1-04
18 February 2004

FINAL ASSESSMENT REPORT

APPLICATION A472

D-TAGATOSE AS A NOVEL FOOD

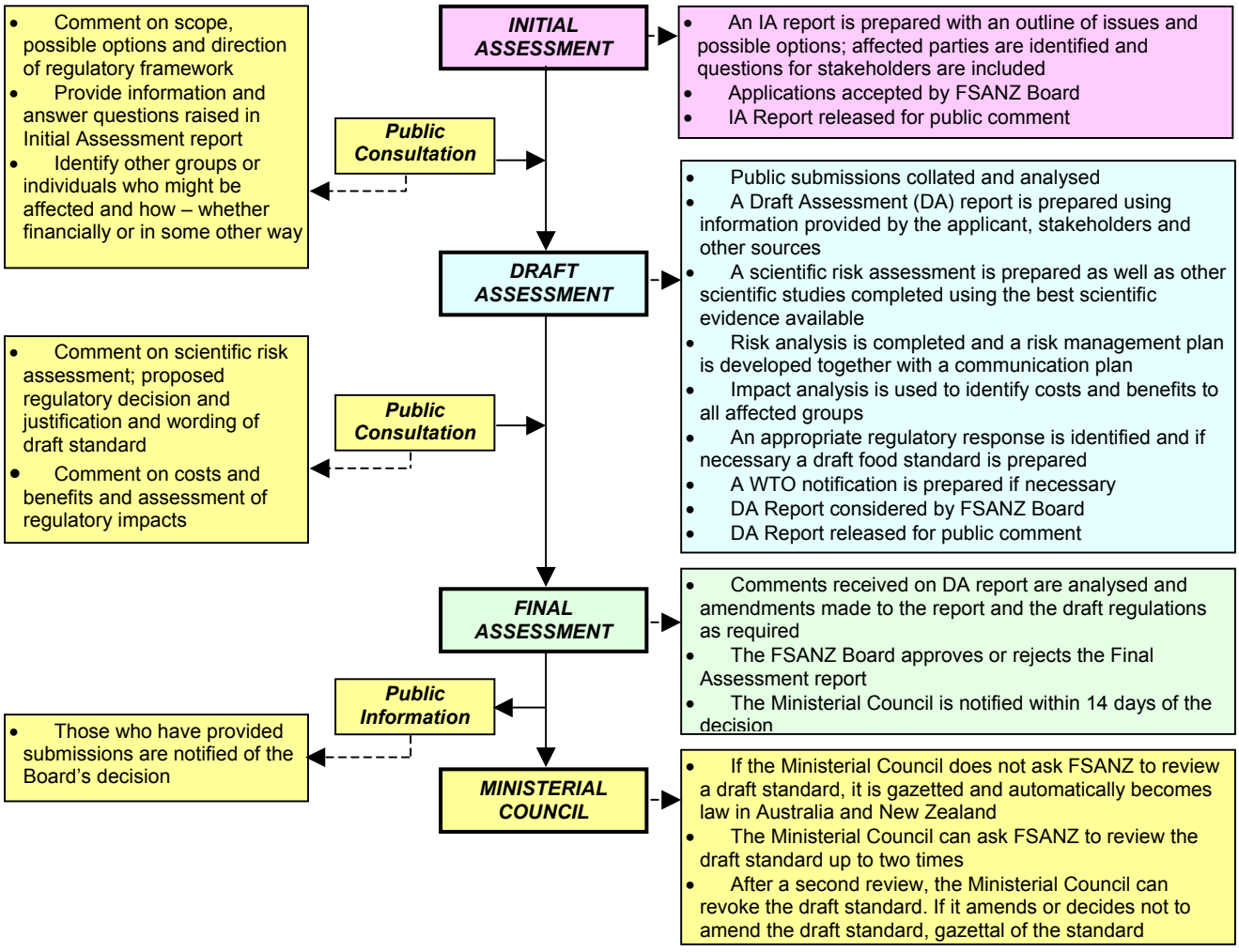
FOOD STANDARDS AUSTRALIA NEW ZEALAND (FSANZ)

FSANZ's role is to protect the health and safety of people in Australia and New Zealand through the maintenance of a safe food supply. FSANZ is a partnership between ten Governments: the Commonwealth; Australian States and Territories; and New Zealand. It is a statutory authority under Commonwealth law and is an independent, expert body.

FSANZ is responsible for developing, varying and reviewing standards and for developing codes of conduct with industry for food available in Australia and New Zealand covering labelling, composition and contaminants. In Australia, FSANZ also develops food standards for food safety, maximum residue limits, primary production and processing and a range of other functions including the coordination of national food surveillance and recall systems, conducting research and assessing policies about imported food.

The FSANZ Board approves new standards or variations to food standards in accordance with policy guidelines set by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) made up of Commonwealth, State and Territory and New Zealand Health Ministers as lead Ministers, with representation from other portfolios. Approved standards are then notified to the Ministerial Council. The Ministerial Council may then request that FSANZ review a proposed or existing standard. If the Ministerial Council does not request that FSANZ review the draft standard, or amends a draft standard, the standard is adopted by reference under the food laws of the Commonwealth, States, Territories and New Zealand. The Ministerial Council can, independently of a notification from FSANZ, request that FSANZ review a standard.

The process for amending the *Australia New Zealand Food Standards Code* is prescribed in the *Food Standards Australia New Zealand Act 1991* (FSANZ Act). The diagram below represents the different stages in the process including when periods of public consultation occur. This process varies for matters that are urgent or minor in significance or complexity.



Final Assessment Stage

FSANZ has now completed two stages of the assessment process and held two rounds of public consultation as part of its assessment of this Application. This Final Assessment Report and its recommendations have been approved by the FSANZ Board and notified to the Ministerial Council.

If the Ministerial Council does not request FSANZ to review the draft amendments to the Code, an amendment to the Code is published in the *Commonwealth Gazette* and the *New Zealand Gazette* and adopted by reference and without amendment under Australian State and Territory food law.

In New Zealand, the New Zealand Minister of Health gazettes the food standard under the New Zealand Food Act. Following gazettal, the standard takes effect 28 days later.

Further Information

Further information on this Application and the assessment process should be addressed to the FSANZ Standards Management Officer at one of the following addresses:

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Assessment reports are available for viewing and downloading from the FSANZ website www.foodstandards.gov.au or alternatively paper copies of reports can be requested from FSANZ's Information Officer at info@foodstandards.gov.au including other general enquiries and requests for information.

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Executive Summary and Statement of Reasons

Food Standards Australia New Zealand (FSANZ) received an Application from Arla Food Ingredients amba (Denmark) on 17 July 2002 seeking to amend Standard 1.5.1 Novel Foods of the *Australia New Zealand Food Standard Code* (the Code) to permit the use of D-tagatose as a novel food ingredient. Standard 1.5.1 requires that novel foods undergo a pre-market safety assessment before they may be sold in Australia and New Zealand.

D-Tagatose can be considered to fall within the scope of the definition of 'sugars' as defined in Standard 2.8.1 - Sugars in the Code and hence can be considered a food. Although D-tagatose is present in small amounts in certain foods, it is regarded as a non-traditional food because it does not have a history of significant human consumption in Australia or New Zealand. D-Tagatose is regarded as a novel food under Standard 1.5.1 because its safety in the context in which it is to be presented had not been determined in the context of the Australian and New Zealand diet.

The objective of this assessment was to determine whether it would be appropriate to amend the Code to permit the use of D-tagatose as a novel food. Such an amendment would need to be consistent with the section 10 objectives of the FSANZ Act.

A range of issues was considered during the assessment of the application. An analysis of the safety and nutritional impact of the use of D-tagatose indicate there are no public health and safety concerns at the anticipated levels of dietary exposure. D-Tagatose has technological properties similar to traditional sugars such as glucose and fructose and can be used as a reducing sugar as it caramelises at elevated temperatures. However, in contrast to traditional sugars, it is only partially absorbed by the body resulting in reduced energy value.

The only regulatory options identified were to approve or not approve the use of D-tagatose as a novel food. The regulatory impact analysis shows that benefits accrue to industry and governments, in terms of enhanced market opportunities and trade (under Australia and New Zealand's requirements under the World Trade Organization), respectively, and to consumers through potentially a greater choice of foods.

Two rounds of public consultation were undertaken. Three submissions were received in the first round and a further six in the second round. The submissions raised a number of scientific and regulatory issues, all of which have been addressed in this Final Assessment Report. Overall, there was general support for the approval of D-tagatose as a novel food.

Conclusions / Statement of Reasons

A variation to the Code, giving approval to the use of D-tagatose as a novel food in Australia and New Zealand is agreed for the following reasons:

- there are no public health and safety concerns associated with the use of D-tagatose as proposed;
- D-tagatose has technological properties similar to traditional sugars;
- the energy value of D-tagatose is lower than traditional sugars;

- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and

- the Regulatory Impact Statement indicates the benefits of the proposed amendment outweigh the costs.

The variation to the Code will come into effect on the date of gazettal.

1. Introduction

An application was received from Arla Food Ingredients amba (Denmark) on 17 July 2002 seeking approval for D-tagatose under Standard 1.5.1 - Novel Foods of the *Australia New Zealand Food Standards Code* (the Code). Work on the Application commenced on 8 August 2002.

2. Regulatory Problem

Under Standard 1.5.1, novel foods are required to undergo a pre-market safety assessment. The purpose of Standard 1.5.1 is to ensure non-traditional foods with features or characteristics that may raise safety concerns will undergo a risk-based safety assessment before they are offered for retail sale in Australia or New Zealand. Novel foods that have been assessed, if approved, are listed in the Table to clause 2 of Standard 1.5.1.

A novel food is defined in Standard 1.5.1 as:

> *... a non-traditional food or food ingredient for which there is insufficient knowledge in the broad community to enable safe use in the form or context in which it is presented, taking into account –*
>
> *(a) the composition or structure of the product;*
> *(b) levels of undesirable substances in the product;*
> *(c) the potential for adverse effects in humans;*
> *(d) traditional preparation and cooking methods; or*
> *(e) patterns and levels of consumption of the product.*

Non-traditional food means a food, which does not have a history of significant human consumption by the broad community in Australia or New Zealand.

D-Tagatose is considered to fall within the scope of the definition of 'sugars' as defined in Standard 2.8.1 - Sugars in the Code and hence is regarded as a food. D-Tagatose is regarded as a non-traditional food because it has no history of significant human consumption in Australia or New Zealand. D-Tagatose is found in small quantities (2 to 800 ppm) in sterilised milk and milk powder as well as in other dairy products, but its safety when added in larger quantities (> 1%, 10000 ppm) to other foods had yet to be determined in the context of the Australia and New Zealand diet. Because of this, D-tagatose was classed as a novel food and therefore required consideration under Standard 1.5.1.

3. Objective

The objective of this assessment was to determine whether it would be appropriate to amend the Code and permit the use of D-tagatose in foods. Such an amendment to the Code needs to be consistent with the section 10 objectives of FSANZ Act.

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives, which are set out in section 10 of the FSANZ Act. These are:

- the protection of public health and safety;

- the provision of adequate information relating to food to enable consumers to make informed choices; and

- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;

- the promotion of consistency between domestic and international food standards;

- the desirability of an efficient and internationally competitive food industry;

- the promotion of fair trading in food; and

- any written policy guidelines formulated by the Ministerial Council.

4. Background

4.1 Properties of D-tagatose

D-Tagatose is a naturally occurring monosaccharide and a stereoisomer of D-fructose. It is an odourless white crystalline solid, with a sweet taste. D-Tagatose is produced from lactose in a two-step process involving enzymatic hydrolysis of lactose to galactose, followed by isomerisation under basic conditions.

D-Tagatose has technological properties similar to traditional sugars such as glucose and fructose and can be used as a reducing sugar as it caramelises at elevated temperatures. However, it is different from traditional sugars in that it is only partially absorbed by the body resulting in reduced energy value. The major fraction of D-tagatose reaches the large intestine unabsorbed (where it undergoes fermentation). D-Tagatose thus offers health advantages as a low energy sugar with low glycaemic index.

4.2 Proposed uses

The Applicant proposes that D-tagatose could be used in the following foods:

- breakfast cereals (ready to eat);
- carbonated diet soft drinks;
- non-carbonated diet soft drinks;
- low fat/fat free ice cream;
- low fat frozen dairy desserts;
- diet/health bars;
- diet soft confectionery;
- hard confectionary;
- icings/frostings; and
- special purpose foods/meal replacements.

4.3 Approvals in other countries

D-Tagatose is available in the United States (US) as a Generally Recognised As Safe (GRAS) dietary ingredient (GRAS Notice No. GRN 000078).

There are no Codex standards relating to D-tagatose.

5. Relevant Issues

5.1 Safety considerations

5.1.1 Safety assessment conducted at Draft Assessment

In the safety assessment conducted at Draft Assessment, FSANZ considered a recent evaluation undertaken at the 57th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2001 and also reviewed more recent studies provided by the Applicant.

The safety assessment of D-tagatose undertaken by JECFA concluded that D-tagatose is a substance of low toxicity, which does not represent a hazard to human health. JECFA allocated an Acceptable Daily Intake (ADI) of '0-80 mg/kg bw/day'[1] for D-tagatose based on concern about its potential to induce glycogen deposition and hypertrophy in the liver and to increase the concentrations of uric acid in serum.

In addition to the above, FSANZ considered new data submitted by the Applicant. The new data consisted of two new studies of toxicity conducted in rats and two new studies of plasma uric acid levels in human volunteers. FSANZ's assessment of the new data confirmed there is no evidence of any public health and safety concern associated with consumption of D-tagatose up to 15 g/day (0.25 g/kg bw/day for a 60 kg adult) even in susceptible individuals (those who have gout or are hyperuricemic). There is some evidence that mild gastrointestinal effects such as nausea, diarrhoea and flatulence may occur in some individuals at doses 30 g/day and above.

FSANZ's toxicology report (**Attachment 2**) contains a summary of JECFA's evaluation from the 57th meeting as well as FSANZ's assessment of the new data.

5.1.2 Additional safety considerations

5.1.2.1 Re-evaluation of D-tagatose at the 61st meeting of JECFA

In June 2003, D-tagatose was re-evaluated by JECFA to consider two new studies of toxicity conducted in rats, and two new studies of plasma uric acid levels in human volunteers[2]. These were the same studies submitted to FSANZ for evaluation by the Applicant.
On the basis of the results from those studies, the Committee concluded that their previous concerns, in relation to liver glycogen deposition and hypertrophy in rats, as well as plasma uric acid levels in humans, had been adequately addressed.

[1] FAO/WHO (2002) Report of fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives, Evaluation of Certain Food Additives and Contaminants, D-Tagatose, p29.
[2] The JECFA report and toxicological monograph are in press

The Committee did however raise new concerns arising from the results of one of the toxicity studies – the two-year study conducted in rats – which demonstrated increased adrenal, kidney and testes weights in rats receiving high doses of D-tagatose. The Committee concluded that the toxicological significance of this finding could not be assessed, as histopathological examination of these tissues had not been undertaken.

The Committee allocated an ADI of 0-125 mg/kg bw/day based on results from human studies which indicate no adverse effects at doses of D-tagatose up to 45 g per day (in three divided doses). In view of the additional uncertainty regarding the nature of the effects observed in the adrenals, kidneys and testes in the two-year rat study, the Committee concluded the new ADI should be temporary.

Following the re-evaluation of D-tagatose by JECFA, a histopathological examination of the adrenals, kidneys and testes retained from the two-year rat study was undertaken and the results were provided to FSANZ for evaluation. The results from the histopathological examinations of these tissues indicated that the effects observed are of no toxicological significance to humans.

Given this, the conclusions reached by FSANZ at Draft Assessment remain valid. That is, there are no public health and safety concerns associated with the use of D-tagatose in food up to 15 g/day (0.25 g/kg bw/day) although mild gastrointestinal effects may be observed at higher dose levels.

5.1.2.2 Individuals with hereditary fructose intolerance

In establishing a temporary ADI for D-tagatose of 0-125 mg/kg bw, JECFA stated that the ADI did not apply to individuals with hereditary fructose intolerance (HFI) due to 1-phosphofructoaldolase (aldolase B) deficiency or fructose 1,6-diphosphatase deficiency.

The question of the suitability of D-tagatose for individuals with HFI has not previously been addressed, nor is FSANZ aware of any direct scientific evidence establishing that individuals with HFI are also intolerant to D-tagatose. However, as D-tagatose is metabolised via the same biochemical pathway as fructose, using the same enzymes, it seems highly probable that D-tagatose would produce the same effects as fructose in individuals with HFI. Because D-tagatose is incompletely absorbed (20%), however, it is expected that such individuals may tolerate several-fold higher intakes of D-tagatose.

This issue raises the question of whether foods containing D-tagatose should carry a mandatory advisory statement to alert individuals with HFI, similar to the statement on foods containing aspartame for individuals with phenylketonuria. The argument being that an individual with HFI would not necessarily recognise D-tagatose as a sugar to be avoided.

HFI is an inherited condition in which affected individuals develop hypoglycaemic and severe abdominal symptoms after ingesting foods containing fructose and its cognate sugars (e.g. sucrose and sorbitol). The condition is considered to be quite rare, the incidence falling somewhere between 1 in 12,000 to 1 in 130,000 live births[3].

[3] James, C.L., Rellos, P., Ali, M., Heeley, A.F. and Cox, T.M. (1996). *J. Med. Genet*. **33:** 837 – 841.

HFI is usually detected in early childhood when infants are weaned from breast milk or infant formula. If the condition remains undiagnosed continued ingestion of these sugars may lead to severe and irreversible liver and kidney damage as well as growth retardation. Once a diagnosis has been established, and provided the tissue damage has not been extensive, the introduction of a fructose-free diet results in rapid alleviation of the acute symptoms followed by recovery. Individuals with HFI typically develop a strong aversion to sweet foods, which serves to protect them from further exposure to the harmful sugars. In addition, diagnosed individuals typically receive dietary counselling to assist them to correctly identify and avoid problem foods.

In Australia and New Zealand, metabolic disorders are managed through a network of clinics, with essentially one clinic in operation per state and New Zealand. In addition, researchers and health professionals working in this field are typically also members of the Australasian Society for Inborn Errors of Metabolism (ASIEM), a special interest group within the Human Genetics Society of Australasia (www.hgsa.com.au/asiem/). Although there is no formal register of individuals with HFI, FSANZ has been advised that most treating physicians would be members of the ASIEM. Individuals with HFI are also assisted directly through the Metabolic Dietary Disorders Association (MDDA) (www.mdda-australia.org), a self-help and support group for sufferers of metabolic disorders and their families.

FSANZ has consulted with the ASIEM regarding the best means of providing information about D-tagatose to individuals with HFI. They advise there can be difficulties when advising patients about the risk associated with specific foods/food ingredients as the content of foods changes often and is not held in any reliable register. In addition to this patients with chronic stable conditions often do not attend specialist clinics and clinic registers are frequently out of date or inaccurate, plus the patient may never have been reviewed by a metabolic physician and may instead be under the care of a general paediatrician or gastroenterologist. For these reasons they consider the best solution would be specific food labelling.

FSANZ has considered this issue and given the very low incidence of HFI, the fact that affected individuals typically display a natural aversion to sweet foods and that D-tagatose will typically be used in foods that a fructose intolerant person would already be avoiding, that most diagnosed individuals are either in the care of a specialist clinic or paediatrician/gastroenterologist, and that there are well established networks for disseminating information regarding metabolic disorders, the use of a mandatory advisory statement was not considered warranted. This is consistent with the labelling of other substances, such as sorbitol, which are also unsuitable for individuals with HFI.

Following a suggestion from the ASIEM, FSANZ will write formally to their Metabolic Physicians and Dietitians Sub Committees and advise them of concerns regarding the suitability of D-tagatose for individuals with HFI and request they advise patients. To ensure that the greatest number of patients are reached, FSANZ will also provide similar advice to the respective Paediatric and Gastroenterology societies in both countries. To assist in the provision of advice to patients, FSANZ will develop a Fact Sheet for distribution to relevant patients and also make this available to the MDDA for placement on their website.

The Applicant has also informed FSANZ they are in the process of preparing the appropriate notifications regarding D-tagatose and HFI for the relevant health professionals and organisations, as well as the medical press.

These notifications concerning the lack of suitability of D-tagatose for individuals with HFI will be circulated before foods containing D-tagatose are placed on the market.

5.2 Food technology assessment

The food technology assessment (**Attachment 3**) concluded that D-tagatose is a naturally occurring sweet-tasting monosaccharide that may be used in a wide range of foods. It could be used in any application permitted by regulation.

5.3 Dietary considerations

Based on US food consumption data (1994-1996, 1998) JECFA has estimated that the mean estimated intake for D-tagatose from all its proposed uses excluding chewing gums and formula diets was approximately 5 g/day and for the 90th percentile group was about 11 g/day. These estimates are based on the use of D-tagatose in all proposed uses at the highest levels. The actual dietary intake would be expected to be much lower.

During Draft Assessment dietary modelling was conducted by FSANZ to estimate the potential dietary intake of D-tagatose in Australia and New Zealand that may result from permitting its use in the foods specified in the application. The full dietary exposure assessment report is attached (**Attachment 4**).

Estimated dietary exposures to D-tagatose were all below 15 g/person/day for all population groups. The estimated mean exposure for consumers of D-tagatose for the Australian population aged 2 years and above was 2.7 g/day. The estimated mean exposure for consumers of D-tagatose for Australian toddlers aged 2 – 4 years was 1.9 g/day and for Australian children aged 5 – 12 years was 3.0 g/day. The estimated mean exposure for consumers of D-tagatose for the New Zealand population aged 15 years and above was 1.9 g/day. The estimated 95th percentile exposures for consumers of D-tagatose for the total Australian and New Zealand populations were 9 g/day and 7.4 g/day respectively. The 95th percentile exposures in children 2-4 years and 5-12 years were 6.9 and 10.5 g/day respectively. Estimates of dietary exposures are not expressed as a per bodyweight figure as it is the bolus dose rather than the per bodyweight dose which is relevant when considering reversible and minor discomforts such as laxation effects.

Estimated short-term exposures were calculated for individual food groups to assess whether gastrointestinal effects were likely. All estimated short-term exposures were below the dose level that mild laxation effects are observed in some individuals.
One exception is individuals consuming large amounts of formulated dietary foods or formulated supplementary sports foods where conservative dietary modelling indicated potential for higher levels of exposure. These products are likely to be infrequently consumed, however, and would mostly be consumed by adults. The modelling for this scenario is also based on the FSANZ estimate of serve size and concentration, which assumes a worst-case scenario. In practice, manufacturers may add lower amounts of D-tagatose.

5.4 Risk assessment for D-tagatose

The data support the safety of D-tagatose at the level of exposure that would be achieved by addition of D-tagatose to a range of foods at the maximum levels provided by the Applicant.

Exposure for all ages for Australian and New Zealand populations is below the level at which mild gastrointestinal effects were observed, even at the 95th percentile (high consumer) exposure level. The highest potential exposure by age group was Australian children 5-12 years at the 95th percentile exposure level (10.5 g/day), which is still below the level at which mild, gastrointestinal effects would be observed (**Attachment 4**).

The potential to exceed the threshold dose for mild gastrointestinal effects is considered low, particularly because the dietary exposure estimates are likely to be over-estimates due to the conservative nature of the assumptions used in the modelling, namely:

- D-tagatose is used in all the foods proposed – this is very unlikely;
- all foods contain D-tagatose at the maximum level proposed;
- food containing tagatose is consumed every day - this tends to overestimate food consumption for high consumers; and
- modelling for short term exposure assumes that individual foods eaten over a 24 hour period were in fact eaten in one hit – food is more likely to be consumed over the course of the day (e.g. confectionery).

The data reflecting a single eating occasion exposure suggested that Australian adults consuming large amounts of formulated dietary foods, or formulated supplementary sports foods (95th percentile consumption level) could potentially have a single consumption of 59 g D-tagatose/day on one eating occasion, however, these products are likely to be infrequently consumed. The estimates are a worst-case scenario based on conservative assumptions.

In conclusion there are no public health and safety concerns associated with the use of D-tagatose in foods as proposed. As better information becomes available on the actual use levels of D-tagatose in various foods, more accurate estimates of dietary exposures will be possible and the public health and safety concerns reassessed, for high intake consumers. It is therefore proposed that FSANZ monitors the use of D-tagatose (and possibly other food ingredients which can cause GI effects at high dose levels) in 3-5 years, in order to obtain a better estimate of dietary exposure and the impact on public health and safety.

5.5 Nutritional considerations

No scientific evidence has been identified linking D-tagatose consumption to a potential decrease in the bioavailability or intake of essential micronutrients. There has been some suggestion that D-tagatose consumption could influence the absorption of the macronutrient fructose due to similarities in the structures of the two substances. However, scientific evidence reviewed at the 55th meeting of JECFA[4] indicated that a high intake of D-tagatose does not significantly affect the intestinal absorption of fructose.

On the basis of the JECFA outcome, it is concluded that the main nutritional effect of D-tagatose consumption will be a reduction in dietary energy intake, which is the intended purpose of using a reduced energy sugar substitute.

[4] FAO/WHO (2001) Report of fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives, Evaluation of Certain Food Additives and Contaminants, D-Tagatose, p13.

Therefore, the use of D-tagatose as a novel food ingredient is unlikely to have a significant impact on any other nutritional aspects when considered in the context of the overall diet.

5.6 Energy value for D-tagatose

About 20-25% of ingested D-tagatose is absorbed from the small intestine. The absorbed fraction is metabolised via the same pathway as fructose, with the remaining unabsorbed fraction being available for fermentation in the large bowel.

Standard 1.2.8 Nutritional Information Requirements lists energy values of approved food ingredients in Table 1 to subclause 2(2). The Applicant initially requested an energy value for D-tagatose based on Net Metabolisable Energy (NME), but withdrew this request when it was identified that Metabolisable Energy (ME) values could only be used in accordance with the requirements of the FSANZ report 'Derivation of energy factors for specific food components not already listed in Standard 1.2.8' (FSANZ Guidelines).

The FSANZ Guidelines have been used as the basis for calculating the energy value of D-tagatose, with the supporting experimental evidence for these calculations considered at Draft Assessment (**Attachment 5**). The metabolisable energy factor for D-tagatose is best reflected by a value of 11 kJ/g. Table 2 of subclause 2(2) of Standard 1.2.8 will be amended to include this energy factor.

5.7 Issues raised in public submissions

5.7.1 Issues raised during Draft Assessment

Comment: Australian Food and Grocery Council argues that before accepting the application as a novel food FSANZ needs to determine that it is a non-traditional food and that there is insufficient knowledge in the broad community to enable its safe use; further, if FSANZ finds that it is safe for human consumption, then it cannot be listed as a novel food.

Response: The object of the Novel Food Standard is to assess the safety of non-traditional food for which there is 'there is insufficient knowledge to enable safe use' in the broader community. Prior to the application, D-tagatose at the proposed levels of use had not undergone a safety assessment in the context of the Australian and New Zealand diets. There was therefore insufficient knowledge in the broad community to ensure safe use in the form in which it is presented. The safety of D-tagatose, in the context of Australia and New Zealand, has been assessed by FSANZ as a consequence of D-tagatose being classified as a novel food. The safety assessment showed subsequently that D-tagatose is safe for human consumption, but without the due process required for novel food assessment, it would not have been possible for FSANZ to determine its safety.

Comment: Department of Health, WA, is 'disappointed that FSANZ had taken significant direction from the USFDA assessment and approval of D-tagatose, and that there was no apparent effort to establish the relevance to the Australian setting and population'.

Response: The Initial Assessment Report merely states the issues and current regulatory status of the product around the world relating to the application. A complete assessment of the product is carried out by FSANZ only after gathering and assessing comments from all sources through the public submission process. The Draft Assessment Report describes toxicological and other evaluations carried out by FSANZ staff.

5.7.2 Issues raised during Final Assessment

Comment: A further submission was received from the AFGC, which stated that D-tagatose is not a novel food and that FSANZ is incorrectly interpreting the definition of *non-traditional food* in Standard 1.5.1. The AFGC argues that:

- as D-tagatose is already standardised as a sugar under Standard 2.8.1, it is not a novel food;

- as D-tagatose is present in milk and because of the widespread use of milk and milk products, D-tagatose cannot be classified as a non-traditional food; and

- as FSANZ is not proposing to place any restrictions on the use of D-tagatose, it can only be concluded that FSANZ considers there is sufficient knowledge in the broad community to enable safe use. This being the case, D-tagatose fails to fit the definition of a novel food.

The AFGC recommends that FSANZ reject the application on the basis that D-tagatose is neither a non-traditional food nor a novel food and that its classification as a sugar under Standard 2.8.1 makes it a standardised food and provides provision for its sale and addition to food as an ingredient.

Response: D-Tagatose, as a hexose monosaccharide, falls within paragraph (a) of the definition of sugars in Standard 2.8.1- Sugars by virtue of its chemical structure. However, this does not give automatic approval as a food, as foods must also meet the requirements of the *General Food Standards* in Chapter 1 of the Code. The purpose of Standard 2.8.1 is to provide a definition and any compositional requirements, not to give authorisation for use.

FSANZ considers D-tagatose to be a non-traditional food because the proposed food uses would lead to a significant increase in consumption by the broad community in Australia or New Zealand. FSANZ acknowledges there has been some consumption of D-tagatose in foods such as milk and other dairy products; however, D-tagatose is present at very low levels in these foods so there is no history of significant human consumption by the broad community in Australia or New Zealand. FSANZ's evaluation therefore classifies it as a non-traditional food as, according to the proposed food uses, there will be a significant increase in consumption in Australia and New Zealand if D-tagatose is permitted as a novel food in Standard 1.5.1.

The object of the Novel Food Standard is to assess the safety of non-traditional food for which there is 'there is insufficient knowledge to enable safe use' in the broader community. Prior to the application, D-tagatose had not undergone a safety assessment in the context of the Australian and New Zealand diets. There was therefore insufficient knowledge in the broad community to enable safe use in the form in which it is presented.

The safety of D-tagatose has now been assessed by FSANZ as a consequence of D-tagatose being classified as a novel food. The safety assessment shows that D-tagatose is safe for human consumption, when used in the manner proposed by the Applicant, which is consistent with Good Manufacturing Practice (GMP).

Even though FSANZ's assessment has shown that D-tagatose can cause gastro-intestinal effects at high levels of exposure, the decision to not impose specific conditions of use on D-tagatose does not mean that D-tagatose should no longer be considered as a novel food. Whether or not there are conditions of use is not a criterion for determining the novelty of the food under Standard 1.5.1, and the standard itself envisages approvals of novel foods without any conditions of use.

Comment: The Food Technology Association of Victoria (FTA Victoria) expressed concern that D-tagatose has only been accepted for food use in the United States and that no additional information was provided by FSANZ on its status in other countries. The New Zealand Food Safety Authority (NZFSA) also asked if the applicant has applied for approval in Denmark or the European Union and whether approval had not been given for any reason.

Response: To FSANZ's knowledge, no other countries other than Australia/New Zealand and the United States have considered D-tagatose. It should be noted however that in addition to the GRAS evaluation done for the United States market and the evaluation conducted by FSANZ, D-tagatose has also been thoroughly evaluated by JECFA, who have found it to be a substance of low toxicity, which does not represent a hazard to human health.

Comment: FTA Victoria is also concerned that although D-tagatose is derived from dairy sources it will not be labelled as such.

Response: D-Tagatose occurs naturally in sterilised milk and milk powder as well as other dairy products but for the proposed food uses it is not derived from these sources and therefore is not a milk product.

Comment: The New Zealand Food Safety Authority (NZFSA) requested guidance on the declaration of D-tagatose, stating that as with trehalose, the limitations on the generic term 'sugar' under Standard 1.2.4[5] mean that D-tagatose could not be described as sugar in the ingredient list.

Response: D-Tagatose would be labelled according to current labelling requirements of any ingredient in food as described in Standard 1.2.4 Labelling of Ingredients, in particular, Clause 4 (b) which pertains to a requirement of a description of the true nature of the ingredient. By virtue of the limitations on the generic name 'sugar' under Standard 1.2.4, the name D-tagatose would be used with the addition of other information to qualify or clarify the name, provided it was not false and misleading to consumers.

[5] Sugar may be used to describe; white sugar, white refined sugar, caster sugar, castor sugar, loaf sugar, or cube sugar, icing sugar, coffee sugar, coffee crystals, raw sugar. The word 'sugars' must not be used in a statement of ingredients.

Comment: The AFGC suggested that the reference to Standard 1.3.4 - Identity and Purity - in the current drafting should be amended to *Must comply with the requirements of Standard 1.3.4* rather than the present words *May only be added to food according to Standard 1.3.4* as Standard 1.3.4 does not set conditions under which substances can be added to food.

Response: FSANZ has determined it is not necessary to make reference to Standard 1.3.4 as a condition of use, as that Standard is of general application in any event. As a consequence, the drafting (**Attachment 1**) has been amended.

Comment: The NZFSA stated that it would be useful for FSANZ to consider if there are any nutritional or public health and safety issues arising from the consumption of both trehalose and D-tagatose. For example, if consumed at around the same time are there differences of any consequence in how the ingredients are metabolised and are there any interactions between the substances.

Response: Trehalose, a disaccharide, is broken down (metabolised) in the small intestine to glucose by the enzyme trehalase. The glucose is readily absorbed and metabolised. The metabolism of trehalose resembles maltose or starch in that both products are absorbed in the form of glucose and very little is absorbed as the parent trehalose. Since trehalose is similar to maltose or starch it may be considered nutritionally equivalent.

In the case of D-tagatose, about 20-25% is absorbed from the small intestine, leaving 75-80%, which is available for fermentation in the large bowel. The absorbed portion is metabolised in the liver by the same pathway as fructose. The metabolites of this pathway are then directly incorporated either into the glycolytic or gluconeogenic pathways.

Trehalose and D-tagatose have the same ultimate metabolic fate, in that their metabolites feed into the same metabolic pathways, but because they are treated differently in the gastrointestinal tract – trehalose is metabolised first to glucose then is readily absorbed whereas D-tagatose is only poorly absorbed and is not metabolised first – it would appear there is no biochemical or physiological basis for concern about an interaction between the two substances in the gastrointestinal tract.

The nutritional assessment concluded that the main nutritional effect of D-tagatose consumption will be a reduction in dietary energy intake, therefore its use is unlikely to have a significant impact on any other nutritional aspects when considered in the context of the overall diet. This includes the consumption of trehalose, which can be considered nutritionally equivalent to maltose or starch.

6. Regulatory Options

FSANZ is required to consider the impact of various regulatory (and non-regulatory) options on all sectors of the community, which includes consumers, the food industry and governments in both Australia and New Zealand. The benefits and costs associated with the proposed amendment to the Code are analysed in a Regulatory Impact Assessment.

The regulatory options under consideration were:

Option 1. Not permit the use of D-tagatose.

Option 2. Permit the use of D-tagatose.

7. Impact Analysis

7.1 Affected Parties

Parties possibly affected by the options outlined include:

1. Food industry wishing to manufacture and sell food products containing D-tagatose.
2. Consumers who may wish to consume foods containing D-tagatose.
3. Government agencies enforcing the food regulations.

7.2 Impact of the regulatory options

7.2.1 Option 1. Not permit the use of D-tagatose

As no safety concerns have been identified, there would be no benefit to government, consumers or industry in maintaining the prohibition on sale on D-tagatose.

Should D-tagatose not be approved there would be no immediate impact on government; however such a decision may be regarded as unnecessarily trade restrictive.

Parties potentially disadvantaged by not permitting this substance are the manufacturers of D-tagatose and producers who wish to use it in the manufacture of their final food products as well as consumers who may benefit from its use.

7.2.2 Option 2. Permit the use of D-tagatose

The benefits of this option would accrue primarily to the food industry and consumers with little or no direct impact on government.

This option is the preferred option because it potentially offers significant benefit to all sectors with very little associated negative impact.

8. Consultation

8.1 Public Consultation

The Initial Assessment of this Application was advertised for public comment between 9 October and 20 November 2002. A total of three submissions were received during this period and a summary of these is included in **Attachment 6** to this Report.

Following the first round of consultation, FSANZ carried out an assessment of the application, including a safety evaluation, taking into account the public comments received. Specific issues raised were addressed in the Draft Assessment Report, which was released for public comment between 21 May and 2 July 2003. In response to the release of the Draft Assessment Report, a further six submissions were received. These are summarised in **Attachment 6** to this Report.

8.2 World Trade Organization (WTO)

Australia and New Zealand are members of the WTO and are bound as parties to WTO agreements. In Australia, an agreement developed by the Council of Australian Governments (COAG) requires States and Territories to be bound as parties to those WTO agreements to which the Commonwealth is a signatory.

Under the agreement between the Governments of Australia and New Zealand on Uniform Food Standards, FSANZ is required to ensure that food standards are consistent with the obligations of both countries as members of the WTO.

In certain circumstances Australia and New Zealand have an obligation to notify the WTO of changes to food standards to enable other member countries of the WTO to make comment. Notification is required in the case of any new or changed standards that may have a significant trade effect and which depart from the relevant international standard (or where no international standard exists).

Amending the Code to allow foods to contain D-tagatose was not notified to the WTO under either the Technical Barrier to Trade (TBT) or Sanitary and Phytosanitary Measure (SPS) agreements as the permission was unlikely to significantly affect trade. Suppliers of food products are not required to take up permissions granted through amendments to the Code.

9. Conclusion and Recommendation

A variation to the Code, giving approval to the use of D-tagatose as a novel food in Australia and New Zealand is agreed for the following reasons:

- there are no public health and safety concerns associated with the use of D-tagatose as proposed;
- D-tagatose has technological properties similar to traditional sugars;
- the energy value of D-tagatose is lower than traditional sugars;
- the proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act; and
- the Regulatory Impact Statement indicates the benefits of the proposed amendment outweigh the costs.

10. Implementation and Review

The draft variation is to come into effect on the date of gazettal.

ATTACHMENTS

1. Draft variation to the *Australia New Zealand Food Standards Code*
2. Safety assessment report
3. Food technology assessment report
4. Dietary exposure assessment report
5. Energy factor for D-tagatose
6. Summary of public submissions

ATTACHMENT 1

DRAFT VARIATIONS TO THE *AUSTRALIA NEW ZEALAND FOOD STANDARDS CODE*

To commence: on gazettal

[1] *Standard 1.2.8 of the Australia New Zealand Food Standards Code is varied by inserting in the* Table 2 to subclause 2(2) –

D-Tagatose	11

[2] *Standard 1.5.1 of the Australia New Zealand Food Standards Code is varied by inserting in the* Table to clause 2 –

D-Tagatose	

ATTACHMENT 2

SAFETY ASSESSMENT REPORT

D-TAGATOSE AS A NOVEL FOOD INGREDIENT

INTRODUCTION

Structure & Properties

D-Tagatose is a stereoisomer (epimer) of D-fructose, differing in the spatial configuration of the hydroxyl group at C-4. D-Tagatose is produced from enzymatic hydrolysis of food-grade lactose to D-galactose followed by chemical isomerisation reaction by calcium hydroxide to form D-tagatose, which is then purified by mineralisation, ion exchange chromatography and re-crystallisation.

Natural occurrence

D-Tagatose is found in sterilised milk and milk powder as well as in other dairy products (between 2 to 800 ppm).

Evaluation by JECFA

D-Tagatose was evaluated in 2000 and 2001 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[1,2] which allocated an ADI of 0-80 mg/kg bw/day based on a NOEL of 0.75 g/kg bw/day and a safety factor of 10. The NOEL was derived from a 28-day study in humans.

Following provision of data from new toxicology and human studies, D-tagatose was re-evaluated by JECFA at their 61st meeting in June 2003[3]. The Committee determined that the previous NOEL of 0.75 g/kg bw/day was still applicable and applied a safety factor of 3 to allow for inter-individual variation. The Committee applied an additional safety factor of 2 to account for uncertainty regarding new findings in a 2-year toxicity study in rats. The previous ADI was therefore removed, and replaced with an ADI of 0-125 mg D-tagatose/kg bw. The new ADI is temporary pending provision of further information regarding new findings in the rat study. The temporary ADI does not apply to individuals with hereditary fructose intolerance due to 1-phosphofructoaldolase (aldolase B) deficiency or fructose 1,6-diphosphatase deficiency.

[1] FAO/WHO (2001) Report of fifty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives, Evaluation of Certain Food Additives and Contaminants, D-Tagatose, p13.

[2] FAO/WHO (2002) Report of fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives, Evaluation of Certain Food Additives and Contaminants, D-Tagatose, p29.

[3] WHO (2003). Report of the 61st Joint FAO/WHO Expert Committee on Food Additives, Rome, 10-19 June 2003.

Current evaluation based on JECFA review plus additional data

FSANZ has not reviewed all studies again in detail – instead FSANZ has reviewed key studies used to establish the ADI.

Condensed versions of the three reviews by JECFA are given below followed by a detailed toxicological assessment of the new data submitted to FSANZ.

REPORT FROM JECFA 55

D-Tagatose is an epimer of D-fructose and is produced from D-galactose by isomerisation under alkaline conditions in the presence of calcium. It is used as a sweetener, texturiser, stabilizer, humectant and formulation aid. The Committee had not previously evaluated D-tagatose.

In a study in rats adapted to consumption of D-tagatose, 80-90% of an oral dose was absorbed.

The predicted daily intake of D-tagatose was determined on the basis of data on food consumption in the United States and the assumption that all foods in the categories being considered contain the additive at the maximum technological level. For the population of the US, intake of this sugar from all proposed uses (except chewing-gum, dietary supplements and meal replacements) was predicted to be 9 g/day for consumers with mean intakes and 18 g/day for those with intakes at the 90th percentile. Intake from chewing gum was predicted to be 4 g/day for consumers with mean intakes and 8 g/day for those with intakes at the 90th percentile. Similar results were obtained for the predicted intakes of young people aged 3-5 years, 6-12 years and 13-19 years. The estimated intakes of D-tagatose from dietary supplements and meal replacements were 3 g and 5 g per eating occasion, respectively. An analysis based on the same assumptions, combined with available data on food consumption from Australia and the European Union, showed that the predicted intake of D-tagatose would be similar in these regions.

D-Tagatose was tested in Sprague-Dawley rats in a series of short-term toxicity studies. The observed increases in liver weights and liver hypertrophy were found to be due, at least in part, to glycogen accumulation. The hepatic changes were partially reversed after exclusion of D-tagatose from the diet. Recovery from the induced liver hypertrophy took longer than recovery from glycogen accumulation. Data from short-term studies of the mechanism of glycogen accumulation suggest that the hepatic changes are due to physiological changes in Sprague-Dawley rats and that Wistar rats are less sensitive to expression of these effects.

The precise metabolic pathway of D-tagatose that leads to gluconeogenesis has not been established. D-Tagatose is metabolized more slowly than fructose. A similar biochemical effect characterized by glycogen accumulation occurs in patients with hereditary fructose intolerance, and this reaction can increase the rates of purine breakdown and accumulation of uric acid. D-Tagatose is more effective than fructose in increasing the concentration of uric acid in serum.

In two studies of developmental toxicity in Sprague-Dawley rats, minimal effects were observed in dams, including reduced food consumption at doses greater than 12 g/kg bw/day and initial depression of weight gain, which returned to normal later in the study.

A dose-related, statistically significant increase in liver weight was found, but histological examination of the livers revealed no abnormalities. No effects were found in either study on reproductive or developmental parameters.

The results of tests for genotoxicity in vitro and in vivo were consistently negative.

A number of studies of gastrointestinal effects have been conducted in healthy human volunteers and in patients with type 2 diabetes[4]. Nausea and adverse gastrointestinal effects were reported in healthy adults given D-tagatose at high doses. Studies in which baseline serum concentrations of insulin and glucose were investigated showed no effect following administration of single or multiple doses, but a decreased glycaemic response was observed when D-tagatose was given before a glucose tolerance test.

Elevated serum uric acid concentrations were reported in three out of six studies in which this parameter was measured; in two of these studies, the values exceeded the normal range.

In the three studies in which parameters indicative of liver function or hepatic changes were measured, no effects were observed.

On the basis of the available data, the Committee concluded that D-tagatose is not genotoxic, embryotoxic or teratogenic. The Committee noted that the increased liver weights and hepatocellular hypertrophy seen in Sprague-Dawley rats occurred concurrently with increased glycogen deposition; however, the reversal of increased glycogen storage after removal of D-tagatose from the feed occurred more rapidly than regression of the liver hypertrophy.

Although the gastrointestinal symptoms seen in adult humans with the expected daily intake of D-tagatose were minor, the Committee was concerned about the increased serum uric acid concentrations observed in a number of studies in humans following administration of either single or repeated doses of D-tagatose. Similar increases are seen with other sugars, such as fructose, but D-tagatose appears to be a more potent inducer of this effect. The Committee noted that the effect of D-tagatose has not been studied in people prone to high serum uric acid concentrations.

The Committee concluded that an ADI could not be allocated to D-tagatose because of concern about its potential to induce liver glycogen deposition and hypertrophy and to increase serum uric acid concentrations. Two studies in Sprague-Dawley and Wistar rats were submitted that might help to resolve the relevance of the induction of liver glycogen deposition and hypertrophy, but the reports were received in draft form and were not suitable for consideration at the present meeting. Before reviewing the compound again, the Committee would wish to evaluate the final reports of these studies and data to clarify the extent, mechanism and toxicological consequences of the increased serum uric acid concentrations observed in humans exposed to D-tagatose.

A toxicological monograph and new specifications were prepared.

[4] Donner TW, Wilber JF, Ostrowski D, *D-Tagatose, a novel hexose: acute effects on carbohydrate tolerance in subjects with and without type 2 diabetes,* **Diabetes Obes Metab 1999 Sep;1(5):285-91.**

REPORT FROM JECFA 57

D-Tagatose is a ketohexose, an epimer of D-fructose inverted at C-4, with a sweet taste. It is obtained from D-galactose by isomerisation under alkaline conditions in the presence of calcium.

D-Tagatose was evaluated by the Committee at its fifty-fifth meeting (Annex 1, reference 149), when it concluded that the available data indicated that D-tagatose is not genotoxic, embryotoxic or teratogenic. It noted that the increased liver weights and hepatocellular hypertrophy seen in Sprague-Dawley rats occurred concurrently with increased glycogen deposition; however, the reversal of increased glycogen storage after removal of D-tagatose from the feed was more rapid than regression of the liver hypertrophy. Although the gastrointestinal symptoms seen in adult humans with the expected daily intake of D-tagatose were minor, the Committee was concerned about the increased serum uric acid concentrations observed in a number of studies in humans after administration of either single or repeated doses of D-tagatose. Similar increases were observed with other sugars, such as fructose, but D-tagatose appeared to he a more potent inducer of this effect. The Committee also noted that this effect of D-tagatose had not been studied in persons prone to high serum uric acid concentrations. The Committee concluded that an ADI could not be allocated for D-tagatose because of concern about its potential to induce glycogen deposition in the liver and liver hypertrophy and to increase the serum concentration of uric acid.

Two studies of up to 7 days' duration in Wistar and Sprague-Dawley rats given repeated doses of D-tagatose were submitted to the Committee at its fifty-fifth meeting, but the reports were received only in draft form and were not suitable for consideration at that time. The Committee therefore asked for the final reports and for further data to clarify the extent, mechanism and toxicological consequences of the increased serum uric acid concentrations observed in humans exposed to D-tagatose. At its present meeting, the Committee reviewed the reports of the two studies in rats, the results of a study in volunteers (on the relevance of the glycogen deposition and liver hypertrophy) and some published studies on the increased uric acid concentrations in serum after intake of D-tagatose, other sugars and other food components.

Biological data: Review of the results of the studies considered by the Committee at its fifty-fifth meeting and comparisons with the data reviewed at the present meeting revealed a difference in sensitivity between Wistar and Sprague-Dawley rats. Sprague-Dawley rats given D-tagatose at a concentration of 50 g/kg of diet for 28 days showed increased hepatic glycogen only when they had not been fasted the night before necropsy, and this effect was not associated with any microscopic changes in the liver. In a 90-day study in which Sprague-Dawley rats were killed after fasting overnight, administration of D-tagatose at a concentration of 50 g/kg of diet had no adverse effect on the liver. In a 6-month study in Wistar rats in which the animals were killed after fasting 7, 14 and 28 days and 3 and 5 months after treatment, administration of D-tagatose at concentrations of up to 100 g/kg of diet had no adverse effects Wistar rats are therefore less susceptible to the hepatic effects of D-tagatose than Sprague-Dawley rats. As D-tagatose stimulated glycogen deposition to a similar degree in the two rat strains in short-term studies, the difference is likely to occur at a later stage, during glycogen-induced or other stimulation of liver growth.

The authors suggested that the increase in normal liver mass seen in fasted rats fed diets containing 100 or 200 g/kg D-tagatose is triggered by increased postprandial storage of liver glycogen resulting from simultaneous feeding of D-tagatose and glucose equivalents. In order to test this hypothesis, the effects of separate and simultaneous administration of D-tagatose and glycogen precursors on liver weight and glycogen level were investigated in Wistar and Sprague-Dawley rats. The results neither supported nor invalidated the hypothesis.

As several studies have been performed in healthy volunteers and in patients with diabetes, the number of persons varying from 4 to 73, the Committee based its toxicological evaluation on the data from these studies. The length of these studies varied from several days to several weeks; one study of 12 months' duration included only a limited number of patients with type 2 diabetes. The toxicological aspects investigated included gastrointestinal effects, increased serum uric acid concentrations and hepatic effects.

Mild gastrointestinal symptoms were reported in only one study, in 3 of 10 patients with type 2 diabetes receiving D-tagatose at 10 g/day for several days, whereas in other studies diarrhoea was observed only in patients receiving 25 g three times daily for 8 weeks. In healthy individuals, administration of a single dose of 30 g induced diarrhoea in some persons only, whereas other studies showed no laxative effect of single doses of D-tagatose as high as 75 g.

The serum or plasma concentration of uric acid was increased transiently in some studies, but the increased uric acid concentration was above the normal range for a number of days in only one study of persons receiving 75 g/day. The other studies showed either no increase or a transient increase in serum uric acid concentrations within the normal range.

In a 28-day study in which 15 g of D-tagatose or 15 g of sucrose were given three times daily to volunteers, magnetic resonance imaging was used to determine liver volume, and glycogen concentrations and several clinical chemical parameters were measured[5]. The results did not reveal any relevant effect on the liver. In addition, no diarrhoea and no increase in serum uric acid concentration were observed. Therefore, the NOEL was 45 g/person per day, equivalent to 0.75 g/kg of body weight per day (for a person weighing 60 kg).

The Committee considered the 28-day study in which humans received a daily dose of 45 g of D-tagatose or sucrose in three divided doses as most representative of human dietary intake and therefore most relevant for assessing the acceptable intake of D-tagatose accurately. While effects were observed after administration of a single dose of 75 g, no effects were seen following administration of three daily doses of 15 g of D-tagatose, equivalent 0.75 g/kg of body weight per day. The Committee established an ADI of 0-80 mg/ kg of body weight on the basis of this NOEL and a safety factor of 10.

Assessment of intake: D-Tagatose is proposed for use as a bulk sweetener in low-energy foods, such as edible ices (at a concentration of 3 g/kg), chewing gum and confectionery (at 15 g/kg), breakfast cereals (at 15 g/kg) and soft drinks (at 1 g/kg). At its present meeting, the Committee considered that the predicted intakes of D-tagatose determined at the fifty-fifth meeting, which were based on the manufacturers' proposed levels of use and individual dietary records in several countries, were conservative.

[5] Boesch C, Ith M, Jung B, Bruegger K, Erban S, Diamantis I, Kreis R, Bar A, *Effect of oral D-tagatose on liver volume and hepatic glycogen accumulation in healthy male volunteers,* **Regul Toxicol Pharmacol 2001 Apr;33(2):257-67**

This was because use had been assumed in the entire food category rather than only in the low-energy food component. The mean consumer intakes of D-tagatose from all proposed uses (except chewing gum, dietary supplements and meal replacements) predicted for Australia, the Member States of the EU and the US ranged from 3 to 9 g/day (63-190% of the ADI), and the predicted intakes by persons at high percentiles of consumption were up to 18 g/day (375% of the ADI). On the basis of the information on possible uses, the Committee concluded that the ADI for D-tagatose may be exceeded by some groups of the population.

A toxicological monograph was prepared. The specifications prepared by the Committee at its fifty-fifth meeting were maintained.

REPORT FROM JECFA 61

At the sixty-first meeting, the Committee reviewed the results of two new studies of toxicity conducted in rats and of two new studies of plasma uric acid levels in human volunteers, which were submitted by the sponsor with a request for a re-evaluation.

Studies in rats previously reviewed by the Committee had focused on the hepatic effects of D-tagatose, in particular, increased liver weight and hypertrophy. These studies indicated that these effects were due, at least in part, to glycogen accumulation, and that the Sprague-Dawley strain of rats was more sensitive to these effects than Wistar rats. The new 28-day study investigating the effects of 20% D-tagatose in the diet has shown that, of six rat strains, the largest increase in liver weight occurred in Sprague-Dawley rats, and the smallest increase in Wistar rats, confirming previous observations of strain differences. The role of glycogen however was not specifically investigated.

In a two-year study in Wistar rats, the administration of diets containing 2.5,5 or 10% D-tagatose and 10% D-tagatose + 10% fructose did not result in histological changes in the liver, although increased liver weights were reported in male and female rats fed on 10% D-tagatose. In addition to this, increased absolute and relative adrenal weights were observed in female rats at all doses of D-tagatose, but not in those receiving fructose alone. Increased adrenal weights were reported in male rats fed on 5% and 10% D-tagatose. The weights of the kidneys in females, the testes in males and the caecums in both sexes were also increased at 10% D-tagatose, and in some cases at 5% D-tagatose. The Committee concluded that in the absence of histopathological confirmation of the nature of the changes induced by D-tagatose in the adrenals, kidneys and testes, it is not possible to assess the toxicological significance of these changes to humans.

Two new human studies showed that a single dose of 30 g D-tagatose to small numbers of health volunteers, or 15 g D-tagatose to hyperuricemic individuals, had no biologically significant effects on uric acid production or excretion, and no recorded gastrointestinal effects. At its forty-eighth meeting, the Committee noted that D-fructose increases uric acid production by accelerating the degradation of purine nucleotides, probably by hepatocellular depletion of inorganic phosphate resulting from accumulation of ketohexose-1-phosphate. Degradation of D-tagatose-1-phosphate is slower than that of D-fructose-1-phosphate, and therefore the hyperuricemic effect of D-tagatose may be greater than that of D-fructose, and hyperuricemic individuals are a potentially vulnerable group for adverse effects of D-tagatose. The new study demonstrated no increase in serum uric acid within four hours of consumption of 15 g of D-tagatose by this vulnerable group.

In studies reviewed previously by the Committee, the maximum increases in serum uric acid and D-tagatose, and the maximum decrease in serum ATP, were seen within one hour of ingesting D-tagatose. It is therefore anticipated that no effect would be expected in hyperuricemic individuals following repeated consumption of 15 g of D-tagatose at subsequent meals.

The Committee concluded that the two-year study in rats demonstrated that the previously reported liver glycogen deposition and hypertrophy did not result in histopathological changes following long term administration of D-tagatose, and thus addressed concerns expressed at the fifty-fifth meeting. However, the study identified new findings, namely increased adrenal, kidney and testes weights. The Committee considered that these changes might have been due to high osmotic load resulting from the high dietary doses administered, but as a histopathological examination of the tissues had not been done this could not be confirmed. Pending provision of the histopathology data, the Committee confirmed that the human data provided the most relevant basis for assessing the acceptable intake of D-tagatose.

At the fifty-seventh meeting, the Committee identified a NOEL for healthy individuals of 45 g D-tagatose per day in three divided doses. The study on hyperuricemic individuals discussed at the current meeting indicated that the NOEL is also applicable to this vulnerable group. The Committee considered that a safety factor of 3 would be appropriate to allow for inter-individual variation. In view of the additional uncertainty regarding the nature of the effects observed in the adrenals, kidneys and testes in the two-year study in rats, the Committee concluded that the ADI should be temporary and applied an additional safety factor of 2. The previous ADI was removed, and on the basis of the NOEL of 0.75 g/kg bw/day, and a safety factor of 6, the Committee allocated a temporary ADI of 0-125 mg D-tagatose/kg bw.

The temporary ADI does not apply to individuals with hereditary fructose intolerance due to 1-phosphofructoaldolase (aldolase B) deficiency or fructose 1,6-diphosphatase deficiency. The Committee requested information on the histological examination of the adrenals, kidneys and testes of the rats from the two-year study by 2006.

REVIEW OF THE NEW TOXICOLOGY DATA

Chronic toxicity and carcinogenicity study with D-tagatose and fructose in Wistar rats. *Report Number V 4533* by Lina BAR and Kuper CF. TNO Nutrition and Food Research, The Netherlands, *August 2002*.

Test materials:	D-tagatose; 20% fructose
Control materials	pregelatinised potato starch
Test Species:	Young (5-6 weeks old) Wistar albino rats (HsdCpb:WU), 50 male and 50 female per group dosed by administration in diet.
Dose:	0, 2.5, 5 or 10% w/w in diet for 24 months.
Guidelines:	USFDA 1982-Toxicological Guidelines, OECD Guideline for Testing of Chemicals 451, May 1981 and EC Guideline 88/302/EC.

Test articles and control material

D-Tagatose and fructose were obtained as a crystalline white powders with > 99% purity. The control substance was a pre-gelatinised potato starch as a coarse white powder.

Study conduct

Four groups of rats (50/sex/group) were treated with D-tagatose in the diet at 2.5, 5, 10 or 10% D-tagatose + 10% fructose (equivalent to 1.0, 2.0 or 4.0 g/kg bw/day for males and 1.2, 2.5 and 4.9 g/kg bw/day for females). The test substance was incorporated in the feed at the expense of 20% barley. The control, low-dose and mid-dose diets were compensated by adding respectively 20%, 17.5%, 15% and 10% pre-gelatinised potato starch.

Clinical observations were recorded daily and bodyweight were measured weekly for the first 13 weeks and subsequently once every month. From 6 months after the start of the study until the end of the study, the animals were palpated weekly to detect palpable masses. Food consumption was assessed on a cage basis, by weighing the feeders, over each 1-week period during the first 13 weeks and subsequently over 1-week periods every month. Blood samples for haematology were taken from all rats after 12 and 24 months. At the end of the study, all animals were sacrificed and a complete necropsy performed (gross examination, organ weights and tissue sampling). Histopathology was performed on liver only.

Results

The highest average intake of the test substance was 4.0 g/kg bw/day in males and 5.0 g/kg bw/day in females of the highest dose group. There were no dose related differences in appearance, general condition or behaviour among the groups. The incidence of grossly visible or palpable masses was not considered treatment-related effect. The test substance did not affect mortality rate.

Mean body weights decreased in males and females at the highest dose. The decrease was statistically significant but there was no dose-response relationship. There were no noticeable differences in overall food intake.

Haematology showed that haemoglobin concentration and packed cell volume tended to be decreased in females fed 10% D-tagatose throughout the study. There were no significant differences in clinical chemistry variables among the groups.

There was a statistically significant increase in the relative weight of the liver in females given the highest doses of D-tagatose and fructose. In addition, increased absolute and relative adrenal weights were observed in female rats at all doses of D-tagatose, but not in those receiving fructose alone. The effect was not clearly dose-related, with the largest increase (79%) being in the group receiving a dietary concentration of 5%. Increased adrenal weights were reported in male rats fed on 5% and 10% D-tagatose. Macroscopic examination revealed a relatively high incidence of enlargement of the adrenals in some treatment groups, which were generally consistent with the increased adrenal weights. The weights of the kidneys in females, the testes in males, and the caecums in both sexes were also increased at 10% D-tagatose, and in some cases at 5% D-tagatose.

[*Comment: These organs have previously been reported to be affected by high doses of low solubility carbohydrates in the rat. Also, gross dietary imbalance due to high doses of polyols may result in metabolic and physiological disturbances in the rat, which have been associated with changes in calcium uptake and excretion accompanied by nephrocalcinosis and adrenal medullary hyperplasia. Such affects are not observed to the same degree in humans and appear to be peculiar to the rat.*]

Histopathological examination was only done on the liver. This examination did not reveal any treatment-related histopathological changes and demonstrated that the increased liver weight was due, at least in part, to glycogen accumulation. There were no observable differences between the treated and control animals in terms of liver tumour incidence.

Conclusions

Based on this two-year study in which the rats were administered with D-tagatose in the diet up to 20%, there was no evidence that the test substance is carcinogenic to the liver of these animals.

There were increases in the relative weights of liver in both D-tagatose and fructose groups but this could be ascribed to additional growth of hepatocytes in reaction to increased glycogen deposition, and is not considered to represent an adverse effect. Likewise, the increased weight seen in the adrenals, kidneys and testes can probably be ascribed to the high osmotic load resulting from the large dietary doses administered and therefore would not be regarded as toxicologically significant. This would need to be confirmed by histopathological examination of these tissues. Such effects are particularly well documented in the adrenals of rats but do not appear to be reproduced to the same extent in human subjects. All other clinical and haematological parameters remained normal.

Based on the above findings, it is concluded that long-term exposure to D-tagatose at dietary levels of up to 10% (4 g/kg bw for males and 5 g/kg bw for females) does not lead to adverse long-term consequences in rats. Based on this study a NOEL of 4 g/kg bw/day is derived.

Histopathological examination of adrenals, kidneys and testes from chronic and carcinogenicity study

Background

A chronic (2-year) toxicity and carcinogenicity study was done in Wistar rats fed a diet of 2.5, 5 and 10% D-tagatose, 20% fructose, and 10% D-tagatose + 10% fructose (50 rats/sex/group). In the original study, histopathological examination was only done for the liver as this had been identified as a potential target organ for toxicity in previous sub-chronic (3-month) studies.

In the 2-year study, the relative liver weight was significantly increased in females in the 10% D-tagatose, 20% fructose and 10% D-tagatose + 10% fructose groups, and in males in the 10% D-tagatose + 10% fructose group. This liver enlargement however was not associated with any histopathological changes.

The relative kidney, adrenal and testes weights were also increased in certain test groups in the study, but although the tissues were embedded in paraffin in preparation for histopathological examination, no such examination was done.

During a re-evaluation of D-tagatose by JECFA it was concluded the toxicological significance of the increased kidney, adrenal and testes weights could not be determined in the absence of histopathological examination.

TNO (Zeist, the Netherlands) was commissioned to undertake the histopathological examinations of the preserved adrenals, kidneys and testes from the 2-year study and the results were provided to FSANZ for evaluation.

Results

Testes

No treatment related histopathological changes were observed in the testes of male rats. Leydig cell hyperplasia and neoplasia occurred with similar frequency in all groups.

Kidneys

The treatment related histopathological changes consisted of:

- increased pelvic mineralisation in males in the 5 and 10% D-tagatose treatment groups, as well as the 10% D-tagatose + 10% fructose group; and

- increased medullary & corticomedullary mineralisation in males in the 10% D-tagatose as well as the 10% D-tagatose + 10% fructose group.

There was a high spontaneous incidence of pelvic and medullary mineralisation in the control group females - 88% exhibiting pelvic mineralisation and 48% exhibiting medullary mineralisation.

Adrenals

The observed treatment related histopathological changes consisted of:

- increased focal medullary hyperplasia in females in the 5 and 10% D-tagatose groups, as well as the 10% D-tagatose + 10% fructose group; and

- increased phaeochromocytomas[6] in males in the 5 and 10% D-tagatose treatment groups, as well as the 10% D-tagatose + 10% fructose group, and in females in the 10% D-tagatose as well as the 10% D-tagatose + 10% fructose groups.

There was a high spontaneous incidence of medullary hyperplasia and phaeochromocytomas in control group males – 60% exhibiting medullary hyperplasia and 30% exhibiting phaeochromocytomas.

[6] a tumour of the adrenal gland that causes excessive release of epinephrine and norepinephrine, hormones that regulate heart rate and blood pressure.

Discussion and conclusion

The only treatment related histopathological changes observed were in the adrenals and kidneys from the medium (5%) and high (10%) dose groups. The effects observed consisted of increased adrenal medullary proliferation and neoplasia and increased pelvic and corticomedullary nephrocalcinosis. The increase in relative testes weight was not associated with any significant histopathological changes.

The histopathological changes observed are identical to those seen following the long-term administration to rats of other slowly digestible carbohydrates (sugars, polyols) (Bär 1985, Bär 1988, Roe 1989, Lynch et al 1996). In this respect, the changes observed in the adrenals and kidneys following administration of D-tagatose are unremarkable.

The increased occurrence of nephrocalcinosis and adrenomedullary proliferative lesions in response to the ingestion of high doses of low digestible sugars and polyols is a well-known phenomenon which appears to be secondary to the treatment-induced hyper-absorption of dietary calcium. The mechanism by which slowly digestible carbohydrates stimulate calcium absorption is largely unknown but it has been suggested that their slow absorption from the GI tract and subsequent intestinal fermentation may play a central role in disturbing calcium homeostasis, at least in the rat (Bär 1988).

The link between increased calcium absorption and nephrocalcinosis is well understood. The increased absorption leads to a several fold increase in urinary calcium excretion (hypercalciuria), which, in turn, is manifest as deposits of calcium phosphate near the corticomedullary junction (cortico-medullary nephrocalcinosis) or in the renal pelvis (pelvic nephrocalcinosis) (Roe 1989). The link between increased calcium absorption and proliferative changes in the adrenal medulla is less well understood. It has been hypothesized that increased intestinal absorption of calcium and subsequent disturbance of the calcium regulating hormonal system influences the functional status of the adrenal medulla in rats and that a prolonged stimulation of the chromaffin cells leads ultimately to a hyperplastic and neoplastic response (Roe & Bar 1985).

There is widespread agreement in the literature that the histopathological changes observed in the rat following long term administration of high doses of low digestible carbohydrates occurs through a common mechanism that has no direct relevance to human safety. In the rat, the occurrence of these effects involves three factors: (1) A high genetic susceptibility to these effects, as evidenced by the high spontaneous incidence of these lesions in the controls and the fact that such lesions are not observed in mice or dogs following ingestion of large amounts of slowly digestible carbohydrates (Lynch et al 1996); (2) an intestinal hyper-absorption of calcium, followed by a disturbance of the calcium homeostatic hormonal system; and (3) a functional and proliferative responsiveness of the adrenal gland to changes in calcium homeostasis. In humans, none of these conditions is fulfilled. The genetic susceptibility is very low as shown by the rare occurrence of phaeochromocytomas (0.005-0.1%) (Manger et al 1985). The ingestion of slow digestible carbohydrates does not measurably affect calcium uptake or homeostasis (Lynch et al 1996) and, there is no known association between hypercalciuria and a higher risk for phaeochromocytomas in humans (Bär 1988). Therefore, the increased urinary calcium excretion and associated proliferative effects on the adrenal medullary tissue seen in rats is likely a species-specific phenomenon, occurring through a mechanism, or mechanisms, that are not operative in humans (Lynch et al 1996).

There is nothing in the results of the histopathological examination of adrenals, kidneys and testes from the 2-year chronic toxicity and carcinogenicity study to suggest that the effects observed with D-tagatose are anything other than the well-described and studied general phenomenon that occurs in rats following high intakes of other low digestible carbohydrates. It seems reasonable to conclude therefore that the effects observed are peculiar to the rat and are of no toxicological significance to humans. Studies on the effect of D-tagatose ingestion on calcium homeostasis in humans would be useful to confirm this conclusion.

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Effect of an oral 30-g dose of D-tagatose on the plasma uric acid levels of healthy male volunteers

by Diamentis I and Bar A. Department of Internal Medicine, University of Crete, Heraklion, Greece, *November 2001.*

Test materials:	D-tagatose
Subjects:	6 male volunteers between 22 and 24 years of age and having body weights of 62-65 kg.
Dose:	marmalade containing 30 g D-tagatose for breakfast.
Guidelines:	in accordance with the declaration of Helsinki approved by the Ethics Committee of the University Hospital of Heraklion.

Test articles and control material

D-Tagatose was obtained as a powder with > 99% purity. Marmalade was prepared with a D-tagatose content of about 40% and a fruit content of about 60%.

Study conduct

Blood samples were collected from the volunteers 1 hour prior to providing them with a light breakfast and blood collection continued just before and up to 4 hours after breakfast. The subjects were required to avoid alcohol the previous night. Six hours after the breakfast, clinical examination was performed on the subjects. Urine was collected over a 24-hour period starting from intake of the test breakfast.

Plasma and urine uric acid concentrations were determined. Plasma glucose and plasma inorganic phosphate were also measured within one hour of blood and urine collection.

Results

All 6 subjects completed the study according to protocol. Plasma glucose concentrations showed statistically significant increase at 1 hour after test breakfast. Plasma uric acid concentrations showed statistically significant increase in all 6 subjects at all postprandial times but no correlation to effect of time (1h to 4h) and they remained within the normal range at all times. Postprandial plasma phosphate levels showed statistically significant decrease 1-2 hour after breakfast, but increased towards the end of the observation period. The levels remained within the normal range throughout the observation period.

The 24-hour urinary excretion of uric acid was within the normal range.

No side effects (flatulence, bloated feeling and laxation) were reported up to 24-hour post treatment observation period.

Conclusions

This study confirms earlier findings using animal models that D-tagatose produces an increase in the plasma uric acid concentrations in humans, however the uric acid levels remain well within the normal range after ingestion of 30 g D-tagatose.

Effect of an oral 15-g dose of D-tagatose on the plasma uric acid levels of hyperuricemic male volunteers

by Diamentis I and Bar A. Department of Internal Medicine, University of Crete, Heraklion, Greece, *December 30, 2002.*

Test materials:	D-tagatose
Subjects:	12 male volunteers (7 hyperuricemic and 5 with gout) between 57 and 64 years of age and having body weights of 72-84 kg.
Dose:	marmalade containing 15 g D-tagatose for breakfast.
Guidelines:	in accordance with the declaration of Helsinki approved by the Ethics Committee of the University Hospital of Heraklion.

Test articles and control material

D-Tagatose was obtained as a powder with > 99% purity. Marmalade was prepared with a D-tagatose content of about 40% and a fruit content of about 60%.

Study conduct

Blood samples were collected from the volunteers 1 hour prior to providing them with a light breakfast and blood collection continued just before and up to 4 hours after breakfast. The subjects were required to avoid alcohol the previous night. Six after the breakfast, clinical examination was performed on the subjects. Urine was collected over a 24-hour period starting from intake of the test breakfast.

Plasma and urine uric acid concentrations were determined. Plasma glucose, plasma inorganic phosphate, creatinine and lactate were also measured within one hour of blood and urine collection.

Results

All 12 subjects completed the study according to protocol. Plasma glucose concentrations showed statistically significant increase from 0.5 to 2 hours after test breakfast. Plasma uric acid concentrations showed statistically significant increase in all 12 subjects at all postprandial times but they remained small and not different from that observed during the pre-treatment period at all times. Postprandial plasma phosphate levels did not vary in response to the intake of test breakfast.

The 24-hour urinary excretion of uric acid was above the normal value in three subjects.

No side effects (flatulence, bloated feeling and laxation) were reported up to 24-hour post treatment observation period.

Conclusions

This study shows that a single dose of 15 g D-tagatose does not produce a clinically significant increase of plasma uric acid concentrations in hyperuricemic and gouty subjects.

ADDITIONAL PUBLISHED LITERATURE ON THE SAFETY/ METABOLISM OF D-TAGATOSE IN HUMANS

Normen L, Laerke HN, Jensen BB, Langkilde AM, Andersson H, *Small-bowel absorption of D-tagatose and related effects on carbohydrate digestibility: an ileostomy study,* **Am J Clin Nutr 2001 Jan;73(1):105-10.**	The aims of this study were to measure the excretion of D-tagatose from the human small bowel, to calculate the apparent absorption of D-tagatose, and to study the effects of D-tagatose on the small-bowel excretion of other carbohydrates. It was concluded that the apparent absorption of 15 g D-tagatose/d was 81%. D-Tagatose had only a minor influence on the apparent absorption of other nutrients.

Buemann B, Gesmar H, Astrup A, Quistorff B, *Effects of oral D-tagatose, a stereoisomer of D-fructose, on liver metabolism in man as examined by 31P-magnetic resonance spectroscopy,* **Metabolism 2000 Oct;49(10):1335-9.**	The effect of 30 g D-tagatose or D-fructose administered orally on ketohexose-1-phosphates, ATP, and inorganic phosphate (Pi) levels in the liver was studied by 31P-magnetic resonance spectroscopy (PMRS) in 5 young male volunteers. Blood and urine were collected to detect a possible increased uric acid production. The results suggest that a moderate intake of D-tagatose may affect liver metabolism by phosphate trapping despite the fact that the sugar may only be incompletely absorbed in the gut.
Buemann B, Toubro S, Astrup A., *Human gastrointestinal tolerance to D-tagatose*, **Regul Toxicol Pharmacol 1999 Apr;29(2 Pt 2):S71-7**	The gastrointestinal effects of D-tagatose on after the consumption of 29 or 30 g of D-tagatose was investigated. Nausea and diarrhea were reported with an incidence of 15.1 and 31.5%, respectively, in 73 healthy young male subjects in a screening study. Increased flatulence after D-tagatose was frequently reported in all the studies and the flatulence did not decline during a 15-day period with intake of 30g in one dose daily. In most cases, symptoms were reported as light or moderate. The results suggest that 30g taken at one time may be above the recommended dose for ordinary use.
Buemann B, Toubro S, Raben A, Blundell J, Astrup A, *The acute effect of D-tagatose on food intake in human subjects,* **Br J Nutr 2000 Aug;84(2):227-31.**	A double-blind randomized crossover study was performed with nineteen normal-weight men to investigate the effect on subsequent ad libitum food intake of replacing 29 g sucrose with 29 g D-tagatose as sweetener to a breakfast meal. The results from this study suggest that D-tagatose may contribute to a reduced energy intake.
Buemann B, Toubro S, Holst JJ, Rehfeld JF, Bibby BM, Astrup A, *D-tagatose, a stereoisomer of D-fructose, increases blood uric acid concentration,* **Metabolism 2000 Aug;49(8):969-76.**	The effect of 30 g oral D-tagatose versus D-fructose on plasma uric acid and other metabolic parameters was tested in 8 male subjects by a double-blind crossover design. Serum uric acid concentration was significantly higher after D-tagatose compared with either 30 g D-fructose or plain water. D-Tagatose attenuated the glycaemic and insulinemic responses to a meal that was consumed 255 minutes after its administration. Moreover, both fructose and D-tagatose increased plasma concentrations of cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1). The metabolic effects of D-tagatose occurred despite its putative poor absorption.
Laerke HN, Jensen BB, Hojsgaard S, *In vitro fermentation pattern of D-tagatose is affected by adaptation of the microbiota from the gastrointestinal tract of pigs,* **J Nutr 2000 Jul;130(7):1772-9.**	*In vitro* fermentation experiments with pig intestinal contents and bacteria harvested from the gastrointestinal tract of pigs were used to investigate the degradation of D-tagatose and the formation of fermentation products. Two groups of eight pigs were fed either a control diet containing 150 g/kg sucrose or a diet which had 100 g/kg of the sucrose replaced by D-tagatose. After 18 d the pigs were killed and the gastrointestinal contents collected for in vitro studies. No microbial fermentation of D-tagatose occurred in the stomach or in the small intestine, whereas the sugar was fermented in the caecum and colon. The authors suggest that D-tagatose is not fermented in the upper gastrointestinal tract, and the ability of the large intestinal microbiota to ferment D-tagatose is dependent on adaptation.

DISCUSSION

At the fifty-seventh meeting of JECFA, a number of issues were raised in relation to the potential for D-tagatose to induce glycogen deposition and hypertrophy in the liver and to increase the concentrations of uric acid in serum. Following identification of these concerns, further studies were conducted with both humans and animals and these studies were evaluated at the sixty-first meeting of JECFA as well as independently by FSANZ. While the additional studies are considered to adequately address the concerns raised at the previous JECFA meeting, additional findings were noted in the two-year rat study, the toxicological significance of which JECFA could not determine because of the absence of histopathological examination of the relevant tissues.

These additional findings namely increased adrenal, kidney and testes weights in the high dose groups were considered by JECFA to possibly be due to high osmotic load resulting from the high dietary doses administered, and as a consequence would not be regarded as toxicologically significant. However, in the absence of histopathological examination of the tissues, this could not be confirmed. Subsequent to this consideration by JECFA, histopathological examination of the preserved adrenals, kidneys and testes from the 2-year toxicity study was completed and do not indicate any unusual findings of toxicological significance to humans.

No significant toxicological effects have thus been observed in the human or animal studies conducted to date. The data indicates no public health and safety concern associated with consumption of D-tagatose up to 15 g/day (0.25 g/kg bw/day) even in susceptible groups, hyperuricemic and gouty subjects.

The application of 6-fold safety factor by JECFA on bulk ingredients is inappropriate, as they cannot be tested above 40-50 g/day due to laxation effects. The new data from human subjects readily demonstrate the safety of D-tagatose consumption by humans up to 15 g/person/day. Therefore no further safety factor needs to be applied in determining its ADI.

CONCLUSIONS

JECFA established a temporary ADI of 0–125 mg/kg bw on the basis of a NOEL of 45 g D-tagatose/day (in three divided doses) from human studies and using a safety factor of 6. However bulk ingredients such as D-tagatose cannot be tested above 40-60 g/day since low-digestible carbohydrates induce intestinal side effects such as laxation at high doses

Further, assessment of new data submitted by the applicant confirms that there is no evidence of any public health and safety concern associated with consumption of D-tagatose up to 15 g/day even in susceptible groups (hyperuricemic and gouty subjects). There is some evidence that gastrointestinal effects such as nausea, diarrhoea and flatulence can occur in some individuals at doses 30 g/day and above. Another human study demonstrated that D-tagatose produces a transient increase in the plasma uric acid concentrations in humans, however the uric acid levels remain well within the normal range after ingestion of 30 g D-tagatose. Therefore applying a 6-fold safety factor in this case is not appropriate.

There were increases in the relative weights of liver, adrenals, kidneys and testes in rats fed D-tagatose but histopathological examination indicates these changes are not toxicologically significant.

It is concluded therefore that D-tagatose is safe for use in food for all individuals up to 15 g/day. Mild gastrointestinal effects may be observed in some individuals at higher dose levels.

ATTACHMENT 3

FOOD TECHNOLOGY ASSESSMENT REPORT

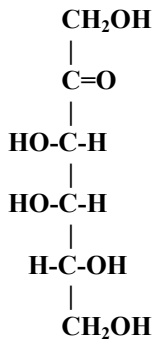
D-TAGATOSE AS A NOVEL FOOD

INTRODUCTION

Structure, function and occurrence

D-Tagatose is a naturally occurring sweet-tasting monosaccharide. D-Tagatose is a ketohexose in which its fourth carbon is chiral and is a mirror image of the respective carbon atom of the common D-sugar, fructose. The CAS number for D-tagatose is 87-81-0. The empirical formula for D-tagatose is $C_6H_{12}O_6$. The molecular weight for D-tagatose is 180.16.

The structural formula of tagatose is**:**



D-Tagatose occurs naturally in *Sterculia setigera* gum, a partially acetylated acidic polysaccharide. D-Tagatose is also found in heated cow's milk. Sterilised cow's milk and milk powder were found to contain tagatose at concentrations between 2 to 20 and 800 ppm, respectively (Troyano et al., 1996).

Production

The production process of D-tagatose occurs in a stepwise manner, starting from the raw material lactose (a disaccharide), which is then altered with the use of enzymes and various fractionating, isomerisation, and purification techniques. Food grade lactose is hydrolyzed to galactose and glucose by passing the solution through an immobilized lactase column.

The sugar mixture from the enzyme hydrolysis is fractionated by chromatography. The chromatographic separation of glucose and galactose is essential and is similar to the normal industrial separation of glucose and fructose, using calcium-based cationic resins. The galactose fraction from the chromatography is converted to D-tagatose under alkaline conditions by adding a suspension of $Ca(OH)_2$ and, optionally, a catalyst $CaCl_2$. The reaction is stopped by adding sulphuric acid. D-Tagatose is stable under the conditions of the isomerisation process. The resulting filtrate is further purified by means of demineralization and chromatography. The purified D-tagatose solution is then concentrated and crystallized to give a white crystalline product which is more than 99% pure.

Physical properties

D-Tagatose is 92% as sweet as sucrose in a 10% aqueous solution (Table 1). D-Tagatose is a white crystalline powder with an appearance very similar to sucrose. The main difference is that the crystal form is a tetragonal bipyramid. Crystallisation from aqueous solution results in anhydrous crystals in an α-pyranose form, with a melting point of 134-137 °C.

Table 1
Relative sweetness of tagatose and other sugars and polyols.

	Relative Sweetness
Sucrose	1
Fructose	0.8-1.7
Tagatose	0.92
Xylitol	0.8-1.0
Glucose	0.5-0.8
Erythritol	0.50
Sorbitol	0.4-0.7
Lactitol	0.4

D-tagatose is a non-hygroscopic product similar to sucrose. This means that D-tagatose will not absorb water from its surrounding atmosphere under normal conditions and does not require special storage.

D-Tagatose exerts a greater osmotic pressure, and hence a lower water activity than does sucrose at equivalent concentrations. The effect of water activity is similar to fructose due to the same molecular weight. Water activity influences product microbial stability and freshness.

D-Tagatose is similar to sucrose in its solubility in water. This makes it suitable for applications where it is substituted for sugar. Compared with polyols, tagatose is more soluble than erythritol and less soluble than sorbitol.

D-Tagatose solutions are lower in viscosity (180 cP at 70% w/w and 20 °C) than sucrose solutions at the same concentrations but slightly higher than fructose and sorbitol.

Chemical properties

D-Tagatose is a reducing saccharide and takes part in Maillard reactions, which leads to a distinct browning effect in food. It also decomposes (caramelizing) more readily than sucrose at high temperatures. At low and high pH, D-tagatose is less stable and converts to various compounds. However, D-tagatose can be used satisfactorily in many different applications at high temperature when process time is kept short.

Applications

D-Tagatose is well suited for confectionery products such as chocolate and hard boiled candies, fondants, fudges, and caramels due to its similar sweetness to sucrose, good ability to crystallize and low caloric value. It could also have applications in ice cream, soft drinks, and breakfast cereals.

Table 2 Conditions of Use Proposed by Applicant	
Food Category	**Use Level in Food (%)**
Breakfast cereals (ready to eat)	4-20 (depending on serving size)
Carbonated diet soft drinks	1
Non-carbonated diet drinks	1
Low fat/fat free Ice-cream	3
Low fat frozen dairy desserts	3
Diet/Health bars	10
Diet soft confectionery	10
Hard confectionery	10-15
Chewing gum	60
Icings/frostings	30
Special purpose foods/Meal replacements	15-20g per serving

Conclusion

D-Tagatose is a naturally occurring sweet-tasting monosaccharide that may be used in a wide range of foods.

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ATTACHMENT 4

DIETARY EXPOSURE ASSESSMENT REPORT

D-TAGATOSE AS A NOVEL FOOD

An application was received by FSANZ in July 2002 requesting approval of the monosaccharide D-tagatose for use as a novel food ingredient in a range of low fat, fat free, diet and reduced energy type and special purpose processed foods. A dietary exposure assessment was conducted to predict exposure of Australians and New Zealanders to D-tagatose when used in foods in accordance with those specified by the applicant. The applicant requested a general permission at GMP to permit its use in all food groups and not just for those specific foods listed in the application.

Summary

Estimated dietary exposures were calculated on a chronic and single eating occasion basis for the Australian and New Zealand populations and Australian children aged 2-4 years and 5-12 years.

Estimated mean chronic dietary exposures to D-tagatose for consumers were 2.7 g/d for the Australian population (2 years and above), 1.9 g/d for Australian toddlers 2-4 years, 3.0 g/d for Australian children aged 5-12 years and 1.9 g/d for the New Zealand population (15 years and above). Estimated 95th percentile exposures to D-tagatose for consumers were 9.0 g/d for the Australian population, 6.9 g/d for children 2-4 years, 10.5 g/d for children 5-12 years and 7.4 g/d for the New Zealand population. Ninety-fifth percentile exposures are overestimated as 24-hour food consumption data exaggerates habitual exposures. These exposures are also based on maximum proposed use levels, also producing an overestimate of exposure.

Estimated short-term exposures for high consumers in a single eating occasion were calculated for individual food groups to assess whether gastro-intestinal effects were likely. All estimated short-term exposures were 24 grams or less for any food for any population group, except for the Australian population consuming large amounts of formulated dietary foods (59 g D-tagatose/day), or formulated supplementary sports foods (56 g D-tagatose/day).

Dietary Exposure Assessment provided by the applicant

The applicant provided a detailed dietary exposure assessment for D-tagatose, based on food groups and levels of use similar to those being proposed for Australia and New Zealand. However this assessment was not considered to be sufficient for assessing the safety of potential exposure to D-tagatose in Australia and New Zealand as the assessment, although detailed, was based on United States food consumption data (US Department of Agriculture Continuing Survey of Food Intakes by Individuals, 1994-96). Therefore FSANZ conducted a dietary exposure assessment.

The exposure assessment submitted by the applicant indicated that mean daily exposure to D-tagatose for consumers of foods containing added D-tagatose (excluding chewing gum and formulated diet foods) was 5 g/day and 11 g/day for the 90th percentile consumer.

Expressed in terms of grams per kilogram body weight per day (g/kg bw/d), the highest exposure is projected for preschool children aged 2-5 years with mean and 90th percentile exposures of 0.17 and 0.33 g/kg bw/d respectively. For the consumers of all age groups combined the estimated exposure is 0.08 and 0.18 g/kg bw/d for the mean and 90th percentile respectively. The additional exposure from chewing gum is estimated at 0.06 – 0.07 g/kg bw/d for the average consumer (assuming a use level of D-tagatose of 60% in the gum). The average daily exposure to D-tagatose from formulated diet foods was considered separately by the applicant as such products are intended to be consumed as meal replacements or as a snack in the context of weight loss or weight control diet. The average daily exposure to D-tagatose from this use is estimated at 0.08 – 0.16 g/kg bw/d for the 20+-year-old consumer who consumes one or two servings of a formulated diet food per day. US food consumption data are based on two days of food records. Use of multiple day records tends to significantly reduce the predicted high consumer exposure (Rutishauser, 2000).

The USFDA estimated the dietary exposure to D-tagatose under the intended conditions of use to be 7.5 g/day for the mean consumer and 15 g/day for the 90th percentile.

The applicant indicated that these estimated exposure levels are likely to be an overestimate since it was presumed that D-tagatose would be used in all foods at the maximum use levels.

The exposure assessment submitted in the application did not estimate exposure to D-tagatose per single eating occasion (e.g. per meal or per snack). Additional information submitted by the applicant did contain data on exposure 'per eating occasion' (e.g. breakfast, lunch, dinner and snack). Per eating occasion for the population (2 years and above), mean exposures were 4.3 grams and 90th percentile exposures were 7.2 grams.

Dietary Modelling

The FSANZ dietary exposure assessment was conducted using dietary modelling techniques that combine food consumption data with food chemical concentration data to estimate the exposure to the food chemical from the diet. The dietary exposure assessment was conducted using FSANZ's dietary modelling computer program, DIAMOND.

Dietary exposure = food chemical concentration x food consumption

The exposure was estimated by combining usual patterns of food consumption, as derived from national nutrition survey (NNS) data, with proposed levels of use of D-tagatose in foods.

The chronic dietary exposure assessment is based on a range of food sources of added D-tagatose in the diet. That is, it includes where consumers may have only eaten one food containing D-tagatose or many foods containing D-tagatose to assess chronic exposures. The exposure assessment also assessed individual foods to determine the likelihood of short-term effects of exposure.

Naturally occurring sources of D-tagatose were not included in the exposure assessment as it was assumed that they would not contribute substantially to the total exposure to D-tagatose.

Dietary Survey Data

DIAMOND contains dietary survey data for both Australia and New Zealand; the 1995 NNS from Australia that surveyed 13 858 people aged 2 years and above, and the 1997 New Zealand NNS that surveyed 4 636 people aged 15 years and above. Both of these surveys used a 24-hour food recall methodology.

The dietary exposure assessment was conducted for both Australian and New Zealand populations. Modelling was conducted for the whole population, as well as for 2 – 4 year olds and 5 – 12 year olds (for Australia only). An exposure assessment was conducted on these younger age groups because children generally have higher exposures due to their smaller body weight, they consume more food per kilogram of body weight compared to adults and because they tend to consume a lot of the food types that are proposed to contain D-tagatose, such as ready-to-eat breakfast cereals, chewing gum, ice creams, gum (soft) type sweets, confectionery and beverages.

D-Tagatose Concentration Levels

The levels of D-tagatose in foods that were used in the exposure assessment were from the application (Table to part 2 (c)). The list of foods and the proposed levels of use, as provided by the applicant, are shown below in Table 1. However, this may not be an extensive list of all foods that D-tagatose could be used in if a general permission for use is given, as D-tagatose can be used as a replacement for other sugars in many foods.

Alternatively sweetened food categories were used, where available, for the exposure assessment. There was no food consumption data available from the NNS for alternatively sweetened ready-to-eat processed breakfast cereals. Based on information supplied by the applicant, that D-tagatose is only likely to be used in reduced fat / reduced-energy type foods, it is unrealistic to assume that D-tagatose would be used in all breakfast cereals. Therefore, FSANZ used the Australian market share for 'healthy' breakfast cereals (11%) (Retail World, 2002) as a more realistic estimate of the amount of cereals that could contain D-tagatose. Where a range of concentrations for a food was reported by the applicant, the highest one was used in the exposure assessment in order to assume a worst-case scenario. The concentration of D-tagatose used in the exposure assessment is shown in Table 2.

Table 1
Proposed use of D-tagatose in foods and levels of use

Food Name	Proposed use level in food	Concentration Level (mg/kg)
Low fat / Fat-free ice cream	3 %	30 000
Chewing gum	60 %	600 000
Diet soft confectionery	10 %	100 000
Hard confectionery	10 – 15 %	100 000 – 150 000
Icings / Frostings	30 %	300 000
Breakfast cereals ready-to-eat	4 – 20% (depending on serve size)	40 000 – 200 000
Special purpose foods / Meal replacements	(15 – 20 g per serve)	*
Non-carbonated diet drinks	1 %	10 000
Carbonated diet soft drinks	1 %	10 000
Low fat frozen dairy desserts	3 %	30 000
Diet / Health bars	10 %	100 000

* depends on serve size assigned. See Table 2.

Table 2
Food groups and concentrations of D-tagatose used in the FSANZ dietary exposure assessment (DEA)

Food Code	Food Name	Concentration Level (mg/kg)	Foods included	Assumptions
3.1.1.8	Low fat / Fat reduced ice cream	30 000	Carbohydrate modified ice cream products, ice confection	
5.2.1	Bubble gum and chewing gum	600 000		
5.3.2	Gum (soft) type sweets confectionery	100 000	Jubes, jellies, Turkish delight, marshmallow	
5.3.3	Hard boil sugar confectionery	150 000		
5.4	Icings and Frostings	300 000		
6.3	Processed cereal and meal products	22 000	"Healthy" breakfast cereals	DEA assumed market share of 11%
13.3	Formula dietary foods	250 000	Diet bars / biscuits	Based on 80 g serve size and 20 g D-tagatose / serve
13.4	Dietetic formulae for slimming and weight loss	53 000		13.4-13.6 Based on a 375g serve size and 20 g D-tagatose / serve
13.5	Supplementary foods for dietetic uses	53 000	Meal replacement drinks	
13.6	Formulated supplementary sports foods	53 000	Sports drinks, high protein drinks	
14.1.3.3	Water based flavoured drinks, artificially sweetened	10 000	Cordial, soft drink	
20.2.2.1	Dairy desserts, artificially sweetened	30 000	Mousse, puddings	Fat reduced chilled yogurt products were not included
20.2.3	Confectionery	100 000	Health bars, muesli bars, chocolate coated health bars, breakfast bars	

A concentration level of 22,000 mg/kg was used for ready-to-eat processed breakfast cereals. Because FSANZ does not have specific consumption data for alternatively sweetened breakfast cereals, a value of 11% (based on market share data) of the total food category's level of use was used, i.e. eleven percent of 200,000 mg/kg (proposed maximum level of use as indicated by the applicant for ready-to-eat breakfast cereals). For the special purpose foods / meal replacements food category, a concentration value of 53 000 mg/kg was used for liquid foods and 250 000 mg/kg for solid foods in this category. This is based on a 375 g serve size for liquid foods and an 80 g serve for solid foods and the upper level of use of 20 grams/serve (as indicated by the applicant) of D-tagatose in these types of products.

How the estimated dietary exposures were calculated

The DIAMOND model allows D-tagatose concentrations to be assigned to food groups. The concentration values in Table 2 were assigned to the alternatively sweetened sub-group of the main food category where a sub category existed. For example, only artificially sweetened carbonated and non-carbonated drinks were assigned the concentration value of 10 000 mg/ kg. Otherwise, the whole group of the normal counterpart of the food group was assigned the D-tagatose concentration (e.g. all icings and frostings).

Individuals' exposure to the additive was calculated using their individual food records from the dietary survey. The DIAMOND program multiplies the specified concentration of D-tagatose by the amount of food that an individual consumed from that group in order to estimate the exposure to each food. Once this has been completed for all of the foods specified to contain D-tagatose, the total amount of D-tagatose consumed from all foods is summed for each individual. Population statistics (mean and high percentile exposures) are then derived from the individuals' ranked exposures.

Where estimated dietary exposures are expressed per kilogram of body weight, each individuals' total dietary exposure is divided by their own body weight, the results ranked, and population statistics derived.

Percentage contributions of each food group to total estimated exposures are calculated by summing the exposures for a food group from each individual in the population group who consumed a food from that group and dividing this by the sum of the exposures of all individuals who consumed from any of the food groups containing D-tagatose and multiplying this by 100.

Food consumption amounts for each individual take into account where each food in a classification code is consumed alone and as an ingredient in mixed foods. For example, breakfast cereal consumed as is, or as part of a slice, are included in the consumption of breakfast cereal.

Estimated exposures for single food groups were calculated using the 95th percentile consumption amount for the food group derived by DIAMOND and multiplying this by the concentration of D-tagatose in the food.

Assumptions in the dietary modelling

Assumptions made in the dietary modelling include:

- where a permission is given to a food category, all foods in that category contain D-tagatose at the specified amount;
- all foods in a group will contain D-tagatose at the maximum proposed use level for the group;
- mean body weight for Australian respondents aged 2 – 4 years is 17 kg;
- mean body weight for Australian respondents aged 5 – 12 years is 32 kg;
- mean body weight for Australian respondents aged 2 years and above is 66 kg;
- mean body weight for New Zealand respondents aged 15 years and above is 71 kg;
- consumption amounts of foods as recorded in the NNSs represent current consumption patterns; and
- consumers always selected the product in the food group that contained D-tagatose.

These assumptions (other than those relating to body weight) are likely to lead to a conservative estimate for D-tagatose dietary exposure. This is because is it unlikely that all foods permitted to contain D-tagatose would in fact contain it, and if they did contain D-tagatose it is unlikely to always be added at the maximum amounts outlined in the application. However the application did not contain information on the likely market share of D-tagatose-containing foods.

The Applicant indicated that D-tagatose is expensive in comparison to sugar and is unlikely to be used in large quantities in an extensive range of foods.

Limitations of the dietary modelling

A limitation of estimating dietary exposure over a period of time associated with the dietary modelling is that only 24-hour dietary survey data were available, and these tend to over-estimate habitual food consumption amounts for high consumers. Therefore, predicted high percentile exposures are likely to be higher than actual high percentile exposures over a lifetime.

In addition, the NNS data used in DIAMOND do not distinguish between eating occasion (e.g. breakfast, lunch, dinner) so it is not possible to report the amount of D-tagatose eaten in one meal/snack. For example, the 240 g of low fat / reduced fat ice cream reportedly eaten by Australian high consumers (95th percentile, see Table 6 below) could have been eaten at one time or over two or more occasions during the day (lunch and dinner, for example). For the purpose of the exposure assessment it is assumed that this amount is eaten at one meal, which is the worst-case scenario.

RESULTS

Estimated dietary exposures to D-tagatose

The estimated dietary exposures to D-tagatose are shown in Table 4. Results are reported for all respondents (i.e. regardless of whether D-tagatose was consumed or not), and for consumers only (i.e. only those individuals that consumed D-tagatose). Only consumer exposures are discussed below in detail because this is the group of the population FSANZ needs to ensure has safe exposure.

The estimated mean exposure for consumers of D-tagatose for the Australian population aged 2 years and above is 2.7 g/day. The estimated mean exposure for consumers of D-tagatose for Australian toddlers aged 2 – 4 years is 1.9 g/day and for children aged 5 – 12 years it is 3.0 g/day. The estimated mean exposure for consumers of D-tagatose for the New Zealand population aged 15 years and above is 1.9 g/day. The estimated 95th percentile exposures for consumers of D-tagatose for the total Australian and New Zealand populations are 9.0 g/day and 7.4 g/day respectively. The estimated 95th percentile exposures for consumers of D-tagatose for Australian toddlers aged 2 – 4 years and children aged 5 – 12 years are 6.9 g/day and 10.5 g/day respectively.

Table 4
Estimated dietary exposures to D-tagatose

Country	Age group	Number of consumers of D-tagatose	Consumers as a % of total respondents[#]	Grams per day		
				Mean all respondents	Mean consumers only	95th percentile consumers only
Australia	Whole population (2 years+)	7341	53	1.4	2.7	9.0
	2-4 years	472	81	1.6	1.9	6.9
	5-12 years	1166	78	2.4	3.0	10.5
New Zealand	Whole population (15 years+)	2311	50	0.9	1.9	7.4

Total number of respondents for Australia: whole population = 13 858, 2-4 years = 583, 5-12 years = 1 496; New Zealand: whole population = 4 636.

Major contributing foods to total estimated dietary exposures

The major foods (>5%) that contributed to the total estimated exposures to D-tagatose are displayed in Table 5. These are displayed for the total population as well as for the younger age groups. The major contributor for each population group assessed was breakfast cereal at around 30% contribution. Other major contributors were gum (soft) type sweets, hard boil sugar confectionery, supplementary foods for dietetic use, formulated supplementary sports foods, water based flavoured drinks and health bars.

The results are based on the 24-hour food recall component of the NNS. The food frequency questionnaire (FFQ) from the Australian NNS (on respondents 12 years and above) showed only 30% of adults and 43% of children 12-18 years consume breakfast cereal on a daily basis. Thirty-three percent of 12-18 year olds and adults eat cereal once to 6 times per week. Twenty-five percent of adults never/less than once per month eat breakfast cereal. As breakfast cereals are the major contributing food to D-tagatose exposure, the estimated exposures to D-tagatose could be lower than estimated on most weekdays over a lifetime.

Table 5
Major contributors to total D-tagatose dietary exposures for Australia and New Zealand, and for different age groups

Country	Age group	Major contributing foods and percent of total D-tagatose exposures
Australia	Whole population (2+ years)	Breakfast cereals (30%) Health bars (14%) Formulated supplementary sports foods (13%) Water based flavoured drinks (11%) Gum (soft) type sweets (9%) Hard boil sugar confectionery (8%) Supplementary foods for dietetic use (5%)

Country	Age group	Major contributing foods and percent of total D-tagatose exposures
	2-4 years	Breakfast cereals (30%) Health bars (22%) Hard boil sugar confectionery (13%) Gum (soft) type sweets (12%) Supplementary foods for dietetic use (12%) Water based flavoured drinks (8%)
	5-12 years	Breakfast cereals (27%) Health bars (21%) Gum (soft) type sweets (14%) Hard boil sugar confectionery (14%) Water based flavoured drinks (6%)
New Zealand	Whole population (15+ years)	Breakfast cereals (29%) Hard boil sugar confectionery (23%) Health bars (19%) Gum (soft) type sweets (12%) Formula diet foods (5%) Supplementary foods for dietetic use (5%)

Comparison of estimated dietary exposure with other studies of D-tagatose exposure

The estimated dietary exposures calculated by FSANZ are slightly lower on a population basis than those submitted by the applicant. Differences in methodology of calculating the exposures (including a different population, consumer consumption patterns, different NNS methodology and calculations) can result in differences in estimated exposures.

The estimated exposures calculated by FSANZ are slightly lower in grams per day than JECFA estimates of 3-9 g/d from a number of countries. High consumers were estimated to be exposed to up to 18 g/d (WHO 2002). This estimate was higher than what FSANZ predicted for high consumers.

Estimated dietary exposures to D-tagatose for single food groups

The dietary exposures to D-tagatose from individual foods were calculated in order to determine whether a consumer could exceed the bolus dose reference health standard, therefore possibly encountering adverse gastro-intestinal effects. They were calculated by multiplying the 95th percentile food consumption amount for a food group by the specified concentration of D-tagatose as outlined in Table 1.

The estimated exposures are shown in Table 6 and 7 for Australia and New Zealand respectively. These dietary exposures differ from the estimated 95th percentile dietary exposures to D-tagatose referred to earlier in the report, in that the results in this section are for 95th percentile consumption amounts for single foods whereas the results earlier in the report refer to the 95th percentile dietary exposure to D-tagatose from consumption of all foods proposed to contain D-tagatose.

Table 6
Estimated dietary exposure to individual food groups at the 95th percentile level of consumption - Australia

Food code	Description	Level of use (mg/kg)	All consumers 2+ years intake		Toddlers aged 2 – 4 years		Children aged 5 – 12 years	
			P95 food intake per day (g)	Grams D-tagatose / day	P95 food intake per day (g)	Grams D-tagatose / day	P95 food intake per day (g)	Grams D-tagatose / day
3.1.1.8	Reduced fat ice cream	30 000	240	**7.2**	82	*	235	**7.1**
5.2.1	Chewing gum	600 000	24.85	**14.9**	18.97	*	31.97	**19.2**
5.3.2	Gum (Soft) type sweets	100 000	133.42	**13.3**	90	**9.0**	125	**12.5**
5.3.3	Hard candy	150 000	64.19	**9.6**	52.56	**7.9**	62.96	**9.4**
5.4	Icings/frostings	300 000	57.3	**17.2**	20	*	40	*
6.3	Ready-to-eat breakfast cereals	200 000	120	**24.0**	67.5	**13.5**	112.5	**22.5**
13.3	Formulated dietary foods	250 000	237	**59.3**	NC		NC	
13.5	Supplementary foods for dietetic use	53 000	40.66	**2.2**	48.22	**2.6**	23.67	**1.3**
13.6	Formulated supplementary sports foods	53 000	1055.3	**55.9**	NC		508	*
14.1.3.3	Water based flavoured drinks, artificially sweetened	10 000	1242	**12.4**	971	*	1103.7	**11.0**
20.2.2.1	Dairy desserts, artificially sweetened	30 000	70.33	*	NC		NC	
20.2.3	Confectionary (health bars)	100 000	85	**8.5**	77.4	**7.7**	62	**6.2**

* <21 respondents therefore not able to be calculated
NC = not consumed

Table 7
Estimated dietary exposure to individual food groups at the 95th percentile level of consumption – New Zealand

Food code	Description	Level of use (mg/kg)	All population (15+ years)	
			P95 food intake per day (g)	Grams D-tagatose / day
3.1.1.8	Reduced fat ice cream	30 000	240	*
5.2.1	Chewing gum	600 000	30	*
5.3.2	Gum (Soft) type sweets	100 000	144.2	**14.4**
5.3.3	Hard candy	150 000	125.12	**18.8**
5.4	Icings/frostings	300 000	24.26	*
6.3	Ready-to-eat breakfast cereals	200 000	75	**15.0**
13.3	Formulated dietary foods	250 000	237.49	*
13.4	Dietetic formula for slimming	53 000	60	*
13.5	Supplementary foods for dietetic use	53 000	25.58	**1.4**

Food code	Description	Level of use (mg/kg)	All population (15+ years) P95 food intake per day (g)	Grams D-tagatose / day
13.6	Formulated supplementary sports foods	53 000	NC	
14.1.3.3	Water based flavoured drinks	10 000	1270.8	*
20.2.2.1	Dairy desserts	30 000	667.5	*
20.2.3	Confectionary (health bars)	100 000	102.25	**10.2**

* <21 respondents therefore not able to be calculated
NC = Not consumed

Where there are less than 21 consumers of a food group, no bolus dose exposures have been calculated from the 95th percentile consumption figure since there are insufficient consumers to derive the figure and for the result to be sufficiently robust. Therefore, the discussion below only includes commodity/ age group combinations for which there were more than 21 consumers.

All estimated short-term exposures from single eating occasion, for any population group, for any food, are 24 grams or lower, except for the Australian population for formulated dietary foods (59.3 g) and formulated supplementary sports foods (55.9 g). These products are likely to be infrequently consumed, and would mostly be consumed by adults. The estimates are also based on the FSANZ estimate of serve size and concentration, which assumes a worst-case scenario. Manufacturers may add lower amounts of D-tagatose in practice.

References

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ATTACHMENT 5

ENERGY FACTOR FOR D-TAGATOSE

D-TAGATOSE AS A NOVEL FOOD

1 Requirements in the *Australia New Zealand Food Standards Code*

Standard 1.2.8 – Nutrition Information Requirements defines 'energy factor' based on metabolisable energy and lists factors, expressed as kJ/g, for a large number of energy-yielding components. Energy factors are used in the calculation of a food's energy content, and components that are recognised as contributing significantly to the energy content of a food (e.g. macronutrients) are assigned values for this purpose. Other food components can contribute to energy intake in a more moderate way, and may be assigned an energy factor where there is sufficient supporting evidence.

As D-tagatose is proposed for use as a sugar substitute, and is not an unavailable carbohydrate, the default energy factor is 17 kJ/g. However, the applicant has submitted data that enables derivation and listing of a more accurately estimated factor.

Energy factors in Standard 1.2.8 are derived using the following formula for metabolisable energy:

ME = GE – FE – UE – GaE – SE

Where ME = metabolisable energy
GE = gross energy
FE = energy lost in faeces
UE = energy lost in urine
GaE = energy lost in gases from large intestine fermentation
SE = energy content of waste products lost from surface areas

In deriving the ME, the information submitted by the applicant has been assessed in accordance with the FSANZ Guidelines "Derivation of energy factors for specific food components not already listed in Standard 1.2.8" (FSANZ Guidelines). These Guidelines can be found at:

http://www.foodstandards.gov.au/standardsdevelopment/informationforapplicants/energyfactorsforspec1683.cfm

2 Conformity of submitted studies to FSANZ guidelines

Eighteen studies were submitted by the applicant providing evidence for use in the determination of both the percentage of D-tagatose absorbed from the upper gastrointestinal tract (intestinal absorption) and the percentage of ingested D-tagatose excreted into the urine. These studies were assessed against the quality criteria established in FSANZ Guidelines; a detailed description of this assessment is provided in the Appendix to this Attachment.

2.1 Excluded Studies

When assessed against FSANZ Guidelines, six of the eighteen submitted studies were excluded from further consideration due to the use of inappropriate subjects. The results from two studies in rats (Saunders et. al. 1999; Whistler et. al. 1974) could not be realistically applied to humans. Four studies, using D-tagatose or other substances, were conducted on humans with an ileostomy (Bär 1990; Jenkins et. al. 1994; Langkilde 1994; Normén et. al. 1999), and were thus considered unsuitable.

2.2 Accepted Studies

Three studies on pigs and nine studies on humans were accepted for assessment against FSANZ Guidelines.

Although the three studies on pigs were deemed relevant for the calculation of energy factors, two did not meet all of the criteria established in FSANZ Guidelines. These studies were not published/peer-reviewed, and did not disclose their source of funding.

Four of the nine human studies did not meet all of the criteria established in FSANZ Guidelines by either the:

- absence of control measures within the experimental design;
- inadequate dietary management during the study;
- nondisclosure of the source of funding; or
- nondisclosure of the means of obtaining informed consent from participants.

Not withstanding these deficiencies, the totality of evidence provides a consistent set of results for each species. The twelve studies have therefore been utilised for the calculation of an energy factor as shown in Table A.

Table A
Application of studies on intestinal absorption and UE

Subject Type for Study	Number of Studies	Used for calculation of intestinal absorption	Used for calculation of UE
Pigs	3	Studies 2 and 3 in Table 1 of the Appendix	Studies 1 and 3 in Table 1 of the Appendix
Humans (healthy)	9	Studies 4 – 10 in Table 1 of the Appendix *	Studies 11 and 12 in Table 1 of the Appendix

* These studies provide only urinary excretion data on L-rhamnose; they were supplied by the applicant for the derivation of a percentage for the intestinal absorption of D-tagatose.

3 Calculating the metabolisable energy of D-tagatose

Each of the components that comprise ME (GE, FE, UE, GaE and SE) requires a separate assessment and calculation. Therefore, an assessment of the evidence for these components has been provided below, with the subsequent derivation of the ME for D-tagatose.

3.1 Gross Energy (GE)

GE or heat of combustion is the total quantity of energy available within a substance. This value is best measured by adiabatic bomb calorimetry, which provides very precise estimates.

A value 15.7 kJ/g can be obtained for the GE of D-tagatose from data supplied by the applicant (Levin et. al. 1995; Livesey 1999). None of this information is based on published bomb calorimetry results, however 15.7 kJ/g is similar to known GE values for glucose and fructose (15.5 kJ/g and 15.2 kJ/g respectively).

A value of **15.7 kJ/g ingested D-tagatose** was assigned to GE.

3.2 Percentage of Gross Energy that is Completely Absorbed in the Upper Intestine

Intestinal absorption is an important consideration, as it determines the energy directly available to the human body from D-tagatose, and the amount of D-tagatose remaining in the large bowel for further fermentation. The percentage of D-tagatose available for fermentation will influence the values obtained for FE and GaE.

Two of the three submitted studies on pigs (Jensen and Laue 1998; Lærke and Jensen 1999) supplied information on intestinal absorption. These studies indicate that approximately 25% of ingested D-tagatose is absorbed from the small intestine, leaving approximately 75% available for further fermentation in the large bowel.

Unlike studies on pigs, human studies cannot ethically undertake invasive portal vein measurements to directly determine the intestinal absorption of D-tagatose. Indirect measurements from urinary excretion values are also unsuitable, as D-tagatose is readily metabolised by the human liver upon absorption from the gastrointestinal tract (Buemann et. al. 1998; Livesey 1999). L-Rhamnose, however, is incompletely metabolised in humans and has a similar chemical structure to D-tagatose. Therefore, seven of the nine accepted human studies (Bjarnason et. al. 1991; Bjarnason et al. 1991; Delahunty and Hollander 1986; Howden et al. 1991; Maxton et. al. 1986; Menzies et al. 1990; Mooradian et. al. 1986) were supplied as a means of deriving the intestinal absorption of D-tagatose in humans from the urinary excretion of ingested L-rhamnose.

In using figures on ingested L-rhamnose, consideration has been given to the influence of lipophilicity and molecular size on intestinal absorption (Hamilton et. al. 1987). L-Rhamnose will thus have a higher (unknown) rate of intestinal absorption than D-tagatose.

The seven human studies indicated that approximately 8-17% of ingested L-rhamnose was excreted into the urine. The applicant has used this information to assign a value of 17-24% to the intestinal absorption of L-rhamnose, and subsequently inferred that no more than 20% of D-tagatose will be absorbed from the gastrointestinal tract in humans (i.e. 80% available for fermentation).

As a number of assumptions are required when using the human studies on L-rhamnose, results from both pigs and humans have been given equal weighting in the determination of intestinal absorption values.

The range of **20-25%** of ingested D-tagatose is to be assigned to intestinal absorption. Consequently, **75-80%** of ingested D-tagatose will be assigned to the percentage of D-tagatose available for fermentation.

3.3 Energy Lost in Faeces (FE)

As specified under FSANZ Guidelines, FE can be calculated by dividing it into three components:

- uFE – the energy lost through excretion of the ingested substance in faeces unchanged,
- mFE – the energy lost in microbial mass through fermentation, and
- oFE – the energy lost through short chain fatty acids that escape large intestinal absorption.

As D-tagatose is completely fermented in humans and appears unchanged in the faeces in minute quantities (Livesey, 1999), uFE can be assigned a value of 0% of fermented D-tagatose.

The applicant has also requested that oFE be set at 0% of fermented D-tagatose, consistent with FSANZ Guidelines.

No data has been made available on mFE; instead the applicant has used the default value of mFE as specified in FSANZ Guidelines. This value is stated as 30% of fermented D-tagatose.

With no energy losses from uFE and oFE, the total value for FE is equivalent to mFE, or **30% of fermented D-tagatose**.

3.4 Percentage of D-Tagatose Excreted into Urine

The UE is derived using the percentage of ingested D-tagatose excreted into the urine multiplied by GE.

Using results from studies on pigs (Jensen and Laue 1998; Jørgensen and Lærke 1998), the excretion of 3-7% of ingested D-tagatose into urine has been observed. A slightly lower range was obtained from two human studies (Buemann et. al. 1998; Buemann et. al. 1999), with the observation that approximately 1-5% of ingested D-tagatose is excreted into the urine.

As the results from pigs align closely with those from humans, the human values have been preferentially used as the basis for calculating UE.

The range of **1-5% of ingested D-tagatose** is to be assigned to the percentage of D-tagatose excreted into the urine.

3.5 Energy Lost in Gases from Large Intestine Fermentation (GaE) and Energy Content of Waste Products Lost from Surface Areas (SE)

The applicant has supplied no information on GaE or SE to suggest that the default values provided in FSANZ Guidelines are inappropriate.

GaE and SE will be assigned values of **5% of fermented D-tagatose and 0 kJ/g of ingested D-tagatose** respectively as specified in FSANZ Guidelines.

3.6 Calculation of the Metabolisable Energy for D-Tagatose

Each of the separate components in the equation for ME are derived as follows:

GE = 15.7 kJ/g ingested D-tagatose
FE = % ingested D-tagatose available for fermentation x 0.3 (30%) x GE
UE = % ingested D-tagatose excreted into the urine x GE
GaE = % ingested D-tagatose available for fermentation x 0.05 (5%) x GE
SE = 0 kJ /g ingested D-tagatose

As a range of values can be obtained for both the percentage of D-tagatose available for fermentation (75-80%) and the percentage of ingested D-tagatose excreted into the urine (1-5%), the calculation of ME produces a range of values as listed in Table B.

Table B
Calculation of ME using the range of percentages for UE and availability of D-tagatose for fermentation

Combination of Different Percentages	GE	FE	UE	GaE	SE	ME
Available for Fermentation = 80% Urinary Excretion = 1%	15.7	3.77	0.16	0.63	0	11.15
Available for Fermentation = 75% Urinary Excretion = 1%	15.7	3.5	0.16	0.6	0	11.42
Available for Fermentation = 80% Urinary Excretion = 5%	15.7	3.77	0.8	0.63	0	10.52
Available for Fermentation = 75% Urinary Excretion = 5%	15.7	3.5	0.8	0.6	0	10.79

All values are in kJ/g ingested D-tagatose

Despite the variation in percentages for intestinal absorption and urinary excretion of D-tagatose, the overall impact on the calculation of ME is small. Therefore, the ME of D-tagatose falls within the range of 10.52 – 11.42 kJ/g, with 11 kJ/g being the most appropriate value when rounded to a whole number (consistent with the listing of other energy factors in Standard 1.2.8).

4 Conclusion

The metabolisable energy factor for D-tagatose is best reflected by a value of 11 kJ/g. It is therefore recommended that this energy factor be inserted into Table 2 of subclause 2(2) of Standard 1.2.8.

5 Acknowledgements

FSANZ would like to thank Dr. Penny Warwick for reviewing the attachment on the energy factor for D-tagatose prior to its public release at Draft Assessment. Dr. Warwick has considerable experience in the area of energy factors, and was instrumental in the development of the guidelines: "Derivation of energy factors for specific food components not already listed in Standard 1.2.8".

6 References

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Appendix to Attachment 5

D-Tagatose
Comparison of Scientific Literature Against FSANZ Criteria

The applicant supplied eighteen references in support of the calculation of an energy factor. As specified in the FSANZ Guidelines for the "Derivation of Energy Factors for Specific Food Components Not already listed in Standard 1.2.8" (the FSANZ Guidelines), these studies were assessed against a set of quality criteria.

In the preamble to the quality criteria for submitted studies (Section 3 of the FSANZ Guidelines), animal studies must meet four requirements:

1. Data is provided to show comparability between the results of animal studies and human studies of the same or similar compounds;
2. Care is taken to eliminate coprophagy in rat experiments;
3. Experiments are done at ranges of intakes and in circumstances relevant to realistic intakes in humans; and
4. Clinical (human) studies are completed to confirm any preliminary data obtained by in vitro or animal experiments.

On this basis, two rat studies (Saunders et. al. 1999; Whistler et. al. 1974) were excluded from further consideration, as the results could not be compared and applied realistically to humans. The three pig studies supplied by the applicant (Jørgensen and Lærke 1998; Lærke et. al. 1998; Jensen and Laue 1998) met these requirements.

Within the FSANZ Guidelines, sixteen criteria are listed:

Studies must –

1. have been published in peer-reviewed literature with international circulation;
2. have adhered to ethical guidelines for experimentation in animals or humans (as appropriate), including informed consent in humans, and have reported details of that adherence;
3. report details of funding arrangements for the study;
4. report details of study design, analytical methodology, duration and statistical analysis, and that discuss the limitations of methodology used;
5. report details of how the food component was administered and how ME was calculated (e.g. results from single bolus dose with ME content determined by difference, or from a range of doses and ME determined statistically using regression techniques);
6. include administration of the food component orally with meals/diets of known energy and nutritional content;
7. are conducted under controlled conditions where possible;
8. are conducted under conditions as close as possible to the normal physiological state of the animal or human;
9. in humans, use healthy subjects rather than patients with diagnosed disorders;
10. use adequate (and appropriate) experimental controls;
11. show appropriate statistical considerations in study design and data analysis;
12. use statistically appropriate numbers (and types) of subjects;

13. use appropriate study durations;
14. be minimally invasive;
15. provide appropriately described details; and
16. explore other factors that might affect the estimation of the energy factor of the food component such as adaptation of subjects, fasted or non-fasted conditions, ingestion as liquid or solid or with or without meals, single large dose versus multiple smaller doses, any effects of the test substance on absorption or digestion of other dietary components, and vice versa, and effects of a range of different background diets.

On the basis of criterion 9, four human studies involving ileostomates as subjects were excluded from further consideration (Normén et. al. 1999; Langkilde 1994; Bär 1990; Jenkins et. al 1994). The remaining twelve studies were assessed against the criteria as listed below in Table 1. The headings of each column in Table 1 correspond to the quality criteria as follows:

Peer Reviewed	– Criterion 1
No. of Subjects	– Criterion 12
Ethical Approval / Informed Consent	– Criterion 2
Funding Publicised	– Criterion 3
Study Design	– Criteria 4, 10, 11
Methodology Criteria Met	– Criteria 7, 8, 13, 14, 15
Administration	– Criteria 5 (partially), 6
Calculation of ME Provided	– Criterion 5 (partially)
Met Dietary Criteria Including Adaptation	– Criterion 16

Of the twelve studies assessed, six comply with all sixteen criteria (Bjarnason et al 1991; Buemann et. al. 1999; Howden et al. 1991; Lærke and Jensen 1998; Menzies et al 1990; Mooradian et al 1986). All twelve studies were considered within the calculation of an energy factor for D-tagatose as the results were consistent across each species. However, the relevant discrepancies were noted for each of the six non-compliant studies.

Table 1
Evidence for Intestinal Absorption and Urinary Excretion Values Assessed Against FSANZ Guidelines

Study	Peer Reviewed	Subject	No. of Subjects	Ethical Approval / Informed Consent	Source of Funding	Study Design	Meth'logy Criteria Met	Administration	Calculation of ME Provided	Met Dietary Criteria Including Adaptation	Results
1. Jørgensen and Lærke (1998)	No – unpublished report	Pigs	n = 6 (2 per diet; rotated through each diet)	Not specified	Not specified	Cross-over, randomised trial, unblinded, controlled.	Yes	Diet 1 – 20% sucrose (control diet) Diet 2 – 10% sucrose + 10% D-tagatose, Diet 3 – 20% D-tagatose Each diet was given over a two-week period.	Yes - ME calculated by the following equation: ME = GEx0.566 (absorption from the gut) – UE – GaE.	Yes – 1 out of the 2 weeks as an adaptation period for each diet. Composition of diets was provided.	5.2% ingested D-tagatose in urine, no D-tagatose in faeces.
2. Lærke and Jensen (1998)	Yes	Pigs	n = 16 (6 per diet)	Handling of animals documented in detail.	Funding from MD Food Ingredients AMBA	Parallel group, controlled	Yes	Diet 1 – 15% sucrose (control diet) Diet 2 – 5% sucrose, 10% D-tagatose Each diet was given over fourteen days.	No	Yes – 4 out of 18 days for experimental diet	25.8% ingested D-tagatose absorbed, No D-tagatose in faeces.
3. Jensen and Laue (1998)	No – unpublished report	Pigs	n = 17	Yes – complied with Danish legislation	Not specified	Cross-over, controlled	Yes	Diet 1 – 20% sucrose (control diet) Diet 2 – 20% tagatose (pigs switched to this diet after control diet).	No	Yes – 1 week adaptation to 20% sucrose, 1 week to 20% D-tagatose. Composition of diets was provided.	26-28% $\pm$ 7% ingested D-tagatose absorbed, 3.3-7% ingested D-tagatose into urine.

Study	Peer Reviewed	Subjects	Number of Subjects	Ethical Approval / Informed Consent	Source of Funding	Study Design	Meth'logy Criteria Met	Administration	Calculation of ME Provided	Met Dietary Criteria Including Adaptation	Results
4. Maxton et. al. (1986)	Yes	Humans	n = 6 (IV) n = 10 (oral)	Yes	Donations of materials for the trial were made by several pharmaceutical companies	Factorial design, not controlled	Yes	L-Rhamnose given intravenously and orally. Oral administration provided as isomolar, hyperosmolar or centrimide containing solutions following fasting period. Cr-EDTA and lactulose also in solution. Dose was given once and urine collected at 0, 2.5, 5, 10 and 24 hours.	No	Not Applicable	11.7% and 13.2% ingested L-rhamnose in urine at 5 and 10 hours respectively for the isomolar solution.
5. Howden et al (1991)	Yes	Humans	n = 59 17 control, 28 with Crohn's disease, 14 with ulcerative colitis.	Yes	Donations of materials for the trial were made by several pharmaceutical companies	Factorial design, controlled	Yes	0.7% bolus solution of L-rhamnose given (1g dose) along with mannitol, cellobiose, lactulose, and Cr-EDTA. Urine collected over 6-24 hours.	No	Not Applicable	10.1% of ingested L-rhamnose in urine of control group at 6 hours.
6. Bjarnason et. al. (1991)	Yes	Humans	n = 12	Yes	Funding from Beecham Pharmaceuticals	Random controlled trial – double blinded	Yes	Test subjects consumed 100 mL bolus solution containing 1g L-rhamnose (control), and the same solution after 7 days of steroid use. Urine was collected over 5 hours following bolus solution.	No	Not Applicable	17.4 $\pm$ 2.5% of ingested L-rhamnose in urine for control dose.

Study	Peer Reviewed	Subjects	Number of Subjects	Ethical Approval / Informed Consent	Source of Funding	Study Design	Meth'logy Criteria Met	Administration	Calculation of ME Provided	Met Dietary Criteria Including Adaptation	Results
7. Bjarnason et al. (1994)	Yes	Humans	n = 37 12 controls 25 with coeliac disease.	Yes	Donations of materials for the trial were made by several pharmaceutical companies	Factorial design, controlled, double blinded	Yes	5g L-rhamnose dissolved into 150 mL and provided as a bolus. Polyethylene glycol, lactulose, and labelled Cr-EDTA were also provided, bringing the solution to 233 mmol/L. Urine collections taken at 0, 2.5, 5 and 10 hours.	No	Not Applicable	11.3 and 13.7% of ingested L-rhamnose excreted into urine at 5 and 10 hours respectively for controls.
8. Mooradian et al (1986)	Yes	Humans	n = 61 13 controls 48 with diabetes	Yes	Not specified	Factorial design, controlled, blinding unknown	Yes	Subjects consumed oral solution of 1g L-rhamnose in hyperosmolar solution (1505 mOsm/L) along with 20g lactose, 20g sucrose, and 5g lactulose. Urine was collected over 5 hours	No	Not Applicable	84.3 $\pm$ 18.4 mg (8-10%) of ingested L-rhamnose was excreted by controls over 5 hours.
9. Delahunty and Hollander (1986)	Yes	Humans, rats, hamsters and guinea pigs	n = 6 humans	Not specified	Funding from Goldsmith foundation, and CCRC research fund	Parallel group (compared between species), not controlled	Yes	Human subjects were given 5 g L-rhamnose, 10 g lactulose, and 1g mannitol in 200 mL solution as a bolus. Urine was collected over 6 hours.	No	Not Applicable	16.3 $\pm$ 2.5% of L-rhamnose into urine of humans.

Study	Peer Reviewed	Subjects	Number of Subjects	Ethical Approval / Informed Consent	Source of Funding	Study Design	Meth'logy Criteria Met	Administration	Calculation of ME Provided	Met Dietary Criteria Including Adaptation	Results
10. Menzies et al (1990)	Yes	Humans	n = 10 (study 1) n = 8 (study 2)	Yes	Funding from the Special Trustees of St Thomas Hospital	Cross-over trial, controlled	Yes	Subjects were given control solutions of 0.2g glucose, 0.5g xylose and 1.0g rhamnose. Subsequent solutions were given with varying concentrations of either mannitol (study 1) or mannitol and lactulose (study 2). Urine was collected after 5 hours and 48 hours was allowed to elapse between the consumption of each solution.	No	Not Applicable	Study 1: 14.7 $\pm$ 1.8% of ingested L-rhamnose into urine (control solutions only). Study 2: 16.7 $\pm$ 1.3% of ingested L-rhamnose into urine (control solutions only).
11. Buemann et. al. (1999)	Yes	Humans	n = 8	Yes	Funding from MD Food Ingredients AMBA	Cross-over, random, double blinded, controlled	Yes	Subjects fasted for 13 hours. Solutions containing either 30g of D-tagatose or 30g fructose were then provided as a bolus, with a 5-33 day washout period between solutions. Urine was collected at 4 and 7 hours after bolus. Energy expenditure measurements and blood tests were also made.	No	Yes – a standardised meal was provided during the seven-hour intervention period.	1.5% of the ingested D-tagatose into urine after 7 hours.

Study	Peer Reviewed	Subjects	Number of Subjects	Ethical Approval / Informed Consent	Source of Funding	Study Design	Meth'logy Criteria Met	Administration	Calculation of ME Provided	Met Dietary Criteria Including Adaptation	Results
12. Buemann et. al. (1998)	Yes	Humans	n = 6	Yes	Funding from MD Food Ingredients AMBA	Cross-over, randomised, double blinded, controlled	Yes	30g of D-tagatose or Sucrose (control diet) were administered each day via cakes that were consumed as part of the normal diet. Subjects acted as own controls and switched between the two diets after a two-month washout period. The sugars were administered over two weeks. Urine samples were taken during this time at three regular periods during the day. Other tests included hydrogen breath tests and energy expenditure tests.	No	No – dietary restrictions were only enforced days of the energy expenditure tests. Otherwise subjects consumed their normal diet.	0.7 – 5.3% of the ingested D-tagatose appeared in the urine. No D-tagatose appeared in the urine when sucrose was consumed. No significant variation between different urine samples was observed.

ATTACHMENT 6

SUMMARY OF PUBLIC SUBMISSIONS

A: Comments at Draft Assessment

1. Food Technology Association, Victoria Inc

- Approve the use of D-tagatose.
- Request that it be maintained on the circulation lists for further changes to this application.

2. Australian Food And Grocery Council

- Argues that FSANZ needs to determine before accepting the application as a novel food, that it is a non-traditional food and that there is not sufficient knowledge in the broad community to enable its safe use;
- Further, if FSANZ finds that it is safe for human consumption, then it cannot be listed as a novel food.

3. Department of Health, Western Australia

- disappointed that FSANZ had taken significant direction from the USFDA assessment and approval of D-tagatose, and that
- there was no apparent effort to establish the relevance to the Australian setting and population.
- undecided regarding which option to support because of insufficient information in the Initial Assessment Report.

B: Comments at Final Assessment

1. Agriculture Forestry & Fisheries, Australia

- does not anticipate the proposed amendment will present any major operational issues for AQIS.
- The proposed amendment to Standard 1.5.1 is a routine amendment to the Code. As such, AQIS expects the proposed amendment to have no regulatory impact under the *Imported Food Control Act 1992*.

2. Food Technology Association of Victoria Inc. (FTA Victoria)

- is concerned that D-tagatose has only been accepted for food use in the USA and no additional information was provided on its status in other countries.
- is also concerned that although D-tagatose is derived from dairy sources it is not required to be labelled as such.
- Notwithstanding the above concerns, accepted Option 2 – to permit the use of D-tagatose as a novel food ingredient.

3. InforMed Systems Pty Ltd

- supports the Application.
- the use of the sugar does not appear to have any potential hazards and since it provides less energy than most metabolisable carbohydrates this may be of some, albeit small, benefit in the current battle against obesity.

4. Public Health Services, Queensland

- cites the Draft Assessment Report which states on page 13: "As better information becomes available on the actual use levels of D-tagatose in various foods, more accurate estimates of dietary exposures will be possible and the public health and safety concerns reassessed, for high intake consumers."
- gives conditional support for Option 2 – to permit the use of D-tagatose, subject to this assessment being completed.

5. Australian Food and Grocery Council

- rejects the FSANZ conclusion that D-tagatose is a novel food.
- considers that D-tagatose is already standardised as a sugar under Standard 1.2.8, it is not a novel food.
- considers that FSANZ, in assessing D-tagatose, has not followed the appropriate procedure according to the FSANZ Act and also that FSANZ persists in interpreting the definitions of non-traditional food and novel food to suit itself, rather than they are written.
- due to the presence of D-tagatose in milk and the widespread use of milk and milk products, considers that FSANZ has erred in classifying D-tagatose as a non-traditional food.
- as FSANZ in not proposing to place any restrictions on the use of D-tagatose, it can only be concluded that FSANZ considers there is sufficient knowledge in the broad community to enable safe use. This being the case, D-tagatose fails to fit the definition of a novel food.
- recommends that FSANZ reject the application on the basis that D-tagatose is neither a non-traditional food nor a novel food and that its classification as a sugar under Standard 1.2.8 makes it a standardised food and provides provision for its sale and addition to food as an ingredient.
- in relation to drafting, states that the wording "may only be added to food according to Standard 1.3.4" under Column 2 of the table to Clause 2, should be reworded to "must comply with the requirements of Standard 1.3.4" as Standard 1.3.4 is the standard that specifies the identity and purity for products, it does not specify how products must be used.

6. New Zealand Food Safety Authority

- agrees that D-tagatose should be classified as a novel food.
- would be interested to find out if the applicant has applied for approval in Denmark or the European Union, and the outcome. For example, has approval not been given, for any reason?

- it would be useful for FSANZ to consider if there are any nutritional or public health and safety issues arising from the consumption of both trehalose and D-tagatose. For example, if both substances are consumed at or around the same time, are there differences of any consequence in how the novel ingredients are metabolised, and are there any interactions between substances? As more of these sugar-type novel substances are approved, it may be important that the substances are not considered in isolation.
- the limitations on the generic term 'sugar' under Standard 1.2.4 that D-tagatose could not be described as sugar in the ingredient list. Guidance on D-tagatose declaration would be helpful.
- notes that in the US, sugar free claims are not permitted, but health claims are authorised to say that D-tagatose does not promote or may reduce the risk of tooth decay. It will be necessary to check imported product to assess compliance with the Code.