FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

8-04
20 October 2004

FINAL ASSESSMENT REPORT

APPLICATION A494

ALPHA-CYCLODEXTRIN AS A NOVEL FOOD

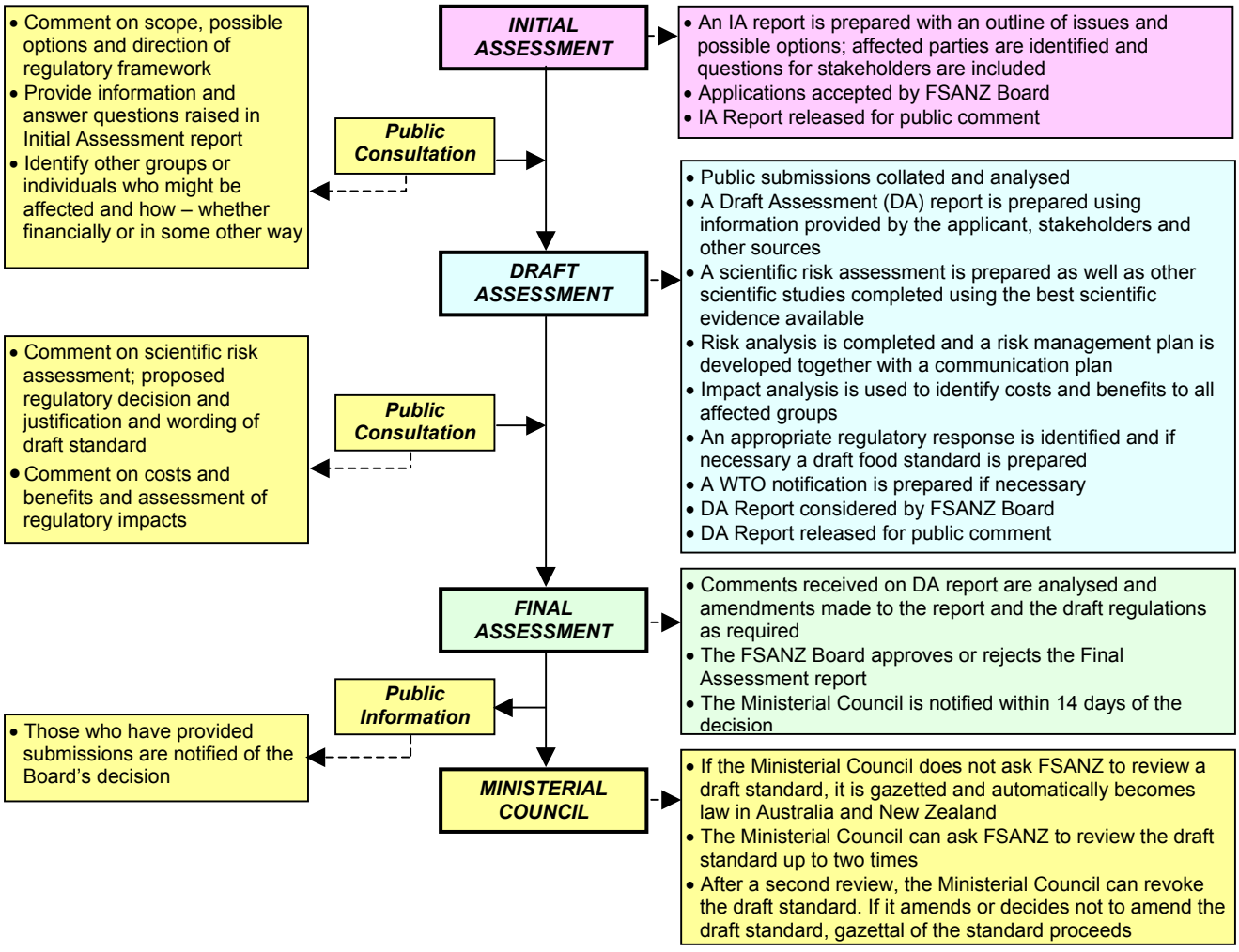
FOOD STANDARDS AUSTRALIA NEW ZEALAND (FSANZ)

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 Australian Government; 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 Australian Government, 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 Australian Government, 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

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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

FSANZ received an Application from Wacker Chemie GmbH on 7 March 2003 to amend Standard 1.5.1 – Novel Foods of the Code to approve the use of alpha-cyclodextrin (α-cyclodextrin) as a novel food.

α-Cyclodextrin is a cyclic polysaccharide consisting of six glucose units linked by α-1,4-bonds. It is produced commercially from liquefied starch by an enzymatic process. It has both technological and nutritional properties. The technological properties include acting as: a carrier for natural colours, flavours and vitamins; a stabiliser of oil in water emulsions; a solubiliser of lipids; and a flavour and aroma modifier by suppression of undesirable flavour characteristics. The main intended use of α-cyclodextrin is as a food ingredient, primarily to replace starch or sugar.

Under the current food standards, novel foods are required to undergo a pre-market safety assessment, as per Standard 1.5.1 – Novel Foods. α-Cyclodextrin is considered to be a non-traditional food because it has no history of significant human consumption in Australia or New Zealand. Its safety in the context in which it is presented in the Australian and New Zealand diet has not yet been determined. For these reasons, α-cyclodextrin is considered to be a novel food and is accordingly considered under Standard 1.5.1.

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

A number of issues were considered during the assessment of this Application. The safety evaluation and dietary exposure assessment of α-cyclodextrin indicate that there are no public health and safety concerns at the anticipated levels of dietary exposure. The potential nutritional impacts of α-cyclodextrin at the proposed levels of exposure were also investigated and it was concluded that α-cyclodextrin is unlikely to affect the absorption of fat-soluble nutrients (fat-soluble vitamins and lipids). The nutrition assessment also concluded that there is sufficient evidence to indicate that α-cyclodextrin is largely indigestible in the small intestine and that the term 'unavailable carbohydrate', with its corresponding energy factor of 8 kJ/g, as provided in Standard 1.2.8 – Nutrition Information Requirements, appropriately describes α-cyclodextrin.

The only regulatory options identified were to approve or not approve the use of α-cyclodextrin as a novel food. The impact analysis indicates, that on balance, there is likely to be a benefit to consumers, public health professionals and industry. There is unlikely to be a significant impact on government enforcement agencies as a result of approval for the use of α-cyclodextrin as a novel food.

Statement of Reasons

It is agreed to approve the use of α-cyclodextrin as a novel food, with no specified conditions of use other than the requirement for the full disclosure of the name ('alpha-cyclodextrin' or 'α-cyclodextrin') when describing the name in the ingredient list, for the following reasons:

- There is no identified public health and safety risk associated with the use of α-cyclodextrin as proposed. The safety evaluation indicates that α-cyclodextrin is a substance of very low toxicity and, in the proposed range of foods at the proposed maximum levels of use as provided by the Applicant, would not raise any safety concerns.

- The nutrition assessment indicates that α-cyclodextrin is unlikely to affect the absorption of fat-soluble nutrients (fat-soluble vitamins and lipids). α-Cyclodextrin is assessed as having a low nutritional impact when used as a food ingredient.

- α-Cyclodextrin can perform certain technological functions normally associated with food additives, in addition to being used as a food ingredient. Classifying α-cyclodextrin as a novel food would not restrict its use to perform a technological function normally associated with a food additive.

- The proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act.

- The Regulatory Impact Statement indicates that for the preferred option, namely, to approve the use of α-cyclodextrin as a novel food, the benefits of the proposed amendment outweigh the costs.

α-Cyclodextrin will be required to meet the specifications listed in Standard 1.3.4 – Identity and Purity – of the Code.

α-Cyclodextrin is largely indigestible in the small intestine and the term 'unavailable carbohydrate', with its corresponding energy factor of 8 kJ/g, as provided in Standard 1.2.8 – Nutrition Information Requirements, can be applied to α-cyclodextrin.

The proposed drafting for amendment to Standard 1.5.1 is at Attachment 1 of the Final Assessment Report.

1. Introduction

FSANZ received an Application from Wacker Chemie GmbH on 7 March 2003 to amend Standard 1.5.1 – Novel Foods of the Code to approve the use of α-cyclodextrin as a novel food.

α-Cyclodextrin is a cyclic polysaccharide consisting of six glucose units linked by α-1,4-bonds. It is produced commercially from liquefied starch by an enzymatic process. It has a torus-shaped molecular structure with a hydrophobic inner cavity, enabling cyclodextrin to form 'inclusion' complexes with a variety of organic compounds. This property allows α-cyclodextrin to perform a range of technical functions, as stated by the Applicant, such as:

- a carrier for natural colours, flavours and vitamins;
- a stabiliser of oil in water emulsions, a solubiliser of lipids; and
- a flavour and aroma modifier by suppressing undesirable characteristics.

However, the Applicant states that α-cyclodextrin is intended to be used primarily as a food ingredient, replacing starch, sugar, fat or fermentable fibres. The Applicant states that the physiological effects of α-cyclodextrin are similar to those of soluble/fermentable fibres and resistant starch, such as increased faecal bulk, decreased levels of plasma triglycerides and cholesterol, and modulation of glycaemic response. As such, the estimated levels of α-cyclodextrin proposed when used as a food ingredient are higher (up to approximately 15%) than when α-cyclodextrin is used for a technological function (approximately 1%).

The Applicant has stated its intention to use the term 'unavailable carbohydrate' to convey nutrition information in relation to products containing α-cyclodextrin. Unavailable carbohydrate is assigned an energy factor of 8 kJ/g in Table 1 to subclause 2(2) of Standard 1.2.8 – Nutrition Information Requirements.

In preparing this Final Assessment Report, FSANZ has assessed:

- the safety of α-cyclodextrin as a food ingredient;
- any potential nutritional implications arising from using α-cyclodextrin as a food ingredient;
- the food technology considerations; and
- the estimated dietary exposure to α-cyclodextrin based on the proposed food uses and proposed levels of use.

2. Regulatory Problem

Under the current food standards, novel foods are required to undergo a pre-market safety assessment, as per Standard 1.5.1 – Novel Foods. The purpose of Standard 1.5.1 is to ensure that non-traditional foods that have 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 Food is defined in the Standard as:

a non-traditional food 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
(d) 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.

Although α-cyclodextrin has technological properties consistent with some of the food additive functions (e.g. carrier, stabiliser), it is also used as a food ingredient. The Applicant states that its intended primary function is as a food ingredient and as such, it is appropriate to consider α-cyclodextrin under Standard 1.5.1. α-Cyclodextrin is considered a non-traditional food because it has no history of significant human consumption in Australia or New Zealand. Although many bacteria are able to produce cyclodextrins from starch, there is no known significant intake of naturally occurring cyclodextrins in food.

The safety of α-cyclodextrin as a food additive or food ingredient has not been evaluated for the Australian and New Zealand populations. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated its safety as a food additive and an Acceptable Daily Intake (ADI) of 'not specified' was assigned[1]. Prior to the Draft Assessment, the safety of α-cyclodextrin as a food ingredient in greater amounts than needed for use as a food additive had not been assessed. Since the Draft Assessment, JECFA has evaluated the use of α-cyclodextrin as a food ingredient in June 2004 and did not raise any safety concerns[2]. The ADI 'not specified'[3] was retained in relating to its use as a food additive. Since foods and food ingredients may have properties associated with food additives, it is appropriate to consider α-cyclodextrin in this broader category and to evaluate it as a novel food in accordance with Standard 1.5.1.

The Novel Foods Standard will be reviewed soon, based on policy guidance from the Ministerial Council issued in December 2003.

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[1] WHO (2002) Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, 49, pp 111-127 (α-cyclodextrin)

[2]WHO (2004) Joint FAO/WHO Expert Committee on Food Additives, Sixty-third meeting Geneva, 8-17 June 2004. Summary and conclusions. Report available at http://www.who.int/ipcs/publications/jecfa/en/summary_final.pdf.

[3] ADI 'not specified' is used to refer to a food substance of very low toxicity, which, on the basis of the available data (chemical, biochemical, toxicological, and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

3. Objective

The objective of this assessment is to determine whether or not it is appropriate to amend the Code to permit the use of α-cyclodextrin as a novel food. Such an amendment to the Code would need to be consistent with the section 10 objectives of the 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 Alpha-Cyclodextrin

α-Cyclodextrin can function as a carrier, stabiliser and solubiliser. In addition, it functions as a flavour and aroma modifier by suppression of undesirable flavour characteristics. However, the Applicant states that the primary food application of α-cyclodextrin is as a food ingredient because of its purported dietary fibre-like properties of increasing faecal bulk, decreased levels of plasma triglycerides and cholesterol and modulation of glycaemic response. These dietary fibre-like properties of α-cyclodextrin are in contrast to gamma-cyclodextrin (see below), which is considered nutritionally equivalent to starch and maltose because it is hydrolysed by salivary and pancreatic amylases to glucose, which is readily absorbed.

4.2 Proposed uses of Alpha-Cyclodextrin

When used as a food ingredient, the applicant states that α-cyclodextrin could potentially be used to partially replace a number of food components or macronutrients. α-Cyclodextrin could be used to replace:

- carbohydrates with a high glycaemic index such as sugar, starch or starch-derived products to reduce the energy value and glycaemic load of the food;
- fat in table spreads;
- fermentable fibres, some of which may be less suitable because of their high viscosity, insufficient stability, taste or presence of by-products.

In other cases, α-cyclodextrin may be added to foods in which it doesn't directly replace any particular component, for example, it could be added to yoghurt or beverages.

The following food applications for α-cyclodextrin are proposed by the Applicant:

- **Bakery products** such as breads, rolls, refrigerated doughs, cakes, muffins, biscuits and baking mixes.
- **Beverages and powders** such as coffee whitener, diet soft drinks, beverage mixes, fruit and vegetable juice drinks, instant coffee and tea, dairy mixes, soy and other non-dairy drinks.
- **Breakfast cereals**.
- **Confectionery** such as chewing gum and hard confectionery.
- **Condiments** such as sauces.
- **Dairy desserts** such as frozen dairy desserts, dessert mixes and yoghurt products.
- **Fat and oil products** such as reduced fat table spreads, dressing and mayonnaise.
- **Formulated meal replacements and supplementary foods**.
- **Grain-based foods** such as instant rice, noodles and pasta.
- **Snack foods** such as cereal bars and salty snacks.

4.3 Prior consideration of gamma-cyclodextrin as a novel food

FSANZ has previously assessed an Application for approval of gamma-cyclodextrin (γ-cyclodextrin) as a novel food (Application A438) submitted by Wacker Chemie GmbH. FSANZ approved the use of γ-cyclodextrin on the basis that there is no evidence of any public health and safety concern associated with consumption of foods containing γ-cyclodextrin and there are no significant nutritional concerns at the proposed levels of use, taking into consideration the section 10 objectives of the FSANZ Act and the Regulatory Impact Statement.

γ-Cyclodextrin serves a variety of functions in food applications including stabilizations of emulsions, elimination of undesirable molecules, solubilisation of ingredients and protection from oxidation. It also serves as a carrier of nutrients and vitamins. As such, γ-cyclodextrin has properties consistent with its classification in certain circumstances as either a food ingredient or as a food additive. When used at levels up to 20% in table spreads, as the applicant suggested as a proposed use, it is more akin to a food ingredient such as starch and maltodextrin than a food additive. For this reason, as well as the fact that a carrier (complexant) is not recognised as a technological function of a food additive in Standard 1.3.1 – Food Additives of the Code, FSANZ assessed γ-cyclodextrin as a novel food ingredient. This is consistent with certain foods and food ingredients being used for their technological function in some cases; examples are egg yolk (emulsifier) and starch (thickener).

The Assessment Reports for Application A438 – Gamma-Cyclodextrin as a Novel Food, are available on the FSANZ website: www.foodstandards.gov.au

4.4 Beta-cyclodextrin as a processing aid

Beta-Cyclodextrin (β-cyclodextrin) is approved as a processing aid under Standard 1.3.3 – Processing Aids, in the table to clause 14, processing aids with miscellaneous functions. β-Cyclodextrin is approved for the function of extraction of cholesterol from eggs at GMP level. β-Cyclodextrin has a different chemical structure and different properties compared with α-cyclodextrin.

4.5 Regulation in other countries

α-Cyclodextrin is permitted as a food in Japan. The Applicant has indicated that Generally Recognised as Safe (GRAS) status in the United States will be sought in the near future. There are no relevant Codex standards for α-cyclodextrin addition as a food ingredient.

5. Relevant Issues

5.1 Safety issues

A detailed safety assessment report is at Attachment 2. As discussed in section 2 of this Report, JECFA evaluated the safety of α-cyclodextrin for food additive use at the 57th meeting in June 2001. An ADI 'not specified' was assigned and a specification was prepared and published. This evaluation only covered the use of α-cyclodextrin as a food additive for certain specified uses with corresponding estimated daily intake of 1.7 g and 3 g for the mean and 90th percentile adult consumer respectively.

The use of α-cyclodextrin as a food ingredient, with corresponding higher levels of use, was recently evaluated by JECFA in June 2004. The conclusion of JECFA was that α-Cyclodextrin does not pose a safety concern at the proposed use levels, as considered by the Committee, and resulting predicted consumption as food ingredient and food additive. The previously established ADI "not specified" for use as a carrier and stabilizer for flavours, colours, and sweeteners, as a water-solubiliser for fatty acids and certain vitamins, as a flavour modifier in soya milk, and as an absorbent in confectionery was maintained.

FSANZ has evaluated the safety of α-cyclodextrin as a food ingredient with higher levels of use, based on the safety data submitted (also submitted for the JECFA evaluation). Safety studies in animals involving very high levels of α-cyclodextrin indicated the only adverse effects were those attributed to the presence of osmotically active substances in the large intestine. There are no long-term studies in animals available, however these are not considered necessary, due to the nature of the observed adverse effects.

One study in human volunteers was submitted to FSANZ, additional to the studies that were considered by JECFA when evaluating α-cyclodextrin as a food additive. This study has now been evaluated by JECFA in 2004 when considering α-cyclodextrin as a food ingredient. This study indicated that acute intake of 10 g α-cyclodextrin with 100 g white bread did not result in adverse effects. Some mild gastrointestinal effects were noted in some individuals following ingestion of 25 g α-cyclodextrin after overnight fasting without the consumption of the white bread or any other food.

Based on the evaluation of the levels of exposure in the animal and human studies and the adverse effects, it is considered that α-cyclodextrin is of very low toxicity and, at the proposed levels of dietary exposure when used as a food ingredient, would not be considered to be of toxicological concern.

5.2 Dietary considerations

A dietary exposure assessment was conducted in order to predict the potential exposures to α-cyclodextrin in Australia and New Zealand in the foods proposed by the Applicant at the proposed levels of use. A detailed dietary exposure assessment report is at Attachment 3. The dietary exposure assessment was conducted for the general Australian and New Zealand populations (2 years and above and 15 years and above, respectively) and for the population considered at potential risk from higher exposures; children (2-12 years, Australia only). The proposed uses of α-cyclodextrin in foods, as provided by the Applicant, are listed in Table 1.

Table 1: Proposed uses of α-cyclodextrin in foods, as provided by the Applicant

Food Name	Concentration Level (%)
Breads and rolls	5
Brownies	7
Cakes (light weight)	5
Crackers (sweet and non-sweet)	10
Bars (grain based)	7
Quick breads	5
Dough (refrigerated)	5
Baking mixes (dry)	5
Beverage mixes (prepared)	1
Diet soft drinks (prepared)	1
Fruit juices	1
Vegetable juices	2
Instant coffee/tea (dry)	1
Coffee whitener (dry)	1
Formula diets (prepared)	1
Soy and non-soy (imitation milk) (prepared)	2
Ready To Eat (RTE) breakfast cereals	2 - 9
Instant rice (prepared)	2
Pasta and noodles (prepared)	2
Condiments	3
Yoghurt	2.5
Pudding mixes (dry)	1
Milk beverage mixes (prepared)	2.5
Frozen dairy desserts	2.5
Reduced fat spreads	20
Dressings and mayonnaise	5
Salty snacks	1
Canned soups (prepared)	2
Dry soups (prepared)	2
Hard candy	15
Chewing gum	10

Estimated mean and 95th percentile dietary exposures for consumers of α-cyclodextrin in the Australian population (2+ years) from all proposed foods were 17.5 grams per day (g/day) and 36.8 g/day, respectively.

Estimated mean and 95th percentile dietary exposures for consumers of α-cyclodextrin in the New Zealand population (15+ years) from all proposed foods were 17.0 g/day and 36.9 g/day, respectively. Australian children (2-12 years) had estimated dietary exposures of 17.5 g/day (mean) and 33.4 g/day (95th percentile). The highest percentage contribution to dietary exposure was from breads and related products for all population groups assessed.

As discussed in section 5.1, in a study in healthy human volunteers, a bolus dose of α-cyclodextrin (doses of α-cyclodextrin consumed in one meal) of 25 grams after overnight fasting without the consumption of anything else produced mild abdominal discomfort in some individuals (see safety assessment report, Attachment 2). Estimated exposures to α-cyclodextrin for high consumers of single food groups were compared to this level. All estimated short-term exposures from a bolus dose, for any population group assessed, for any food, are less than 25 grams, with the exception of muesli (25.7g/day) for the 95th percentile Australian children 2-12 years and fruit and vegetable juice products (27.5g/day) for the 95th percentile New Zealanders 15+ years. The estimated bolus doses presented above are based on 24-hour food consumption data and may include consumption on more than one occasion during a day. This may lead to an overestimate of bolus dose exposure to α-cyclodextrin for some foods that are likely to be eaten more than once per day.

5.3 Nutritional considerations

A detailed Nutrition Assessment is at Attachment 4.

5.3.1 Nutrient absorption

As discussed in section 2 of this Report, JECFA evaluated α-cyclodextrin for food additive use at the 57th meeting in June 2001. Within this assessment the impact of α-cyclodextrin on nutrient absorption was assessed.

Because α-cyclodextrin can form inclusion complexes with certain vitamins, minerals and fatty acids, the absorption of these essential nutrients in the presence of α-cyclodextrin has been investigated. In its assessment of α-cyclodextrin as a food additive, JECFA used studies on β-cyclodextrin to estimate the potential impact of α-cyclodextrin on nutrient absorption and concluded that it is unlikely that the potential interaction between α-cyclodextrin and lipophilic vitamins would impair these vitamins' bioavailability.

Fat-soluble nutrients (fat-soluble vitamins A, D, E and K and lipids) and their absorption are considered the most likely nutrients to be potentially affected by the presence of α-cyclodextrin because of the ability of α-cyclodextrin to complex these nutrients in its hydrophobic core.

5.3.1.1 Fat-soluble vitamins (vitamins A, D, E and K)

Only one *in vitro* study was available that investigated the solubility of vitamins A, D, E and K in an isotonic buffered saline solution in the presence of α-, β-, and γ-cyclodextrins and a control. This *in vitro* study is not sufficient for evaluating the potential for α-cyclodextrin to affect the absorption of fat-soluble vitamins, so relevant studies using β-cyclodextrin were considered.

Four studies in animals have evaluated the impact of β-cyclodextrin on the fat-soluble vitamins A, D and E, using both bolus doses and continuous administration. These studies indicate that β-cyclodextrin had no adverse impact on the absorption of the fat-soluble vitamins A, D or E when compared to control groups.

There are no *in vivo* studies on the impact of any of the cyclodextrins on the absorption of vitamin K available however, information on the biochemistry and physiology of vitamin K and cyclodextrin – vitamin K interactions does not provide evidence that vitamin K absorption would be influenced.

5.3.1.2 Lipids

There are some studies available that assess the impact of β-cyclodextrin on lipid absorption, which can be used as an indirect indication of the potential impact of α-cyclodextrin. These studies do not indicate that α-cyclodextrin would adversely affect the absorption of fat-soluble nutrients.

5.3.1.3 Summary

The available scientific literature demonstrates that β-cyclodextrin does not impair the absorption of vitamins A, D and E, an outcome that is considered applicable to α-cyclodextrin. One *in vitro* study indicates that α-cyclodextrin has greater capacity to form inclusion complexes with vitamin K than other cyclodextrins. However, considering the biochemistry and physiology of vitamin K, it is unlikely that α-cyclodextrin will adversely impact on vitamin K status. Data on lipid absorption also indicates that α-cyclodextrin is unlikely to affect the absorption of fat-soluble macronutrients.

Therefore it is determined that the use of α-cyclodextrin in food will have only a minor impact, if any, on the ability to obtain adequate amounts of fat-soluble nutrients from the diet.

5.3.2 Alpha-cyclodextrin as unavailable carbohydrate

The Applicant states that for energy nutritional labelling purposes, α-cyclodextrin could be classified as 'unavailable carbohydrate'. 'Unavailable carbohydrate' is recognised in Table 1 to subclause 2(2) of Standard 1.2.8 – Nutrition Information Requirements – of the Code as having an energy value of 8 kJ/g. Available carbohydrates are those carbohydrates that are fully absorbed from the small intestine and are available for metabolism.

There is no definition of 'unavailable carbohydrate' in the Code. The term 'unavailable carbohydrate' has been used historically to distinguish indigestible fibre (cellulose and hemicellulose) from other fully digestible and metabolically available carbohydrates. Considering the current knowledge on dietary fibre and its various forms, the term 'unavailable carbohydrate' may best apply to carbohydrates that are indigestible in the small intestine, even if there is additional fermentation in the large intestine. Such a classification is consistent with the energy factor of 8 kJ/g applied to unavailable carbohydrate in the Code; if these substances were fully indigestible throughout the entire gastrointestinal system then an energy factor of 0 kJ/g would be more appropriate.

FSANZ has reviewed the available data in order to determine whether α-cyclodextrin is appropriately characterized as 'unavailable carbohydrate', that is, not absorbed or available for metabolism to any significant extent. The nutrition assessment concludes that there is sufficient evidence to indicate that α-cyclodextrin is largely indigestible in the small intestine. This is consistent with the findings of the JECFA evaluation that approximately 2% of α-cyclodextrin is absorbed from the small intestine. It is therefore appropriate to use the term 'unavailable carbohydrate' to describe α-cyclodextrin and apply the energy factor of 8 kJ/g assigned to 'unavailable carbohydrate' to α-cyclodextrin.

5.3.3 Digestion and dietary fibre-like properties

The Applicant claims that α-cyclodextrin would meet the definition for dietary fibre in Standard 1.2.8 – Nutrition Information Requirements of the Code, however, it cannot be claimed as dietary fibre because the analytical methods specified in the table to subclause 18(1) are not applicable to α-cyclodextrin. The Applicant is not seeking to have a method for determining the dietary fibre content of foods containing α-cyclodextrin recognised in Standard 1.2.8 because there is no official method recognised by the Association of Analytical Chemists (AOAC). As such, the purported dietary fibre-like effects of α-cyclodextrin, other than indigestibility in the small intestine, have not been assessed as part of this Application.

5.4 Risk characterisation

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

The dietary exposure to α-cyclodextrin in Australia and New Zealand was compared to the consumption of 25 g α-cyclodextrin, which caused some mild gastrointestinal discomfort under certain circumstances in one safety study only.

Two high consuming population groups exceeded the intake of 25 g by a small margin. However, it is unlikely that an individual would reach 25 g in one meal. The dietary modelling is likely to give an overestimate because of the high levels of use that were assigned in the dietary modelling, and the estimated doses are based on 24-hour consumption data and may included consumption on more than one occasion.

In addition, the gastrointestinal discomfort at this level (i.e. 25 g α-cyclodextrin) noted in the study occurred on an empty stomach and when administered in liquid form. Therefore, if the α-cyclodextrin had been administered in combination with food, it is unlikely that the mild gastrointestinal effects would have occurred at this level, and might also be self-limiting.

This study was considered by JECFA in evaluating the safety of α-cyclodextrin as a food ingredient in 2004. JECFA explained the abdominal discomfort as a well-known effect of carbohydrates of low digestibility, particularly if ingested in liquid form on an empty stomach. It is partly caused by an influx of water in the small intestine (achieving isotonicity) and partly by the ensuing fermentation process in the more distal parts of the gut.

The nutritional assessment indicates that α-cyclodextrin is unlikely to affect the absorption of fat-soluble nutrients (fat-soluble vitamins and lipids). α-Cyclodextrin is assessed as having a low nutritional impact when used as a food ingredient.

In conclusion, there are no public health and safety concerns associated with the use of α-cyclodextrin in foods as proposed.

5.5 Food technology considerations

Food technology issues have been considered in preparing this Final Assessment Report and the Food Technology Report is at Attachment 5. The following points are derived from the Food Technology Report:

- Cyclodextrins are formed by converting linear starch chains into cyclic molecules by using an enzyme; cyclodextrin glucanotransferase (CGTase). CGTase reactions produce α, β and γ cyclodextrins with six, seven and eight units of glucose respectively, linked by α-1,4 bonds.

- Two different types of cyclodextrin production processes can be distinguished: 'solvent processes' in which an organic complexing agent precipitates one type of cyclodextrin selectively and as such directs the enzyme reaction to produce mainly this type of cyclodextrin; and 'non-solvent processes' where no complexing agent is added and a mix of different cyclodextrins are formed.

- The annular structure of α-cyclodextrin provides a hydrophobic cavity which allows the formation of inclusion complexes with a variety of non-polar organic molecules of appropriate size. The hydrophilic nature of the outer surface of the cyclic structure makes α-cyclodextrin water-soluble.

- α-Cyclodextrin can function as: a carrier and stabilizer for flavours, colours and sweeteners; an absorbent for suppression of undesirable flavours and odours in foods; and absorbent for suppression of halitosis (breath-freshening preparations); and as a water-solubiliser for fatty acids and fat-soluble vitamins.

- α-Cyclodextrin is a starch product that can provide specialised functions in place of some alternative food ingredients such as starches or maltodextrins in food. Proposed levels of use, as indicated by the Applicant, are more consistent with that of a food ingredient rather than an additive.

- Classifying α-cyclodextrin as a food would not restrict its use to perform a technological function normally associated with a food additive.

- α-Cyclodextrin is suitable for use in a wide range of foods providing benefits of low viscosity as well as temperature and pH stability.

5.6 Risk management

Standard 1.5.1 of the Code, in the Table to clause 2, makes provision for conditions of use for a particular novel food to be specified in column 2 of that table, associated with permission for that novel food.

Conditions of use may be specified where a particular public health and safety risk is identified for either the general population or an identified population sub-group. Such conditions of use may be referred to as risk management strategies and include limiting the maximum level of use of the novel food or novel food ingredient, limiting the categories of foods to which the novel food ingredient may be added, or requiring statements to be provided on novel foods that advise against consumption by particular sub-groups of the population or provide the consumer with information about the appropriate use of the novel food.

The nutrition assessment indicates that α-cyclodextrin is unlikely to affect the absorption of fat-soluble nutrients (fat-soluble vitamins and lipids). α-Cyclodextrin is assessed as having a low nutritional impact when used as a food ingredient. Based on the nutrition assessment, no specific risk management strategies are necessary.

The safety evaluation indicates that α-cyclodextrin is a substance of very low toxicity and, at the proposed levels of dietary exposure when used as a food ingredient, would not raise any safety concerns. JECFA have also evaluated the safety of α-cyclodextrin as food ingredient and raised no safety concerns. JECFA have retained the previously established ADI 'not specified' in relation to its use as a food additive.

In one study in human volunteers, some mild gastrointestinal effects were noted in some individuals following ingestion of 25 g α-cyclodextrin after overnight fasting without the consumption of food. JECFA noted, in their evaluation of α-cyclodextrin as a food ingredient, ingestion of 20 g or more of α-cyclodextrin on a single eating occasion may cause gastrointestinal effects in humans. Short-term exposures from a bolus dose were greater than 20 grams for only two foods - muesli (25.7g/day) for the 95th percentile Australian children 2-12 years and fruit and vegetable juice products (27.5g/day) for the 95th percentile New Zealanders 15+ years. As such, consideration has been given to whether any risk management strategies are required with respect to potential gastrointestinal effects.

5.6.1 Consideration of limiting the maximum level of use of α-cyclodextrin or the categories of foods to which α-cyclodextrin may be added

The estimated bolus doses are based on 24-hour food consumption data and may include consumption on more than one occasion during a day. This may lead to an overestimate of bolus dose exposure to α-cyclodextrin for some foods that are likely to be eaten more then once per day (e.g. milk). It may not lead to as much of an overestimate for foods more likely to only be eaten once per day (e.g. ice cream).

The estimated short-term exposures to α-cyclodextrin which exceed 20 g/day, are for muesli and fruit and vegetable juice products. Fruit and vegetable juice products are likely to be consumed more than once over a 24 hour period and the predicted exposure is likely to be an overestimate of what is consumed during a single eating occasion. Therefore, it is not necessary to consider risk management strategies in relation to fruit and vegetable juice products. It is likely that muesli will be eaten only once per day and therefore, the predicted exposure based on 24 hour consumption data may not be an overestimate.

α-Cyclodextrin is proposed to be used at a level of 2-9 g/100 g muesli, while a level of 9 g/100 g food was assigned to muesli for the dietary modelling resulting in an overestimate of the likely consumption.

The 95th percentile consumer for children aged 2-12 years is consuming 285 g muesli in a single eating occasion to achieve the predicted exposure for this group of 25.7 g of α-cyclodextrin. Only two children consumed more than 285 g of muesli on that day with an 11 year old and an 8 year old both consuming 303 g and a third child aged 11 years consumed 262 g. No other children consumed more than 160 g muesli. Muesli is usually consumed with milk or yoghurt and so when α-cyclodextrin is included in muesli, it is being consumed within the food matrix in a meal providing significant amounts of carbohydrate, protein and fibre. Many muesli products are already high in fibre, so any gastrointestinal effects following consumption of muesli containing α-cyclodextrin could equally be attributed to the naturally occurring fibre.

It is concluded that it is not necessary to limit the maximum level of use of α-cyclodextrin or the categories of foods to which α-cyclodextrin may be added because:

- There are no limits placed on the use of other unavailable carbohydrates or polyols in foods, which have similar physiological effects.

- The gastrointestinal effects observed in the study are mild and only occurred in 4/12 overnight-fasted subjects given a single dose of 25 g of α-cyclodextrin in water. When sold as a food ingredient, α-cyclodextrin would always be included in a food matrix, therefore it would not be possible for an individual to consume the α-cyclodextrin in combination with water only.

- Although it is possible for the 95th percentile consumer in Australian children aged 2-12 years to exceed 25 g α-cyclodextrin during a single eating occasion of muesli (25.7g/day), this is likely to be an overestimate of consumption given the proposed level of use is 2-9 g/100 g (rather than the 9 g/100 g food assigned in dietary modelling). In addition, the estimate for the 95th percentile is attributed to three children only consuming large quantities of muesli.

5.6.2 Consideration of requiring labelling statements on foods containing α-cyclodextrin

The Applicant states that α-cyclodextrin has dietary fibre-like properties of increasing faecal bulk, decreased levels of plasma triglycerides and cholesterol and modulation of glycaemic response. α-Cyclodextrin cannot be claimed as dietary fibre because the analytical methods specified in the table to subclause 18(1) are not applicable to α-cyclodextrin. It could be argued that consumers will be unable to identify that a food containing α-cyclodextrin may have a dietary fibre-like effect because it cannot be claimed as dietary fibre. The inclusion of α-cyclodextrin in the ingredient list only would not provide consumers with the information that it may cause abdominal discomfort. α-Cyclodextrin has been assessed as largely indigestible in the small intestine and will be identified as 'unavailable carbohydrate' in the Nutrition Information Panel.

Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations – of the Code, currently requires all food containing more than 10 g of some polyols and more than 25 g polydextrose and some polyols either singularly or in combination per 100 g of food to carry an advisory statement regarding the laxative effects of the food when consumed in excess.

The content levels which trigger the required labelling were derived based on tolerance studies noting that: intra- and inter-individual responses to the same substance may vary depending on the frequency and nature (i.e. in combination with other foods or alone) of consumption; and children are more vulnerable to the laxative effects. The trigger level of 10 g/100 g of food was established for substances which produce laxative symptoms at approximately 30 g/day in adults. The trigger level of 25 g/100 g food was established for substances which produce laxative symptoms at approximately 40 g/day or higher in adults.

Ingestion of 20-25 g or more of α-cyclodextrin on a single eating occasion may cause gastrointestinal effects in humans, particularly if eaten alone. This tolerance level is similar to those polyols for which a labelling statement regarding the laxative effects is triggered at a level of 10 g/100 g food. However, the gastrointestinal effects noted after consumption of α-cyclodextrin were abdominal discomfort in a small number of subjects and only one subject experienced diarrhoea after ingestion of 25 g α-cyclodextrin on an empty stomach. Therefore, it would not be accurate or appropriate to apply the labelling statement relating to polyols and polydextrose to α-cyclodextrin.

An alternative statement referring to gastrointestinal effects when consumed in excess could be considered for α-cyclodextrin with a trigger level of 10 g/100 g food, consistent with the trigger level for the statement required for polyols based on the occurrence of symptoms at similar dose levels. The proposed use levels for α-cyclodextrin according to the Applicant are primarily less than this 10 g/100 g food, with the exception of reduced fat spreads (20%), crackers (10%), hard candy (15%) and chewing gum (10%) and none of these foods are consumed in quantities sufficient to approach 25 g α-cyclodextrin at a single eating occasion. It is unlikely that α-cyclodextrin will be used at levels beyond that proposed due to the target formulation of the product and the role of α-cyclodextrin in the particular food.

It is concluded that it is not considered necessary to require a statement relating to excessive consumption potentially causing gastrointestinal effects because:

- α-Cyclodextrin will be declared as unavailable carbohydrate in the Nutrition Information Panel.

- The abdominal discomfort reported is mild, symptoms vary between and within individuals and are unlikely to be experienced given the proposed uses of α-cyclodextrin.

- The proposed levels of use of the food are primarily lower than a likely trigger level, with the exception of a few foods that would not be eaten in quantities sufficient to cause gastrointestinal upset at a single eating occasion.

5.6.3 Risk management conclusions

The use of risk management strategies in conjunction with permission for α-cyclodextrin as a novel food, in the form of either a limit on its use or requiring a labelling statement, is not deemed necessary.

The name ('alpha-cyclodextrin' or 'α-cyclodextrin') would need to be used when describing the ingredient in the ingredient list, as prescribed in Standard 1.2.4 – Labelling of Ingredients – of the Code. This should be specified as a condition of use in column 2 of the table to clause 2 of Standard 1.5.1 of the Code. This condition of use is consistent with that required for γ-cyclodextrin.

α-Cyclodextrin will be required to meet the specifications listed in Standard 1.3.4 – Identity and Purity – of the Code. The specifications for α-cyclodextrin, as established by JECFA, are stated in the reference listed in clause 2(a) of Standard 1.3.4.

When assessing the use of trehalose as a novel food FSANZ proposed that, given the increasing use of food and ingredients, which may potentially cause gastro-intestinal effects at high doses of exposure, it would monitor the use of these ingredients in 3-5 years in order to obtain a better estimate of dietary exposure and its impact on public health and safety. FSANZ will also undertake to monitor the use of α-cyclodextrin. The uptake of existing permissions for novel foods by industry will be considered during the review of novel foods.

5.7 Issues raised in submissions

5.7.1 Issues raised in response to the Initial Assessment Report

5.7.1.1 Safety considerations

Some submitters indicated conditional support for the approval of α-cyclodextrin as a novel food pending the outcome of a safety evaluation. The Applicant indicated that α-cyclodextrin has been used as a food ingredient only in Japan. Because of its limited use in other countries, one submitter expressed the view that the safety assessment should be extremely thorough.

FSANZ consideration
A safety assessment for α-cyclodextrin as a food ingredient has now been completed. The outcomes of the safety assessment were discussed in section 5.1 of this Report and more detail is available in the safety assessment report at Attachment 2. Based on the evaluation of the levels of exposure in the animal and human studies and the adverse effects, it is considered that α-cyclodextrin is of very low toxicity and, at the proposed levels of dietary exposure, would not be considered to be of toxicological concern.

5.7.1.2 Effect of α-cyclodextrin on the absorption of nutrients

Two submitters expressed concern about the potential for α-cyclodextrin to inhibit the absorption of certain vitamins, minerals and fatty acids. One submitter stated concern that because α-cyclodextrin acts as a carrier, it may be able to carry nutrients beyond their sites of absorption in the gut and subsequently lead to deficiencies.

FSANZ consideration
As discussed in section 5.4.2 of this Report, FSANZ has evaluated the potential effect of α-cyclodextrin on the absorption of the fat-soluble vitamins (vitamins A, D, E and K) and lipids. Fat-soluble nutrients (fat-soluble vitamins and lipids) and their absorption are considered the most likely nutrients to be affected by the presence of α-cyclodextrin because of the ability of α-cyclodextrin to complex these nutrients in its hydrophobic core.

This information is provided in the Nutrition Assessment Report at Attachment 4.

The Nutrition Assessment Report concludes that β-cyclodextrin does not impair the absorption of vitamins A, D or E and that, based on the structural similarity of α-cyclodextrin with β-cyclodextrin and a relevant *in vitro* study comparing the complexing capacity of the cyclodextrins, α-cyclodextrin is unlikely to affect the absorption of these fat-soluble vitamins. An *in vitro* study indicates that α-cyclodextrin is more likely to form complexes with vitamin K than the other cyclodextrins, however, it is considered unlikely that α-cyclodextrin will adversely affect the vitamin K status of individuals due to the biochemistry and physiology of vitamin K.

5.7.1.3 Alpha-cyclodextrin as 'unavailable carbohydrate'

One submitter expressed concern that the term unavailable carbohydrate may be confusing to the general public and did not support its use as a nutrition claim.

FSANZ consideration
As discussed in section 5.4.3 FSANZ has reviewed the available data in order to determine whether or not α-cyclodextrin is appropriately characterized as 'unavailable carbohydrate', that is, not absorbed or available for metabolism to any significant extent. This evaluation is presented in the Nutrition Assessment Report at Attachment 4.

The nutrition assessment concludes that there is sufficient evidence to indicate that α-cyclodextrin is largely indigestible in the small intestine. It therefore seems appropriate to classify α-cyclodextrin as 'unavailable carbohydrate' and apply the energy factor of 8 kJ/g assigned to 'unavailable carbohydrate' to α-cyclodextrin.

While 'unavailable carbohydrate' may be a term that is not well understood by the general public, there is provision in Standard 1.2.8 – Nutrition Information Requirements – of the Code for using the energy factor assigned to unavailable carbohydrate in order to calculate the energy of the food for the purposes of inclusion in a Nutrition Information Panel. In accordance with Standard 1.2.8, clause 5 (6) the Nutrition Information Panel must include declarations of unavailable carbohydrate where the unavailable carbohydrate has been substracted in the calculation of 'carbohydrate by difference'. The declaration of unavailable carbohydrate in the Nutrition Information Panel would be considered mandatory information and as such, while not considered to be a claim, appears to be rarely utilised by industry.

5.7.1.4 Consideration of α-cyclodextrin against Standard 1.5.1 – Novel Foods

AFGC argued, in its submission, that FSANZ did not provide justification in the Initial Assessment Report for considering α-cyclodextrin as a novel food. AFGC suggest that α-cyclodextrin meets the definitions for sugars, contained in Standard 2.8 – Sugars – of the Code, and also dietary fibre, contained in Standard 1.2.8 – Nutrition Information Requirements – of the Code.

FSANZ consideration
The possibility of a food meeting a particular definition in the Code does not exclude that food from also being considered novel. For example, a definition is provided in Standard 1.2.8 – Nutrition Information Requirements – of the Code for 'biologically active substances', however, many substances that meet this definition would also be considered to be novel.

While α-cyclodextrin may meet the definition for dietary fibre, it cannot be claimed as dietary fibre because the analytical methods specified in the table to subclause 18(1) are not applicable to α-cyclodextrin. AFGC argue that α-cyclodextrin can be considered to be starch hydrosylate, which is covered in the definition for 'sugars'. However, α-cyclodextrin is a product of a starch hydrosylate formed by the action of the enzyme CGTase, rather than it being a starch hydrosylate itself.

α-Cyclodextrin is considered a non-traditional food because it has no history of significant human consumption in Australia or New Zealand. Although many bacteria are able to produce cyclodextrins from starch, there is no known significant intake of naturally occurring cyclodextrins in food. The safety of α-cyclodextrin as a food ingredient in greater amounts than needed for use as a food additive, had not been assessed prior to this Application. There were some adverse effects noted in some of the studies at higher levels of use as indicated in the safety assessment report at Attachment 2. As such, α-cyclodextrin is considered a novel food in accordance with the definition provided in Standard 1.5.1 because it is a non-traditional food 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 both the potential for adverse effects in humans and the patterns and levels of consumption of the product.

AFGC has regularly provided submissions in response to assessment reports for novel food applications indicating that, in their opinion, the novel food being assessed does not meet the definition of novel food and should not require pre-market assessment. The Novel Foods Standard will be reviewed soon based on policy guidance from the *Australia New Zealand Food Regulation Ministerial Council* issued in December 2003. The review of the Standard will give consideration to the definitions for both 'non-traditional food' and 'novel food'.

5.7.2 Issues raised in response to the Draft Assessment Report

5.7.2.1 Safety considerations

Two issues have been raised in relation to the safety assessment for α-cyclodextrin as follows:

- Because α-cyclodextrin is likely to be used as a premium or special purpose food, the safety of α-cyclodextrin for the likely consumer sub-groups (e.g. those with concerns about weight control or blood glucose control) should be evaluated.

- The safety of the enzyme cyclodextrin-glycosyl transferase (CGTase), sourced from a genetically modified strain of *E. coli* K-12, used for the production of α-cyclodextrin, should be assessed.

A further issue relates to risk management. Based on the safety assessment, NZFSA have requested that some consideration should be given to limiting the amount of α-cyclodextrin per serve, or per 100 g of food. They have suggested a maximum limit of 10% α-cyclodextrin in any food based on the occurrence of gastrointestinal effects at higher levels.

FSANZ consideration
Although some products containing α-cyclodextrin will be marketed as special purpose foods to a target sub-group of the population, many products containing α-cyclodextrin will be marketed to the general community.

It would only be necessary to address the safety of α-cyclodextrin for particular sub-groups of the population if the potential existed for them to be at a greater risk. Based on all the safety studies available and the nature of the only adverse effect found (mild gastrointestinal discomfort), there is no evidence to suggest that any population sub-group would be at increased risk of experiencing adverse effects. JECFA explained the abdominal discomfort in this study as a well-known effect of carbohydrates of low digestibility, particularly if ingested in liquid form on an empty stomach, which is partly caused by an influx of water in the small intestine (achieving isotonicity) and partly by the ensuing fermentation process in the more distal parts of the gut. There is no evidence to indicate that individuals with concerns about weight control or blood glucose control would have greater susceptibility to the adverse effect of abdominal discomfort.

In relation to the enzyme CGTase, it is not necessary or appropriate to assess its safety for the following reasons:

- The Application is for the use of α-cyclodextrin as a final food/food ingredient, not for the chemicals used in its productions. The specifications would address any concerns due to the carry-over of components resulting from the production methods. A limited evaluation for this purpose has been undertaken by JECFA, which concluded that the enzyme CGTases, which is used in the production of α-cyclodextrin, is derived from a non-genotoxic, non-toxinogenic source and is completely removed from α-cyclodextrin during purification and is therefore of no safety concern.

- It is not appropriate for an Application for use of α-cyclodextrin, which is to be imported as a finished product, to be dependent on approval for an enzyme used in its production. The enzyme will not be used in Australia or New Zealand and no permission to do so is sought.

- It is not appropriate to extend the Application to include permission for an enzyme used in the production. A separate application is required for new enzymes such as CGTase, if permission for their use is sought in Australia or New Zealand. This would allow the safety of the enzyme to be fully considered in the context of all possible uses.

FSANZ has given consideration to limiting the maximum amount of α-cyclodextrin in the final food in section 5.6 of this Report – Risk Management. Based on the nature of the adverse effects (gastrointestinal discomfort) it is concluded that limiting the maximum amount of α-cyclodextrin used in a final food product is not necessary as a condition of use for the following reasons:

- There are no limits placed on the use of other unavailable carbohydrates or polyols in foods, which have similar physiological effects.

- The gastrointestinal effects observed in the study are mild and only occurred in 4/12 overnight-fasted subjects given a single dose of 25 g of α-cyclodextrin in water. When sold as a food ingredient, α-cyclodextrin would always be included in a food matrix, therefore it would not be possible for an individual to consume the α-cyclodextrin in combination with water only as was administered in the study.

- Although it is possible for the 95th percentile consumer in Australian children aged 2-12 years to exceed 25 g α-cyclodextrin during a single eating occasion of muesli (25.7g/day), this is likely to be an overestimate of consumption given the proposed level of use is 2-9 g/100 g (rather than the 9 g/100 g food assigned in dietary modelling). In addition, the estimate for the 95th percentile is attributed to three children only consuming large quantities of muesli.

- The proposed levels of use of the food are primarily lower than 10%, with the exception of a few foods that would not be eaten in quantities sufficient to cause gastrointestinal upset at a single eating occasion.

5.7.2.2 Claims and representation of α-cyclodextrin

Dietary fibre-like properties cannot be claimed

NZFSA argue that while α-cyclodextrin is purported to have dietary fibre-like effects, the dietary fibre cannot be claimed in accordance with Standard 1.2.8, therefore consumers may not be able to identify the potential dietary fibre-like effects and this is potentially misleading.

FSANZ consideration
α-Cyclodextrin cannot be claimed as dietary fibre, but it can be considered to be 'unavailable carbohydrate' for inclusion in the Nutrition Information Panel. The issue was considered in section 5.6 of this Report, and it was concluded that no additional labelling as a condition of use of α-cyclodextrin was necessary.

Consideration of low GI, low joule and dietary fibre claims

Queensland Health requested that FSANZ consider the likely claims associated with foods containing α-cyclodextrin, e.g. low glycaemic index (GI) claims, low energy claims and potentially, in the future, dietary fibre claims.

FSANZ consideration
There are no specific regulations for GI claims in the Code. Any claims made on the label of foods need to comply with fair trading laws in addition to any relevant regulations in the Code. Therefore, any statements made on the label of a food about the GI should not mislead consumers. A GI symbol program is in operation that does not involve FSANZ and foods currently on the market carry low GI claims.

Low joule claims are regulated by Standard 1.2.8, clause 14. Because α-cyclodextrin can be considered unavailable carbohydrate, an energy value of 8 kJ/g can be used to calculate the energy content of the final food containing α-cyclodextrin. This may enable low joule claims to be made about the final food containing α-cyclodextrin. In order to make a low joule claim, the requirements of clause 14 of Standard 1.2.8 must be met for the final food.

Dietary fibre claims cannot be made for α-cyclodextrin because the analytical methods specified in Standard 1.2.8, the table to subclause 18(1), are not applicable to α-cyclodextrin. The Applicant is not seeking to have a method for determining the dietary fibre content of foods containing α-cyclodextrin recognised in Standard 1.2.8 because there is no official method recognised by the Association of Analytical Chemists (AOAC).

In order for such a method to be included in Standard 1.2.8, thus enabling claims to be made in relation to dietary fibre, an Application would need to be made to FSANZ, which would be assessed in the same way that applications of a similar nature have been assessed for polydextrose and resistant maltodextrin.

5.7.2.3 Consideration of α-cyclodextrin against the novel foods standard

Both NSW Food Authority and AFGC have questioned why α-cyclodextrin should be considered a novel food rather than simply a food since the assessment concludes that α-cyclodextrin does not pose any public health and safety concern and no conditions of use are necessary. The NSW Food Authority has requested that this issue be addressed in the review of the novel foods standard.

FSANZ consideration
Standard 1.5.1, clause 2 states that:

> *a novel food must not be sold by way of retail sale as food or for use as a food ingredient unless it is listed in column 1 of the Table to this clause and complies with the conditions of use, if any, specified in column 2*.

In referring to the conditions of use, if any, a food can still be considered novel even if no conditions of use are specified.

The Novel Foods Standard will be reviewed based on policy guidance from the *Australia New Zealand Food Regulation Ministerial Council* issued in December 2003. The review of the Standard will give consideration to the definitions for both 'non-traditional food' and 'novel food' and the requirements of the Standard.

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, governments in both Australia and New Zealand and often public health professionals. The benefits and costs associated with the proposed amendment to the Code will be analysed in a Regulatory Impact Assessment.

Novel foods or novel food ingredients used in Australia and New Zealand are required to be listed in Standard 1.5.1 – Novel Foods. As the use of α-cyclodextrin is being considered as a novel food ingredient, which requires pre-market approval under Standard 1.5.1 – Novel Foods, it is not appropriate to consider non-regulatory options to address this Application.

Two regulatory options have been identified for this Application:

Option 1 – Not permit the use of α-cyclodextrin as a novel food.

Option 2 – Permit the use of α-cyclodextrin as a novel food.

7. Impact Analysis

7.1 Affected Parties

Parties possibly affected by the options outlined in section 6 include:

1. Consumers who may benefit as a result of new products containing α-cyclodextrin.

2. Public health professions because of the desire to ensure consistency in the education message regarding the potential promotion of α-cyclodextrin as 'unavailable carbohydrate' and having dietary fibre-like properties.

3. Those sectors of the food industry wishing to market foods containing α-cyclodextrin as a food ingredient including potential importers, manufacturers of α-cyclodextrin and manufacturers of foods that may potentially contain α-cyclodextrin.

4. Government agencies enforcing the food regulations.

7.2 Impact analysis

7.3.1 Option 1 – Not permit the use of α-cyclodextrin as a novel food ingredient

7.3.1.1 Consumers

There are no significant costs or benefits of not permitting the use of α-cyclodextrin identified for consumers. Consumers wishing to purchase foods with reduced energy value or low to medium glycaemic index already have access to such food products, many of which are marketed in such a way to target consumers interested products with these properties.

7.3.1.2 Public health professionals

There is no clear cost or benefit to public health professionals by not permitting α-cyclodextrin as a food ingredient. There are a number of foods available with reduced energy and low to medium glycaemic index which health professionals can recommend to clients.

7.3.1.3 Industry

The current situation of no permission for the use of α-cyclodextrin represents a cost to industry sectors wishing to manufacture or import α-cyclodextrin for incorporation into food products or those wishing to manufacture or import final food products containing α-cyclodextrin (currently only available in Japan). The food products containing α-cyclodextrin are likely to be premium or special purpose foods due to the cost of producing α-cyclodextrin and will therefore represent only a small sector of the market, at least initially.

7.3.1.4 Government

There is no cost or benefit identified to government by not permitting α-cyclodextrin as a novel food ingredient.

7.3.2 Option 2 – Permit the use of α-cyclodextrin as a novel food ingredient

7.3.2.1 Consumers

Consumers may benefit from additional choice. Where α-cyclodextrin is intended for use as a food ingredient, replacing starch or sugar for example, the resultant products are likely to be more expensive than the traditional counterpart. For industrial application, α-cyclodextrin is likely to cost approximately US$ 20-25 per kg[4]. Because the products containing α-cyclodextrin may be more expensive, the products are likely to be targeted at consumers looking for foods with particular attributes such as reduced energy or reduced glycaemic index, who will incur the cost by choice. This means that there is not likely to be any cost to the consumer looking to purchase general foods. The ability of α-cyclodextrin to moderate the flavour and aroma or undesirable characteristics of a food component, as stated by the applicant, may present an additional benefit to consumers. The improved quality and stability afforded by the addition of α-cyclodextrin (due to the technical properties) of some foods may benefit consumers.

7.3.2.2 Public health professionals

Public health professionals may benefit from a wider range of foods with particular nutritional characteristics to recommend or suggest to their clients. α-Cyclodextrin cannot be declared as dietary fibre and so it is not anticipated that there will be any confusion about the nutrition education message regarding fibre.

7.3.2.3 Industry

Food manufacturers are likely to benefit from permitting α-cyclodextrin as a novel food both in terms of processing and the end quality product. Food manufactures and importers are likely to benefit from the potential to develop and market new processed foods with potentially enhanced nutritional characteristics. Manufacturers of α-cyclodextrin will benefit from sales to food manufacturers.

7.3.2.4 Government

There are no significant costs or benefits identified to government agencies enforcing the food regulations. The Department of Agriculture, Fisheries and Forestry (DAFF) indicated that approval for α-cyclodextrin as a novel food would represent a routine amendment to the Code and, if adopted, would not have an adverse regulatory impact on DAFF or the Australian Quarantine and Inspection Service (AQIS). Approval of α-cyclodextrin as a novel food ingredient would promote international trade in food products, potentially benefiting government.

7.3.3 Assessment of impacts

On the basis of this Final Assessment, there is likely to be a benefit to consumers, public health professionals, industry and potentially government in permitting α-cyclodextrin as a novel food ingredient.

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[4] Biwer, A., Antranikian, G. and Heinzle, E. (2002) **Enzymatic production of cyclodextrins**. *Appl. Microbiol. Biotechnol,* 59, pp 609-617.

The Department of Agriculture, Fisheries and Forestry indicated that there would be no anticipated impact on enforcement operation. No further information relevant to the impact analysis was received in submissions to either the Initial or the Draft Assessment Reports.

8. Consultation

8.1 Public consultation

8.1.1 Initial assessment

FSANZ received seven submissions in response to the Initial Assessment Report. Five of these submitters support Option 2, to permit α-cyclodextrin as a novel food, subject to the assessment of safety, nutrition and dietary exposure at Draft Assessment. A summary of submissions is at Attachment 6. Issues raised in submissions have been addressed in section 5 of this Report.

8.1.2 Draft assessment

FSANZ received four submissions in response to the Draft Assessment Report. Three submitters supported Option 2, to permit the use of α-cyclodextrin as a novel food, while New Zealand Food Safety Authority stated that they thought it would be premature to approve the use of α-cyclodextrin as a novel food. A summary of these submissions is at Attachment 6. Issues raised in submissions have been addressed in section 5 of this Report.

8.2 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade. This enables other member countries of the WTO to make comment.

Amending the Code to permit the use of α-cyclodextrin as a novel food was not be notified to the WTO under either the Technical Barrier to Trade (TBT) or Sanitary and Phytosanitary Measure (SPS) agreements as the permission is unlikely to significantly effect trade, particularly since FSANZ would be expanding permissions. There are no relevant international standards and the potential food applications for α-cyclodextrin are limited in terms of market size. Because the products containing α-cyclodextrin may be more expensive, the products are likely to be targeted at consumers looking for foods with particular attributes. Therefore this matter was not notified to the WTO.

9. Conclusion

It is agreed to approve the use of α-cyclodextrin as a novel food, with no specified conditions of use other than the requirement for the full disclosure of the name (‘alpha-cyclodextrin’ or ‘α-cyclodextrin’) when describing the name in the ingredient list, for the following reasons:

- There is no identified public health and safety risk associated with the use of α-cyclodextrin as proposed. The safety evaluation indicates that α-cyclodextrin is a substance of very low toxicity and, in the proposed range of foods at the proposed maximum levels of use as provided by the Applicant, would not raise any safety concerns.

- The nutrition assessment indicates that α-cyclodextrin is unlikely to affect the absorption of fat-soluble nutrients (fat-soluble vitamins and lipids). α-Cyclodextrin is assessed as having a low nutritional impact when used as a food ingredient.

- α-Cyclodextrin can perform technological functions in addition to being used as a food ingredient. Classifying α-cyclodextrin as a novel food would not restrict its use to perform a technological function normally associated with a food additive.

- The proposed changes to the Code are consistent with the section 10 objectives of the FSANZ Act.

- The Regulatory Impact Statement indicates that for the preferred option, namely, to approve the use of α-cyclodextrin as a novel food, the benefits of the proposed amendment outweigh the costs.

α-Cyclodextrin will be required to meet the specifications listed in Standard 1.3.4 – Identity and Purity – of the Code.

α-Cyclodextrin is largely indigestible in the small intestine and the term 'unavailable carbohydrate', with its corresponding energy factor of 8 kJ/g, as provided in Standard 1.2.8 – Nutrition Information Requirements, can be applied to α-cyclodextrin.

The proposed drafting for amendment to Standard 1.5.1 is at Attachment 1 of the Final Assessment Report.

10. Implementation and review

The amendment to Standard 1.5.1 – Novel Foods – of the Code, to permit the use of α-cyclodextrin as a novel food, will come into effect upon gazettal, subject to any request from the Ministerial Council for a review.

ATTACHMENTS

1. Draft variation to the *Australia New Zealand Food Standards Code*
2. Safety Assessment Report
3. Dietary Exposure Assessment Report
4. Nutrition Assessment Report
5. Food Technology Report
6. Summary of Submissions

ATTACHMENT 1

Draft variation to the *Australia New Zealand Food Standards Code*

To commence: on gazettal

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

α-cyclodextrin	The name 'alpha cyclodextrin' or 'α-cyclodextrin' must be used when declaring the ingredient in the ingredient list, as prescribed in Standard 1.2.4.

ATTACHMENT 2

SAFETY ASSESSMENT REPORT

Safety of α-cyclodextrin

Summary and Conclusion

JECFA has evaluated α-cyclodextrin as a food additive in 2001 and concluded that an ADI 'not specified'[5] as appropriate (WHO, 2002). In addition, JECFA evaluated α-cyclodextrin in 2004 for its use as a food ingredient (WHO, 2004) and retained the ADI 'not specified'. The safety data, as provided by the Applicant, were similar to the data provided by to the JECFA evaluation in 2001. The safety studies in animals, involving very high levels of α-cyclodextrin, indicated the only adverse effects were those attributed to the presence of osmotically active substances. There are no long-term studies in animals available, however these are not considered necessary, since the adverse effects of α-cyclodextrin are related to the presence of osmotically active substances. α-Cyclodextrin has no mutagenic or teratogenic potential.

One study in human volunteers was submitted to FSANZ, additional to the studies that were evaluated by JECFA, which indicated that acute intake of 10 g α-cyclodextrin with 100 g white bread did not result in adverse effects. This study has been evaluated by JECFA in 2004. These data are considered sufficient for the assessment of α-cyclodextrin as a novel food.

After evaluation of the levels of exposure in the animal and human studies and the adverse effects, it was considered that α-cyclodextrin is of very low toxicity and, at the proposed levels of dietary exposure, would not be considered to be of toxicological concern. Therefore, it is not necessary to set an ADI for the use of α-cyclodextrin.

Introduction

Application A494 seeks approval for the use of α-cyclodextrin as a novel food. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated α-cyclodextrin as a food additive in 2001. However, JECFA did not evaluate the proposed higher exposure of α-cyclodextrin through the use as a novel food in 2001. The Applicant has submitted all the studies available to JECFA, as well as one recent study in human volunteers, which tested the gastrointestinal tolerance of α-cyclodextrin. Since, the JECFA evaluation was so recently published (2002), the studies in the JECFA report have not been re-evaluated, but the summary of the JECFA report was directly copied in this safety assessment report.

[5] ADI 'not specified' is used to refer to a food substance of very low toxicity, which, on the basis of the available data (chemical, biochemical, toxicological, and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

In 2004, JECFA evaluated α-cyclodextrin for use as a food ingredient. The conclusion of JECFA was that α-Cyclodextrin does not pose a safety concern at the proposed use levels considered by the Committee and resulting predicted consumption as food ingredient and food additive. The previously established ADI "not specified" for use as a carrier and stabilizer for flavours, colours, and sweeteners, as a water-solubiliser for fatty acids and certain vitamins, as a flavour modifier in soya milk, and as an absorbent in confectionery was maintained (WHO, 2004).

For the production of α-cyclodextrin, the enzyme cyclodextrin-glycosyl transferase (CGTase), sourced from a genetically modified strain of *E coli* K-12, was used. The gene coding for CGTase was obtained from a non-pathogenic and non-toxigenic strain of *Klebsiella oxytoca*. It is not necessary to assess the safety of this enzyme as part of this Application because the specifications would address any concerns due to carry-over of components resulting from the production methods and JECFA undertook a limited evaluation for this purpose.

Summary of JECFA evaluation (2001)

α-Cyclodextrin, like β-cyclodextrin, is not digested in the gastrointestinal tract but is fermented by the intestinal microflora. In germ-free rats, α-cyclodextrin is almost completely excreted in the faeces, whereas γ-cyclodextrin is readily digested to glucose by the luminal and/or epithelial enzymes of the gastrointestinal tract. α-Cyclodextrin is absorbed intact at low levels (approximately 2%) from the small intestine. Absorbed α-cyclodextrin is then excreted rapidly in the urine. The majority of the absorption takes place after metabolism by the microflora in the caecum. Although no studies of metabolism in humans *in vivo* were available, α-cyclodextrin and β-cyclodextrin, unlike γ-cyclodextrin, cannot be hydrolysed by human salivary and pancreatic amylases *in vitro*.

The acute toxicity of α-cyclodextrin when given by the intraperitoneal or intravenous route indicates that it can cause osmotic nephrosis, probably because it is not degraded by lysosomal amylases. At high doses, this leads to renal failure.

The results of short-term (28- and 90-day) studies of toxicity indicated that α-cyclodextrin has little effect when given orally to rats or dogs. After administration of a very high dietary concentration (20%), caecal enlargement and associated changes were seen in both species. This effect is likely to result from the presence of a high concentration of an osmotically active substance in the large intestine. No studies of intravenous administration were available to permit a comparison of the systemic toxicity of this compound with that of β- and γ-cyclodextrin.

Studies conducted in mice, rats, and rabbits with α-cyclodextrin at concentrations in the diet of up to 20% did not indicate any teratogenic effects. Similarly, the results of assays for genotoxicity were negative. No long-term studies of toxicity, carcinogenicity, or reproductive toxicity have been conducted with α-cyclodextrin, but the Committee concluded that, given the known fate of this compound in the gastrointestinal tract, such studies were not required for an evaluation.

In vitro, α-cyclodextrin, like β-cyclodextrin, sequestered components of the membranes of erythrocytes, causing haemolysis. The threshold concentration for this effect was, however, higher than that observed with β-cyclodextrin.

The enzyme CGTase, which is used in the production of α-cyclodextrin, is derived from a non-genotoxic, non-toxinogenic source and is completely removed from α-cyclodextrin during purification and is therefore of no safety concern.

The predicted mean intake of α-cyclodextrin by consumers, based on individual dietary records for 1994–98 for the USA and proposed maximum levels of use in a variety of foods, would be 1.7 g/day (32 mg/kg bw per day) for the whole population and 1.6 g/day (87 mg/kg bw per day) for children aged 2–6 years. The main contributors to the total intake of α-cyclodextrin are likely to be soya milk and sweets.
For consumers at the 90th percentile of intake, the predicted intake of α-cyclodextrin would be 3 g/day (67 mg/kg bw per day) for the whole population and 2.6 g/day (140 mg/kg bw per day) for children aged 2–6 years.
No studies of human tolerance to α-cyclodextrin were submitted to the Committee, despite its potentially high dietary intake. Nevertheless, the Committee was reassured by the relatively low toxicity of this compound in animals and the fact that it was less toxic than β-cyclodextrin, for which studies of human tolerance were available. Furthermore, the fact that it is fermented in the gastrointestinal tract in an analogous manner to β-cyclodextrin supported the conclusion that, as in laboratory animals, it would be fermented to innocuous metabolites before its absorption by humans.

The Committee concluded that, on the basis of the available studies on α-cyclodextrin and studies on the related compounds β-cyclodextrin and γ-cyclodextrin, for which ADIs had been allocated, there was sufficient information to allocate an ADI "not specified". This ADI was based on the known current uses of α-cyclodextrin under good manufacturing practices as a carrier and stabilizer for flavours, colours, and sweeteners; as a water-solubiliser for fatty acids and certain vitamins; as a flavour modifier in soya milk; and as an absorbent in confectionery.

Additional studies not assessed in the JECFA evaluation in 2001

Acute α-cyclodextrin intake study in healthy male volunteers (Diamantis and Bär, 2002)

Test material:	α-cyclodextrin dissolved in 250 ml water
Control material:	starch (in the form of about 100 g fresh white bread) with 250 ml of water
Dose levels	0, 10 or 25 g α-cyclodextrin
Test groups:	12 healthy male volunteers (age 23-24 years, non-smoking)
GLP:	Not stated.

Study conduct

The subjects were comprised of twelve male volunteers who orally took, on three separate days: 1) 50 g starch (in the form of about 100 g fresh white bread) together with 250 ml water; 2) 50 g starch (100 g white bread) together with 10 g α-cyclodextrin dissolved in 250 ml water; and 3) 25 g α-cyclodextrin dissolved in 250 ml water after overnight fasting. The study was of a single blind design. Two rest days were allocated between treatment days. During the 3-hour following intake, water consumption was allowed, however it was recommended not to drink more than 300 ml.

Blood was taken before and 15, 30, 45, 60, 75, 90, 120, 150 and 180 min intake of test material for measurement of glucose and insulin.

Results

All subjects completed the study. After completion of the last treatment (25 g α-cyclodextrin, without bread intake) three subjects reported mild abdominal discomfort and one subject reported diarrhoea. 10 g α-cyclodextrin combined with white bread intake did not result in any clinical effect.

This study was assessed by JECFA in 2004. JECFA explained the abdominal discomfort as a well-known effect of carbohydrates of low digestibility, particularly when taken outside the food matrix on an empty stomach. It is partly caused by an influx of water in the small intestine (achieving isotonicity) and partly by the ensuing fermentation process in the more distal parts of the gut.

References:

Diamantis I, Bär A. (2002). Effect of α-cyclodextrin on the glycaemic index (GI) and insulinemic index (II) of starch in healthy human volunteers. Unpublished study report.

WHO (2002). Safety evaluation of certain food additives and contaminants. WHO Food Additives Series 48: 111-127 (α-cyclodextrin). Full report available at http://www.inchem.org/documents/jecfa/jecmono/v48je10.htm

WHO (2004). Joint FAO/WHO Expert Committee on Food Additives, Sixty-third meeting Geneva, 8-17 June 2004. Summary and conclusions Report available at http://www.who.int/ipcs/publications/jecfa/en/summary_final.pdf

WHO (in preparation). Safety evaluation of certain food additives, WHO Food Additives Series xx (α-cyclodextrin), in preparation.

ATTACHMENT 3

DIETARY EXPOSURE ASSESSMENT REPORT

Application A494 – *Alpha*-cyclodextrin as a novel food

Summary

An Application was received by FSANZ requesting amendment of the Food Standards Code (the Code) to allow the use of *alpha*-cyclodextrin (α-cyclodextrin) as a novel food ingredient, under Standard 1.5.1 – Novel Foods, for use in a variety of foods including milk and milk products, breads, confectionery and various other products. A dietary exposure assessment was deemed necessary in order to predict the potential exposures to α-cyclodextrin in Australia and New Zealand if it were to be approved for use at the proposed levels in foods.

The Applicant proposed to use α-cyclodextrin as a food ingredient because of its purported dietary fibre-like properties. A dietary exposure assessment was conducted for the general Australian and New Zealand populations (2 years and above and 15 years and above, respectively) and for the population considered at potential risk from higher exposures; children (2-12 years, Australia only). Food consumption data were derived from the 1995 Australian National Nutrition Survey (NNS) and the 1997 New Zealand NNS. α-Cyclodextrin concentration data were derived from levels proposed in the Application.

Estimated mean and 95th percentile dietary exposures for consumers of α-cyclodextrin in the Australian population (2+ years) from all proposed foods were 17.5 grams per day (g/day) and 36.8 g/day, respectively. Estimated mean and 95th percentile dietary exposures for consumers of α-cyclodextrin in the New Zealand population (15+ years) from all proposed foods were 17.0 g/day and 36.9 g/day, respectively. Australian children (2-12 years) had estimated dietary exposures of 17.5 g/day (mean) and 33.4 g/day (95th percentile). The highest percentage contribution to dietary exposure was from breads and related products for all population groups assessed.

Bolus doses of α-cyclodextrin based on high consumers of individual foods over a 24-hour period do not exceed 28 grams for any food for either the Australian or New Zealand populations. This is higher than the level of 25 grams at which mild adverse affects can occur when consumed diluted in water.

Background

α-Cyclodextrin is a cyclic polysaccharide that is produced commercially from liquefied starch by an enzymatic process. Due to its torus-shaped molecular structure with a hydrophobic inner cavity, α-cyclodextrin is able to form 'inclusion' complexes with a variety of organic compounds. This enables α-cyclodextrin to perform a range of technical functions including:

- carrier for natural colours, flavours and vitamins;
- stabiliser of oil-in-water emulsions, a solubiliser of lipids; and
- flavour and aroma modifier by suppressing undesirable characteristics.

However, the Applicant's primary intended use of α-cyclodextrin is as a food ingredient because of its purported dietary fibre-like properties. These properties include increasing faecal bulk, decreased levels of plasma triglycerides and cholesterol and attenuation of glycaemic response.

The Applicant provided information that α-cyclodextrin is permitted as a food in Japan. Further to this, the Applicant has indicated that they intend to seek Generally Recognised as Safe (GRAS) status in the United States. There are no relevant Codex standards or Acceptable Daily Intakes (ADIs) for α-cyclodextrin as a food ingredient.

Table 1: Proposed uses of α-cyclodextrin in foods, as provided by the Applicant

Food Name	Concentration Level (%)
Breads and rolls	5
Brownies	7
Cakes (light weight)	5
Crackers (sweet and non-sweet)	10
Bars (grain based)	7
Quick breads	5
Dough (refrigerated)	5
Baking mixes (dry)	5
Beverage mixes (prepared)	1
Diet soft drinks (prepared)	1
Fruit juices	1
Vegetable juices	2
Instant coffee/tea (dry)	1
Coffee whitener (dry)	1
Formula diets (prepared)	1
Soy and non-soy (imitation milk) (prepared)	2
Ready To Eat (RTE) breakfast cereals	2 - 9
Instant rice (prepared)	2
Pasta and noodles (prepared)	2
Condiments	3
Yoghurt	2.5
Pudding mixes (dry)	1
Milk beverage mixes (prepared)	2.5
Frozen dairy desserts	2.5
Reduced fat spreads	20
Dressings and mayonnaise	5
Salty snacks	1
Canned soups (prepared)	2
Dry soups (prepared)	2
Hard candy	15
Chewing gum	10

Dietary Exposure Assessment provided by the Applicant (or submissions)

The Applicant provided a dietary exposure assessment for α-cyclodextrin, based on food groups similar to those being proposed for Australia and New Zealand. The dietary exposure assessment provided by the Applicant was based on United States food consumption data (US Department of Agriculture Continuing Survey of Food Intakes by Individuals, 1994-96 and 1998).

The dietary exposure assessment submitted by the Applicant indicated that mean consumer (2 years and above) exposure to α-cyclodextrin is estimated at 11.4 g/person/day and 19.8 g/person/day at the 90th percentile consumer. It was also noted that additional amounts of α-cyclodextrin may be ingested with chewing gum (0.9 g/person/day). These calculations are based on simultaneous use in all foods at the maximum proposed level. Children aged 2 – 5 years and 6 – 12 years had estimated α-cyclodextrin mean exposure of 10.2 g/day and 11.8 g/day (mean) and 90th percentile exposure of 16.2 g/day and 18.7 g/day.

The Applicant indicated that although dietary exposure had not been specifically calculated for Australia and New Zealand, US consumption of processed foods is higher than for Australia and New Zealand and therefore dietary exposure is likely to be less than reported using US data.

The dietary exposure assessment provided by the Applicant was not considered to be sufficient for assessing the level and safety of potential exposure to α-cyclodextrin in Australia and New Zealand. Therefore, FSANZ conducted a dietary exposure assessment using the Australian and New Zealand consumption data from the NNSs to estimate the potential exposure to α-cyclodextrin if it was permitted to be used in the foods requested in the Application.

Dietary Modelling

The 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 α-cyclodextrin in foods.

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 the NNSs used a 24-hour food recall methodology.

The dietary exposure assessment was conducted for both Australian and New Zealand populations. An assessment was conducted for the whole population 2+ years and 15+ years for Australia and New Zealand, respectively, as well as for children aged 2-12 years (Australia only). An exposure assessment was conducted for children because children generally have higher dietary exposures due to their smaller body weight, and greater consumption of food per kilogram of body weight compared to adults. A particular concern is the fact that children are likely to consume the types of products that are proposed to have α-cyclodextrin added, such as biscuits, cakes, bread and breakfast cereal.

Additional Food Consumption Data or Other Relevant Data

No further information was required or identified for the purpose of refining the dietary exposure estimates for this Application.

α-Cyclodextrin Concentration Levels

The levels of α-cyclodextrin in foods that were used in the exposure assessment were derived from the Application. The foods and proposed levels of use are shown below in Table 2. Hydration factors were applied to the proposed concentration levels in the dietary modelling for dry mixes puddings, and for instant coffee and tea to represent the levels of α-cyclodextrin that would be present in these foods when 'made up' or 'ready to consume'. This was necessary as most food consumption data in DIAMOND are in the 'ready to consume' state. Pasta and rice food consumption data in DIAMOND are in the 'raw' state. Consequently α-cyclodextrin concentrations have been adjusted to account for this. The factors used and the resulting concentration levels in foods are also shown in Table 2.

Concentrations of α-cyclodextrin were assigned to food groups using DIAMOND food classification codes. These codes are based on the Australian New Zealand Food Classification System (ANZFCS) used in Standard 1.3.1 Food Additives (for example 14.1.3 represents water based flavoured drinks). The foods proposed by the Applicant to contain α-cyclodextrin were matched to the most appropriate ANZFSC code(s) for dietary modelling purposes.

Where the Applicant provided a range of possible concentrations, the highest level in the range was used for calculating the estimated exposures in order to assume a worst-case scenario. The Applicant provided concentrations of α-cyclodextrin in foods as percentages. These were converted to mg/kg concentrations for use in the DIAMOND program.

Table 2: Proposed use of α-Cyclodextrin in foods and levels of use for estimating dietary exposure

ANZFCS Food Code	Food Name	Proposed Concentration Level (%)	Hydration factor	Level used in modelling (mg/kg)
1.2.1	Fermented milk and rennetted milk	2.5		25 000
1.2.2	Fermented milk products and rennetted milk products	2.5		25 000
2.2.2	Oil emulsions (<80% fat)	20		200 000
3.1.1	Ice cream	2.5		25 000
3.1.2	Ice confection	2.5		25 000
4.3.4	Fruit and vegetable spreads including chutney, peels and marmalades	3.0		30 000
4.3.6.4	Mustard	3.0		30 000
4.3.8.4	Soy beverages only	2.0		20 000
5.2.1	Bubble gum and chewing gum	10		100 000
5.3.3	Hard boil sugar confectionery	15		150 000
6.3	Processed cereal and meal products	9.0		90 000
6.4	Flour products (excluding pancakes, pikelets and crumpets)	2.0	0.33	60 600
6.4.3	Instant noodles and flavoured rice	2.0	0.33	60 600
7.1	Breads and related products	5.0		50 000

7.2.1	Biscuits	10.0		100 000
7.2.2	Cakes and muffins	5.0		50 000
7.2.3	Slices	7.0		70 000
7.2.4	Pastries	5.0		50 000
12.1.1	Salt	3.0		30 000
12.3	Vinegars and related products	3.0		30 000
13.3.2	Liquid supplementary foods for dietetic uses	1.0		10 000
14.1.2	Fruit and vegetable juice products	2.0		20 000
14.1.3.3	Water based flavoured drinks, artificially sweetened (except cordial)	1.0		10 000
14.1.6.2	Instant coffee	1.0	113	88
14.1.6.5	Instant coffee - decaffeinated	1.0	113	88
14.1.6.6	Instant tea	1.0	113	88
20.1.1	Beverage flavourings	2.5		25 000
20.2.1	Desserts (non-dairy)	1.0	2.2	4 500
20.2.2	Dairy desserts	1.0	7.8	1 300
20.2.3.1	Cereal bars only	7.0		70 000
20.2.4	Sauces, mayonnaise and salad dressings	5.0		50 000
20.2.7	Savoury snacks	1.0		10 000
20.2.8.1	Beverage whitener	1.0		10 000
20.2.9	Soups	2.0		20 000
21.1.6	Muesli	9.0		90 000

How were the estimated dietary exposures calculated?

The DIAMOND program allows α-cyclodextrin concentrations to be assigned to food groups. All foods in this group are assigned the concentration of α-cyclodextrin shown in Table 1.

Each individuals' exposure to the α-cyclodextrin was calculated using their individual food records from the dietary survey. The DIAMOND program multiplies the specified concentration of α-cyclodextrin 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 α-cyclodextrin, the total amount of α-cyclodextrin 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 dividing the sum of consumers' exposures from a food group by the sum of all consumers' exposures from all foods, 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, where milk products are used in cooking.

Bolus doses were calculated by multiplying the 95th percentile food consumption amount, for consumers only for a food group, by the specified concentration of α-cyclodextrin as outlined in Table 2. Only food consumption figures over a 24-hour period were available from DIAMOND. It was assumed that these figures represent the amount of the food consumed in one sitting.

Assumptions in the dietary modelling

The aim of the dietary exposure assessment was to make as realistic an estimate of dietary exposure as possible. However, where significant uncertainties in the data existed conservative assumptions were generally used to ensure that the dietary exposure assessment did not underestimate exposure.

Assumptions made in the dietary modelling include:

- where a permission is given to a food classification, all foods in that group contain α-cyclodextrin;
- all the foods within the group contain α-cyclodextrin at the proposed levels;
- where a range of α-cyclodextrin concentrations was proposed for a food category it has been assumed that the maximum concentration would be used;
- consumption of foods as recorded in the NNS represent current food consumption patterns;
- condiments include pickles, relishes, mustard, salt, vinegar, jams and other fruit and vegetable spreads;
- 'dough' refers to pastry;
- 2.2 grams of coffee powder makes 250 ml of liquid coffee; and
- consumers always selected the products containing α-cyclodextrin.

These assumptions are likely to lead to a conservative estimate for α-cyclodextrin dietary exposure.

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. However, in the case of foods such as milks and breads the majority of consumers will be daily consumers of these foods, therefore 24 hour dietary data will more closely represent habitual exposures.

Results

Estimating risk

Estimated dietary exposures are usually compared to a reference health standard in order to determine the potential risk to health of a population or its sub-groups. While an Acceptable Daily Intake (ADI) 'not specified' has been assigned for use of α-cyclodextrin as a food additive, this is not relevant to the consideration of α-cyclodextrin as a food ingredient. The use of α-cyclodextrin as a food ingredient has not been assigned an ADI.

Therefore, estimated exposures based on all proposed foods and α-cyclodextrin use levels were simply reported in gram amounts per day.

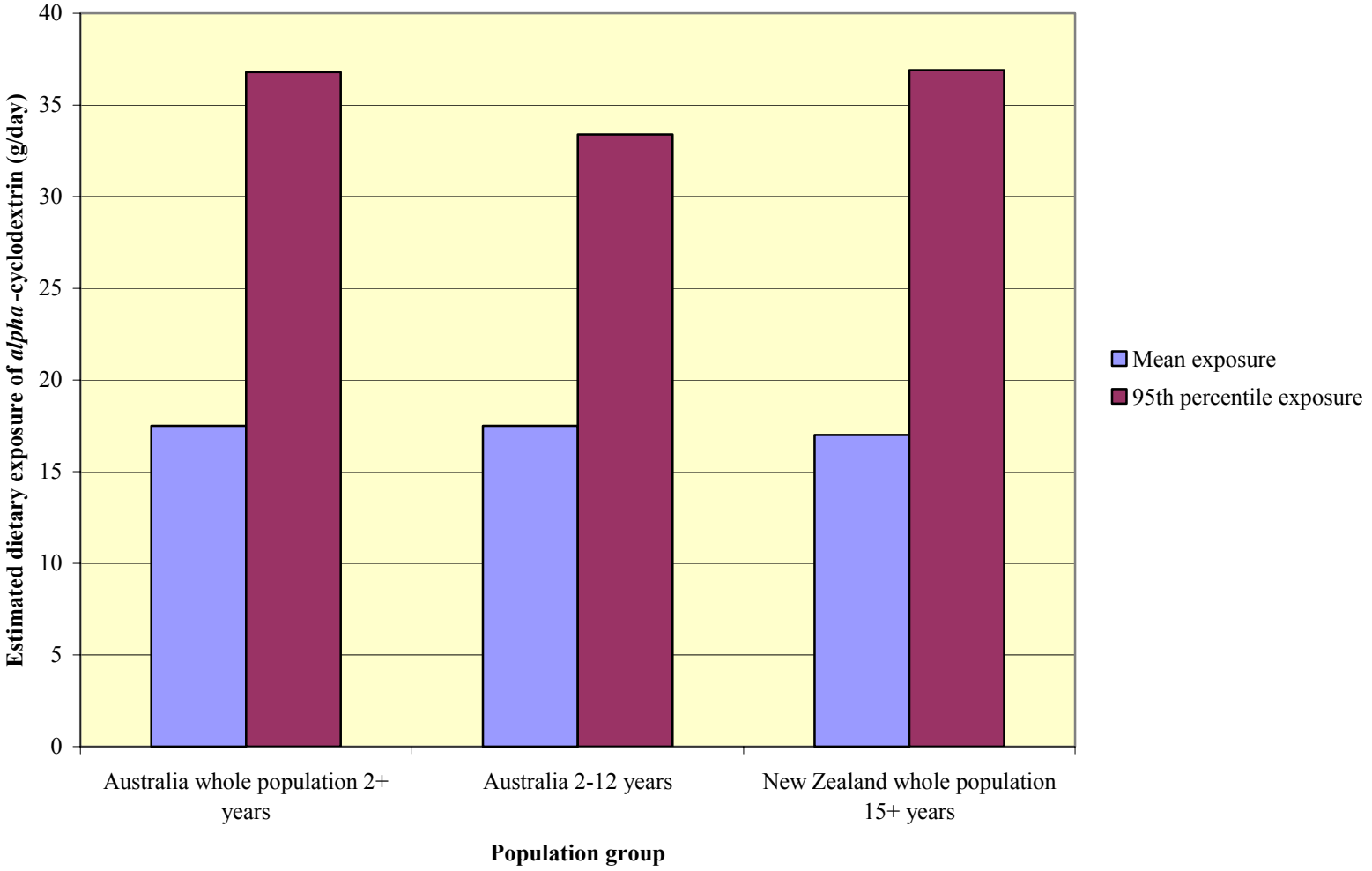
In one study in healthy human volunteers a bolus dose of α-cyclodextrin (doses of α-cyclodextrin consumed in one meal) of 25 grams after overnight fasting without the consumption of anything else produced mild abdominal discomfort in some individuals (see safety assessment report, attachment 2). Estimated exposures to α-cyclodextrin for high consumers of single food groups are compared to this level.

Estimated dietary exposures to α-cyclodextrin

The estimated dietary exposures, based on all proposed foods, for α-cyclodextrin are shown in summary in Figure 1 and in more detail in Appendix 1.

Estimated mean exposures from all proposed foods for all Australian consumers of α-cyclodextrin are 17.5 g/day, and 17.0 g/day for New Zealand consumers of α-cyclodextrin. Estimated 95th percentile exposures for consumers of α-cyclodextrin from all proposed foods are 36.8 g/day and 36.9 g/day for Australia and New Zealand, respectively. Australian children 2-12 years had estimated mean dietary exposures of 17.5 g/day and estimated 95th percentile exposures of 33.4 g/day for consumers of α-cyclodextrin.

Figure 1: Estimated mean and 95th percentile dietary exposures for consumers of α-cyclodextrin from all proposed foods for Australia and New Zealand



Major contributing foods to total estimated dietary exposures

The foods and their corresponding contribution to the total estimated exposures to α-cyclodextrin are displayed in detail in Appendix 2.

A summary of the percentage contributions of different food groups to total estimated dietary exposures to α-cyclodextrin are displayed in Figure 2 (Australia 2+ years), Figure 3 (Australia 2-12 years) and Figure 4 (New Zealand 15+ years). These contributions are calculated assuming all the proposed foods contain α-cyclodextrin. Breads and related products were the major contributors for each population group, contributing 27% – 37%. Processed cereals and meal products including cereals (9-14%), and biscuits (7% - 9%) were the other major contributors for each population group. Sauces, mayonnaise and salad dressings (6% -8%) were another major contributor for the Australia 2+ years and New Zealand 15+ years population groups. Cakes and muffins (7%) and flour products (5%) also came up as high contributor for the New Zealand 15+ years population group, while oil emulsions (<80% oil) (7% - 9%) came up as a significant contributor for the Australia 2+ years and Australia 2-12 years population groups.

Foods from the fruit and vegetable products group were also significant contributors (8%) to α-cyclodextrin dietary exposure for Australian children 2-12 years.

Figure 2: Percent contribution to estimated α-cyclodextrin dietary exposure for Australians aged 2+ years

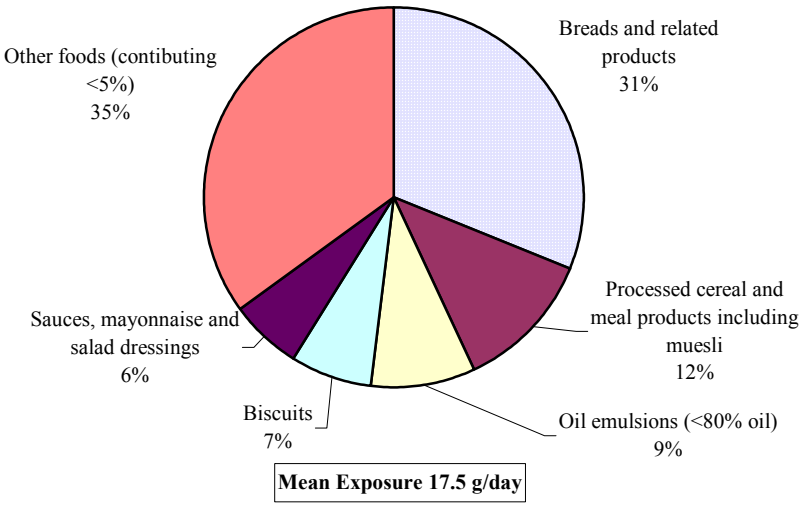


Figure 3: Percent contribution to estimated α-cyclodextrin dietary exposure for Australians aged 2-12 years

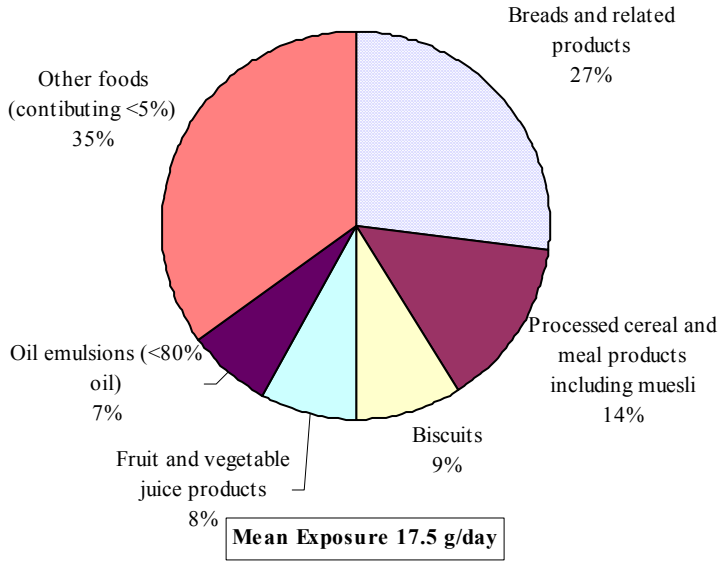
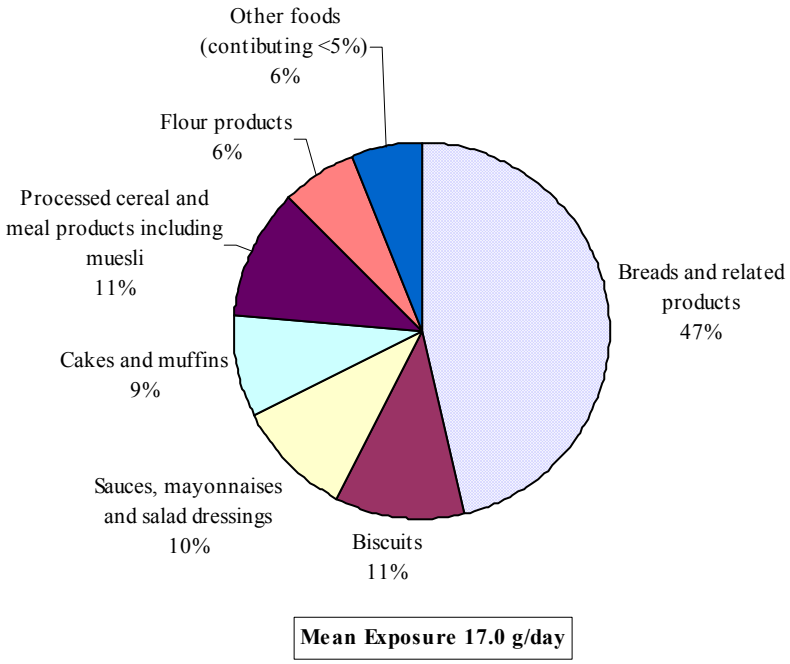


Figure 4: Percent contribution to estimated α-cyclodextrin dietary exposure for New Zealanders aged 15+ years



Estimated dietary exposures to α-cyclodextrin from single food groups

The dietary exposures to α-cyclodextrin from individual foods were calculated in order to determine whether a consumer could exceed the bolus dose reference health standard from a single meal, therefore possibly encountering adverse affects such as gastrointestinal effects. They were calculated by multiplying the 95th percentile food consumption amount for consumers only for a food group by the specified concentration of α-cyclodextrin as outlined in Table 2.

The estimated exposures are shown in Tables 3, 4 and 5 for Australia 2+ years, Australia 2-12 years and New Zealand 15+ years, respectively. These dietary exposures differ from the estimated 95th percentile dietary exposures to α-cyclodextrin 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 95th percentile dietary exposure to α-cyclodextrin selected from a distribution of ranked individuals' exposures based on consumption of a range of foods proposed to contain α-cyclodextrin.

Where there are less than 21 consumers of a food group, no bolus dose exposures have been calculated since there are insufficient consumers to derive a statistically robust 95th percentile. Therefore, only foods or food groups for which there were more than 21 consumers were included.

All estimated short-term exposures from a bolus dose, for any population group assessed, for any food, are less than 25 grams, with the exception of muesli (25.7g/day) for Australian children 2-12 years and fruit and vegetable juice products (27.5g/day) for New Zealanders 15+ years.

The estimated bolus doses presented above are based on 24-hour food consumption data and may include consumption on more then one occasion during a day. Due to the way DIAMOND is programmed, single eating occasion data are unable to be derived. This may lead to an overestimate of bolus dose exposure to α-cyclodextrin for some foods that are likely to be eaten more then once per day (e.g. milk). It may not lead to as much of an overestimate for foods more likely to only be eaten once per day (e.g. ice cream).

Table 3: Estimated dietary exposure to individual foods groups at the 95th percentile (P95) level of consumption for Australia 2+ years

Food description	Number of consumers	Level of use (g/100g)	P95 food consumption g/day	Grams α-cyclodextrin g/day
Fermented milk and rennetted milk	340	2.5	259	6.5
Fermented milk products and rennetted milk products	1282	2.5	329	8.2
Oil emulsions (<80% fat)	7010	20	44	8.8
Ice cream	2435	2.5	258	6.5
Ice confection	807	2.5	296	7.4
Fruit and vegetable spreads including chutney, peels and marmalades	3649	3.0	54	1.6
Mustard	690	3.0	11	0.3
Soy beverages only	297	2.0	530	10.6
Bubble gum and chewing gum	235	10	84	8.4
Hard boil sugar confectionery	504	15	64	9.6
Processed cereal and meal products	5582	9.0	120	10.8
Flour products (excluding pancakes, pikelets and crumpets)	2414	6.06	190	11.5
Instant noodles and flavoured rice	61	6.06	116	7.0
Breads and related products	12342	5.0	279	14.0
Biscuits	5169	10.0	92	9.2
Cakes and muffins	2059	5.0	241	12.1
Slices	268	7.0	177	12.4
Pastries	2444	5.0	179	9.0
Salt	90	3.0	1.3	0.0
Vinegars and related products	1170	3.0	22	0.7
Liquid supplementary foods for dietetic uses	126	1.0	766	7.7
Fruit and vegetable juice products	1201	2.0	924	18.5
Water based flavoured drinks, artificially sweetened (excluding cordials)	1153	1.0	1287	12.9
Instant coffee	5563	0.0088	1827	0.2
Instant coffee - decaffeinated	414	0.0088	1402	0.1
Beverage flavourings	1496	2.5	344	8.6
Desserts (non-dairy)	478	0.45	280	1.3
Dairy desserts	316	0.13	420	0.5
Cereal bars only	479	7.0	66	4.6
Sauces, mayonnaise and salad dressings	4956	5.0	195	9.8
Savoury snacks	1355	1.0	100	1.0

Beverage whitener	44	1.0	16	0.2
Soups	1379	2.0	929	18.6
Muesli	708	9.0	202	18.2

Total number of respondents for Australia: = 13 858.
* Food groups that did not have ≥21 consumers are not included in this calculation.

Table 4: Estimated dietary exposure to individual foods groups at the 95th percentile (P95) level of consumption for Australia 2 – 12 years

Food description	Number of consumers	Level of use (g/100g)	P95 food consumption g/day	Grams α-cyclodextrin g/day
Fermented milk and rennetted milk	23	2.5	259	6.5
Fermented milk products and rennetted milk products	267	2.5	365	9.1
Oil emulsions (<80% fat)	1042	20	31	6.2
Ice cream	583	2.5	256	6.4
Ice confection	359	2.5	259	6.5
Fruit and vegetable spreads including chutney, peels and marmalades	415	3.0	41	1.2
Mustard	61	3.0	13	0.4
Soy beverages only	47	2.0	777	15.5
Bubble gum and chewing gum	58	10	59	5.9
Hard boil sugar confectionery	196	15	58	8.7
Processed cereal and meal products	1269	9.0	96	8.6
Flour products (excluding pancakes, pikelets and crumpets)	464	6.06	131	7.9
Breads and related products	1904	5.0	233	11.7
Biscuits	1014	10.0	83	8.3
Cakes and muffins	314	5.0	223	11.2
Slices	30	7.0	91	6.4
Pastries	353	5.0	132	6.6
Vinegars and related products	113	3.0	19	0.6
Liquid supplementary foods for dietetic uses	21	1.0	792	15.8
Fruit and vegetable juice products	404	2.0	729	14.6
Water based flavoured drinks, artificially sweetened (excluding cordial)	158	2.0	750	0.05
Instant coffee	25	0.0088	609	0.05
Beverage flavourings	518	2.5	245	6.1
Desserts (non-dairy)	91	0.45	336	1.5
Dairy desserts	59	0.13	420	0.5
Cereal bars only	210	7.0	62	4.3
Sauces, mayonnaise and salad dressings	570	5.0	133	6.7
Savoury snacks	472	1.0	75	0.8
Soups	103	2.0	764	15.3
Muesli	48	9.0	285	25.7

Total number of respondents for Australia 2 – 12 years: = 2 079.
* Food groups that did not have ≥21 consumers are not included in this calculation.

Table 5: Estimated dietary exposure to individual foods groups at the 95th percentile (P95) level of consumption for New Zealand 15+ years

Food description	Number of consumers	Level of use (g/100g)	P95 food consumption g/day	Grams α-cyclodextrin g/day
Fermented milk and rennetted milk	180	2.5	336	8.4
Fermented milk products and rennetted milk products	303	2.5	282	7.1
Oil emulsions (<80% fat)	1193	20	32	6.4
Ice cream	683	2.5	262	6.6
Ice confection	22	2.5	251	6.3
Fruit and vegetable spreads including chutney, peels and marmalades	1347	3.0	52	1.6
Mustard	254	3.0	11	0.3
Soy beverages only	50	2.0	518	10.4
Bubble gum and chewing gum	46	10	76	7.6
Hard boil sugar confectionery	198	15	125	18.8
Processed cereal and meal products	1502	9.0	76	6.8
Flour products (excluding pancakes, pikelets and crumpets)	799	6.06	293	17.8
Breads and related products	4125	5.0	320	16.0
Biscuits	1821	10.0	96	9.6
Cakes and muffins	975	5.0	311	15.6
Slices	273	7.0	211	14.8
Pastries	778	5.0	151	7.6
Salt	1419	3.0	4.3	0.1
Vinegars and related products	147	3.0	30	0.9
Liquid supplementary foods for dietetic uses	525	1.0	281	2.8
Fruit and vegetable juice products	97	2.0	1377	27.5
Water based flavoured drinks, artificially sweetened (excluding cordials)	178	1.0	1272	12.7
Instant coffee	2185	0.0088	949	0.08
Instant coffee - decaffeinated	113	0.0088	583	0.05
Beverage flavourings	137	2.5	350	8.8
Desserts (non-dairy)	231	0.45	384	1.7
Dairy desserts	119	0.13	502	0.7
Cereal bars only	150	7.0	100	7.0
Sauces, mayonnaise and salad dressings	2168	5.0	203	10.2
Savoury snacks	402	1.0	151	1.5
Soups	610	2.0	634	12.7
Muesli	274	9.0	177	15.9

Total number of respondents for New Zealand: = 4 636.
* Food groups that did not have ≥21 consumers are not included in this calculation.

Appendix I

Estimated dietary exposures to α-cyclodextrin from all proposed foods for Australia and New Zealand and for different population groups

Country	Population group	Number of consumers of α-cyclodextrin	Consumers as a % of total respondents[#]	Mean consumers grams/day	95th percentile consumers grams/day
Australia	Whole population (2+ years)	13 828	99.8	17.5	36.8
	2-12 years	2 079	100	17.5	33.4
New Zealand	Whole population (15+ years)	4 608	99.4	17.0	36.9

Total number of respondents for Australia: whole population = 13 858, 2-12 years = 2 079; New Zealand: whole population = 4 636.

Appendix 2

Contribution of each food group to total α-cyclodextrin dietary exposure for Australia 2+ years, Australia 2-12 years and New Zealand 15+ years

Description	Australia 2+ years % total exposure	Australia 2-12 years % total exposure	New Zealand 15+ years % total exposure
Fermented milk and rennetted milk	0.4	0.2	0.7
Fermented milk products and rennetted milk products	2.1	2.5	1.3
Oil emulsions (<80% fat)	9.0	6.6	3.8
Ice cream	2.7	4.4	2.1
Ice confection	1.0	2.7	0.07
Fruit and vegetable spreads including chutney, peels and marmalades	0.8	0.5	1.0
Mustard	0.02	0.02	0.04
Soy beverages only	0.6	0.8	0.3
Bubble gum and chewing gum	0.2	0.3	0.2
Hard boil sugar confectionery	0.7	1.7	1.3
Processed cereal and meal products	10.2	13.8	6.5
Flour products (excluding pancakes, pikelets and crumpets)	4.0	4.0	5.3
Instant noodles and flavoured rice	0.01	0.02	-
Breads and related products	31.2	26.8	37.1
Biscuits	7.4	8.9	9.0
Cakes and muffins	3.8	3.6	7.3
Slices	0.5	0.2	1.8
Pastries	3.8	2.8	2.9
Salt	0.0	0.0	0.09
Vinegars and related products	0.1	0.05	0.05
Liquid supplementary foods for dietary foods	0.1	0.1	0.7
Fruit and vegetable juice products	3.8	7.7	1.2
Water based flavoured drinks, artificially sweetened (except cordial)	2.5	1.4	1.0
Instant coffee	0.1	0.0	0.08
Instant coffee - decaffeinated	0.01	0.0	0.0
Instant tea	0.0	-	0.0
Beverage flavourings	1.7	3.4	0.5
Desserts (non-dairy)	0.1	0.2	0.2
Dairy desserts	0.03	0.04	0.03
Cereal bars only	0.5	1.4	0.6
Sauces, mayonnaise and salad dressings	5.8	3.3	7.7
Savoury snacks	0.2	0.4	0.3
Beverage whitener	0.0	-	0.01
Soups	4.6	1.7	4.6
Muesli	2.1	0.6	2.4

ATTACHMENT 4

Nutrition Assessment Report

1. Introduction

α-Cyclodextrin is a cyclic polysaccharide consisting of six glucose units linked by α(1,4) bonds. It has a torus-shaped molecular structure with a hydrophobic inner cavity, enabling the substance to form 'inclusion' complexes with a variety of organic compounds. α-Cyclodextrin is chemically similar to β-cyclodextrin (seven glucose units) and γ-cyclodextrin (eight glucose units).

α-Cyclodextrin may impact on the absorption of fat-soluble nutrients from the intestine by its recognised property of binding to, and forming inclusion complexes with fat-soluble chemicals. There is also an indication that α-cyclodextrin itself may not be fully digested by the human intestine, and may not supply as much energy to the body as other carbohydrates. The Applicant has therefore suggested that the energy factor allocated to 'unavailable carbohydrates' in the Code (8 kJ/g) is more appropriate for α-cyclodextrin than the one typically used for other 'available carbohydrates' (17 kJ/g).

This assessment will examine both the potential impact of α-cyclodextrin on nutrient absorption, and the digestion of α-cyclodextrin at the maximum levels in the range of foods proposed by the Applicant.

1.1 Dietary Fibre Status

The Applicant states that α-cyclodextrin is to be used primarily as a food ingredient because of its purported dietary fibre-like properties. It is mentioned that the physiological effects of α-cyclodextrin are similar to those of soluble/fermentable fibres and resistant starch, such as increased faecal bulk, decreased levels of plasma triglycerides and cholesterol, and attenuation of the glycaemic response.

The 'dietary fibre-like properties' mentioned by the Applicant have some importance for this nutrition assessment (e.g. indigestibility). However, the Applicant has not requested recognition of α-cyclodextrin as dietary fibre, and therefore this assessment will not address the dietary fibre status of α-cyclodextrin. For the same reason, this assessment will not evaluate the appropriateness or capability for products containing α-cyclodextrins to bear dietary fibre claims.

2. Impact on Nutrient Absorption

The impact of α-cyclodextrin on nutrient absorption has not been evaluated in currently available scientific literature. This lack of data identified in a previous α-cyclodextrin assessment made by the Joint Expert Committee on Food Additives (JECFA) of Codex Alimtentarius[2]. JECFA instead used evidence on β-cyclodextrin for its α-cyclodextrin assessment, as there is greater information on its nutritional impact. The close chemical similarity between α-cyclodextrin and β-cyclodextrin was considered sufficient by JECFA to allow for comparisons between the metabolism and toxicity of the substances[2].

Because the α-cyclodextrin has the ability to trap lipid-based substances in its interior, fat-soluble nutrients are considered to be at the greatest risk of malabsorption and are thus the focus of this section.

2.1 Fat-Soluble Vitamins (Vitamins A, D, E, and K)

The actual chemistry of the interaction between cyclodextrins and fat-soluble vitamins is not fully understood, although there is some indication of the processes that occur. It has been theorised that fat-soluble vitamins are not adversely affected by α- or β-cyclodextrins because the cavity in these substances is small compared to other cyclodextrins, and that such cavities do not readily permit the entry of vitamin molecules[3]. The ability for cyclodextrins to increase the water solubility of lipid-based substances may even improve their intestinal absorption[3,4], however this outcome is based on speculation only, and has not been demonstrated in the current literature.

Although there is no direct evidence of α-cyclodextrin having an inhibitory effect on nutrient absorption, there is one *in vitro* study that provides some indication of the consequences for fat-soluble vitamins. α-, β- and γ-Cyclodextrin were examined for their influence on the solubility of vitamins A, D, E and K in an isotonic buffered saline solution at concentrations up to 5%[3]. Because these vitamins are fat-soluble and have very poor solubility in water, an increase in water solubility indicates a stronger binding between the cyclodextrin and the vitamin. The results of the study (see Table 1 below) indicate that α-cyclodextrin produced a lower solubility for vitamin A in comparison to the solubility for β- and γ-cyclodextrins, but more than the control; and did not solubilise vitamins D and E (as was also observed for the control and β- / γ-cyclodextrin). However, the presence of α-cyclodextrin produced a significantly higher solubility for Vitamin K than was observed for the control and other cyclodextrins.

Table 1: Solubility (μg/mL) in Water of Vitamins A, D, E and K with different cyclodextrins at a concentration of 5% and as measured by mass spectrometry[3]

Vitamin	Control (saline) solution	α-cyclodextrin solution	β-cyclodextrin solution	γ-cyclodextrin solution
Vitamin A acetate	<4	7	9	4
Vitamin A (retinol)	<1	1	4	11
Vitamin D_2	<0.5	0	0	0
Vitamin D_3	<0.1	0	0	<1
Vitamin E acetate	0	0	0	0
Vitamin K_1	<0.5	5	<0.5	2

These results indicate that vitamins A and K are the most likely fat-soluble vitamins to be affected by any intake of α-cyclodextrin. However, without any other information on α-cyclodextrin, it is difficult to assess whether these *in vitro* studies have the potential to impact on the nutritional status of humans. Therefore, consistent with the approach taken by JECFA, this report will draw on available β- cyclodextrin studies to further assess the nutritional impact on fat-soluble vitamins.

2.1.1 β-Cyclodextrin Studies on Vitamins A, D, and E

Four studies have been identified that evaluate the impact of β-cyclodextrin on the fat-soluble vitamins A, D and E[5-8] in animals; a summary of these studies can be found in Table A-1 of the Appendix to this Attachment. All of these studies indicate that at various doses over periods of 8-48 hours (bolus test) and 4-52 weeks (continuous administration), β-cyclodextrin had no adverse impact on the absorption of fat-soluble vitamins when compared to control groups. Bellringer *et al* 1995[6] did observe a significant decrease in serum vitamin A levels of female dog subjects at a dose of 50 g/kg feed, however the authors argued that the female dog results showed very wide variability between individual subjects, and therefore represented some unknown experimental error.

2.1.2 Vitamin K

There are no *in vivo* studies that directly assess the impact of α-, β- or γ-cyclodextrins on the absorption of vitamin K, or on the vitamin K status of animals or humans. Even so, the above-mentioned *in vitro* result for vitamin K can be indirectly qualified *in vivo* by assessing the intake, biochemistry and physiology of vitamin K, and cyclodextrin – vitamin K interactions.

Unlike most other vitamins, vitamin K status is not solely dependent on its dietary intake. Vitamin K can be manufactured by the microflora of the gut, and the intestinal uptake of the vitamin can be partially obtained from this source[9]. Most of the remaining vitamin K intake from foods is poorly absorbed, with liver stores acting as the body's primary source of the vitamin to ensure that a constant supply is available[10]. There is no data available on the vitamin K status of the Australian or New Zealand populations because this was data was not collected in either National Nutrition Survey. However, limited information on the populations of other developed nations shows that mean consumption of vitamin K is above identified levels of adequacy[11,12]. Because of all these factors, vitamin K deficiency is rarely seen and only in situations where liver stores have not developed fully (e.g. newborn infants) or where gut microflora is significantly harmed (such as through high exposure to oral antibiotics).

Vitamin K is absorbed from the gut within the vicinity of the terminal ileum (end of the small intestine). *In vitro* evidence indicates that cyclodextrins – including α-cyclodextrin – have a stronger affinity for cholesterol and bile salts compared to fat-soluble vitamins[7,13], and therefore are likely to be complexed with these substances instead of vitamin K by the time a meal reaches the terminal ileum. In this environment, vitamin K is likely to be only partially affected by the presence of α-cyclodextrin.

There is also some evidence in nutritionally healthy dogs[14] and rats[15], that prothrombin times (an indicator of vitamin K status) are not significantly affected by the consumption of α-cyclodextrin over 90 days at a dose up to 20% in the diet, and neither was bleeding reported as a clinical effect in either study. These results are further indication that Vitamin K status is unlikely to be adversely affected by α-cyclodextrin intake.

Therefore, while one *in vitro* study indicates that α-cyclodextrin is more likely to form an inclusion complex with vitamin K than other cyclodextrins, it is not possible to draw any conclusions from this study on the potential impact of α-cyclodextrin on vitamin K status.

Any potential impact on vitamin K status is reduced substantially by the ready supply and uptake of the vitamin in a normal healthy diet, and by the competition with other substances for binding sites on α-cyclodextrin molecules. Overall there is an absence of evidence on the direct impact that α-cyclodextrin intakes will have on vitamin K status, however available (indirect) information has not indicated any potential for concern.

2.2 Lipids

Similar to fat-soluble vitamins, there are no studies that evaluate the impact of α-cyclodextrin intake on lipid absorption. Therefore, available β-cyclodextrin studies will be used to this part of the nutrition assessment.

Férézou *et al* 1997[7] is the only identified study that has assessed the impact of β-cyclodextrin intake on postprandial lipid absorption. Férézou *et al* monitored the levels of serum cholesterol, triglycerides and HDL-cholesterol following a meal as shown in Table 1 below. The results of this study demonstrate that the administration of 5-10% β-cyclodextrin bolus doses to pigs (a good animal for the modelling of human digestion) produce no significant alterations in the postprandial absorption of lipids.

Table 2: 6-hour Postprandial Serum Lipid Results from Pigs Fed Cyclodextrins[7]

Study Groups	**CD Dose (g/day)**	**Serum Cholesterol**		**Serum Triglycerides**		**Serum HDL-cholesterol**	
		Final level at 6 hours (mg/dL)	*Significant Difference ? ($p<0.05$)*	*Result as area under the curve for 6 hour period (mg/dL/h)*	*Significant Difference ? ($p<0.05$)*	*Final level at 6 hours (mg/dL)*	*Significant Difference ? ($p<0.05$)*
Control meal	0	84±5	Yes between cholesterol rich meal and the other three meals. The other three meals were not different from each other.	386±55	No	35±5	No
Cholesterol rich meal	0	173±5		505±104		48±10	
Low β-CD meal with cholesterol	5 g/100g feed	102±9		424±33		45±8	
High β-CD meal with cholesterol	10 g/100g feed	85±3		467±118		46±12	

Férézou *et al*[7] and three other studies[6,16,17] also examined the influence of β-cyclodextrin intake on lipid absorption over a continuous period of time. The details of these studies can be found in Table A-2 of the Appendix to this Attachment. Although these studies do not illustrate how β-cyclodextrin affects the absorption of lipids immediately after a meal, they indicate that fat absorption sensitive biomarkers do not decrease with a prolonged exposure to β-cyclodextrin. Such results further reinforce the postprandial findings of Férézou *et al*.

2.3 Evaluation

The available scientific literature demonstrates that β-cyclodextrin does not impair the absorption of vitamins A, D and E, an outcome that is considered applicable to α-cyclodextrin. There is some *in vitro* evidence that α-cyclodextrin has greater capacity to form inclusion complexes with vitamin K than occurs with other cyclodextrins, however there is an overall absence of direct evidence on the interaction between α-cyclodextrin and vitamin K. Considering the biochemistry and physiology of vitamin K, it is unlikely that α-cyclodextrin will adversely impact on vitamin K status. Data on lipid absorption also indicates that α-cyclodextrin is unlikely to adversely affect the absorption of fat-soluble macronutrients.

Therefore it is determined that the use of α-cyclodextrin in food will have only a minor impact, if any, on the ability to obtain adequate amounts of fat-soluble nutrients from the diet.

3. Application of an Energy Factor to Alpha-Cyclodextrin

The Applicant has stated an intention to use the term 'unavailable carbohydrate' to convey nutrition information in relation to products containing α-cyclodextrin. Unavailable carbohydrate is assigned an energy factor of 8 kJ/g in Table 1 to subclause 2(2) of Standard 1.2.8 – Nutrition Information Requirements.

'Unavailable carbohydrate' has no prescribed definition within the Code. This term has its origins in 1929 with the classification of carbohydrate into 'available' and 'unavailable' forms, where the intention was to distinguish completely indigestible crude fibre (cellulose and hemicellulose) from other fully digestible and metabolically available carbohydrates[18]. However, with current knowledge on dietary fibre and its various forms, the term 'unavailable' may best apply to carbohydrates that are indigestible in the small intestine, even if there is additional fermentation in the large intestine. Such classification is consistent with the 8 kJ/g energy factor applied to unavailable carbohydrates in the Code; if these substances were fully indigestible throughout the entire gastrointestinal system then an energy factor of 0 kJ/g would be more appropriate.

3.1 In Vitro *Studies*

The digestion of α-cyclodextrin has been examined in both *in vitro* and *in vivo* environments. Dexter French first reported *in vitro* results in 1957[19], although this was in reference to an unpublished study (the results were not documented). French stated that α-cyclodextrin was completely resistant to amylase digestion, while β- and γ-cyclodextrins could be partially hydrolysed in the presence of amylases. The only other *in vitro* study that has examined the digestion of α-cyclodextrin was published by Kondo *et al* in 1990[20].

This study found that under appropriate conditions (50 mM sodium glycerophosphate buffer at 37°C, pH 7.0; with NaCl and calcium acetate added at 25 mM) and assessed by high-pressure liquid chromatography; porcine pancreatic α-amylase, human pancreatic α-amylase, and human salivary α-amylase were unable to hydrolyse α-cyclodextrin.

3.2 In Vivo *Studies*

There are three *in vivo* studies that assess the digestibility of α-cyclodextrin in rats[21-23] and one that assessed the digestibility of α-cyclodextrin in humans[24]. The results of the rat studies and the human study can be found in Tables A-3 and A-4 of the Appendix to this Attachment respectively.

The rat studies showed that very little α-cyclodextrin is excreted into the faeces, thus providing evidence that it had been almost completed digested. The rat studies also tracked labelled (^{14}C) α-cyclodextrin through various excretion pathways, and found that increasing doses of α-cyclodextrin resulted in greater levels of CO_2 production and a constant level of urinary excretion. These results indicate that although α-cyclodextrin was digested by the time it had passed through the entire gastrointestinal system of rats, this digestion occurred only to a minor degree in the small intestine (thus producing the noticeable but constant urinary excretion) and with the remainder almost completely fermented within the large intestine (resulting in the increased CO_2 production).

The human study by Diamantis and Bär provides results comparable to those of the rat studies. This study shows that α-cyclodextrin significantly reduced the glycaemic response when consumed together with white bread, and produced no significant increase in blood glucose levels from baseline when consumed alone. The small increase in blood insulin levels following ingestion of α-cyclodextrin alone is also consistent with the outcomes of the rat studies, showing that a small yet insignificant proportion of α-cyclodextrin may be absorbed within the small intestine.

3.3 Evaluation

There is sufficient evidence to indicate that α-cyclodextrin is largely indigestible in the small intestine. This is consistent with the findings of the JECFA evaluation that approximately 2% of α-cyclodextrin is absorbed from the small intestine[2]. It is therefore appropriate to use the term 'unavailable carbohydrate' to describe α-cyclodextrin and apply the energy factor of 8 kJ/g assigned to 'unavailable carbohydrate' to α-cyclodextrin. From animal studies, α-cyclodextrin has been shown to partially fermented within the large intestine, however the totality of evidence supports the application of a lower energy factor to α-cyclodextrin than the one applied to fully digested carbohydrates.

4. Conclusion

α-Cyclodextrin is assessed as having a low nutritional impact when used as an ingredient in food. There is a potential impact on nutrient absorption (vitamin K) based on *in vitro* solubility studies only, however this impact appears to be minor. It is also appropriate to consider α-cyclodextrin as 'unavailable carbohydrate' for the purposes of assigning an energy factor, as suggested by the Applicant.

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Table A-1: Influence of β-Cyclodextrin Consumption on Serum and Liver Vitamin A, D and E Levels

Study	Study Period	Study Design	No. and type of Subjects		Beta-CD Dose	Results - Vitamin A				Results - Vitamin D		Results - Vitamin E	
						Baseline Serum Level	*Final serum level*	*Final liver level*	*Significant Difference (p<0.05)?*	*Final serum level*	*Significant Difference (p<0.05)?*	*Final serum level*	*Significant Difference (p<0.05)?*
Bárdos *et al*, 1989	8 hours (bolus dose as capsule)	RCT, blinding unknown	15 rabbits, 5 per group	Control (lactose bolus)	0	1020±126 μg/L	583±45 μg/L	-	Yes - control serum levels significantly decreased from baseline; diets 1 and 2 remained unchanged from baseline.	-	-	-	-
				Diet 1 (lactose and retinyl palmitate)	0	907±81 μg/L	874±199 μg/L	-		-		-	
				Diet 2 (b-CD and retinyl palmitate)	13.1 g/100g	974±307 μg/L	1170±361 μg/L	-		-		-	
Bellringer *et al*, 1995	1 year	RCT	8 dogs; 4 male and 4 female	Male	0 (Control)	-	635±120 mg/dL	151±36 μg/g	No difference observed between groups	96±33	No difference observed between groups	4.7±1.1	No difference observed between groups
					6.2 g/kg feed	-	892±107 mg/dL	-		-		-	
					12.5 g/kg feed	-	856±191 mg/dL	-		-		-	
					50 g/kg feed	-	636±106 mg/dL	103±49 μg/g		87±18		4.6±3.3	
				Female	0 (Control)	-	809±34 mg/dL	162±55 μg/g	Yes – for serums results between control and 12500, and control and	113±29	No difference observed between groups	5.2±1.0	No difference observed between groups
					6.2 g/kg feed	-	840±95 mg/dL	-		-		-	
					12.5 g/kg feed	-	1083±152 mg/dL	-		-		-	

Study	Study Period	Study Design	No. and type of Subjects		Beta-CD Dose	Results - Vitamin A				Results - Vitamin D		Results - Vitamin E	
						Baseline Serum Level	*Final serum level*	*Final liver level*	*Significant Difference ($p<0.05$)?*	*Final serum level*	*Significant Difference ($p<0.05$)?*	*Final serum level*	*Significant Difference ($p<0.05$)?*
					50 g/kg feed	-	627±97 mg/dL	116±10 μg/g	50000. Yes – for liver results between control and 50000.	90±46		3.6±3.2	
Férézou *et al*, 1997	1 month	RCT, postprandial results on day 28 as area-under-the-curve	24 pigs, 6 pigs per group	Control diet	0	-	1052±138 μg/L/hr	-	Yes between cholesterol rich diet and other three diets. Other three diets were not different from each other.	-	-	-	-
				Cholesterol rich diet	0	-	2327±269 μg/L/hr	-		-		-	
				Low B-CD diet ± chol	5 g/100g feed	-	1304±73 μg/L/hr	-		-		-	
				High B-CD diet ± chol	10 g/100g feed	-	1316±235 μg/L/hr	-		-		-	
Szejtli *et al*, 1983	48 hours (bolus dose)	Cross-over study, blinding unknown. Results as radioactivity from labelled vitamin D.	Control (Vitamin D only), 5 rats	0.5 hrs	0	-	-	-	-	55±6 Bq/kg	Unknown	-	-
				1.5 hrs	0	-	-	-		371±32 Bq/kg		-	
				3.0 hrs	0	-	-	-		1199±389 Bq/kg		-	
				6.0 hrs	0	-	-	-		2542±569 Bq/kg		-	
				48.0 hrs	0	-	-	-		3356±231 Bq/kg		-	
			Vitamin D ± β-CD, 5 rats	0.5 hrs	2.7 mg/kg body wt	-	-	-	-	123±59 Bq/kg	Unknown	-	-
				1.5 hrs	2.7 mg/kg body wt	-		-		852±253 Bq/kg		-	
				3.0 hrs	2.7 mg/kg body wt	-		-		1852±806 Bq/kg		-	

Study	Study Period	Study Design	No. and type of Subjects		Beta-CD Dose	Results - Vitamin A				Results - Vitamin D		Results - Vitamin E	
						Baseline Serum Level	*Final serum level*	*Final liver level*	*Significant Difference ($p<0.05$)?*	*Final serum level*	*Significant Difference ($p<0.05$)?*	*Final serum level*	*Significant Difference ($p<0.05$)?*
				6.0 hrs	2.7 mg/kg body wt	-		-		3805±1423 Bq/kg		-	
				48.0 hrs	2.7 mg/kg body wt	-	-	-		3271±310 Bq/kg		-	

- Not assessed as part of the study

Table A-2: Influence of Cyclodextrin Intake on Serum Lipid Levels

Study	Study Period (weeks)	Study Design	Number of Subjects		β-CD Dose (g/day)	Fasting Serum Chol Results			Fasting Serum Triglyceride Results			Fasting Serum HDL-Chol Results		
						Baseline level	*Final level*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*
Bellringer *et al*, 1995	52	RCT	40 rats; 20 male and 20 female	Male	0 (Control)	73±9 *mg/dL*	98±25 *mg/dL*	No	104±18	223±53	Yes but only between the control and the 50 g/kg group.	49±4	72±19	No
					6200 ppm	81±14 *mg/dL*	119±41 *mg/dL*		105±30	201±55		51±6	85±22	
					12500 ppm	82±13 *mg/dL*	132±64 *mg/dL*		121±25	175±63		53±8	100±41	
					50000 ppm	76±16 *mg/dL*	100±24 *mg/dL*		98±22	138±48		50±11	78±21	
				Female	0 (Control)	85±13 *mg/dL*	124±35 *mg/dL*	No	77±18	255±245	No	62±10	86±23	Yes but only between the control the 50 g/kg group.
					6200 ppm	88±15 *mg/dL*	126±29 *mg/dL*		85±22	201±55		66±9	109±27	
					12500 ppm	75±10 *mg/dL*	121±30 *mg/dL*		82±14	179±81		53±8	96±24	
					50000 ppm	84±7 *mg/dL*	129±23 *mg/dL*		80±15	105±25		65±7	110±24	
	52	RCT	8 dogs; 4 male and 4 female	Male	0 (Control)	120±13 *mg/dL*	104±12 *mg/dL*	No	30±6	27±8	No	113±15	96±26	No
					6200 ppm	116±16 *mg/dL*	99±17 *mg/dL*		27±7	24±3		109±17	114±19	
					12500 ppm	120±21 *mg/dL*	108±11 *mg/dL*		28±1	25±4		108±20	120±20	
					50000 ppm	121±34 *mg/dL*	105±34 *mg/dL*		26±2	28±2		110±32	118±14	
				Female	0 (Control)	101±21 *mg/dL*	112±11 *mg/dL*	No	27±6	30±4	No	101±14	105±11	No

Study	Study Period (weeks)	Study Design	Number of Subjects		β-CD Dose (g/day)	Fasting Serum Chol Results			Fasting Serum Triglyceride Results			Fasting Serum HDL-Chol Results		
						Baseline level	*Final level*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*
					6200 ppm	117±15 *mg/dL*	113±27 *mg/dL*		26±5	28±1		97±12	107±22	
					12500 ppm	127±17 *mg/dL*	186±55 *mg/dL*		29±3	41±12		101±11	166±44	
					50000 ppm	127±13 *mg/dL*	114±29 *mg/dL*		23±3	31±4		97±31	107±25	
Férézou *et al*, 1997	1	RCT, double blinded	24 pigs, 6 pigs per group	Control meal	0	-	89±5 *mg/dL*	Yes between cholesterol rich diet and other three diets. Other three diets were not different from each other.	-	28±6	No	-	31±2	No
				Cholesterol rich meal	0	-	185±5 *mg/dL*		-	29±2		-	39±3	
				Low β-CD meal with cholesterol	5 g/100g feed	-	104±9 *mg/dL*		-	33±8		-	36±6	
				High β-CD meal with cholesterol	10 g/100g feed	-	85±2 *mg/dL*		-	28±6		-	32±2	
Favier *et al*, 1995	3	RCT, blinding unknown	Sample size unknown	Control diet	0	-	1.52±0.08 mmol/L	Yes – β-CD diets were significantly lower than control	-	1.24±0.02 mmol/L	Yes β-CD diets were significantly lower than control, and were significantly different between each other	-	0.29±0.03 mmol/L	Yes – High β-CD diet was significantly lower than control
				Low β-CD diet	2.5 g/100g feed	-	1.30±0.05 mmol/L		-	0.84±0.02 mmol/L		-	0.25±0.01 mmol/L	
				High β-CD diet	5.0 g/100g feed	-	1.21±0.05 mmol/L		-	0.70±0.06 mmol/L		-	0.20±0.01 mmol/L	

Study	Study Period (weeks)	Study Design	Number of Subjects		β-CD Dose (g/day)	Fasting Serum Chol Results			Fasting Serum Triglyceride Results			Fasting Serum HDL-Chol Results		
						Baseline level	*Final level*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*
Garcia-Mediavilla *et al*, 2003	7	RCT, blinding unknown	32 Male Wistar rats, 8 per group	Control diet	0	-	1.25±0.13 mmol/L	Yes between control diet and other three diets. A, B and C diets were not different from each other.	-	-	-	-	-	-
				Diet A (control with 2% chol)	0	-	2.32±0.18 mmol/L		-	-		-	-	
				Diet B (diet A ± β-cyclodextrin)	2.5g/100 g feed	-	2.78±0.21 mmol/L		-	-		-	-	
				Diet C (diet A ± β-cyclodextrin)	5.0g/100 g feed	-	3.22±0.46 mmol/L		-	-		-	-	
Toyoda *et al*, 1997	104	RCT, double blinded.	Male Fischer rats, 50 per group	Control	0	-	166±40 *mg/dL*	No	-	-	-	-	-	-
				Low β-CD diet	2.5 g/100g feed	-	142±40 *mg/dL*		-	-		-	-	
				High β-CD diet	5.0 g/100g feed	-	140±50 *mg/dL*		-	-		-	-	
			Female Fischer rats, 50 per group	Control	0	-	138±17 *mg/dL*	No	-	-	-	-	-	-
				Low β-CD diet	2.5 g/100g feed	-	146±12 *mg/dL*		-	-		-	-	

Study	Study Period (weeks)	Study Design	Number of Subjects	β-CD Dose (g/day)	Fasting Serum Chol Results			Fasting Serum Triglyceride Results			Fasting Serum HDL-Chol Results		
					Baseline level	*Final level*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*	*Baseline level (mg/dL)*	*Final level (mg/dL)*	*Significant Difference? (p<0.05)*
			High β-CD diet	5.0 g/100g feed	-	124±20 *mg/dL*		-	-		-	-	

- Not assessed as part of the study

Table A-3: Small Intestine Digestion – Rat Studies

Study	Study Period	Study Design	Number of Subjects		CD Dose	Mean Faecal Excretion of Test Substance		Mean Excretion as CO_2	Mean Excretion into Urine	Mean Residual Content in Body Organs
						Time 1 (% ingested)	*Time 2 (% ingested)*	*Time 2 (% ingested)*	*Time 2 (% ingested)*	*Time 2 (% ingested)*
Anderson *et al*, 1963	23 hours (time 2), Intermediate testing at 17 hours (time 1)	RCT, blinding unknown	6 rats, 2 per group	Control (starch bolus)	0	0	0	61.5	2.4	28.5
				α-CD bolus	2.5 g α-CD/100 mL	14.4	0	60.3	5.8	27.9
				β-CD bolus	2.5 g β-CD/100 mL	5.8	0	57.7	4.4	28.1
Suzuki and Sato, 1985[#]	60 hours (time 2)	RCT, blinding unknown, no control	8 rats, 4 per group	α-CD bolus	1500 g α-CD	-	79.5	-	-	-
				β-CD bolus	1200 g β-CD	-	1.8	-	-	-
Van Ommen *et al*, 2004	24 hours all diets (time 1), 48 hours A3, A4, B1, B2 diets only (time 2)	RCT, blinding unknown, no control	Male Wistar rats, 4 per group	Group A1	200 mg α-CD/kg bw	12.0±2.5	-	58.1±1.4	2.6±0.9	20.8±1.5
				Group B1	200 mg α-CD/kg bw	11.5±7.0	18.0±1.9	53.8±3.6	18.0±1.9	10.4±1.5
				Group A3	1000 mg α-CD/kg bw	12.6±4.3	17.9±2.8	65.7±4.7	3.1±0.37	10.5±2.2
			Female Wistar rats, 4 per group	Group A2	200 mg α-CD/kg bw	4.2±3.1	-	58.3±2.7	2.8±0.3	28.3±3.1
				Group B2	200 mg α-CD /kg bw	11.0±7.8	16.4±4.6	60.0±4.3	16.4±4.6	9.2±2.0
				Group A4	1000 mg α-CD /kg bw	5.6±4.2	16.9±1.7	67.7±0.5	3.1±0.1	12.3±0.6

- Not assessed as part of the study

Suzuki and Sato also examined the α-cyclodextrin percentage of small and large intestine contents, however these results have not been included as they did not account for previous absorption prior to examination of the intestines.

Table A-4: Small Intestine Digestion – Human Study by Diamantis and Bär, 2004.

Study Period	Study Design	Number of Subjects		α-CD Dose	Serum Blood Glucose (mg/dL)					Serum Blood Insulin (μIU/mL)				
					Baseline	*45 min*	*90 min*	*180 min*	*Significant Difference? (p<0.05)*	*Baseline*	*45 min*	*90 min*	*180 min*	*Significant Difference? (p<0.05)*
3 hours on 3 separate days, with a washout of ≥2 days	Crossover trial, single blinding	12 males	Control bolus (100g white bread± water)	0	96.0	148.9	118.4	96.4	Yes – test bolus 1 results were significantly different to the control, and test bolus 2 was significantly different to both test bolus 1 and the control.	10.3	117.5	26.5	8.9	Yes – test bolus 1 and 2 results were significantly different to the control. The test boluses did not significantly vary between each other.
			Test Bolus 1 (100g white bread ± a-CD ± water)	10g bolus in water	89.6	96.1	106.1	90.4		11.6	22.2	29.3	11.7	
			Test Bolus 2 (a-CD ± water)	25g bolus in water	89.8	92.3	89.0	92.1		13.1	21.5	21.8	13.2	

ATTACHMENT 5

FOOD TECHNOLOGY REPORT

Alpha-Cyclodextrins

Introduction

Cyclodextrins are formed by converting linear starch chains into cyclic molecules by using an enzyme; cyclodextrin glucanotransferase. Cyclodextrin glucanotransferase reactions produce alpha (α), beta (β) and gamma (γ) cyclodextrins with six, seven, and eight units of glucose respectively, linked by α(1–4) bonds. The empirical formula of alpha-cyclodextrin is $C_{36}H_{60}O_{30}$ and the molecular weight is 972.85.

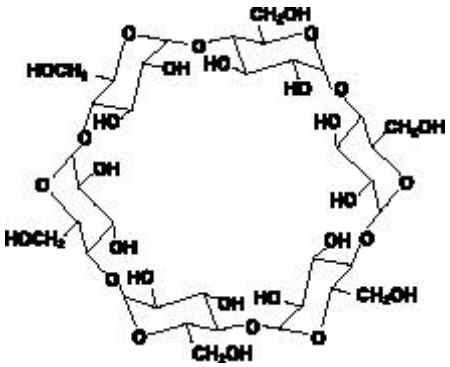

Figure 1. Alpha-cyclodextrin chemical structure. (Biwer, Antranikian, and Heinzle, 2002).

α-Cyclodextrin (synonyms, cyclohexaamylose, cyclomaltohexaose, alpha-Schar-dinger dextrin) is a non-reducing cyclic saccharide comprised of six glucose units.

The Food & Agriculture Organization/World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives (JECFA) has evaluated alpha-cyclodextrin and in 2001 allocated an acceptable daily intake (ADI) of "not specified."

Manufacturing processes

In general, two different types of cyclodextrin production processes can be distinguished: In "Solvent Processes" an organic complexing agent precipitates one type of cyclodextrin selectively and as such directs the enzyme reaction to produce mainly this type of cyclodextrin. In the "Non-solvent Process" no complexing agent is added and therefore a mixture of different cyclodextrins is formed. The ratio of cyclodextrins produced depends on the cyclodextrin glucosyltransferase used and on the reaction conditions.

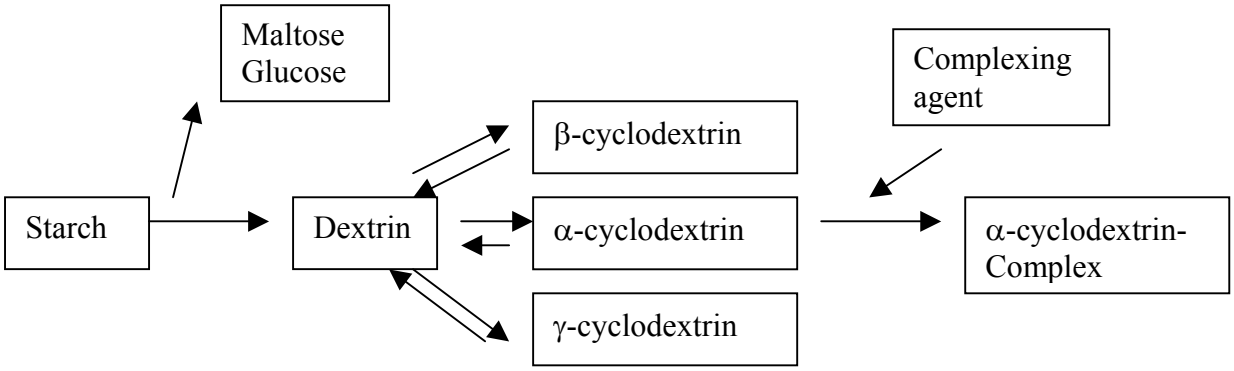

Figure 2. Reaction scheme for cyclodextrin formation using a complexing agent. (Biwer, Antranikian, and Heinzle, 2002).

α-Cyclodextrin may be produced by the action of (CGTase, EC 2.4.1.19) on hydrolysed starch syrups at neutral pH (6.0–7.0) and moderate temperature (35–40 °C). The annular (or doughnut-shaped) structure of α-cyclodextrin provides a hydrophobic cavity that allows formation of inclusion complexes with a variety of non-polar organic molecules of appropriate size. The hydrophilic nature of the outer surface of the cyclic structure makes α-cyclodextrin water-soluble.

The hydrophobic cavity and the hydrophilic outer surface of α--cyclodextrin form the basis for its use in the food industry. α-cyclodextrin, like its homologues β- and γ-cyclodextrin, can function as a carrier and stabilizer for flavours, colours, and sweeteners; as an absorbent for suppression of undesirable flavours and odours in foods; as an absorbent for suppression of halitosis (in breath-freshening preparations); and as a water-solubiliser for fatty acids and vitamins.

Cyclodextrins are normally sold as a dry, fine and crystalline powder, which remains stable long term. For industrial applications α-cyclodextrins cost around US$20-25/kg compared to β-cyclodextrins (US$3-4/kg) and γ-cyclodextrins (US$ 80-100/kg). Most cyclodextrin sold is low-priced beta-cyclodextrin but, with their prices coming down, market shares of α- and γ- cyclodextrin are expected to increase significantly in the next decade (Biwer, Antranikian, and Heinzle, 2002).

Functional properties and applications

Cyclodextrins can function to dissolve other hydrophobic (water-disliking) substances. The advantage of cyclodextrins is that they offer a hydrophobic cavity of average size ((1.5 nm x 0.7 nm x 0.8 nm) whereas the molecule is hydrophilic on the outside. This toric structure allows stable inclusion complexes to form, with a wide diversity of organic substances and also with salts and halogens. Depending on their respective size, the ‘guest’ molecule is encapsulated fully or partially, with cyclodextrin acting as the ‘host’ molecule or receptor. In addition, the complex improves the stability of the ‘guest’ molecule not only in water but also in air in the case of dry products, as well as in relation to heat, oxidation and hydrolysis.

The most important parameter for complex formation with hydrophobic substances is their three-dimensional size (Table 1).

Table 1. Properties of Cyclodextrins

	Molecular Size (A^o)				Water solubility (g/100 ml; 25 °C
Type	**Glucose units**	**Inside diameter**	**Outside diameter**	**Height**	
α	6	5.7	13.7	7.0	14.50
β	7	7.8	15.3	7.0	1.85
γ	8	9.5	16.9	7.0	23.20

α-Cyclodextrin uses include: carrier; encapsulating agent for food additives, flavourings and vitamins; stabilizer; and absorbent. α-Cyclodextrin is used as a carrier for flavours, colours, and sweeteners in foods such as dry mixes, baked goods, and instant teas and coffee, as a stabilizer for flavours, colours, vitamins, and polyunsaturated fatty acids in dry mixes and dietary supplements (< 1% of the final product), as a flavour modifier in soy milk (< 1%), and as an absorbent (breath freshener) in confectionery (10–15% of the final product).

α-Cyclodextrin use in food is not primarily as a food additive although it may perform some of the technological functions set out in Schedule 5 of Standard 1.3.1 - Food Additives, in the *Australia New Zealand Food Standards Code* such as a stabilizer and flavour modifier. α-Cyclodextrin levels of use are more consistent with that of a food ingredient rather than an additive. Starch, maltodextrins and starch hydrolysates are considered as food ingredients by the food industry and enforcement agencies.

As a food ingredient the labelling regulations would require the disclosure of its name in full on the food label. α-Cyclodextrin can be used a carrier of other ingredients or flavours, and this use is consistent with other food ingredients such as starches or sugars that can be used as a carrier. The function of a carrier is not a technological function set out in Schedule 5 of Standard 1.3.1 –Food Additives.

Table 2. Applicant's proposed maximum use of α-cyclodextrin

Food Application	Maximum proposed use (%)
breads, rolls, doughs (refrigerated)	5
cakes, muffins	5-7
biscuits	1
baking mixes	5 (dry)
beverage mixes (prepared)	1
coffee whitener (dry)*	1
diet soft drinks	1
fruit and vegetable juice drinks (dry)	1-2
instant coffee/tea*	1

dairy mixes (prepared)	2.5
soy and other non-dairy drinks	2
breakfast cereals	2-9
condiments*	3
hard confectionery	15
chewing gum	10
frozen dairy desserts	2.5
dessert mixes (dry)	1
yoghurt products	2.5
reduced fat table spreads	20
dressing and mayonnaise	5
formulated meal replacements (prepared)	1
instant rice prepared)	2
noodles	2
pasta	2
cereal bars	7
salty snacks	1

* The use is for a technological function corresponding to use level.

Stability in processing

α-Cyclodextrin is stable under the pH conditions encountered in many food products. It is hydrolysed by strong acids but the rate of hydrolysis is lower than for linear malto-oligosaccharides. No degradation occurs under alkaline conditions. Since α-cyclodextrin had no reducing end, it does not undergo Maillard type reactions. Furthermore, because it does not have any reactive functional groups, it does not react chemically with other food components.

α-Cyclodextrin is stable under the temperature conditions encountered in food processing and storage. With increasing temperature bound water is lost. Thermal decomposition occurs at about 250-278 °C (melting point).

α-Cyclodextrin is hydrolysed by α-amylases of fungal or bacterial origin. Conversely, salivary (human) and pancreatic (human, porcine) amylases are unable to hydrolyse α-cyclodextrin to any extent.

Conclusion

The properties of starches can be modified by treatments which result in products suitable for specific purposes in the food industry. α-Cyclodextrin is a starch product that can provide specialised functions in place of some of the alternative food ingredients such as starches or maltodextrins in a food.

α-Cyclodextrin is suitable for use in a wide range of foods providing benefits of low viscosity and temperature and pH stability. The ability of α-cyclodextrin to form complexes with a wide variety of organic molecules, coupled with its water solubility, make it a versatile food ingredient.

The proposed main use of α-cyclodextrin is as a food ingredient. As a food ingredient, it undergoes the normal processing or preparation requirements for the particular food to which it is added. Foods are not restricted from use to perform a technological function in another food. Foods are also generally permitted processing aids.

References

Biwer A., Antranikian G., and Heinzle E. Enzymatic production of cyclodextrins. Appl. Microbiol. Biotechnol (2002) 59:609-617.

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Linden G and Lorient D. New ingredients in food processing. Biochemistry and agriculture. CRC Press 2000 Woodhead Publishing Ltd, Cambridge, England.

World Health Organization, Geneva, 2003. Food Additives Series: 48 Safety Evaluation Of Certain Food Additives. Prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). IPCS - International Programme on Chemical Safety alpha-Cyclodextrin. *Dr A.S. Prakash and Dr P.J. Abbott*

ATTACHMENT 6

Summary of submissions

Submissions received in response to the Initial Assessment Report

A total of seven submissions were received in response to the Initial Assessment Report. Five of these submitters support Option 2, to permit α-cyclodextrin as a novel food, subject to the assessment of safety, nutrition and dietary exposure at Draft Assessment. Issues raised in submissions include concern about the use of the term 'unavailable carbohydrate', the potential of α-cyclodextrin to inhibit the absorption of nutrients, the marketing of foods containing α-cyclodextrin as having dietary fibre-like properties, and that α-cyclodextrin should not be considered as a novel food.

Submitter	Preferred regulatory option	Safety issues	Nutrition issues	Other comments
Dietitians Association of Australia (DAA)	Option 2 (subject to further consideration at Draft Assessment)	Support Option 2 subject to FSANZ preparing a safety assessment including consideration of the JECFA evaluation of α-cyclodextrin as a food additive, and additional studies on the safety of α-cyclodextrin.	Concerned about the potential for α-cyclodextrin to inhibit the absorption of certain vitamins, minerals and fatty acids.	Concern that the addition of functional fibres to foods of otherwise poor nutritional value will enable nutrition claims to be made about these products.
Food Technology Association of Victoria (FTA Victoria)	Option 2	No specific comment.	No specific comment.	No further comments.
New Zealand Food Safety Authority (NZFSA)	Option 2 (subject to further consideration at Draft Assessment)	Support a thorough safety assessment since α-cyclodextrin is only approved for use in Japan.	Support a thorough nutrition assessment including the investigation of any negative impacts. Believe that the term 'unavailable carbohydrate' may be confusing to the general public and do not supports its use as a nutrition claim.	No further comments.

New Zealand Crop and Food Research	No preferred regulatory option stated. α-Cyclodextrin should not be allowed to be included as part of the dietary fibre component of foods unless present as less than a certain proportion of the total dietary fibre and unless tested in subject groups in which there may be concerns regarding deficiency.	No specific comment.	Concerns regarding α-cyclodextrin being marketed as having dietary-fibre like properties. Dietary fibre is associated with a spectrum of beneficial properties which α-cyclodextrin does not posses. Concern that because α-cyclodextrin acts as a carrier it may be able to carry nutrients beyond their sites of absorption in the gut and subsequently lead to deficiencies.	No further comments.
Department of Agriculture, Fisheries and Forestry (DAFF)	Option 2 considered a routine amendment and, if adopted, would not have an adverse regulatory impact on DAFF or the Australian Quarantine and Inspection Service (AQIS).	No specific comment.	No specific comment.	Permitting the use of α-cyclodextrin as a novel food is not expected to have any impact on DAFF or AQIS under the *Imported Food Control Act 1992*.
Australian Food and Grocery Council (AFGC)	No preferred regulatory option stated. Considers that FSANZ has not adequately justified that the Application relates to a matter that warrants a variation to a food regulatory measure. Believes that FSANZ has failed to determine that α-cyclodextrin is a novel food.	No specific comment.	No specific comment.	Believe that although FSANZ has determined α-cyclodextrin to be a non-traditional food, FSANZ has not provided justification that it is a novel food. Believe that α-cyclodextrin meets the definitions for sugars contained in Standard 2.8 of the Code and dietary fibre contained in Standard 1.2.8 of the Code.

Confectionery Manufacturers of Australasia Limited	Option 2 (subject to a risk based safety assessment)			Permission for α-cyclodextrin as a novel food will provide scope for innovation, potential for a wider range of products with properties such as reduced energy and GI.

Submissions received in response to the Draft Assessment Report

A total of five submissions were received in response to the Draft Assessment Report. Three submitters supported Option 2, to permit the use of α-cyclodextrin as a novel food, while New Zealand Food Safety Authority stated that they thought it would be premature to approve the use of α-cyclodextrin as a novel food. The Australian Food and Grocery Council support the safety of α-cyclodextrin but requested that FSANZ review the recommendation such that α-cyclodextrin is considered a food and not a novel food.

Submitter	Preferred regulatory option	Specific comments
Environmental Health Unit, Queensland Health	Option 2	• While the types of foods in which α-cyclodextrin is used are likely to be premium or special purpose foods rather than generally consumed foods, studies in humans have involved only healthy male volunteers. Human toleration studies should be conducted on subjects likely to be concerned with weight control or blood glucose control. • FSANZ has not adequately considered the likely claims associated with foods containing α-cyclodextrin, e.g. low GI claims or low energy claims and potentially in the future dietary fibre claims.
NSW Food Authority	Option 2	• No specific technical comment on this assessment. • Questioned why α-cyclodextrin should be an entry in the table to clause 2 of Standard 1.5.1 if the assessment shows that no conditions of use are to be specified. This is a general question to be addressed in the review of the novel food standard.
Food Technology Association of Victoria (FTA Victoria)	Option 2	No further comments

New Zealand Food Safety Authority (NZFSA)	Believe that it is premature to approve the use of α-cyclodextrin as a novel food. If this application is progressed, NZFSA suggest that there should be some limitation on the amount of α-cyclodextrin that can be added to food.	• Suggest that some consideration should be given to limiting the amount of α-cyclodextrin per serve, or the amount per 100g of food. Based on the limited human data, a maximum figure of 10% could be suggested. This is because mild gastrointestinal symptoms were observed at levels of 25 g α-cyclodextrin (not incorporated into food) while the dietary modelling indicated the potential for both the mean and 95th percentile consumer to exceed this amount. • The safety of the enzyme CGTase used in the production of α-cyclodextrin, which is sourced from a genetically modified strain of *E. coli*, should be addressed in the Final Assessment. • As dietary fibre claims cannot be made, the foods containing α-cyclodextrin will be marketed using the other benefits of reduced energy or reduced glycaemic index. Consumers might not anticipate an associated increase in dietary fibre, which could be potentially misleading. • Edit on page 42 of the report where there is a reference to RMD.
Australian Food and Grocery Council (AFGC)	Support permission for the use of α-cyclodextrin. Requested that recommendation reviewed so that α-cyclodextrin is recognised simply as a food rather than a novel food.	• AFGC considers that FSANZ's assessment has shown that there is sufficient knowledge in the broad community to allow safe use of α-cyclodextrin and therefore it should not be regulated as a novel food, but rather as a food. • FSANZ's assessment of α-cyclodextrin as unavailable carbohydrate should be reflected in section 9 – Conclusions and Recommendations in the Final Assessment Report.