

6 July 2011
[13-11]

APPLICATION A1034 ADVANTAME AS A HIGH INTENSITY SWEETENER APPROVAL REPORT

Executive Summary

Purpose

An Application was received from Ajinomoto Co Inc. to amend Standard 1.3.1 – Food Additives in 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 two rounds of public consultation have been conducted.

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

FSANZ has independently evaluated the submitted toxicity studies on Advantame including studies on kinetics, metabolism, acute toxicity, repeat-dose toxicity, genotoxicity, immunotoxicity, reproductive toxicity and developmental toxicity. Four human studies were also evaluated.

The acute toxicity in rats was assessed as very low. There was no evidence that Advantame was genotoxic or carcinogenic. In human studies, doses up to 0.5 mg/kg bw were well tolerated by volunteers with and without type-2 diabetes following a single dose or repeated dosing for up to 12 weeks. An Acceptable Daily Intake (ADI) has been set at 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. The NOAEL was based on maternotoxicity at the next higher dose of 1000 mg/kg bw/day.

Comparisons of the modelled dietary exposure to Advantame with the ADI of 5 mg/kg bw indicated that for all groups of Australian and New Zealand consumers assessed (including children), estimated dietary exposures were well below this safe level of exposure. On this basis, there are no public health and safety issues associated with the proposed addition of Advantame to food. The key risk assessment findings are detailed in **Supporting Document 1**.

FSANZ concludes that approval of Advantame as an intense sweetener does not raise any public health and safety issues for Australian or New Zealand consumers. Furthermore, Advantame is technologically justified as it provides the function of an intense sweetener¹ in foods.

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 has considered that it is appropriate that Advantame is included in Schedule 2 of Standard 1.3.1 for the following reasons:

- There is no specific risk that needs to be managed by setting a maximum permitted level in foods.
- It allows a wider variety of foods to use Advantame to formulate food preparations that 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.
- Even when used at the levels proposed by the Applicant, the dietary exposure for the highest consumer is well below the ADI.

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.

Assessing the Application

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.

Decision

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

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

Reasons for Decision

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. Consultation on the 2nd Assessment Report was conducted over a period of four weeks with eight submissions received.

Summaries of these are in **Attachment 2** of this Report. FSANZ has taken all submitters' comments into consideration in completing the Approval Report.

² <http://www.foodstandards.gov.au/foodstandards/changingthecode/ministerialcouncilpolicyguidelines/>

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SUPPORTING DOCUMENTS

The following documents, which were used in the preparation of this Approval Report, is available on the FSANZ website at

<http://www.foodstandards.gov.au/foodstandards/applications/applicationa1034adva4493.cfm>

SD1: Risk Assessment Report (Approval)

SD2: Overview of the food irradiation process and a glossary of technical terms (Approval)

SD3: Summary of literature on consumers and food irradiation (Assessment)

SD4: Proposed amendments to Standard 1.5.3 (marked up) (Approval)

Introduction

An Application was received from Ajinomoto Company Incorporated on 18 August 2009 to amend Standard 1.3.1 – Food Additives in 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 substantial data base of toxicological data that needed to be assessed.

The Applicant supplied an extensive toxicological data set that required a detailed review. There were over 50 detailed studies, many unpublished, to assess. No other country in the world has yet completed a toxicological assessment and established an acceptable daily intake (ADI) for Advantame.

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 initially 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 levels of Advantame likely to be used as a sugar replacement in a range of common food products.

1. The Issue

The Applicant is requesting permission to add Advantame to a range of foods. 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. 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 has been 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 pose an unacceptable risk for public health and safety for any consumer group?

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, it 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 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.

FSANZ sought an external peer review of the toxicology report in parallel with the public consultation for the 1st Assessment Report. The reviewer concurred with the conclusions drawn by FSANZ in the Hazard Assessment Report and commented that FSANZ's evaluation was scientifically defensible. A few suggestions were made to improve the clarity of the report, which were adopted in the final version of the Risk and Technical Assessment Report.

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 Addressing the objectives

The legislative objectives that FSANZ is required to meet when developing or varying a food standard are noted in section 3. FSANZ considers the primary objectives of most relevance to this Application is protecting public health and safety and the provision of adequate information relating to food to enable consumers to make informed choices. The other objective of prevention of misleading and deceptive conduct has less direct relevance but was also taken into consideration. These are addressed in sections 6.2 to 6.4.

6.2 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. Initially, 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.

6.3 Labelling of Advantame-containing products

Labelling addresses the objective set out in section 18(1)(b) of the FSANZ Act; the provision of adequate information relating to food to enable consumers to make informed choices. 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 food products containing Advantame, or formed in the digestive tract prior to absorption (similar to aspartame³), 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, FSANZ has concluded that this 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.

³<http://www.foodstandards.gov.au/scienceandeducation/factsheets/factsheets2009/aspartamejuly2009.cfm>

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 international additive number 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 Code⁵, 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 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.

Other claims in accordance with the conditions specified in *The Code of Practice on Nutrient Claims in Food Labels and in Advertisements* (CoPoNC)⁶ 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 also 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 further consideration by Ministers. For further information about Proposal P293, refer to <http://www.foodstandards.gov.au/foodstandards/proposals/proposalp293nutritionhealthandrelatedclaims/index.cfm>.

6.3.4 *Labelling for food intolerances*

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

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

⁶ CoPoNC is a voluntary code of practice for food suppliers in Australia and is used by some manufacturers in New Zealand.

- 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 indicate any additional labelling requirements in order 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 or information requirements are proposed for Advantame.

6.4 Prevention of misleading and deceptive conduct

FSANZ has considered this objective and concludes there are no misleading or deceptive conduct aspects to this assessment.

6.5 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'.

In regard to Policy principle sec.18 (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 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. 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*.

CoPoNC specifies certain conditions for claims, such as 'low sugar', which may be applicable for foods containing Advantame.

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 and fair trade legislation 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 technological function of a food sweetener (SD1).
- The proposed addition of Advantame to food is safe for human consumption (SD1).
- The proposed amounts of Advantame added are consistent with achieving the technological function and Advantame would be added in a quantity and a form which is consistent with delivering the stated purpose of sweetening the food (SD1).
- 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.

6.6 Specifications for Advantame

Standard 1.3.4 includes 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 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 included in the draft variations arising from this Application (**Attachment 1**).

6.7 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 table top sweeteners and powdered beverages. A calibration curve based on standard Advantame or Advantame-acid solutions is used.

6.8 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 be regulated in Standard 1.3.1 in either Schedule 1 with specific maximum limits or be generally permitted in Schedule 2 under GMP.

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 the food additive in foods.

FSANZ has calculated that a 60 kg person would have to consume 300 mg Advantame/day to exceed the ADI of 5 mg/kg bw/day. As Advantame is 20,000 times sweeter than sucrose, 300 mg Advantame is equivalent to a consumption 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 a wider variety of foods to use Advantame to formulate food preparations that 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.
- Even when used at the levels proposed by the Applicant, the dietary exposure for the highest consumer is well below the ADI.

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 were identified for this Application:

Option 1: Reject the draft variations, 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 potential role of Advantame in managing energy intake
- 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 the draft variations*

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 Council⁷ (CCC) indicated that it has been conducting nationally projectable consumer research in the United States for over 20 years. 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. FSANZ requested a copy of this survey from the CCC in order that it can be evaluated. However, the CCC has not responded to FSANZ's requests; therefore, FSANZ cannot provide an independent opinion on conclusions from that report.

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 potentially assist in weight management.

Since there are no public health and safety risks from consumption of Advantame-containing products, there would not appear to be any benefits to consumers from rejection of the draft variations.

⁷ The Calorie Control Council is an international association representing companies that make and use intense sweeteners.

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 potential advantages that the use of Advantame may give.

8.2.1.3 Government

There would be no impact on jurisdictional authorities if the current situation remained. At an international level, lack of approval may be regarded as 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. It is noted that this is a voluntary permission and industry can elect to use Advantame if it provides an overall benefit to the company.

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 and industry are expected to be the same as for option 2A. However, the costs may be less for jurisdictions if they do not need to analyse Advantame due to permissions being granted at GMP levels. Additionally, this option provides a greater innovation potential for industry. It may also lead to increased efficiency for FSANZ and other regulators as there would not need to be a case-by-case assessment of each new food type. 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 when approved overseas.

Consumers would be provided with an increased choice of products with the potential to aid weight management programs. 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 associated 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. A second round of consultation was conducted over a period of 4 weeks. Eight submissions were received.

Summaries of these are in **Attachment 2** of this report. FSANZ has taken all submitters' comments into consideration in completing the Approval Report. The key issues raised in both submission periods are addressed below.

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

Approval of Advantame as either a Schedule 1 or 2 food additive has also been addressed in Section 6.8 Risk Management Strategy. It was suggested by some submitters that FSANZ should take a Schedule 1 approach and incorporate in the Code restricted maximum limits in table top sugar substitutes (powdered only), a range of powdered beverages including fruit flavoured drinks, milks and flavoured milk drinks, instant tea and coffee, and protein drinks. This was suggested as more appropriate than a Schedule 2 GMP approach on the basis of the following:

- The technological function in foods other than those originally proposed by the Applicant has not been demonstrated.
- A dietary exposure assessment has not been undertaken on permissions in other foods.
- A robust method of detection is not available for all food matrices.

FSANZ has assessed that the proposed use of Advantame as an intense sweetener is technologically justified in the foods that were proposed for permission by the Applicant. It is likely that if Advantame performs the function of sweetening these foods, that it would also do so in other food matrices. Furthermore, manufacturers are not likely to use Advantame in foods where it does not perform that function.

FSANZ reiterates its conclusion that GMP permissions for Advantame in Schedule 2 are 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 a wider variety of foods to use Advantame.
- Due to the intense sweetness of Advantame and minimal amounts needed to sweeten foods, the use of Advantame is self-limiting.

Dietary exposure calculations have not been undertaken on permissions in other foods, as the dietary exposure assessment that has been conducted made very conservative assumptions about the foods that were likely to contain Advantame. In particular, dietary exposure assessment was modelled on the very conservative assumption that all of the foods that the Applicant proposed would contain Advantame at the maximum proposed level.

Despite these very broad assumptions, the assessment indicated that estimated exposures to Advantame would be very low (less than 3% of the ADI for all population groups assessed, at the 90th percentile). Additionally, a simple calculation indicates that a 60 kg person would have to consume more than 300 mg Advantame/day to exceed the ADI of 5 mg/kg bw/day. As Advantame is 20,000 times sweeter than sucrose, then 300 mg Advantame is equivalent to a consumption of approximately 6 kg sugar. Similarly, a 19 kg child would have to consume the equivalent of about 1.9 kg sugar on a daily basis to exceed the ADI.

The third issue raised was in relation to a need to have robust method of detection available for a broader range of food matrices if approved as a Schedule 2 additive. 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 table top sweeteners and powdered beverages; therefore, the current analytical method is sufficient for these uses.

FSANZ understands that it is usual that manufacturers in their quality control schemes ensure that a method of analysis is available for newly developed foods. This allows them to analyse the precise level needed to sweeten the proposed foods. It also serves to restrict costs to the manufacturers by only using the amounts needed in the foods.

While the requirement for analytical methods for applications has been longstanding, FSANZ has agreed at a recent meeting of the Implementation Sub-Committee⁸ (ISC), to be more stringent on this requirement, ensuring that the methods of analysis section is adequately addressed in all new applications.

For applications that do not adequately address this requirement, FSANZ will either request additional information from the applicant to ensure this is addressed within the administrative assessment period of 15 working days, or reject the application. This decision will be made on a case-by-case basis and remains at the discretion of FSANZ.

⁸ <http://www.health.gov.au/internet/main/publishing.nsf/content/foodsecretariat-isc.htm>

However, it should be noted that the provision of an analytical method may not be required in all circumstances. For example, if a processing aid such as an enzyme is used in the production of a food but is not present or is denatured in the final product, or where processing aids and food additives are requested to be permitted according to GMP as is the case with Advantame, the provision of an analytical method is not necessary. In these cases, a short explanation or statement from the applicant regarding this is sufficient.

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. It is envisaged that the EAG would work alongside the standards development process to provide expert advice on analytical methodology as required. This advice could then be incorporated into the assessment reports so it is clear to jurisdictions what methods are fit-for-purpose and are available for enforcement purposes. If needed, this may be an area where advice is sought from the EAG by FSANZ, when the ISC EAG is established.

9.1.2 Risk to public health and safety from addition of Advantame to foods

Submitters raised a number of issues in relation to the safety of Advantame. These have been addressed below.

9.1.2.1 Establishing an acceptable daily intake (ADI) of 5 mg/kg bw/day

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 observed 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). In 2000, the European Commission's Scientific Committee on Food (SCF)⁹ 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.

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.

⁹ 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

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 (2000) have suggested a third possibility for prolonged GIT exposure to sucralose in rabbits, namely their pronounced coprophagic¹⁰ 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.

GE Free New Zealand also suggested that the submission from the New Zealand Food Safety Authority (NZFSA) was ignored by FSANZ. However, the submission received from the NZFSA noted that the approach taken by FSANZ in using the adverse findings in rabbits as the basis of the ADI was conservative. The Applicant was given the opportunity to provide additional data to show that the rabbit findings were not relevant to humans, such as evidence that the metabolism in rabbits is different to humans. However, no such data has been provided to FSANZ. As discussed in the 2nd Assessment Report prepared in relation to this Application, 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 to humans. The adverse effects observed in rabbits are currently the most appropriate basis to establish an ADI for Advantame.

9.1.2.2 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.

Issue 1

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

¹⁰ Coprophagia is the consumption of faeces.

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.

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.

Issue 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.

Issue 3

The ADI for Neotame is based on impacts on LDH (lactate dehydrogenase) 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.

9.1.2.3 Implications for public health and safety associated with the proposed addition of Advantame to food.

One submitter claimed that there are serious implications for public health and safety issues associated with the proposed addition of Advantame to food. The submitter raised a number of issues which have been addressed below.

Issue 4

FSANZ has relied on unpublished industry data

Concern was expressed that FSANZ's assessment of Advantame is based on unpublished industry data. However, the studies assessed for this Application were conducted according to Good Laboratory Practice (GLP) and international guidelines for toxicological testing. The studies were also peer reviewed by an independent expert in toxicology who concurred with FSANZ's interpretation of the data and conclusions on the safety of Advantame.

Issue 5

There are no data on the new metabolite Advantame-acid

Standard toxicity studies cover the effects due to all metabolites formed following ingestion of a particular compound.

There is an extensive toxicological database for Advantame, which is directly applicable to Advantame-acid and any other metabolites formed following ingestion. While the starting material added to the diet and then fed to laboratory animals or humans was Advantame, it is not the form which animals or humans are systemically exposed to. In all species examined, Advantame is converted to Advantame-acid in the digestive tract prior to absorption, with virtually no systemic exposure to the parent compound. The majority of systemic exposure is to Advantame-acid and other related metabolites.

Issue 6

Animals that died or were sacrificed in a moribund condition were not reported in any studies

The purpose of a Hazard Assessment is not to reproduce original study reports but to evaluate the data in these reports and describe results by exception.

Stating that there were no treatment-related mortalities or clinical signs or effects on haematology parameters etc. indicates that the endpoints were not biologically different from the concurrent control group.

Mortalities and clinical signs are standard toxicological endpoints reported in all studies. In nearly all studies conducted on Advantame, the number of deaths occurring in groups of laboratory animals treated with Advantame occurred at no greater frequency than the concurrent control group. The only study where treatment-related clinical signs and sacrifices occurred was in the rabbit developmental study. The results of the study have formed the basis of the ADI.

Issue 7

Lack of data on the sulphate conjugate of Advantame

The lack of data to corroborate the presence of a sulphate conjugate of Advantame-acid in dogs is of no toxicological relevance. As mentioned above, the toxicity studies cover the adverse effects occurring following exposure to all metabolites formed following ingestion.

Issue 8

Loose, green or pale stools could be indicative of irritable bowel, abnormal liver function or over-production of bile

There is no evidence including any histopathology of the digestive tract or liver/gall bladder, to support this hypothesis or any suggestion of liver dysfunction including any perturbations of clinical chemistry parameters. As discussed in the Risk and Technical Assessment Report (Supporting Document 1), the occurrence of pale faeces in laboratory animals was attributable to the high concentration of unabsorbed Advantame/Advantame-acid in the digestive tract, both of which are white substances. The green or purple faeces that were observed in rats are most likely attributable to coloured metabolites. The occurrences of discoloured faeces without evidence of systemic toxicity indicate that the findings are not adverse.

Issue 9

Statistically significant differences in the occurrence of benign mammary tumours, lower uterine weight and ovary weights in female rats, and increased pancreatic islet cell carcinoma, renal and bladder cell changes in males need to be studied further.

Whether differences between a treated and control group are statistically significant (or not) does not determine whether a finding is treatment-related. There are a range of factors taken into consideration in evaluating whether an observed difference is treatment-related (and potentially adverse) or reflects normal biological variability. In the case of the selected differences cited by the submitter and which were reported in the FSANZ evaluation of the 2-year rat study, all were within the normal range of biological variability for the particular rat strain, showed no dose-response relationship and/or were not corroborated by other toxicological endpoints.

Issue 10

Adverse effects in humans have been disregarded by FSANZ. Longer term studies with larger trial numbers should be conducted before Advantame is approved.

FSANZ has evaluated all the adverse events reported in the 4 human studies and concluded that none are attributable to Advantame. The rationale for this conclusion is provided in the respective evaluation reports for each of the studies, which can be found in Section 3.2.10 of Supporting Document 1. FSANZ considers that the toxicological database for Advantame is extensive and includes studies conducted with adequate numbers of subjects and of sufficient duration.

A number of other issues were raised in relation to the human studies.

- It was stated that there were no records of how many people undertook the first study (by Warrington 2004) and 3 subjects experienced 5 adverse effects. It was claimed that the 'adverse effects point to hypersensitivity reactions affecting blood pressure, namely respiratory distress and headache and dizziness'. The number of subjects participating in each of the 4 human studies was provided in each of the respective evaluation reports in Section 3.2.10 of Supporting Document 1. In the study of Warrington (2004), Advantame was administered to 'groups of eight fasted male volunteers at 0.1, 0.25 or 0.5 mg/kg bw'. There was no effect on blood pressure and no evidence of respiratory distress, which argues against 'hypersensitivity reactions'. In this study, adverse events were self-reported by 3 of the 24 subjects; 1 at the mid-dose (headache) and 2 subjects at the top dose (dizziness/light headedness or headache followed by either an upper respiratory tract infection or pharyngitis several days later). None of these findings were considered treatment-related predominantly because dizziness/light headedness or a headache were not reported in any of the other 3 human studies conducted on larger groups of subjects over longer periods of time (up to 12 weeks).

- It was stated that in the second oral dosing study (Warrington 2005), 8 adverse events were recorded in 5 subjects treated with Advantame, which were dismissed by FSANZ. In this study, 6 subjects were dosed with Advantame (0.25 mg/kg bw) once. No control group was included because, similar to Warrington et al (2004), the study was designed to examine the metabolism of Advantame. Five of the 6 subjects experienced mild adverse events; 4 reported dental injury (broken teeth, lost dental filling) attributed to the consumption of hard, crusty bread rolls and the fifth experienced back pain. One of the subjects with dental injury also had insect bites (classified as mild), pain at the cannula site (where blood was withdrawn for testing) and rectal haemorrhage (classified as moderate), with the latter commencing six days after dosing, when no Advantame is detectable, and therefore not associated with treatment. None of these findings are attributable to Advantame because their cause has already been established.
- It was stated that the metabolites, HF-1 and HU-1, could cause parathyroid effects (due to high vitamin D conversion) or inhibit the uptake of vitamins and minerals. As no treatment-related effects were determined in a large number of studies conducted in laboratory animals and humans, including studies conducted over long durations at the maximum practical dietary concentration, such a statement is not substantiated by the data.
- It was stated that in the 12-week study (by Pirage 2006), which was conducted in type II diabetics, there were no records of whether the control or test subjects consumed other artificial sweeteners. It was implied that such exposure could confound the study results particularly as some Advantame-treated subjects experienced adverse events. FSANZ considers that there are no grounds to support this suggestion on the basis of the following:
 - The number of control subjects reporting adverse events actually outweighed the number for Advantame-treated subjects (9 *versus* 5). Such a finding illustrates the variability in background events occurring within a study group.
 - From a biological perspective, no rationale was provided to illustrate how background exposure to non-caloric sweeteners already permitted in food could interfere with any effects of Advantame. Indeed, a comprehensive physiological and biochemical assessment of all subjects prior to and during the study indicated that apart from their diabetes, all subjects were of sound health.

Issue 11

Methanol produced from the metabolism of Advantame is of concern because it is metabolised to produce formaldehyde and formic acid, which are highly toxic.

Humans are already exposed to methanol in the diet by virtue of its natural occurrence in a wide range of foods (including fruits and vegetables) and as a by-product of protein synthesis. The amount of methanol released during GIT hydrolysis of Advantame would be of a lesser magnitude than exposure via these other sources. The toxicological consequence of such dietary exposure to methanol has been assessed by various food regulatory authorities.

For example, the UK's Committee on Toxicity (COT) has recently concluded that exposure to methanol in food, including that resulting from the consumption of aspartame, is unlikely to be harmful to human health¹¹.

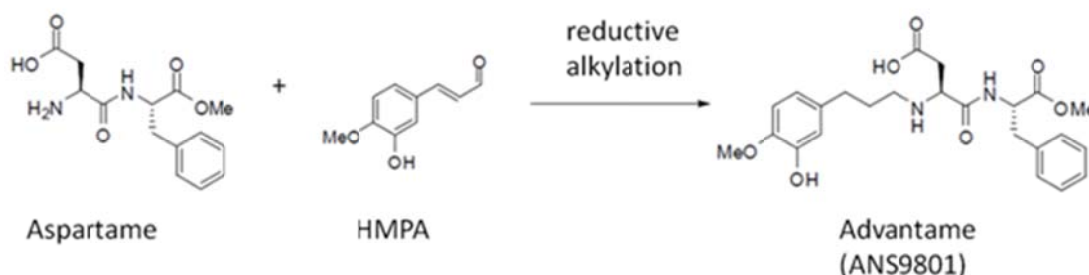
¹¹ <http://cot.food.gov.uk/pdfs/cotstatementmethanol201102.pdf>

9.1.3 FSANZ and its obligations under the FSANZ Act

A submitter suggested that FSANZ had breached its obligations under the FSANZ Act by misleading consumers in two key areas:

- not informing consumers that aspartame is made from genetically engineered bacteria
- the serious public health and safety issues that is evident in the data on Advantame.

FSANZ does not have any data or information from the Application that shows that there is any use of genetic engineering in the production of aspartame or Advantame. Advantame is synthesised from aspartame and a chemical named 3-(3-hydroxy-4-methoxyphenyl)-propionaldehyde (HMPA) in a one step process summarised below:



For further information on this process, refer to Supporting Document 1 Risk and Technical Assessment report¹².

Under the current requirements of Standard 1.5.2 – Food produced using Gene Technology, there is a mandatory requirement that food products must be labelled as ‘genetically modified’ where novel DNA and novel protein is present in the final food. The Applicant provided a statement to the effect that Advantame ‘does not fall under the definitions of products consisting of products consisting of, nor containing genetically modified organisms (GM) and genetically modified microorganisms’. Since there are no genetically modified organisms or novel protein in Advantame-containing food products, there is no requirement for labelling under Standard 1.5.2.

In Australia and New Zealand, aspartame is permitted for use as an intense sweetener in a range of foods to specified levels. The safety of aspartame has been the subject of comprehensive reviews by FSANZ, the FAO/WHO Joint Expert Committee on Food Additives (JECFA), the European Food Safety Authority (EFSA) and the US Food and Drug Administration (USFDA). Scientific evidence to date supports the safety of aspartame for use as a sweetener in food.

In regard to the suggestion that there are serious public health and safety issues that are evident in the data on Advantame, FSANZ concludes that Advantame does not raise any public health and safety issues for any age group at expected levels of dietary exposure (see Section 9.1.2).

9.1.4 Advantame and trademark

One of the submitters raised an issue around the status of Advantame as a trademark. Advantame is listed as a trademarked name for the chemical preparation. However, the submitter has claimed that information on their website states that it is a generic name for the sweetener, not a registered brand name.

¹²<http://www.foodstandards.gov.au/srcfiles/A1034%20Advantame%20AR%20SD1%20Risk%20Assess%20AM ENDED.pdf>

FSANZ liaised with the Applicant who indicated that they assigned Advantame to their new sweetener as a generic name, and do not intend to use this name as a trademarked name. However, they submitted an application for a trademark because Advantame is quite a new name and there was a possibility that a third party would register Advantame as a trademarked name and this would cause issues with using Advantame as a generic name. Their application and registration aims to allow the Applicant or a customer to use this name as a generic name without any problems. The Applicant indicated that they would not claim infringement of trademark, if Advantame is used as generic name for their new sweetener by third parties.

9.1.5 FSANZ and the peer-review process

One submitter suggested that FSANZ considers reviewing its approach to toxicological assessments, in particular, the external peer review process. They suggest a panel review process similar to the European Food Safety Authority (EFSA).

FSANZ thanks the submitter for their suggestion but notes that a system is already in place for expert peer review when needed that works well on a case-by-case basis.

FSANZ has given consideration to the development of a scientific committee before; however, given the size of the Australian and New Zealand community, and the number of qualified people in regulatory toxicology and risk assessment, the cost of that approach would need to be weighed up against any specific benefits. Where a particularly complex or critical issue is involved FSANZ will set up a panel to address specific issues but to do so routinely would have significant time and resource costs for FSANZ.

With Advantame the issues were not particularly difficult and the peer review sought was adequate, sufficient and appropriate for the assessment of this Application.

10. Consultation

Comments received in the second consultation period were 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 was no need to notify this Application under the Sanitary or Phytosanitary Measures (SPS) Agreement.

Conclusion

11. Conclusion and Decision

It is concluded that approval for the use of Advantame as a food additive does not raise any public health and safety issues for Australian or New Zealand consumers and satisfies the requirements in the FSANZ Act.

FSANZ has considered the primary objective of protection of public health and safety and has concluded that safety assessment did not identify any public health concerns.

FSANZ considers that current labelling requirements meet the objective of providing adequate information to enable informed choice, and that prevention of misleading and deceptive conduct is not directly relevant to this application.

Decision

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

Reasons for Decision

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 Council policy guidance on the *Addition to Food of Substances other than Vitamins and Minerals*¹³.
- 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. Implementation and Review

The FSANZ Board's decision will 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.

REFERENCES

Fulcher SM, Renaut SD & Bottomly AM (2003) ANS9801: Study of effect on embryo-fetal toxicity in the rabbit by gavage administration. Report No. AJO 190/022479. Lab: Huntingdon Life Sciences Ltd, Huntingdon, Cambridgeshire, England. Sponsor: Ajinomoto Co Inc, Tokyo, Japan. *Unpublished*.

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

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

Pirage V (2006) Safety and tolerability assessment of multiple daily doses of ANS9801: Part 2 – A 12-week safety study of ANS9801 administered to subjects with type 2 diabetes. Study No. ANSE-103b. Lab: Stradins Clinical University Hospital, Riga, Latvia. Sponsor: Ajinomoto Co Inc, Tokyo, Japan. *Unpublished*.

¹³ <http://www.foodstandards.gov.au/foodstandards/changingthecode/ministerialcouncilpolicyguidelines/>

Warrington S (2004) An open, dose escalating study to determine the safety, tolerability and pharmacokinetic profile of ANS9801 in health male volunteers. Study No. ANSE-101. Lab: Hammersmith Medicines Research Ltd, Central Middlesex Hospital, London, UK. Sponsor: Ajinomoto Co Inc, Tokyo, Japan. *Unpublished*.

Warrington S (2005) An open label study to investigate the adsorption, pharmacokinetics, metabolism and excretion of a single oral dose of ^{14}C -ANS9801 in healthy male volunteers. Study No. ANSE-102. Lab: Hammersmith Medicines Research Ltd, Central Middlesex Hospital, London, UK. Sponsor: Ajinomoto Co Inc, Tokyo, Japan. *Unpublished*.

ATTACHMENTS

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

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



Food Standards (Food Standards (Application A1034 – Advantame as a High Intensity Sweetener) Variation)

The Board of Food Standards Australia New Zealand gives notice of the making of this variation under section 92 of the *Food Standards Australia New Zealand Act 1991*. The Standard commences on the date specified in clause 3 of this variation.

Dated DATE OF GAZETTAL

Standards Management Officer
Delegate of the Board of Food Standards Australia New Zealand

1 Name

This instrument is the *Food Standards (Application A1034 – Advantame as a High Intensity Sweetener) Variation*.

2 Variation to Standards in the *Australia New Zealand Food Standards Code*

The Schedule varies the Standards in the *Australia New Zealand Food Standards Code*.

3 Commencement

These variations commence on **DATE OF GAZETTAL**.

SCHEDULE

[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 |

Submissions Summary

1st Assessment

| Submitter | Comment |
|--|--|
| The Australian Food and Grocery Council (AFGC) | <p>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.</p> <p>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.</p> <p>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.</p> |
| The NSW Food Authority | <p>Seeks clarification about some of the toxicological studies referred to in the Risk Assessment report:</p> <p>Pharmacokinetics (SD1: pages 29 - 31)</p> <ul style="list-style-type: none"> • FSANZ has identified some problems with the studies but appears to have provided alternative explanations rather than seeking clarification from the applicant. <p>Comparison with other intense sweeteners (SD1: pages 93 - 94)</p> <ul style="list-style-type: none"> • 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. • 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 | <p>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 at this time.</p> <p>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).</p> |
| The New Zealand Food Safety Authority (NZFSA) | <p>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. Questioned whether the rabbit is an appropriate model for humans and that a higher ADI may have been justifiable if the rabbit is found not to be a good surrogate for humans.</p> |
| Ajinomoto Co., Inc. | <p>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'.</p> <p>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.</p> |

| Submitter | Comment |
|--|--|
| | 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 | <p>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.</p> <p>The analytical procedure described in the 1st Assessment report may be appropriate for some food matrices such as soft drinks and table top 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.</p> <p>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.</p> |
| International Sweeteners Association | Supports approval. |
| The Calorie Control Council | <p>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.</p> <p>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.</p> |
| 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. 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. |

2nd Assessment

| Submitter | Comment |
|--|---|
| GE Free NZ | <p>Opposes the approval on the following grounds:</p> <ul style="list-style-type: none"> • FSANZ has breached its obligations under the FSANZ Act • not informing consumers that aspartame is made from genetically engineered bacteria • data do not support the safety of Advantame • FSANZ ignored the submission by the NZFSA |
| Ministry of Agriculture and Forestry New Zealand ¹⁴ | Supports the use of Advantame as an additive according to GMP in Schedule 2 of Standard 1.3.1, Option 2B. |
| Queensland Health | Supports Option 2A at restricted maximum limits to prevent widespread uptake of this new sweetener if it was approved according to GMP in Schedule 2 of Standard 1.3.1, Option 2B. Have concerns over approval in additional foods with no methods of analysis available for determining the levels of Advantame in these foods. |
| Dietitians Association of Australia | Supports the approval of Advantame |
| 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. |

¹⁴ Previously the New Zealand Food Safety Authority

| Submitter | Comment |
|--|---|
| South Australia Health | <p>Supports Option 2A as they are concerned over Option 2B that there is no evidence to support the suitability of Advantame in other food matrices and no methods of analysis available for determining the levels of Advantame in these foods.</p> <p>Required clarification of the status of Advantame as a trademark.</p> |
| Department of Health Victoria | <p>Supports Option 2A at restricted maximum limits 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. Believe that seeking a Schedule 2 permission (Option 2B) is not supported on three main grounds:</p> <ul style="list-style-type: none"> • The technological function in foods other than those originally proposed by the Applicant has not been demonstrated. • A dietary exposure assessment has not been undertaken on permissions in other foods. • A robust method of detection is not available for all food matrices. <p>Suggests that FSANZ considers reviewing its approach to toxicological assessments, in particular, the external peer review process. They suggest a panel review process similar to the European Food Safety Authority (EFSA).</p> |
| New Zealand Food & Grocery Council (FGC) | <p>Supports the Application and the preferred approach to permit the use of Advantame as a Schedule 2 food additive.</p> |