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

14 February 2011
[3-11]

APPLICATION A1034
ADVANTAME AS A HIGH INTENSITY SWEETENER
2nd ASSESSMENT REPORT

Executive Summary

Purpose

An Application was received from Ajinomoto Co Inc to amend Standard 1.3.1 – Food Additives of the *Australia New Zealand Food Standards Code* (the Code) to approve the use of a new intense sweetener Advantame for use in a range of foods.

This Application is being assessed under the Major Procedure and will include two rounds of public consultation, with this being the second round.

The specific objectives in considering this Application are to:

- protect public health and safety in relation to the proposed addition of Advantame to a range of foods
- ensure adequate information relating to Advantame is provided to consumers to enable informed choice

In order to ensure appropriate use of Advantame FSANZ has considered two options. Firstly, establishing maximum limits (MLs) in Schedule 1 of the Code, or secondly giving approval for use according to Good Manufacturing Practice (GMP) in Schedule 2 of Standard 1.3.1.

FSANZ concludes that approval of Advantame as an intense sweetener in Schedule 2 of Standard 1.3.1 does not pose a significant human health risk for Australian or New Zealand consumers. Furthermore, Advantame is technologically justified as it provides the function of an intense sweetener[1] in foods at the use levels proposed by the Applicant. The key risk assessment findings are detailed in **Supporting Document 1**.

The general labelling requirements of the Code, including the mandatory declaration of food additives, will provide adequate information to consumers regarding foods containing Advantame. Advantame must be declared in the ingredient list by its class name 'sweetener' followed by its specific name 'Advantame'. Based on the risk assessment findings, no additional mandatory labelling is proposed.

[1] replaces the sweetness normally provided by sugars in foods without contributing significantly to their available energy

Assessing the Application/Proposal

In assessing the Application FSANZ has had regard to the following matters as prescribed in section 29 of the *Food Standards Australia New Zealand Act 1991* (FSANZ Act):

- whether costs that would arise from a food regulatory measure developed or varied as a result of the Application outweigh the direct and indirect benefits to the community, Government or industry that would arise from the development or variation of the food regulatory measure
- there are no other measures that would be more cost-effective than a variation to Standard 1.3.1 that could achieve the same end
- any relevant New Zealand standards
- any other relevant matters.

Preferred Approach

To prepare draft variations to permit the use of Advantame as a Schedule 2 food additive in Standard 1.3.1 for use according to Good Manufacturing Practice (GMP) in foods specified in Schedule 1.

Reasons for Preferred Approach

The development of an amendment to the Code to give approval to the sale and use of food with added Advantame in Australia and New Zealand is proposed on the basis of the available scientific evidence, for the following reasons:

- the safety assessment did not identify any public health and safety issues
- use of Advantame is technologically justified
- approval for addition of Advantame to food is consistent with Ministerial policy guidance on the *Addition to Food of Substances other than Vitamins and Minerals*[2]
- a regulation impact assessment process has been undertaken that fulfils the requirement in Australia and New Zealand for an assessment of compliance costs. The assessment concluded that the approval of Advantame as an intense sweetener in Schedule 2 of Standard 1.3.1 provides a net benefit
- there are no other measures that would be more cost-effective than a variation to Standard 1.3.1 that could achieve the same end.

Consultation

Consultation on the 1st Assessment was conducted over a period of six weeks; eleven submissions were received. Summaries of these are in **Attachment 2** of this report. FSANZ has taken all submitters' comments into consideration in completing the Second Assessment Report. Public comment is now invited on this Report, which includes a draft variation to Standard 1.3.1. Comments received in the second consultation period will be used to assist in preparing the Approval Report.

[2] http://www.foodstandards.gov.au/foodstandards/changingthecode/ministerialcouncilpolicyguidelines/

Invitation for Submissions

FSANZ invites public comment on this Report based on regulation impact principles for the purpose of preparing an amendment to the Code for approval by the FSANZ Board.

Written submissions are invited from interested individuals and organisations to assist FSANZ in further considering this Application. Submissions should, where possible, address the objectives of FSANZ as set out in section 18 of the FSANZ Act. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant studies, research findings, trials, surveys etc. Technical information should be in sufficient detail to allow independent scientific assessment.

The processes of FSANZ are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of FSANZ and made available for inspection. If you wish any information contained in a submission to remain confidential to FSANZ, you should clearly identify the sensitive information, separate it from your submission and provide justification for treating it as confidential commercial material. Section 114 of the FSANZ Act requires FSANZ to treat in-confidence, trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

Submissions must be made in writing and should clearly be marked with the word 'Submission' and quote the correct project number and name. While FSANZ accepts submissions in hard copy to our offices, it is more convenient and quicker to receive submissions electronically through the FSANZ website using the Standards Development tab and then through Documents for Public Comment. Alternatively, you may email your submission directly to the Standards Management Officer at submissions@foodstandards.gov.au. There is no need to send a hard copy of your submission if you have submitted it by email or the FSANZ website. FSANZ endeavours to formally acknowledge receipt of submissions within 3 business days.

DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 15 March 2011

SUBMISSIONS RECEIVED AFTER THIS DEADLINE WILL NOT BE CONSIDERED

Submissions received after this date will only be considered if agreement for an extension has been given prior to this closing date. Agreement to an extension of time will only be given if extraordinary circumstances warrant an extension to the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.

Questions relating to making submissions or the application process can be directed to the Standards Management Officer at standards.management@foodstandards.gov.au.

If you are unable to submit your submission electronically, hard copy submissions may be sent to one of the following addresses:

Food Standards Australia New Zealand
PO Box 7186
Canberra BC ACT 2610
AUSTRALIA
Tel (02) 6271 2222

Food Standards Australia New Zealand
PO Box 10559
The Terrace WELLINGTON 6143
NEW ZEALAND
Tel (04) 978 5630

CONTENTS

SUPPORTING DOCUMENTS

The following materials, which were used in the preparation of this Assessment Report, are available on the FSANZ website at:
http://www.foodstandards.gov.au/foodstandards/applications/applicationa1034adva4493.cfm

SD1: Risk Assessment report (Amended)

Introduction

An Application was received from Ajinomoto Company Incorporated on 18 August 2009 to amend Standard 1.3.1 – Food Additives of the *Australia New Zealand Food Standards Code* (the Code). The Applicant is seeking approval for the use of Advantame, a new intense sweetener in a range of foods. This Application is being assessed under the major procedure due to the complexity of the risk assessment that needs to be undertaken.

The Applicant supplied an extensive toxicological data set that required a detailed review. There were over 50 detailed studies, many unpublished, to assess and these have required careful consideration by FSANZ toxicologists. No other country in the world has yet completed a toxicological assessment and established an acceptable daily intake (ADI) for Advantame. FSANZ sought an external peer review of the toxicology report in parallel with the public consultation period for the 1st Assessment Report. The reviewer concurred with the conclusions drawn by FSANZ in the Hazard Assessment Report and suggested some minor amendments to the Report which will be taken into consideration in the preparation of the Approval Report.

The Applicant advised FSANZ that the purpose of using Advantame as a food additive is to provide assistance to people as part of their weight management or weight loss regime by lowering the caloric value of foods while maintaining the flavour of the foods. Advantame is proposed for use in Australia and New Zealand in table top sugar substitutes (powdered only) and a range of powdered beverages including fruit flavoured drinks, milks and flavoured milk drinks, instant tea and coffee, and protein drinks. The Applicant provided data to estimate the maximum limits of Advantame likely to be used as a sugar replacement in a range of common food products.

This 2nd Assessment Report discusses the issues involved in the proposed addition of Advantame to food, and seeks further comments from stakeholders under this second round of public consultation on the proposed amendments to Standard 1.3.1.

1. The Issue

The Applicant is requesting permission to add Advantame to a range of foods, in order to increase the variety of intense sweetener products available on the market for consumers seeking calorie reduced foods in their diets.

The use of Advantame in food is not currently permitted in the Code. Therefore Advantame requires a pre-market safety assessment under Standard 1.3.1 before this product can be sold in Australia or New Zealand.

2. Current Standard

2.1 Background

A food additive is any substance not normally consumed as a food in itself and not normally used as an ingredient of food, but which is intentionally added to a food to achieve one or more of the technological functions specified in Schedule 5 of Standard 1.3.1 (e.g. a sweetener).

Standard 1.3.1 regulates the use of food additives in the production and processing of food. A food additive may only be added to food where expressly permitted in this standard. Additives can only be added to food in order to achieve an identified technological function according to Good Manufacturing Practice.

Standard 1.3.4 – Identity and Purity prescribes standards for the identity and purity of food additives.

Advantame is a novel sweetener that has yet to reach the market and no international standards that are relevant to the use of Advantame have been identified. However, FSANZ is of the understanding that a Petition for use of Advantame as a food additive is currently under review by the United States Food and Drug Administration.

Of the technological functions listed in Schedule 5 of Standard 1.3.1, Advantame is classified as an intense sweetener as it 'replaces the sweetness normally provided by sugars in foods without contributing significantly to the available energy of the food'.

3. Objectives

The specific objectives in considering this Application are to:

- protect public health and safety in relation to the proposed addition of Advantame to a range of foods
- ensure adequate information relating to Advantame is provided to consumers to enable informed choice.

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives which are set out in section 18 of the FSANZ Act. These are:

- the protection of public health and safety; and
- 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.

3.1 Policy Guideline on Addition to Food of Substances other than Vitamins and Minerals

Under its section 18 objectives, FSANZ must have regard to any written policy guidelines formulated by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council). The Ministerial Council has provided a Policy Guideline on the *Addition to Food of Substances other than Vitamins and Minerals*.

The Policy Guideline provides 'high order' and 'specific order' policy principles and additional guidelines for the addition of substances other than vitamins and minerals to food. The 'high order' principles reflect FSANZ's statutory objectives described above.

'Specific order' policy principles are provided both for substances added for a 'technological function' as well as for 'Any Other Purpose'. The purpose for addition of Advantame to food falls under 'Technological Function' and therefore regard will be given to the policy guidance in the assessment of this Application. The relevant specific order policy principles are stated below:

The addition of substances other than vitamins and minerals to food where the purpose of the addition is to achieve a solely technological function should be permitted where:

a) the purpose for addition can be articulated clearly by the manufacturer (i.e. the stated purpose); and
b) the addition of the substance to food is safe for human consumption; and
c) the amounts added are consistent with achieving the technological function; and
d) the substance is added in a quantity and a form which is consistent with delivering the stated purpose; and
e) no nutrition, health or related claims are to be made in regard to the substance.

4. Questions to be answered

The key questions which FSANZ has considered as part of this assessment are:

- Has the stated purpose for adding Advantame been articulated clearly?
- Is Advantame proposed to be added in a quantity and form which is consistent with achieving the stated purpose and technological functions?
- Is there a need to establish a reference health standard for Advantame in order to protect public health and safety?
- If Advantame enters the food supply would the resulting exposure for all consumers pose an unacceptable risk for public health and safety?

RISK ASSESSMENT

5. Risk & Technical Assessment Summary

A comprehensive risk and technical assessment was undertaken to: (1) determine whether Advantame can deliver the intended technological function in the final food; (2) evaluate the toxicity of Advantame and establish an acceptable daily intake (ADI); and (3) compare the estimated levels of intake of Advantame with the ADI to ascertain the potential dietary risk to consumers (**Supporting Document 1**).

Following this detailed assessment, the following was concluded:

- the proposed use of Advantame as an intense sweetener is technologically justified
- the toxicity of Advantame has been well characterised based on an extensive database. The ADI for Advantame is set at 0-5 mg/kg bw/day
- for all groups of Australian and New Zealand consumers assessed (including children), estimated dietary exposures were well below the ADI
- there are no public health and safety issues associated with the proposed addition of Advantame to food.

Risk Management

6. Risk Management Issues

FSANZ's regulatory approach differs depending on the nature of the risks identified and there are a number of approaches used to manage identified risks. These may include prescribing specifications for the identity and purity of the substance, compositional and/or labelling requirements, and where necessary, restriction or prohibition. Drawing on the conclusions from the risk assessment, the following sections discuss approaches to managing any identified public health and safety risks and other broader issues requiring consideration in the development of regulations for addition of Advantame to specific foods.

6.1 Risk to public health and safety

FSANZ concludes that approval of Advantame as a Schedule 2 food additive in Standard 1.3.1 poses negligible risk to public health and safety for Australian or New Zealand consumers. Currently, proposed uses are in table top sugar substitutes (powdered only) and a range of powdered beverages including fruit flavoured drinks, milks and flavoured milk drinks, instant tea and coffee, and protein drinks.

6.2 Consistency with Policy Guidelines

As noted in Section 3.1, FSANZ is required to have regard to the Policy Guideline on the Addition of Substances other than Vitamins and Minerals to foods. Since the purpose for addition of Advantame to food falls under 'Technological Function' regard has been given particularly to the specific order policy principles for 'Technological Function'.

It has been determined that the Applicant provided a clear stated purpose, Advantame is safe for human consumption, there is a clear technological function and Advantame is added in a quantity and form which is consistent with delivering the stated purpose. Therefore, FSANZ concludes that the addition of Advantame to a range of foods is consistent with the first four of the specific order policy principles for 'Technological Function' (refer to Section 3.1).

In regard to Policy principle (e), the Applicant has stated that the purpose of using Advantame as an additive is also to provide assistance to people as part of their weight management or weight loss regime by lowering the caloric value of foods. Therefore, products containing Advantame may seek to make claims potentially causing inconsistency with this policy principle. However, FSANZ considers that as long as the claims made are in accordance with the requirements and conditions set out in Standard 1.1A.2 (Transitional Standard – Health Claims), and Standard 1.2.8 (Nutrition Information Requirements), there are no reasons to apply additional requirements for such claims. This is consistent with permitted claims on products containing other similar intense sweeteners.

Although it relates to the addition of substances other than for a technological purpose, FSANZ has also given regard to the last policy principle related to the addition of substances other than vitamins and minerals to food where the purpose of the addition is for other than to achieve a solely technological function ('Any Other Purpose'). This principle states that *the presence of the substance does not mislead the consumer as to the nutritional quality of the food*.

Nutrition information requirements are specified in Standard 1.2.8. This Standard requires the declaration of certain nutrients in the nutrition information panel (NIP) on packaged foods, subject to certain exemptions. In general, the NIP must include the energy, protein, carbohydrate, sugars, total fat, saturated fat and sodium content of the food.

The total energy content declared in the NIP captures the energy content of all the ingredients used in that food. Any lowering of the energy value of a food as a result of replacing ingredients such as sugars with Advantame will be reflected in the total energy content declared in the NIP and thereby provide consumers with nutrition information to assist their food choice.

The Code also specifies conditions that should be met for certain nutrition claims which may be relevant to foods containing intense sweeteners like Advantame. For example clause 14 of Standard 1.2.8 contains requirements that must be met for low joule claims. Furthermore in relation to health claims, there is currently no specific permission in the Code for weight loss or weight management claims; Standard 1.1A.2 prohibits the presence of a claim or statement in a label or an advertisement that *the food is a slimming food or has intrinsic weight reducing properties.*

The Code of Practice on Nutrient Claims in Food Labels and in Advertisements (CoPoNC) specifies certain conditions for claims, such as 'low sugar', which may be applicable for foods containing Advantame. CoPoNC is a voluntary code of practice for food suppliers in Australia and is used by some manufacturers in New Zealand. Should a manufacturer in Australia or New Zealand choose to make low energy, low sugar or similar claims, on food labels or advertisements, the fair trade legislation requires that such representations about food must not mislead, deceive or be false.

Therefore, FSANZ considers that there are sufficient requirements in the Code that, when adhered to, would provide adequate information to enable consumers to make an informed choice in relation to the nutritional quality of Advantame containing foods.

Having given regard to policy guidance, FSANZ concluded that the addition of Advantame can be permitted as proposed for the following reasons:

- the purpose for adding Advantame to food as proposed has been articulated clearly by the manufacturer as achieving a solely technological function of a food sweetener (Supporting Document 1)

- the proposed addition of Advantame to food is safe for human consumption (Supporting Document 1)

- the proposed amounts of Advantame added are consistent with achieving the technological function (Supporting Document 1)

- Advantame would be added in a quantity and a form which is consistent with delivering the stated purpose of sweetening the food (Supporting Document 1)

- the existing labelling requirements in the Code, including those for nutrition and health claims, enable consumers to make an informed choice in relation to the nutritional quality of Advantame containing foods.

6.3 Labelling of Advantame-containing products

Labelling provisions are included within the Code to protect public health and safety and to provide adequate information to enable consumers to make informed choices.

6.3.1 Mandatory advisory statements

Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations requires foods containing aspartame or aspartame-acesulphame salt to be labelled with an advisory statement to the effect that the food contains phenylalanine for consumers with phenylketonuria. The risk assessment has determined that while there is no phenylalanine in the final food products, or formed in the digestive tract prior to absorption (similar to Aspartame[3]), phenylalanine is likely to be formed *in vivo* (after absorption) similar to Neotame (refer to SD1). In considering Neotame, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that with regard to phenylketonuria, the formation of phenylalanine from the normal use of Neotame 'would not be significant in relation to this condition' (WHO 2004). Based on the similarity in metabolism this conclusion is also true for Advantame. Therefore, an advisory statement for consumers with phenylketonuria in the Code is not required.

6.3.2. Labelling of ingredients

It is proposed that the general labelling requirements in the Code, applicable to foods for retail sale required to bear a label, including the mandatory declaration of food additives (Standard 1.2.4 – Labelling of Ingredients) would apply. In accordance with these existing requirements, where a food for retail sale is required to bear a label and contains Advantame, the sweetener would be declared in the ingredient list by its class name 'sweetener' followed by its specific name 'Advantame'. There is currently no additive number internationally or in the Code for Advantame.[4] Until a code number is established, the specific name Advantame must be used in the ingredients list. However, when a number is assigned and placed into the Code[5], then declaration of Advantame as a food additive would then be possible by name or number. This requirement will also apply to the retail sale of table top sugar substitute formulations containing Advantame. The declaration of Advantame on the label of a food will therefore alert consumers to its presence and may be used by consumers to choose or avoid foods containing Advantame if they so wish.

Where foods for retail sale are exempt from the requirement to bear a label, such as unpackaged foods, the Code does not require the presence of non-allergenic food additives to be declared. As the risk assessment concludes that the use of Advantame at GMP in the different food categories considered in this Application does not raise any public health and safety issues, FSANZ considers the current food additive declaration requirements in Standard 1.2.4 are appropriate for all foods permitted to contain Advantame.

Consumers who wish to avoid Advantame in foods that are not required to bear a label may request information from the food retailer about its presence or otherwise, although provision of this information is not mandated by the Code. This approach is consistent in the Code for the use of all permissible non-allergenic food additives in foods that are not required to bear a label.

6.3.3 Nutrition, health and related claims

It is proposed that similar to other intense sweeteners that are currently in the market place, claims in accordance with the requirements in Standards 1.1A.2 – Transitional Standard – Health Claims and 1.2.8 – Nutrition Information Requirements may be made about foods containing Advantame.

---

[3] http://www.foodstandards.gov.au/scienceandeducation/factsheets/factsheets2009/aspartamejuly2009.cfm

[4] To date there is no international Code for Advantame established. This will be considered by the Codex Alimentarius in due course.

[5] Via a Code maintenance Proposal

Other claims in accordance with the conditions specified in CoPoNC may also be applicable for foods containing Advantame. For all claims, the requirements of fair trade legislation (i.e. representations about food must not mislead, deceive or be false) must be met.

FSANZ has proposed a draft Standard – Standard 1.2.7 – Nutrition, Health and Related Claims, under Proposal P293 – Nutrition, Health & Related Claims which includes requirements for a number of nutrition, health and related claims. However, draft Standard 1.2.7 is currently under review due for completion in October 2011. For further information about Proposal P293, refer to http://www.foodstandards.gov.au/consumerinformation/labellingoffood/nutritionhealthandrelatedclaims/.

6.3.4 Labelling for food intolerances

In regard to Advantame, the evidence indicates that intolerance reactions are highly unlikely for the following reasons:

- the human studies conducted on Advantame, at doses much higher than consumers would be exposed to, provided no suggestion of intolerance
- the conclusion of the hazard assessment is that Advantame is well tolerated by humans
- this conclusion for humans is supported by numerous laboratory animal studies using very high doses of Advantame
- although intolerance reactions have been reported with Aspartame, this is not a useful surrogate for Advantame because it is metabolised differently
- there are no reports in the scientific literature of intolerance reactions to Neotame, which is chemically and metabolically similar to Advantame.

There is no evidence to propose any additional labelling requirements to alert consumers of possible intolerances to Advantame.

6.3.5 Labelling summary

On the basis of the risk assessment, FSANZ considers the current general labelling requirements of the Code are appropriate for all foods, including table top sugar substitutes, should the use of Advantame be permitted in foods. No additional mandatory labelling is proposed.

6.4 Specifications for Advantame

Standard 1.3.4 – Identity and Purity adopts specifications for food additives (and other substances in foods) by reference to specific sources, including specifications established by JECFA. Standard 1.3.4 also contains distinct specifications for some ingredients and substances where there is not a suitable specification included in the sources referenced in that Standard.

The Purpose of Standard 1.3.4 is to regulate the identity and purity of substances. Advantame is not covered by a specification from one of the published sources identified in Standard 1.3.4 – Identity and Purity or in any of the primary or secondary specification sources approved for use by FSANZ. In the absence of an appropriate published monograph, a detailed specification is provided in SD1. This specification is now included in the drafting for this Application (**Attachment 1**).

6.5 Methods of analysis

The assay for Advantame and the validation of this method is presented in full detail in the Application. This can be viewed by interested parties as part of the public register. This method employs high-performance liquid chromatography (HPLC) coupled with an ultraviolet absorption detector (refer to Section 2.1.3 of SD1).

The HPLC method employed in the analysis of the Advantame also quantifies Advantame-acid (a breakdown product of Advantame) and other related substances in tabletop sweeteners and powdered beverages. A calibration curve based on standard Advantame or Advantame-acid solutions is used.

6.6 Risk Management Strategy

The risk assessment concluded that permitting the use of Advantame as an intense sweetener is technologically justified and poses no significant risk to public health and safety. The general labelling requirements of the Code will provide adequate information to consumers regarding foods containing Advantame. Based on the risk assessment findings, no additional mandatory labelling is proposed.

Advantame could either be regulated in Schedule 1 with specific maximum limits or be generally permitted in general purpose processed foods via Schedule 2 under GMP to Standard 1.3.1.

Schedule 1 permissions usually apply when the risk assessment determines that an exceedance of the reference health level, namely the ADI, would be possible for any population group and it would be appropriate to restrict levels of Advantame in foods.

Alternatively, approval for use of Advantame could be granted to a wide range of food types in Schedule 1 according to GMP by listing in Schedule 2 of Standard 1.3.1. This approach is similar to the previous approval of Neotame in January 2000, whereby Schedule 2 permissions were granted at that time, based on the low level of risk that Neotame posed to any population group.

FSANZ has calculated that a 60 kg person would have to consume 300 mg Advantame/day to exceed the ADI of 0-5 mg/kg bw/day. As Advantame is 20,000 times sweeter than sucrose, then 300 mg Advantame is equivalent to a consumption of the equivalent of 6 kg sugar. Similarly, a 19 kg child would have to consume the equivalent of about 1.9 kg sugar.

Therefore, FSANZ has concluded that the second option to recommend GMP permissions for Advantame in Schedule 2 is the most appropriate for the following reasons:

- there is no specific risk that needs to be managed by setting a maximum permitted level in foods
- it allows manufacturers to formulate food preparations that, when used following manufacturer's instructions, suit a variety of broader food applications
- due to the intense sweetness of Advantame and minimal amounts needed to sweeten foods, the use of Advantame is self-limiting.

7. Options

FSANZ is required to consider the impact of various regulatory (and non-regulatory) options on all sectors of the community, which includes consumers, food industries and governments in Australia and New Zealand.

Food additives used in Australia and New Zealand are required to be listed in Standard 1.3.1. As Advantame is considered a food additive and requires a pre-market approval under Standard 1.3.1, it is not appropriate to consider non-regulatory options to address this Application.

Three regulatory options have been identified for this Application:

Option 1: Reject Application, thus not approving the use of Advantame as an intense sweetener

This option maintains the *status quo* by not permitting the use of Advantame as a food additive in Standard 1.3.1.

Option 2A: Approve the use of Advantame as an intense sweetener in Schedule 1 of Standard 1.3.1

This option will result in an amendment to Schedule 1 of Standard 1.3.1 to permit the use of Advantame as a food additive in a specified range of foods at restricted maximum levels. This option will also result in a subsequent amendment to Standard 1.2.4 to include Advantame in the list of food additives in Schedule 2.

Option 2B: Approve the use of Advantame as an intense sweetener in Schedule 2 of Standard 1.3.1

This option will result in an amendment to Schedule 2 of Standard 1.3.1 to permit the use of Advantame as a food additive at levels according to GMP in foods specified in Schedule 1 of Standard 1.3.1. This option would result in a wider range of foods being permitted to contain added Advantame than for Option 2. This option will also result in a subsequent amendment to Standard 1.2.4 to include Advantame in the list of food additives in Schedule 2.

8. Impact Analysis

8.1 Affected Parties

Parties possibly affected by the regulatory options outlined above include:

- consumers who may be affected by new products containing Advantame
- public health professionals because of the role of Advantame in reducing weight for obese individuals
- those sectors of the food industry wishing to market foods containing Advantame, including potential importers, manufacturers of Advantame and manufacturers of foods that may potentially contain Advantame
- government generally, where a regulatory decision may impact on trade or World Trade Organization (WTO) obligations, and State, Territory and New Zealand enforcement agencies.

8.2 Benefit Cost Analysis (RIS Number: 10838)

In developing food regulatory measures for adoption in Australia and New Zealand, FSANZ is required to consider the impact of all options on all sectors of the community, including consumers, the relevant food industries and governments.

The regulatory impact assessment identifies and evaluates, though is not limited to, the costs and benefits arising from the regulation and its health, economic and social impacts.

The regulatory impact analysis is designed to assist in the process of identifying the affected parties and the likely or potential impacts the regulatory provisions will have on each affected party. Where medium to significant competitive impacts or compliance costs are likely, FSANZ has sought advice from the Office of Best Practice Regulation (OBPR) to estimate compliance costs of regulatory options.

The OBPR has approved a preliminary assessment of this Application which concluded that there were no business compliance costs involved and/or minimal impact and consequently a detailed Regulation Impact Statement (RIS) is not required.

8.2.1 Option 1: Reject Application, thus not approving the use of Advantame as an intense sweetener

8.2.1.1 Consumers

FSANZ was initially of the understanding that there is either no or limited research from consumers as to whether they are satisfied with the current range of intense sweeteners or whether those consumers currently consuming approved sweeteners would prefer additional food choices.

At 1st Assessment, the Calorie Control Council[6] (CCC) indicated that it has been conducting nationally projectable consumer research in the United States for over 20 years. FSANZ has requested a copy of this survey from the CCC in order that it can be evaluated. The CCC claims that, even with the availability of a wide range of intense sweeteners and products containing them, consumers have indicated that they would like more products available. Of the consumers using low-calorie, reduced sugar and sugar free products (86% of the USA population over 18 years of age) responding to the CCC's most recent survey, 87% are interested in being offered additional low-calorie products. Of the products listed, 61% would like more low-calorie snacks, 57% low-calorie cereals, 56% low-calorie ice cream/frozen yogurt, 52% cakes/pies, 46% candy, 41% yogurt, 39% soft drinks, 36% jam/jellies/preserves, and 36% puddings and gelatins.

There is a potential cost to consumers with this option in terms of the lack of availability of a newer product with ability to lower energy values in food and assist in weight reduction.

Since there are no public health and safety risks from consumption of Advantame-containing products there are no benefits to consumers from rejection of this Application.

8.2.1.2 Industry

There is an identifiable opportunity cost to the food industry in terms of a loss of product range and marketing opportunities.

There are other intense sweeteners permitted for use, such as steviol glycosides, saccharin, cyclamate, aspartame, acesulphame potassium, thaumatin, sucralose, and alitame which industry can currently use. The use of Advantame compared to aspartame however, may result in lower costs and improved function in specific foods because of its stability. Maintaining the status quo would deny industry any advantages that the use of Advantame may give.

[6] The Calorie Control Council is an international association representing companies that make and use intense sweeteners.

8.2.1.3 Government

There would be no impact on government. There are no benefits to Governments in maintaining a prohibition as there are no perceived costs on jurisdictions that enforce the food regulations. Lack of approval may be regarded as unnecessarily trade restrictive.

8.2.2 Option 2A: Approve the use of Advantame as an intense sweetener in schedule 1 of Standard 1.3.1

8.2.2.1 Consumers

Consumers may benefit from foods containing Advantame as this would provide an alternative intense sweetener on the market, possibly with a preferred taste profile.

8.2.2.2 Industry

This option would provide an alternative sweetener and would increase market and product opportunities for the food industry.

8.2.2.3 Government

There may be a small cost to Government agencies that enforce the regulations to validate the analytical method of analysis for Advantame. There may also be further costs if they choose to analyse for the presence of this sweetener at a higher rate than they are currently doing for existing intense sweeteners.

8.2.3 Option 2B: Approve the use of Advantame as an intense sweetener in schedule 2 of Standard 1.3.1

The costs and benefits for consumers, industry and Government are expected to be the same as for option 2A but additionally this option provides a greater innovation potential for industry and would provide a reduced cost for new applications to extend the range of foods. FSANZ would not need to provide a case-by-case assessment of each new food type usage should there be further requests to permit its use in other food types. Therefore, this option would be efficient in the long-term in regard to approval of more foods containing Advantame.

8.3 Comparison of Options

It is anticipated that the introduction of a range of food products containing Advantame would provide greater opportunities for innovation by manufacturers and allow them to benefit from increased market development both domestically and overseas. As Advantame has been demonstrated to be approximately 20,000 times sweeter than sucrose, the use of Advantame by manufacturers would allow for the formulation of energy-reduced food products with a flavour profile that is similar to that of the original food. Consumers would be provided with an increased choice of products with the potential to aid weight management and weight loss regimes. There are no significant impacts on government enforcement agencies by the addition of Advantame as an ingredient to foods; although it is acknowledged that there may be costs to validate the method of analysis for Advantame should these agencies elect to test for the presence or level of Advantame.

Option 1 appears to provide no benefits to industry, consumers or government. Option 1 denies industry access to a new food additive which has been assessed as safe. It also denies consumers access to foods containing Advantame and any associated benefits.

Option 2A does not appear to impose any significant costs on industry, consumers, public or Government. Option 2 provides benefits to industry in terms of product innovation and development and potential sales of foods containing Advantame, while consumers may benefit from possible improved flavour/taste profiles.

Option 2B would provide industry with a greater potential for innovation due to a wider range of foods being permitted to contain added Advantame than would be permitted under Option 2A and lower costs association with avoiding the need for further applications to extend the range of permitted food types.

An assessment of the costs and benefits of the three options indicates that there would be a net benefit in permitting the use of Advantame as a Schedule 2 additive (Option 2B).

Communication and Consultation Strategy

9. Communication

9.1 Response to public consultation

Consultation on the 1st Assessment was conducted over a period of six weeks. Eleven submissions were received. Summaries of these are in **Attachment 2** of this report. FSANZ has taken all submitters' comments into consideration in completing the Second Assessment Report. The key issues raised are addressed below.

9.1.1 Approval of Advantame as either a Schedule 1 or 2 food additive

This has been addressed in Section 6.6 Risk Management Strategy.

9.1.2 Establishing an acceptable daily intake (ADI) of 5 mg/kg bw/day based on the rabbit developmental toxicity study

FSANZ has set an ADI of 5 mg/kg bw/day, by applying a 100-fold safety factor to the no observed adverse effect level (NOAEL) of 500 mg/kg bw/day in a rabbit developmental toxicity study (Fulcher et al 2003). The NOAEL was based on maternotoxicity at the next higher dose of 1000 mg/kg bw/day. The Applicant does not consider that the ADI should be based on this study because it believes that the maternotoxicity was not due to a systemic effect of Advantame 'but a result of inappetence and gastrointestinal tract distress associated with oral ingestion of large amounts of poorly absorbed material.'

Since Advantame has limited absorption from the gastrointestinal tract (GIT) in rats, dogs and humans, coupled with the known sensitivity of rabbits to gastrointestinal disturbances, the hypothesis may seem plausible. In support of this hypothesis, the Applicant cited another rabbit developmental toxicity study in which marked gastrointestinal irritation occurred following gavage dosing with sucralose (another intense sweetener) at 700 mg/kg bw/day (Kille et al 2000)[7]. In 2000, the European Commission's Scientific Committee on Food (SCF)[8] considered that these gastrointestinal effects were not toxicologically relevant and therefore could not serve as the basis to set an ADI for sucralose. The rationale given by the SCF was the sensitivity of rabbits to GIT distress resulting from a poorly digestible substance exerting an osmotic effect in the GIT.

[7] Kille JW et al (2000) Sucralose: Assessment of teratogenic potential in the rat and rabbit. Food & Chemical Toxicology **38** (Suppl. 2): S43-S52

[8] European Commission (2000) Opinion of the Scientific Committee on Food on sucralose SCF/CS/ADDS/EDUL/190 Final. Available at: http://ec.europa.eu/food/fs/sc/scf/out68_en.pdf

Unfortunately the Kille et al study cited by the Applicant to support their hypothesis regarding a possible osmotic effect for Advantame is not applicable because of key differences in physicochemical properties between sucralose and Advantame. In order for an ingested compound to be osmotically active in the GIT it needs to possess two important characteristics, i.e. it must be water soluble and undergo limited absorption. Whilst high water solubility is common to many ingested compounds it is rarely coupled with poor absorption from the GIT. Sucralose is very soluble in water and undergoes around 35% absorption from the GIT in pregnant rabbits, albeit very slowly over 5 days. Unlike Advantame, sucralose has been shown to cause peri-anal soiling, scouring and caecal enlargement in rats and rabbits. This suggests that if sucralose is osmotically active then it needs to either undergo extensive enterohepatic re-circulation or be efficiently secreted into the GI tract (Kille et al 2000). John et al[9] (2000) have suggested a third possibility for prolonged GIT exposure to sucralose in rabbits, namely their pronounced coprophagic[10] behaviour. While these three possibilities also exist for Advantame there is no kinetic information available on the rate of Advantame excretion in the pregnant rabbit.

In contrast to the high water solubility of sucralose (283 g/L at 20°C), Advantame has relatively poor water solubility (0.76 g/L at 15°C) and consequently is not particularly osmotically active. A physicochemically-related intense sweetener, Neotame, is more water soluble (12.5 g/L at 20°C) and, like Advantame, around 10% of an ingested amount is absorbed. Neotame did not cause GIT disturbances in rabbits up to the highest tested dose (1000 mg/kg bw/day).

FSANZ maintains that the adverse, treatment-related findings observed in rabbits cannot be discounted without additional data to show that the findings are not toxicologically relevant. Hence the hypothesis proposed by the Applicant is not considered to be supported by the available data on Advantame.

In summary, FSANZ does not agree that the adverse effects observed in rabbits dosed with Advantame can be discounted as:

- there is no adequate scientific justification to do so
- discoloured urine observed in rabbits suggests systemic exposure to a metabolite or metabolites either not present in rats and dogs, or present at much lower levels
- the maternotoxicity observed in rabbits cannot be attributed to a localised irritant effect on the GIT without any histopathological confirmation of irritation.

9.1.3 Clarification on specific technical aspects of the toxicological data

A submitter raised an issue that Advantame and Neotame were chemically similar and metabolised similarly, but that there were differences in their effects e.g. on serum lactate dehydrogenase (LDH). FSANZ discussed these issues with the submitter and they were satisfied with FSANZ's response. The issues raised by the submitter at 1st Assessment are addressed below.

9.1.3.1 FSANZ had identified some problems with the pharmacokinetic studies, but had addressed these independently without seeking clarification from the Applicant.

FSANZ did not consider it necessary to clarify any aspects of the pharmacokinetic studies because the Applicant had clearly identified the limitations to the method of analysis of Advantame in plasma and excreta during the product development process, and as a result developed a 'new' method to address these limitations.

[9] John BA et al (2000) The pharmacokinetics and metabolism of sucralose in the rabbit. Food & Chemical Toxicology **38** (Suppl. 2): S111-S113

[10] Coprophagia is the consumption of faeces.

The 'old' method had the potential to overestimate the concentration of Advantame by a maximum of 5%, with a corresponding underestimation of the concentration of Advantame-acid. The Application therefore included data generated using both the 'old' and the 'new' analytical methods, which are identified in the Risk and Technical Assessment Report (SD1). Collectively, the data provided by the Applicant were considered adequate to characterise the absorption, distribution, metabolism and elimination of Advantame in rats and dogs.

9.1.3.2 The Application relied upon comparisons between Advantame and Neotame, without any comparative data being provided. It was suggested that details on the relative propensity to metabolise Advantame to methanol and phenylalanine would be useful.

A comprehensive toxicological database on Advantame was submitted by the Applicant and independently assessed by FSANZ. The Hazard Assessment (see Section 3 of SD1) was based on this Advantame-specific data and does not rely on data on other intense sweeteners, including Neotame. Some general comparisons were made with Neotame and Aspartame in the discussion (see Section 3.3 of SD1) because Advantame is a derivative of Aspartame, and is chemically and metabolically similar to Neotame. FSANZ did not consider it necessary to obtain any further details on the metabolism of Advantame to methanol and phenylalanine because: (1) these compounds are naturally-occurring food compounds; (2) oral dosing studies in laboratory animals and humans (in which these compounds would have been formed) found no evidence of toxicity; and (3) such details would not inform the risk assessment.

9.1.3.3 The ADI for Neotame is based on impacts on LDH and it seems that there is no evidence that Advantame caused a similar impact, but SD1 includes no LDH results.

Advantame did not increase serum lactate dehydrogenase (LDH) in rats, dogs or humans as previously observed for Neotame in dogs. In all repeat-dose toxicity studies on Advantame in rats, dogs and humans, LDH was analysed as a standard toxicological endpoint consistent with international test guidelines (see Appendix 1 of SD1). Where a toxicological endpoint shows no change relative to the control group or pre-treatment baseline value, it would not normally be specifically reported; that is, results are reported by exception. The general statement 'there was no treatment-related effect on any clinical chemistry parameter' used throughout the Hazard Assessment Report (Section 3 of SD1) is intended to cover the absence of any perturbation of LDH or any other standard clinical chemistry endpoint.

9.1.4 Suitability of the analytical method of detection for more complex matrices like dairy-based products and meal replacements

FSANZ was satisfied that the analytical method supplied by the Applicant was suitable for the food types requested – which included powdered dairy products. At this stage Advantame will be added only to tabletop sweeteners and powdered beverages; therefore, the current analytical method is sufficient for these uses.

The Implementation Sub-Committee[11] (ISC) is currently considering the establishment of an Expert Advisory Group (EAG) to provide expert advice on analytical methodology as required during the standards development process. If Advantame was added to more complex food, this may be an area where advice is sought from the EAG if and when the ISC EAG was established.

[11] http://www.health.gov.au/internet/main/publishing.nsf/content/foodsecretariat-isc.htm

10. Consultation

Public comment is now invited on this 2nd Assessment Report, which includes a draft variation to Standard 1.3.1. Comments received in the second consultation period will be used to assist in preparing the Approval Report, to complete the Application.

10.1 World Trade Organization (WTO)

As members of the 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.

The inclusion of Advantame would have a trade enabling effect as it would permit specific foods containing Advantame to be imported into Australia and New Zealand and sold, where currently they would be prohibited. For this reason, there is no need to notify this Application under the Sanitary or Phytosanitary Measures (SPS) Agreement.

Conclusion

11. Conclusion and Preferred Option

It is concluded that approval for the use of Advantame as a food additive does not pose a significant human health risk for Australian or New Zealand consumers and satisfies the requirements in the FSANZ Act.

Preferred Approach

To prepare draft variations to permit the use of Advantame as a Schedule 2 food additive in Standard 1.3.1 for use according to Good Manufacturing Practice (GMP) in foods specified in Schedule 1.

Reasons for Preferred Approach

The development of an amendment to the Code to give approval to the sale and use of food with added Advantame in Australia and New Zealand is proposed on the basis of the available scientific evidence, for the following reasons:

- the safety assessment did not identify any public health and safety issues
- use of Advantame is technologically justified
- approval for addition of Advantame to food is consistent with Ministerial policy guidance on the *Addition to Food of Substances other than Vitamins and Minerals*[12]
- a regulation impact assessment process has been undertaken that fulfils the requirement in Australia and New Zealand for an assessment of compliance costs. The assessment concluded that the approval of Advantame as an intense sweetener in schedule 2 of Standard 1.3.1 (Option 2B) provides a net benefit
- there are no other measures that would be more cost-effective than a variation to Standard 1.3.1 that could achieve the same end.

[12] http://www.foodstandards.gov.au/foodstandards/changingthecode/ministerialcouncilpolicyguidelines/

12. Implementation and Review

Following the second round of public consultation, an Approval Report will be completed and the draft variation will be considered for approval by the FSANZ Board. The FSANZ Board's decision will then be notified to the Ministerial Council. Following notification, the proposed draft variation to the Code is expected to come into effect on gazettal, subject to any request from the Ministerial Council for a review of FSANZ's decision.

ATTACHMENTS

1. Draft variations to the *Australia New Zealand Food Standards Code*
2. Summary of submissions

Attachment 1

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

Section 94 of the FSANZ Act provides that standards or variations to standards are legislative instruments, but are not subject to disallowance or sunsetting

Commencement: On gazettal

[1] ***Standard 1.2.4*** *is varied by –*

[1.1] *inserting in* Part 1 *of* Schedule 2 –

Advantame	-

[1.2] *inserting in* Part 2 *of* Schedule 2 –

Advantame	-

[2] ***Standard 1.3.1*** *is varied by –*

[2.1] *inserting in* Schedule 2 *in* Alphabetical Listing *and* Numeric Listing –

- Advantame

[3] ***Standard 1.3.4*** *is varied by –*

[3.1] *inserting in the* Schedule –

Specifications for Advantame

1. Purity

Specification Parameter	Specification Value	Analytical Methodology
Assay	Not less than 97.0% and not more than 102.0% on anhydrous basis	High pressure liquid chromatography (HPLC)
Specific rotation $[\alpha]^{20}$ D	Between -45^0 and -38^0	Japanese Pharmacopeia
Advantame-acid	Not more than 1.0%	HPLC
Total other related substances	Not more than 1.5%	HPLC
Water	Not more than 5.0%	Karl Fischer coulometric titration
Residue on ignition	No more than 0.2%	Japanese Pharmacopeia

2. Residual Solvents

Specification Parameter	Specification Value	Analytical Methodology
Methyl Acetate	No more than 500 mg/kg	Gas chromatography
Isopropyl Acetate	No more than 2000 mg/kg	Gas chromatography
Methanol	No more than 500 mg/kg	Gas chromatography
2-Propanol	No more than 500 mg/kg	Gas chromatography

Attachment 2

Summary of submissions

Submitter	Comment
The Australian Food and Grocery Council (AFGC)	Supports on the basis that there is no identified risk to public health and safety, and that the intense sweetener performs a technological function, as intended. Considers that the availability of this sweetener to the food industry will provide significant opportunities for product development, and significant potential benefit to consumers in the greater availability and choice of foods that may help assist in the management of energy consumption, and therefore weight management. Supports Option 2B to approve the use of Advantame as an intense sweetener in Schedule 2 of Standard 1.3.1 on the basis of efficiency in amending the Code to provide the broadest possible permission for use and to avoid having to make further application to extend the range of foods permitted to add Advantame. However, also supports option 2A as a schedule 1 additive if that approach is more appropriate.
The NSW Food Authority	Seeks clarification about some of the toxicological studies referred to in the Risk Assessment report. 1. Pharmacokinetics (SD1: 29 - 31) FSANZ has identified some problems with the studies but appears to have provided alternative explanations rather than seeking clarification from the applicant. 2. Comparison with other intense sweeteners (SD1: 93 - 94) a) The application relies upon comparisons between Advantame to Neotame but comparative data are not provided. For example, some details about relative propensity to metabolise to methanol and phenylalanine would be useful. b) The ADI for Neotame is apparently based on impacts on LDH and it seems that there is no evidence that Advantame caused a similar impact, but SD1 includes no LDH results.
The Victorian Department of Health	No concerns at this time relating to the use of Advantame as a table-top sweetener and added to a range of powdered beverages and protein drinks (conditional on support of the toxicology report by the external peer reviewers). There are no nutritional issues identified as this time. Supports Option 2A: to approve the use of Advantame as an intense sweetener in schedule 1 of Standard 1.3.1 at restricted maximum levels to prevent the potential widespread uptake of this new intense sweetener into a wide range of foods that might occur if it were listed under Schedule 2 (Option 2B).
The New Zealand Food Safety Authority (NZFSA)	Based on the data presented and subject to further exposure assessment, supports, in principle, Option 2B to list Advantame in Schedule 2 of Standard 1.3.1.
Ajinomoto Co., Inc.	The ADI should be established on the basis of the NOAEL values obtained from the long-term rat study, as is customary, given that no species-specific toxicity (systemic) is present. In the case of Advantame, given that the NOAEL in the long-term rat study and in the other toxicity studies in rats and dogs was the highest dietary concentration tested of 50,000 ppm, the data support an ADI of 'not specified'. Advantame should be included in Schedule 2 of Standard 1.3.1 which would enable it to be used in a wide range of foods in accordance with GMP. The appropriate wording for the Schedule 2 entry would be: 'Advantame (technological use consistent with clause 4)' which is consistent with the use of other similar high intensity sweeteners. In order to be consistent with the specifications proposed in the USFDA petition, Ajinomoto, Inc. would like the specification value for water content to be changed from '2.5 to 5.0%' to 'not more than 5%'.
Queensland Health	Supports the preferred approach – To proceed to develop a food regulatory measure, to amend Standard 1.3.1 – Food Additives, to permit the use of Advantame in specified foods at specified levels or, alternatively, consider the use of Advantame as an additive according to GMP in Schedule 2 of Standard 1.3.1. The analytical procedure described in the 1st Assessment report may be appropriate for some food matrices such as soft drinks and tabletop sweeteners, but might not be adequate for more complex matrices like dairy-based products and meal replacements. These might require an extraction and purification step.

Submitter	Comment
	If FSANZ decides to proceed to the second stage of the assessment, Queensland would appreciate the provision of full analytical method details so that Queensland Health Forensic and Scientific Services can comment on it.
International Sweeteners Association	Supports approval.
The Calorie Control Council	Supports the use of Advantame as an additive according to GMP in Schedule 2 of Standard 1.3.1, Option 2B. Use in accordance with GMP is a good option for intense sweeteners as their use is self limiting, that is off tastes may develop if too much intense sweetener is used in a food or beverage product. In addition, for cost reasons food manufacturers would not use more of an intense sweetener than necessary and they are more and more frequently using sweetener blends which decreases the overall amount of sweetener needed as most sweeteners are synergistic when combined.
Leo Adler (NZ)	Does not support the Application. Artificial sweeteners are commonly associated with consumer health risk factors and the alternative of pure natural sugar or stevia are already very suitable for all food and drink products. I would prefer all artificial sweeteners to be removed from all products and Advantame is no exception.
Food Technology Association of Australia	Agrees with Option 2A – to approve the use of Advantame as an Intense Sweetener in Schedule 1 of Standard 1.3.1. No reason provided as to why it specifically preferred a Schedule 1 permission over a more broader Schedule 2.
New Zealand Food & Grocery Council (FGC)	Supportive of the Application and the Code should be amended to enable its use. This is primarily because the safety assessment did not identify any public health or safety concerns with use of Advantame. Furthermore, enabling the use of Advantame is an opportunity for members to perhaps extend or improve their product range, thus fostering innovation.