Application for the use of steviol glycosides as a food additive in foods for special medical purposes.

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List of Appendices:

3.1.1 GENERAL REQUIREMENTS

1 Applicant details

(addressing section 3.1.1.B of the FSANZ Application Handbook)

[redacted]	[redacted]

2 Purpose of the application

(addressing section 3.1.1.C of the FSANZ Application Handbook)

This application requests amendment to the Australia New Zealand Food Standards Code (**the Food Standards Code**) to permit the use of steviol glycosides (otherwise known as stevia) as a permitted food additive for use in foods for special medical purposes (**FSMPs**) up to a maximum level of 330 mg/kg to align with international permissions and previous safety assessments of stevia conducted by FSANZ.

Stevia is a sweetener that is already permitted for use in several food product categories in accordance with Standard 1.3.1 and Schedule 15 of the Food Standards Code. Food Standards Australia New Zealand (**FSANZ**) has considered and approved applications extending the use of stevia in food, including the following applications:

Application	Year of FSANZ approval	Purpose
Application A540	2008	To permit stevia as an intense sweetener in several product categories.
Application A1037	2011	To increase the maximum permitted levels of stevia in ice cream, water based beverages, brewed soft drinks, formulated beverages, and soy beverages
Application A1108	2015	To add rebaudioside M to the approved list of steviol glycosides.
Application A1132	2017	To extend the permission for use of stevia to include all steviol glycosides present in the *Stevia rebaudiana* Bertoni leaf
Application A1149	2019	To extend the permission for stevia to fruit drinks
Application A1157	2018	To permit steviol glycoside rebaudioside M produced from enzymatic conversion
Application A1172	2019	To permit steviol glycoside rebaudioside D produced from enzymatic conversion
Application A1176	2019	To permit an enzymatic conversion method to produce stevia preparations

Application	Year of FSANZ approval	Purpose
Application A1183	2020	To permit steviol glycoside rebaudioside E produced from enzymatic conversion
Application A1207	2021	To permit rebaudioside M produced from fermentation by a genetically modified *Saccharomyces cerevisiae* strain
Application A1222	2021	To permit the use of a new stevia mixture produced by genetically modified *Y. lipolytica* VRM0014

Throughout this application, unless identified otherwise, a reference to a specific level of stevia is a reference to the amount of steviol equivalents calculated in accordance with Section 1.3.1-4(7) of Standard 1.3.1. This facilitates simple comparison with international stevia limits, which are also expressed in steviol equivalents.

Policy guidelines from the Food Ministers' Meeting are relevant to the assessment by FSANZ of this application, namely:

- Policy Guideline on the addition of substances other than vitamins and minerals; and
- Policy Guideline on the intent of Part 2.9 of the Food Standards Code – Special Purpose Foods.

FSANZ must have regard to these policy guidelines when assessing whether to amend the Code. The FSANZ Application Handbook sets out application requirements that are consistent with addressing the policy guidelines, including, for example, the provision of information that addresses public health and safety, ensuring the purpose for adding the substance is articulated clearly, and that the levels of addition of the substance are consistent with the purpose and do not create significant negative public health impacts. This application has been prepared in accordance with all Application Handbook requirements, including those requirements relating to policy guidelines.

3 Justification for the application

(addressing section 3.1.1.D of the FSANZ Application Handbook)

Regulatory justification

Stevia meets the Standard 1.1.2 definition of a substance that is used as a food additive as it is:

- Identified in Schedule 15 as a substance that may be used as a food additive; and
- Is added to food to perform a technological purpose listed in Schedule 14 (as a sweetener).

FSMPs are permitted to contain food additives listed at item 13.5 of the table to Section 15-5 of Schedule 15 of the Food Standards Code. Item 13.5 does not currently list stevia. As such, stevia may only be compliantly used in FSMPs if there is an amendment to the Food Standards Code.

Net benefits for consumers and industry

The inclusion of stevia in FSMPs can be justified on the basis that it would provide a net benefit to consumers and industry.

Consumers

Stevia is currently permitted to be used as a food additive in FSMPs in numerous international jurisdictions (see Section 3.1.1-9 below). Many FSMP products are imported to Australia and New Zealand from other countries. As FSMPs are intended to be consumed by limited population groups, consumers often rely on accessing FSMPs from countries outside of Australia and New Zealand.

Currently, FSMPs that contain stevia as a food additive are not permitted to be imported into Australia or New Zealand in commercial quantities, effectively preventing Australian and New Zealand consumers from accessing these products.

There can be legitimate medical or other reasons to specifically formulate FSMPs to use stevia as a sweetener. For example, sweeteners – just like Stevia – are commonly used in FSMPs to improve the product palatability without affecting carbohydrates/protein/fat ratio and, as such, improve patient's compliance to the nutritional intervention.

This application seeks to permit the use of stevia as a food additive in FSMPs at a maximum level of 330 mg/kg, excluding products for infants under 12 months of age. This level is consistent with equivalent permissions that exist internationally, including in the European Union and in *Codex Alimentarius*. If successful, this application would allow consumers in Australia and New Zealand to access products containing stevia that are already available internationally.

We believe that any potential concerns regarding the use of stevia in FSMPs would be addressed by the fact that:

- The use of stevia at the proposed amount does not present a safety risk (see Section 3.3.1-B below). Stevia has been assessed numerous times by FSANZ and the proposed level of use in FSMPs aligns with permissions that already exist internationally.
- FSMPs are not consumed by the wider population and consumers of FSMPs containing stevia would do so in the context of medical supervision.
- FSMPs may be used as a sole source of nutrition (i.e. not used together with other food products). In this usage scenario, the use of Stevia in FSMPs should not increase the overall population exposure to this sweetener.

Industry

If the application is successful, Australian and New Zealand manufacturers and importers would have greater flexibility in introducing FSMPs to Australia and New Zealand for the dietary management of specific medical conditions. Businesses that sell FSMPs containing stevia in other markets would be able to introduce these products to Australia and New Zealand, and manufacturers producing FSMPs domestically will be able to introduce stevia into product formulations.

FSMPs are typically nutrient-dense, and as a result may not be palatable for consumers. As stevia has a better taste than other synthetic sweeteners, and is plant-derived, permission to use stevia as a sweetener in FSMPs would allow industry to supply products with better taste, palatability and consumer acceptability without increasing sugar intake. Improved taste and palatability will also help prevent consumers from being discouraged from continuing to consume an FSMP where it is required for medical purposes. This is a significant benefit in certain medical conditions where sugar should not be used in the FSMP formulations.

Government

Due to the relatively small market for FSMPs in Australia and the fact that the addition of stevia does not present a safety risk, it is unlikely that this application would result in increased regulatory or other government costs. Any costs incurred in enforcing the use of stevia in FSMPs are unlikely to be significantly higher than the costs of enforcing stevia use in other product categories.

4 Information to support the application

(addressing section 3.1.1.E of the FSANZ Application Handbook)

The application contains supporting information in accordance with the Application Handbook's requirements in Guideline 3.1 – General requirements, Guideline 3.3.1 – Food additives and Guideline 3.6.3 in relation to special purpose foods (other than infant formula). As noted above, FSANZ has assessed information relating to the use of stevia as a food additive on numerous occasions in the context of previous applications to amend the Food Standards Code. We therefore refer to supporting information that has already been assessed by FSANZ at various points throughout this application. Any such instances are clearly highlighted and justified below.

5 Assessment procedure

(addressing section 3.1.1.F of the FSANZ Application Handbook)

The applicant considers that the application should be assessed under the general procedure level 2 (maximum 380 variable hours). Stevia has been assessed by FSANZ and is already permitted under several food product categories. This application seeks to extend the use of stevia to the specific category of FSMP.

6 Confidential commercial information

(addressing section 3.1.1.G of the FSANZ Application Handbook)

The application contains CCI as summarised in the table below. The detailed CCI has been provided separately to FSANZ and summarised in a general nature throughout the relevant sections of this Application.

Information requested to be considered as confidential	Justification
Appendix C	The information contains proprietary sales data for the applicant's products that is not in the public domain.

7 Other confidential information

(addressing section 3.1.1.H of the FSANZ Application Handbook)

The application does not include any other confidential information, aside from the confidential commercial information identified above.

8 Exclusive capturable commercial benefit

(addressing section 3.1.1.I of the FSANZ Application Handbook)

If successful, this application will confer a benefit on consumers and the industry at large by permitting the import, manufacture and sale of FSMPs containing stevia in Australia or New Zealand. This application will not confer an exclusive capturable commercial benefit on the applicant.

9 International and other national standards

(addressing section 3.1.1.J of the FSANZ Application Handbook)

As identified above, stevia is permitted for use in FSMPs and equivalent products under *Codex Alimentarius* and other international standards in jurisdictions including the European Union, United States, Canada, Singapore, Turkey, and Japan. The permission to use stevia in FSMPs in Australia and New Zealand would be consistent with existing permissions in these jurisdictions. We summarise the international permissions for the use of stevia in FSMPs in the below table.

Jurisdiction	Permission to use stevia in FSMPs (or equivalent products)	Relevant regulation or standard
Codex Alimentarius	Permitted up to 350 mg/kg (excluding products for infants and young children)	General Standard for Food Additives Codex Stan 192-1995
Europe	Permitted up to 330 mg/kg (excluding products for infants and young children)	Annex II of Regulation (EC) No 1333/2008 (as amended by Regulation 1131/2011)
Singapore	Permitted up to 175 mg/kg	Singapore Food Regulations (made under the Singapore Sale of Food Act)
Canada	Permitted in beverages, beverage mixes and beverage concentrates up to 0.02%	Health Canada List of Permitted Food Additives
United States	Permitted so long as vendor provides a Generally Recognised as Safe (**GRAS**) notice covering the intended use or the use of the ingredient aligns with an existing GRAS notice and intended use that has been approved by the Food and Drug Administration. There are currently 54 no objection GRN's and 4 pending for stevia based ingredients.	
Turkey	Permitted up to 330 mg/kg (excluding products for infants and young children)	
Japan	Permitted in all food categories with no usage limit (there is no FSMP or equivalent regulatory category in Japan)	Japan Food Chemical Research Foundation List of Existing Food Additives

This application seeks permission to use stevia at a level of 330 mg/kg for all FSMP products, excluding products for infants under 12 months of age. This approach is justified on the basis that:

- Stevia is safe for use across the general population at the proposed level and previous FSANZ assessments of stevia have not identified specific concern relating to consumption by young children of foods containing stevia (see section 3.3.1-B below);
- The general population, including young children, is exposed to stevia in the diet through other product categories without any safety concern (as part of Application A1037, FSANZ assessed stevia intake in numerous age groups including children aged 2-6);
- It is highly likely that FSMPs for use by young children would only be formulated using stevia where this is necessary for the relevant medical purpose, taking into account the age of the intended user (e.g. where it is necessary to sweeten the product with a substance other than sugar for a medical reason);
- FSMPs are subject to additional regulatory controls to ensure safe consumption by vulnerable persons including that they must be consumed in the context of medical supervision; and

- Other countries including the US, Canada and Singapore do not exclude products for young children from the permission to use stevia in FSMPs.

10 Statutory declaration

(addressing section 3.1.1.K of the FSANZ Application Handbook)

A statutory declaration has been provided with this application and is included in Appendix A.

11 Checklist

(addressing section 3.1.1.L of the FSANZ Application Handbook)

Completed checklists for sections 3.1.1, 3.1.3 and 3.6.3 of the Application Handbook are included in Appendix B.

3.3.1 FOOD ADDITIVES

A Technical information on the food additive

(addressing section 3.3.1.A of the FSANZ Application Handbook)

A.1 Nature and Technological purpose of the additive

Stevia is a plant-based sweetener extracted from the leaves of Stevia rebaudiana. The sweetness of S. rebaudiana comes from diterpene glycosides, commonly known as steviol glycosides. Steviol glycosides would be used in FSMPs to perform the function of an intense sweetener, which would enable the reduction of sugar in foods for special medical purposes.

Steviol glycosides are currently used widely in the Australian and international food industry as an intense sweetener to partially or completely replace the use of sugar in product formulations.

The flavour and sweetness qualities of steviol glycosides, coupled with their high stability, mean these extracts are capable of wide use and can function as multi-purpose, low-calorie sweeteners. The stability of steviol glycosides was last reviewed by FSANZ in 2021 as part of Application A1222.[1] Steviol glycosides have been the subject of several safety assessments by FSANZ and are permitted in the Food Standards Code as a food additive for multiple food types.

Commercial stevia sweeteners generally contain ≥95% steviol glycosides (dry weight basis), where the steviol glycosides are defined as rebaudioside A, rebaudioside B, rebaudioside C, rubusoside, stevioside, steviolbioside, dulcoside A, rebaudioside D, rebaudioside F, rebaudioside M. In most commercial sweeteners where the extract is produced via fermentation, ratios would be different.

A.2 Information to enable identification of the additive

JECFA has defined steviol glycosides (steviol conjugated with glucose, xylose, and/or rhamnose) as natural constituents of the Stevia rebaudiana (Bertoni) plant leaves.[2] Steviol glycosides have the food additive number INS 960.[3]

As outlined below, specifications for the identity and purity of steviol glycosides are already included in Schedule 3 of the Food Standards Code. Where it does not list specifications for a particular ingredient or substance, Schedule 3 incorporates relevant specifications from JECFA monographs. This application does not seek to introduce new types of stevia or modify or extend the specifications for the different types of stevia that may be used in food in Schedule 3.

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[1] FSANZ (2021). Application A1222: Steviol glycosides from Yarrowia lipolytica – Supporting Document 1. Canberra, Australia / Wellington, NZ: Foods Standards Australia New Zealand (FSANZ). Available at: http://www.foodstandards.gov.au/code/applications/Pages/A1132Definition-of-Steviol-Glycosides.aspx

[2] JECFA (2010). Steviol glycosides [Prepared at the 73rd JECFA, 2010) and published in FAO JECFA Monographs 10, 2010)]. In: Combined Compendium of Food Additive Specifications. (FAO JECFA Monographs 10). 73rd Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 8-17, 2010, Geneva, Switz. Food and Agriculture Organization of the United Nations (FAO), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome, Italy. Available at: https://www.fao.org/3/i1782e/i1782e.pdf

[3] JECFA (2005). Steviol glycosides. In: Evaluation of certain food additives. Sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 8-17, 2004, Geneva. Geneva: World Health Organization (WHO); 34-39, 138. (WHO Technical Report Series, no. 928; Available at: http://apps.who.int/iris/bitstream/10665/43141/1/WHO TRS 928.pdf

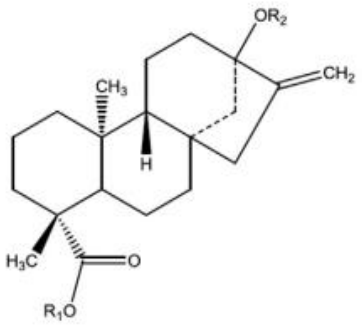
Synonyms, Trade Names, and Abbreviations

Steviol glycosides are referred to using several other common and brand names including stevia, rebiana, rebaudioside A, Truvia™.

Rebaudioside A and stevioside are the most abundant steviol glycosides naturally occurring in S. Rebaudiana leaf. Stevioside and rebaudioside A constitute at least 90% of weight of all glycosides present in the leaves. A number of other Steviol glycosides are present in minor quantities. However, optimised extraction, purification and enrichment techniques including fermentation has allowed the production of *S. Rebaudiana* extracts with different steviol glycoside ratios and better sensory attributes that are suitable for various food applications. For example, some commercial stevia sweeteners are enriched with rebaudioside M and rebaudioside D.

Structurally, steviol glycosides consist of an aglycone (steviol), which is connected at C-4 and C-13 to mono-, di-, or tri-saccharides (containing predominantly glucose and/or rhamnose). The structural details for the relevant steviol glycosides are given in Figure 1.

Rebaudioside A, has the chemical name 13-[(2-O-β-D glucopyranosyl-3-O-β-D'glucopyranosyl-β-D-glucopyranosyl)oxy] kaur-16-en-18-oic acid β-D-glucopyranosyl ester (CAS No. 58543-16-1), while stevioside has the chemical name: 13-[(2-O-β-D-glucopyranosyl-β-D'glucopyranosyl)oxy] kaur-16-en-18-oic acid β-D-glucopyranosyl ester. All other minor steviol glycosides have the structural backbone or aglycone structure of steviol with a varying number of glycoside linkages.



Compound	R1	R2
Steviol	H-	H-
Stevioside	Glcß1-	Glcß(1-2)Glcß1-
Rebaudioside A	Glcß1-	Glcß(1-2)[Glcß(1-3)]Glcß1-
Rebaudioside B	H-	Glcß(1-2)[Glcß(1-3)]Glcß1-
Rebaudioside C	Glcß1-	Rhaα(1-2)[Glcβ(1-3)]Glcβ-
Rebaudioside D	Glcβ(1-2)Glcβ1-	Glcß(1-2)[Glcß(1-3)]Glcß1-
Rebaudioside E	Glcβ(1-2)Glcβ1-	Glcβ(1-2)Glcβ1-
Rebaudioside F	Glcβ1-	Xylβ(1-2)[Glcβ(1-3)]Glcβ1-
Rebaudioside M	Glcß(1-2)[Glcß(1-3)]Glcß1-	Glcß(1-2)[Glcß(1-3)]Glcß1-
Steviolbioside	H-	Glcβ(1-2)Glcβ1-
Dulcoside A	Glcβ1-	Rhaα(1-2)Glcβ1-
Rubusoside	Glcß1-	Glcß1-
Glc, Rha, and Xyl represent glucose, rhamnose, and xylose sugar moieties, respectively		

Figure 1. Molecular structures of major steviol glycosides. Steviol refers to the basic aglycone.

In application A1132, FSANZ approved an extension to the specifications for steviol glycoside preparations. This extension goes beyond the previously approved 10 steviol glycosides (stevioside; rebaudioside, A, B, C, D, E, F and M; steviolbioside; rubusoside and dulcoside), to also include all of the various steviol glycosides that can be extracted from the stevia leaf. They are claimed to reduce

the unwanted taste characteristics associated with commercial steviol glycoside preparations used to replace sugar or in blends with other intense sweeteners, with or without sugar.

FSANZ has approved further additions to permitted specifications for stevia contained in Schedule 3 of the Food Standards Code, resulting from the following applications:

- In application A1222, FSANZ approved the use of Rebaudioside MD produced by fermentation from a genetically modified *Yarrowia lipolytica.*
- In application A1207, FSANZ approved the use of Rebaudioside M produced by fermentation from a genetically modified *Saccharomyces cerevisiae.*
- In application A1176, FSANZ approved the use of Rebaudioside D, M and AM produced from enzymatic conversion using specific enzymes derived from genetically modified strains of *Escherichia coli.*
- In application A1183, FSANZ approved the use of Rebaudioside E produced from enzymatic conversion using a specific protein engineered enzyme derived from a genetically modified strain of *Pichia pastoris.*

A.3 Information on the chemical and physical properties of the additive

All forms of stevia used in food must meet relevant chemical and physical specifications included in Schedule 3 of the Food Standards Code.

Food grade specifications for steviol glycosides, finalised by JECFA, require not less than 95% of the total preparation to be comprised of ten named steviol glycosides, on a dried weight basis.[4]

Preparations of steviol glycosides are white or light-yellow powders that are either odourless or have a slight odour.

Steviol glycoside powder preparations are freely soluble in water and ethanol. Steviol glycoside solutions have a pH between 4.5 – 7.0 (1 in 100 solution) and have sweetness profiles that range between 200-300-fold (compared to sucrose) depending on the particular steviol glycoside present in a JECFA-defined 95% pure preparation and the testing methodology details.[5]

A.4 Information on the impurity profile

All forms of stevia used in food must meet relevant purity specifications included in Schedule 3 of the Food Standards Code.

The major component of high-purity steviol glycoside preparations that adhere to JECFA specifications (>95% purity) are one or a mixture of steviol glycosides. Generally, the composition of

[4] JECFA (2010). Steviol glycosides [Prepared at the 73rd JECFA, 2010) and published in FAO JECFA Monographs 10, 2010)]. In: Combined Compendium of Food Additive Specifications. (FAO JECFA Monographs 10). 73rd Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 8-17, 2010, Geneva, Switz. Food and Agriculture Organization of the United Nations (FAO), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome, Italy. Available at: https://www.fao.org/3/i1782e/i1782e.pdf

[5] JECFA (2010). Steviol glycosides [Prepared at the 73rd JECFA, 2010) and published in FAO JECFA Monographs 10, 2010)]. In: Combined Compendium of Food Additive Specifications. (FAO JECFA Monographs 10). 73rd Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 8-17, 2010, Geneva, Switz. Food and Agriculture Organization of the United Nations (FAO), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome, Italy. Available at: https://www.fao.org/3/i1782e/i1782e.pdf

the steviol glycoside mixtures can vary depending to the S. rebaudiana cultivar from which the steviol glycosides are extracted, as well as differences in the manufacturing process. [6]

According to JECFA specifications, the impurities representing the other 5% of the material must not include more than 1% total ash, nor should residual methanol or ethanol be present at greater than 200ppm and 5000ppm, respectively. In addition, the specifications state that arsenic and lead levels should not exceed 1 ppm in the high purity steviol glycoside preparations.[7] Any product in which stevia is used must also comply with relevant limits for contaminants and toxicants in Schedule 19 of the Food Standards Code.

This application seeks only to extend the use of permitted forms of stevia to a new product category. As such, it is not necessary to consider the impurity profile of any new forms of stevia.

A.5 Manufacturing process

Manufacturers use the same basic steps to extract steviol glycosides from the leaves of the stevia plant, although there is some variation in the later stages of purification and separation of glycosides. The process generally involves:

- Extraction from the leaves by dissolving the steviol glycosides in warm/hot water in a batch system, 3 – 5 times, or by a continuous reverse flow system;
- Flocculation and precipitation of suspended matter;
- Filtration;
- Concentration by vacuum assisted evaporation;
- Adsorption (and release by alcohol) in a resin exchange process;
- Ion-exchange purification;
- Further filtration and concentration; and
- Spray drying or crystallisation.

Further processing to concentrate and separate a specific steviol glycoside product is often undertaken and may involve patented procedures, such as fermentation or enzymatic modification.

A.6 Specification for identity and purity

Specifications for steviol glycoside mixtures are outlined in Schedule 3 of the Food Standards Code. Section S3-2 of Schedule 3 incorporates specifications from relevant JECFA monographs.

Section S3-39 and S3-35 of Schedule 3 also provide specifications for steviol glycosides that have been produced by fermentation and enzymatic conversion respectively. Fermentation is typically carried out using approved yeast or bacterial strains with gene modifications for rebaudiosides and allows production of steviol glycoside mixtures with favourable sensory properties. In May 2021,

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[6] EFSA (2010). EFSA Panel on Food Additives and Nutrient Sources (ANS); Scientific Opinion on safety of steviol glycosides for the proposed uses as a food additive (question no EFSA-Q-2007-071, EFSA-Q-2008-387, EFSA-Q-2008-401, adopted on 10 March 2010 by European Food Safety Authority). EFSA J 8(4):1537. [85 pp.]. doi:10.2903/j.efsa.2010.1537. Available at: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1537/full

[7] JECFA (2010). Steviol glycosides [Prepared at the 73rd JECFA, 2010) and published in FAO JECFA Monographs 10, 2010)]. In: Combined Compendium of Food Additive Specifications. (FAO JECFA Monographs 10). 73rd Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 8-17, 2010, Geneva, Switz. Food and Agriculture Organization of the United Nations (FAO), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Rome, Italy. Available at: https://www.fao.org/3/i1782e/i1782e.pdf

FSANZ approved application A1207 to permit the use of Steviol glycosides Rebaudioside ("Reb") M that is produced by fermentation from Saccharomyces cerevisiae, expressing steviol glycoside biosynthesis pathway genes, as a general-purpose sweetening agent. In September 2021, FSANZ approved A1222 to include *Yarrowia lipolytica* strain VRM0014, containing pathway genes for the production of steviol glycosides, in addition to previously listed Saccharomyces cerevisiae strain CD15407 containing novel genes for the production of rebaudiosides. In A1183, FSANZ approved the use of an enzymatic conversion method (using an enzyme derived from genetically modified strain of Pichia pastoris) for production of high purity rebaudioside E (≥85% rebaudioside E; ≥95% total steviol glycosides). The production method has previously been assessed for two other rebaudiosides, rebaudioside M and rebaudioside D, in applications A1157 and A1172 respectively.

This Application does not seek to introduce any forms of stevia which are not already permitted for use and subject to specifications identified in Schedule 3. Commercial stevia sweeteners proposed to be used by the applicant only include those steviol glycosides that have already been assessed and approved by FSANZ in previous applications.

A.7 Information for food labelling

Steviol glycosides are considered to be intense sweeteners and flavour enhancers when added to various food products. Steviol glycosides have been assigned the INS number of 960. The Food Standards Code permits steviol glycosides to be listed in a statement of ingredients as either "sweetener (steviol glycosides)" or "sweetener (960)".

A.8 Analytical method for detection

Reverse-phase high-performance liquid chromatography (RP-HPLC) coupled with tandem mass spectrometry is used to detect steviol glycosides, due to its high selectivity and multianalyte capability since different sweeteners are frequently used in mixtures to achieve the desired taste, flavour or mouthfeel (Kubica, Namiesnik & Wasick, 2015). HPLC-MS based detection and quantification continues to be the recognised method for steviol glycosides, however advances have been made to increase to achieve high efficiency, simplicity, versatility, and low solvent consumption. For example, these include fast gradient UHPLC coupled with charged aerosol detection (Hollá et al., 2022), hydrophilic interaction liquid chromatography (HILIC) (Wang et al., 2022).

A.9 Potential additional purposes of the food additive when added to food

Steviol glycosides are added to food either as an intense sweetener, or to replace the sweetness normally provided by sugars.[8] The main purpose for using stevia in food is to reduce or replace the sugar content of the product.

Steviol glycosides differ from other permitted intense sweeteners as these are sourced from plant material rather than chemical synthesis. The use of steviol glycosides presents greater flexibility for manufacturers and addresses consumer demand for fewer synthetically derived ingredients. It also presents greater dietary choice to consumers who might not be able to consume average quantities of sugar.

[8] FSANZ (2016a). Standard 1.3.1 - Food Additives. In: Australia New Zealand Food Standards Code. Canberra, Australia / Wellington, New Zealand: Food Standards Australia New Zealand (FSANZ). Available at: https://www.legislation.gov.au/Series/F2015L00396.

It is unlikely that stevia would be used for a purpose other than an intense sweetener. Any other use (e.g. as a food ingredient) would be subject to controls under the Food Standards Code, including restrictions on the use of novel foods and nutritive substances.

B Information related to the safety of steviol glycoside

(addressing section 3.3.1.B of the FSANZ Application Handbook)

Steviol glycosides are currently permitted for use in numerous food product categories, and have been used safely in food products sold in Australia and New Zealand for years. FSANZ has specifically assessed the safety of steviol glycosides several times. FSANZ first approved the use of steviol glycosides as an intense sweetener in a wide variety of foods in 2008 (FSANZ, 2008). FSANZ allowed an increase in the maximum permitted level of steviol glycosides in ice cream, water-based beverages, brewed soft drinks, formulated beverages and flavoured soy beverages, of up to 200 mg/kg and in plain soy beverages, of up to 100 mg/kg, following the assessment of A1037 (FSANZ, 2011). A new steviol glycoside, rebaudioside M, was approved for use in the same food categories and at the same use levels are previously permitted steviol glycoside products by FSANZ in 2015 (FSANZ, 2015). Also, the rebaudioside MD form of steviol glycoside, purified from fermentation using Saccharomyces cerevisiae (strain CD15407) was approved for use in foods by FSANZ in 2019. FSANZ approved a broader definition of steviol glycosides through assessment of A1132 (FSANZ, 2017).

As part of Application A1037, FSANZ conducted a dietary exposure assessment of stevia in relation to a proposed increase in permitted maximum stevia levels in several categories. This assessment included a scenario where the level of stevia consumed by children aged 2-6 could slightly exceed the ADI for stevia for this age group. FSANZ did not identify any safety concerns with the proposed level of stevia in the diet.

FSANZ has assessed the safety of stevia in food in several applications (see Section 3.1.1-2 above), and most recently in 2021 through application A1222. A review of literature identifies several relevant articles that have been published since that time, including Abbas Momtazi-Borojeni et al. (2021); Chappell et al. (2021); EFSA (2018, 2021); Lea et al. (2021); Rotimi et al. (2018); Uçar et al. (2018); Ji et al. (2023); and Orellana-Paucar (2023). These papers are incorporated into the below discussion of safety.

B.1 Information on the toxicokinetics and metabolism of steviol glycoside

Rebaudioside A and stevioside have the same metabolic characteristics. Rebaudioside A and stevioside are also the most abundant glycosides in Stevia leaf naturally, although commercial stevia sweeteners are produced to contain higher concentrations of other steviol glycosides. Following oral intake, rebaudioside A is resistant to degradation by the digestive enzymes and gastric acid of the upper gastrointestinal tract and passes through to the colon. In the colon, gut microflora metabolise rebaudioside A into steviol by removing the glycosyl moieties (de-glycosylation), resulting in steviol. Steviol is subsequently absorbed and conjugated in the liver to steviol glucuronide, which is excreted via the urine. The absorption of the parent steviol glycosides in vitro and in vivo is presumably very low. Plasma concentrations of Steviol in humans remain very low after oral intake, and steviol glucuronide is the primary circulating compound when rebaudioside A or stevioside is consumed (Lea et al., 2021; Abbas Momtazi-Borojeni et al., 2017, Simoens et al., 2022).

There is evidence to suggest other steviol glycosides are metabolised into same primary metabolites. In an in-vitro study by Purkayastha et al. (2014) demonstrated that rebaudiosides B, D, and M are metabolized to steviol in the same manner as rebaudioside A, which supported the use of toxicology

data available on steviol, and on steviol glycosides metabolized to steviol (i.e., rebaudioside A) to substantiate the safety of rebaudiosides B, D, and M.

Steviol glycosides are widely used commercially as a healthy, noncariogenic, zero-calorie alternative for sucrose. In addition, many studies with both animal models and human volunteers have shown that Steviol glycosides is safe for consumption (Marković et al., 2008; Ceunen & Geuns, 2013; Rajab et al., 2009; Awney et al., 2011; Rotimi et al., 2018). Much of the toxicology literature of steviol glycosides has focused on its potential mutagenicity and genotoxicity, as summarised in previous FSANZ safety evaluations. Overall, in vitro and in vivo studies have consistently demonstrated that steviol glycosides and its permitted equivalents, are not mutagenic or genotoxic (Brusick, 2008; Urban et al., 2013). There is a single exception, an in vivo study by Nunes et al. (2007), with significant methodological limitations that led experts and regulators to conclude that the study is irrelevant to the health and safety of high purity steviol glycosides in animals or humans (Brusick, 2008; JECFA, 2008; EFSA, 2010; EFSA, 2018; Urban et al., 2013; EFSA Panel on Food Additives and Flavourings et al., 2021).

According to Chappell et al. (2021) the safety of steviol glycosides at approved use levels has been reviewed by multiple investigators and organizations, including regulatory agencies, which have concluded that steviol glycosides do not present a health concern to humans (i.e., lack of carcinogenicity, genotoxicity or reproductive/developmental toxicity) based on data collected from both in vitro and in vivo studies (Carakostas et al., 2008; Carakostas et al., 2016; EFSA, 2010; JECFA, 2016). Various steviol glycoside preparations have been determined to be generally recognized as safe (GRAS) by notifiers, and the US FDA has responded with “no questions” regarding the GRAS determination of such preparations.

Besides a relevant genotoxicity study included in FSANZ safety evaluations of A1132 assessment published in 2009 by Williams and Burdock, more recently, Ucar et al. (2017) conducted a study on the genotoxicity of stevia in human lymphocytes. Their results supported previous findings by showing that steviol glycosides have no genotoxic activity in chromosomal aberrations and micronuclei groups.

This study used Stevia (including steviol glycoside, purity 99%, CAS No: 8016–24-8) and Mitomycin C (MMC) (CAS No: 200–008-6), cytochalasin B (CAS No: 14930–96-2) for in vitro tests. In order to evaluate the genotoxic potential of stevia, ADI value was used for dose selection. ADI/4, ADI/2, ADI, ADI × 2 and ADI × 4 which were equivalent to 1, 2, 4, 8 and 16 µg/ml concentrations were chosen for best evidencing cytogenetic damage. Peripheral venous blood was collected from non-smoking, healthy two female and two male adults (aged 25–26 years). The donors fulfilled the following criteria: <30 years old, non-smokers, no medication for at least 3 weeks prior, and not having undergone radiological examination within 3 months prior. All procedures were applied according to the IPCS guidelines. The two repeated experiments were conducted using the same blood samples. Whole blood (0.2 ml) was added to 2.5 ml Chromosome Medium B. For Chromosomal aberrations test Clare (2012) method was applied with some modifications and for Micronucleus test Fenech (2000) method was followed.

No significant difference in the induction of chromosomal aberrations and micronuclei was observed between the groups treated with the concentrations of stevia (1, 2, 4, 8 and 16 µg/ml) and the negative control at both treatment periods. The most dominant types of aberrations were chromatid breaks followed by sister chromatid union, chromosome breaks, fragments and polyploidy. In micronucleus test, only one micronuclated binucleate cells were observed in treated cultures. A slight but non-significant increase was observed at both treatment periods.In recent review articles by Ji et al. (2023) and Orellana-Paucar (2023), it was concluded that, based on published reports, oral consumption of steviol glycosides at recommended doses is not teratogenic or cancerogenic. Ji et al

(2023) further reviewed evidence of other bioactivities of Stevia rebaudiana extract, such as antioxidant, antidiabetics, anti-inflammation, and antimicrobial, given its historical use in south America as a sweetening ingredient, however further human trials are required to fully establish these beneficial bioactive effects In summary, these genotoxicity study results add to the large database of safety data for steviol glycosides and its permitted equivalents and support the interpretation that steviol glycosides are safe for use in FSMPs.

B.2 Information on the toxicity of steviol glycoside

Several acute toxicology studies on rebaudioside A (98% purity) conducted by Eurofins/Product Safety Laboratories were included in a 2012 FDA GRAS notification (Mini Star Intl. GRN418, 2012). Oral (0.233 – 5 g/kg) and dermal (2 g/kg) rebaudioside A exposures in rats produced no acute toxicity effects. In addition, rebaudioside A did not elicit primary skin irritation (0.5 g) or primary eye irritation (0.04 g) in rabbits upon dermal or ocular exposures.

Previous FSANZ application A1132 discusses the following study. A single subacute animal assay was conducted as a bridging toxicity study to investigate whether previous toxicity studies on rebaudioside A would be appropriate to support the safety evaluation of rebaudioside D. The study by Nikiforov et al. (2013) was performed in accordance with US FDA testing guidelines. The study design included the oral administration of 0, 500, 1000, or 2000 mg/kg/day rebaudioside D (purity = 93.5%, with the remaining 6.5% comprised mostly of other steviol glycosides), or 2000 mg/kg/day rebaudioside A (purity = 98.9%), to five groups of 20 Crl:CD(SD) rats (10 male, 10 female) respectively, for 28 consecutive days. Doses normalised to consumption rates and body weights for the males and females in each test group were 506 and 495, 1027 and 1012, 2042 and 2016, and 2043 and 1965 mg/kg/day, respectively. There were no adverse changes observed in clinical observations, terminal body weights, organ weights, or food consumption, or any remarkable differences in hematological, serum chemistry or urinalysis endpoints between control animals and those administered either rebaudiosides A or D. With one exception, functional observational battery and motor activity endpoints were not impacted by either steviol glycoside at tested doses relative to control animals. The females in all rebaudioside D dose groups had significantly lower ambulatory activity relative to control, though the authors hypothesised that this was the result of quicker habituation of these animals, and not related to treatment. In fact, no differences in ambulation were observed in the highest dose rebaudiosides A and D treatment group females, and no differences were reported in any of the treatment group males relative to control group males. Nikiforov et al. (2013) concluded that the study was appropriate as a bridging study for rebaudioside D, and that it verified the safety of rebaudioside D for human consumption.

As summarised in the FSANZ safety evaluations of high purity steviol glycoside preparations, clinical studies have demonstrated that steviol glycosides are well tolerated in humans and are not associated with adverse effects in healthy humans as well as individuals with type-2 diabetes or who are hypotensive. In addition to the clinical research summarised in the previous safety evaluations, it should be noted that in another study that compared the impact of pre-meal ingestion of stevia (Whole Foods 365 brand; steviol glycoside purity not reported) with that of other sweeteners (i.e., aspartame or sucrose) on food intake, satiety, and postprandial glucose and insulin levels in healthy lean and obese individuals between the ages of 18-50 (Anton et al., 2010). The study reported that stevia significantly lowered post-meal glucose levels relative to sucrose preloads, and significantly lowered post-meal insulin levels compared to both aspartame and sucrose preloads. The effects on hunger and satiety were not different between the three sweeteners. However, critical study limitations (e.g., no reported steviol glycoside composition, purity, or even relevant dose metric)

suggest that the results of this study are not likely to influence the current regulatory position regarding the safety of steviol glycoside in humans.

In a more recent study, the toxicokinetic profiles of steviol and steviol glucuronide following administration of high-dose stevioside were determined in two groups of male and female Sprague–Dawley (Crl:CD(SD)) rats (72 animals/sex per dose group) (Roberts et al., 2016). Animals were administered by gavage stevioside (≥ 95% purity) single oral doses of 40 or 1,000 mg/kg body weight (bw) (equivalent to 16 or 396 mg steviol equivalents/kg bw). Additionally, the pharmacokinetics of steviol and steviol glucuronide following consumption of stevioside were examined in an open-label, single dose trial in 10 healthy adult males between the ages of 20 and 45 years. The subjects were provided 40 mg/kg bw of stevioside (equivalent to 16 mg steviol equivalents/kg bw) in an aqueous solution. The available subchronic toxicity studies on steviol glycosides show no adverse effect to animals or humans (Roberts et al., 2016). The only effects noted in the steviol glycoside animal toxicity studies have been related to decreases in body weight gain, which have previously been described for a number of other sweetener products including sucralose and neotame as result of palatability, caloric reduction, and subtle decrements in food consumption at study initiation (Carakostas et al., 2008).

One study by Yılmaz (2022) investigated the effect of very high doses of steviol glycosides (940 mg/kg and 1880 mg/kg bodyweight) using a mice model. The study found that consumption of stevia at this level slightly increased the oxidative damage, cell cycle activity, and chromosomal aberration frequency. The dosage of stevia considered in this study is extremely high, and exceeds commonly accepted ADIs for stevia of up to 4 mg/kg by approximately 200-400-fold. As such, the results of this study are not relevant to this application, as the safety concerns identified would not arise at the proposed level of use.

Overall, the results of these most recent additions to the toxicology and clinical literature of high purity steviol glycosides support the safety of high purity preparations. Therefore, this application is supported by the prior findings in the published literature showing that steviol glycosides are not acutely toxic in laboratory animals or humans. The safety data does not demonstrate any risk of toxicity should steviol glycosides be added to FSMPs.

B.3 Safety assessment reports prepared by international agencies or other national government agencies

The safety of steviol glycosides has been assessed by many international scientific and regulatory bodies, including JECFA, FDA, EFSA, Codex Alimentarius, FCC, GB Standards, Japanese Regulations and Health Canada. Due to the significant interest in the use of steviol glycosides extensive testing has been carried out.

JECFA has reviewed the safety of steviol glycosides in four separate meetings and has established an ADI for steviol glycosides of 0 to 4 mg/kg body weight expressed as steviol equivalents (JECFA 2005, 2007, 2008, 2010). This ADI has been adopted by FSANZ. The proposed usage of stevia in FSMPs is consistent with this ADI.

C Information related to the dietary exposure to steviol glycosides

(addressing section 3.3.1.C of the FSANZ Application Handbook)

C.1 A list of the food groups or foods proposed to contain steviol glycosides

This application seeks approval of the use of stevia in food for special medical purposes (category 13.5 in Schedule 15 of the Food Standards Code), excluding products for infants under 12 months.

C.2 The maximum proposed level or the concentration range of steviol glycosides for FSMPs

This application seeks to amend Schedule 15 relating to Standard 1.3.1 to allow steviol glycosides in FSMPs (excluding products for infants under 12 months) to a maximum level of 330 mg/kg (steviol equivalents). This proposed level would align with existing limits in the EU (330 mg/kg) and *Codex Alimentarius* (350 mg/kg), and would not present a risk to safety.

The proposed level is lower than the maximum permitted level for other food product categories including fruit and vegetable spreads (permitted up to 450 mg/kg), chocolate and cocoa products (permitted up to 550 mg/kg), sugar confectionary (permitted up to 1,100 mg/kg), and tabletop sweeteners (permitted up to the minimum level required at GMP). It is expected that the majority of FSMP products containing stevia would fall below the proposed maximum limit; however, the limit of 330 mg/kg would give manufacturers and importers flexibility in providing products that have been formulated using stevia at levels that are consistent with the relevant technological requirements to achieve the medical purpose of the product. As many FSMP products are manufactured in and exported from the European Union, implementing a maximum limit of 330 mg/kg would facilitate trade and minimise barriers to the supply of FSMPs in Australia and New Zealand.

FSMPs may be formulated as a sole source of nutrition. Where stevia is used in an FSMP that is a sole source of nutrition, it is unlikely that the consumer would be consuming stevia from other sources. In this scenario, the consumer's overall exposure to stevia is therefore unlikely to increase.

Refer to Appendix C for a summary of the stevia levels used in the applicant's products which are sold in international jurisdictions, including intended population groups and length of time of use, and estimated stevia exposure per day. As FSMPs may be developed to perform a wide range of medical functions, the information in Appendix C is not intended to be exhaustive. However, it indicates that the proposed use of stevia in FSMPs would fall within accepted ADIs.

C.3 Information on likely level of consumption of food groups not currently listed in NNSs

The Application Handbook requests information on the likely consumption of foods not currently listed in Australian and New Zealand national nutrition surveys (**NNSs**). Data on the consumption of FSMPs may not be available from these NNSs, and is not included in the Australian Health Survey for 2017-2018.

FSMPs are specifically formulated to achieve a medical purpose. The amount of stevia that is used in an FSMP may therefore vary according to the medical purpose of the product and whether it is intended to be used as a sole source of nutrition. In all cases, FSMPs (and any stevia contained in an FSMP) would be consumed in the context of medical supervision. The use of stevia in FSMPs is likely to be analogous with the use of other intense sweeteners that are already permitted for use in FSMPs at GMP.

FSMPs are consumed by a relatively small portion of the population. It is expected that the amount of stevia consumed by the general population through FSMP products would be substantially lower than that which is consumed through other categories of products which are permitted to contain stevia (e.g. various beverage categories, formulated supplementary sports foods).

We have included information relating to the usage levels of stevia in the applicant's products in section 3.6.3-B of this application.

C.4 The percentage of FSMPs in which steviol glycosides is proposed to be used

Internationally, stevia is used in a minority of FSMPs. Stevia is typically only used in FSMPs where it is necessary to achieve the relevant medical purpose (e.g. where it is appropriate to reduce sugar intake) and/or to perform the technological function as an intense sweetener. It is expected that stevia will be used in a minority of FSMP products in Australia and New Zealand.

C.5 Information relating to the use of steviol glycosides in FSMPs in other countries

Please refer to Section 3.1.1-9 for a table summarising the permissions for the use of stevia in FSMPs and equivalent products in countries outside of Australia and New Zealand. These countries include Europe[9], USA[10], Canada[11], Singapore[12], Mainland China[13], Japan[14] and Turkey[15]. FSMPs containing stevia are sold in each of these countries, but they do not make up the majority of the market.

There is no label warning required for the use of steviol glycosides (E960) in FSMPs in the countries stated above and at that maximum level. Steviol glycosides (E960) was first allowed to be used in FSMPs products in 2010 in the United States.

C.6 For foods where consumption has changed in recent years, information on likely current food consumption

As identified above, there is likely to be little information on the consumption of FSMPs in relevant NNSs. Globally, there has been some recent growth in the demand for FSMPs attributable to factors including lifestyle factors which have increased the need for dietary management of disease, and government initiatives (Fortune Business Insights, 2020, Global Market Monitor, 2020). This growth has not been specifically targeted towards FSMPs containing stevia; however, the permission to use stevia in FSMPs would allow manufacturers and importers to be more flexible in meeting consumer demand.

As FSMPs are designed for the dietary management of specific conditions, it is not expected that there will be significant growth in FSMP consumption as a portion of overall food intake in Australia and New Zealand.

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[9] Annex II of Regulation (EC) No 1333/2008. Available at: https://food.ec.europa.eu/safety/food-improvement-agents/additives/database_en

[10] Codex Alimentarius Food Additives Commission. Available at: https://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/gsfa/en/

[11] Canada Standards for Permitted Sweeteners. Available at: https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/lists-permitted/9-sweeteners.html

[12] Singapore Food Additives Regulation. Available at: https://www.sfa.gov.sg/docs/default-source/legislation/sale-of-food-act/food_regulations.pdf

[13] Centre for Food Safety. Food Additives. Available at: https://www.cfs.gov.hk/english/programme/programme_rafs/files/2010_amendment_to_sweeteners_in_food_regulation_Legco_brief.pdf

[14] The Japan Food Chemical Research Foundation. Food Additives. Available at: https://www.ffcr.or.jp/en/tenka/list-of-existing-food-additives/list-of-existing-food-additives.html

[15] Turkish Food Codex. Food Additives Regulation. Available at: https://www.fao.org/faolex/results/details/en/c/LEX-FAOC152534

3.6.3 SPECIAL PURPOSE FOODS – OTHER FOODS

A Information related to general compositional requirements

(addressing section 3.6.3.A of the FSANZ Application Handbook)

A.1 Information on the identity and physical and physiological need of the target population

This application does not seek to change the compositional requirements for FSMPs or any other product category. Rather, this application requests that stevia be permitted for use as a food additive in FSMPs.

This application seeks to permit the use of stevia up to 330 mg/kg in all FSMP products, other than products for infants under 12 months. This would include:

- FSMPs that are presented as a partial source of nutrition;
- FSMPs that are presented as a sole source of nutrition; and
- Very Low Energy Diet (**VLED**) products.

Stevia would be used in FSMPs to perform the technological function of an intense sweetener. As stevia performs a technological, rather than nutritional function, its application to FSMPs may be relatively broad. The target population for FSMPs containing stevia is likely to be consumers that have a medical condition that requires dietary management using products that have been sweetened with a substance other than sugar.

By way of example, the role of stevia in FSMPs is critical in the dietary management of obesity and diabetes. Replacing sugar with stevia has the benefit of reducing fructose, which has been shown to have negative effects on liver health. This is particularly relevant for patients with diabetes or obesity who are at risk of developing non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (Jenson etal 2018). Complete sugar replacement with stevia could be applied when it is not suitable to use sugar in FSMP formulations. In this scenario, stevia would provide a better taste compared to other synthetic sweeteners, and would therefore help improve patient compliance.

A multicentre clinical trial using Optifast (a VLED FSMP product containing stevia) by Ard et al (2018) demonstrated that a comprehensive behavioural weight-loss intervention with Total meal replacement (TMR), led to greater clinically significant weight loss at 26 and 52 weeks compared with a well-established food -based behavioural intervention. It also showed the feasibility of such an intervention for motivated individuals, indicating that stevia has good acceptability in the target population, and is safe for use in FSMPs (especially very low energy foods).

A.2 Purpose of the compositional change

As detailed in Section 3.1.1-3, the permission to add stevia to FSMPs as a food additive would provide greater choice for consumers and give industry greater flexibility in formulating products designed for the dietary management of specific conditions. It would also allow consumers to access a greater range of products that are already sold internationally in jurisdictions that permit the use of stevia in FSMPs.

Stevia would perform a technological function, not a nutritive or health-related function, in FSMPs. The use of stevia as a food additive may assist industry and consumers in achieving health-related goals where the medical purpose of a particular FSMP product requires a reduced intake of sugar.

A.3 Information related to the safety of the proposed compositional change

Based on the safety data considered at Section 3.3.1-B above, there is no demonstrated negative safety effects that can be associated with the use of stevia in FSMPs. Stevia is already a well-known substance that has an established history of use in many food categories with no adverse effects. Extension of this permission to FSMPs would not create any new safety risk.

Sections 3.3.1-B.1 and 3.3.1-B.2 details relevant studies on metabolism and toxicology of steviol glycosides. Generally, steviol glycosides are deglycosylated by intestinal microflora prior to the absorption of steviol and conjugation to steviol glucuronide. As detailed in Sections 3.3.1-B.1 and 3.3.1-B.2, pharmacokinetic and toxicological studies including human trials have not found any adverse effects on human health. Consumption levels of FSMPs are more heavily regulated and controlled due to the presence of medical supervision compared to regular food products, therefore the exposure levels of steviol glycosides are highly unlikely to exceed ADIs for healthy individuals. Manufacturers would be subject to the maximum limit that set for stevia in FSMPs (proposed to be 330 mg/kg) and would still be subject to overarching requirements in Standard 2.9.5 to ensure that their product composition is safe and is appropriate for the specific dietary purpose for which the product has been designed.

A.4 Information related to the nutritional impact or performance impact of the proposed compositional change

This application seeks to permit stevia for use as a food additive to perform a technological function (intense sweetener) in FSMPs. It does not seek to permit stevia for use as a nutritive substance or to perform any specific nutrition, health or performance-related function.

The use of stevia would give manufacturers and importers a greater ability to deliver products that are suited to the relevant medical purpose, where the medical purpose requires the product to be sweetened with a substance other than sugar. It would do this by allowing the products to achieve the desired flavour and level of sweetness without using sugar. Stevia would not of itself be used to achieve a broader medical purpose as a functional ingredient that provides a nutritional or health benefit.

Clinical trials have been conducted to investigate antihyperglycemic, blood pressure reducing effects of stevioside in diabetic rats and humans with positive findings to support the use of stevia in food for special medical purposes (Jeppesen et al., 2003; Gregersen et al., 2004; Boonkaewwan et al., 2006; Chatsudthipong & Muanprasat, 2009; Brahmachari et al., 2011; Yadav & Guleria, 2012; Jeppesen et al., 2000).

B Information related to the dietary intake or dietary exposure

(addressing section 3.6.3.B of the FSANZ Application Handbook)

B.1 Data to enable the dietary exposure of the target population to be estimated

The level of consumption of stevia in FSMP products will vary according to: the medical purpose that the product is formulated to assist with; the serve size that is required to achieve the medical purpose; and whether the product is intended for use as a sole source of nutrition.

It is expected that consumption of stevia would be analogous with consumption of FSMPs that are sweetened with other intense sweeteners that are already permitted to be used at GMP.

The applicant has provided a CCI summary of its FSMP products that contain stevia and that are sold in countries other than Australia and New Zealand. This includes products that would be classified as VLED products in Australia and New Zealand. This information also includes the intended population

and estimated daily dosage for each product. The products included in this summary each contain stevia within the proposed level of 330 mg/kg when made up as directed. We include this summary in Appendix C.

B.2 Data on the recommended level of consumption of the special purpose food for the target population

In FSMP products sold in the US and EU markets, the steviol glycoside content ranges from as low as 30mg/kg to 258mg/L (see Appendix C). This application requests a maximum level of stevia in FSMPs of 330 mg/kg, in line with EU and other international requirements.

As discussed above, the level of consumption of FSMPs containing stevia will vary according to several factors. In all cases, FSMPs containing stevia must undergo stringent testing to ensure that they are safe, and will be consumed in the context of medical supervision.

C Information related to labelling requirements under Part 2.9 of the Code

(addressing section 3.6.3.C of the FSANZ Application Handbook)

C.1 Information related to safety or nutritional impact of the proposed labelling change

This application does not request any change to the labelling requirements for FSMPs under the Food Standards Code. The existing labelling requirements for FSMPs would ensure that any FSMP containing stevia can be consumed safely. Relevantly, any FSMP that contains stevia must still declare the presence of stevia in accordance with 2.9.5-11, in addition to the mandatory statements and declarations prescribed by Section 2.9.5-10.

FSMPs must also be used under medical supervision, and their distribution is limited such that a consumer will generally purchase an FSMP from an appropriately qualified professional. In addition to the strict labelling requirements, this means that a consumer of an FSMP is likely to have access to additional information regarding the suitability of the product from a qualified person.

C.2 Information to demonstrate that the proposed labelling change will be understood and will assist consumers

No labelling change would be required if stevia is permitted to be used in FSMPs. As noted above, consumers would be able to identify the presence of stevia in an FSMPs through the mandatory ingredient declaration that is required under Section 2.9.5-11.

D Information related to internationally recognized codes of practice and guidelines

(addressing section 3.6.3.D of the FSANZ Application Handbook)

Stevia is already permitted for use in FSMPs in several international jurisdictions (refer to sections 3.1.1-9 and 3.3.1-C.5 of this application). None of these jurisdictions require specific warning statements relating to the use of stevia in FSMPs. The use of stevia in FSMPs (excluding products for infants under 12 months) at a level up to 330 mg/kg would therefore be consistent with internationally recognised standards.

References

Abbas Momtazi-Borojeni, A., Esmaeili, S. A., Abdollahi, E., & Sahebkar, A. (2021). A review on the pharmacology and toxicology of steviol glycosides extracted from Stevia rebaudiana. *Current Pharmaceutical Design*, 23(11), 1616-1622.

Anton, S. D., Martin, C. K., Han, H., Coulon, S., Cefalu, W. T., Geiselman, P., & Williamson, D. A. (2010). Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. *Appetite*, *55*(1), 37-43.

Ard, J. D., Lewis, K. H., Rothberg, A., Auriemma, A., Coburn, S. L., Cohen, S. S., Loper, J., Matarese, L., Pories, W. J., & Periman, S. (2019). Effectiveness of a Total Meal Replacement Program (OPTIFAST Program) on Weight Loss: Results from the OPTIWIN Study. Obesity (Silver Spring), 27(1), 22-29. https://doi.org/10.1002/oby.22303

Australian Bureau of Statistics (ABS). (2018). National Health Survey: First results. Accessed in November, 2021. Available online at: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey-first-results/latest-release#:~:text=%20National%20Health%20Survey%3A%20First%20results%20%201,Survey%20material.%20%206%20Endnotes.%20%20More%20

Awney, H. A., Massoud, M. I., & El-Maghrabi, S. (2011). Long-term feeding effects of stevioside sweetener on some toxicological parameters of growing male rats. *Journal of Applied Toxicology*, 31(5), 431-438.

Boonkaewwan, C., Toskulkao, C., & Vongsakul, M. (2006). Anti-inflammatory and immunomodulatory activities of stevioside and its metabolite steviol on THP-1 cells. Journal of Agricultural and Food Chemistry, 54(3), 785-789.

Brahmachari, G., Mandal, L. C., Roy, R., Mondal, S., & Brahmachari, A. K. (2011). Stevioside and related compounds–molecules of pharmaceutical promise: a critical overview. Archiv der Pharmazie, 344(1), 5-19.

Brusick, D. J. (2008). A critical review of the genetic toxicity of steviol and steviol glycosides. *Food and Chemical Toxicology*, 46(7), S83-S91.

Carakostas, M. C., Curry, L. L., Boileau, A. C., & Brusick, D. J. (2008). Overview: the history, technical function and safety of rebaudioside A, a naturally occurring steviol glycoside, for use in food and beverages. *Food and Chemical Toxicology*, *46*(7), S1-S10.

Ceunen, S., & Geuns, J. M. (2013). Steviol glycosides: chemical diversity, metabolism, and function. *Journal of Natural Products*, 76(6), 1201-1228.

Chan, P., Tomlinson, B., Chen, Y. J., Liu, J. C., Hsieh, M. H., & Cheng, J. T. (2000). A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. British journal of clinical pharmacology, 50(3), 215-220.

Chappell, G. A., Heintz, M. M., Borghoff, S. J., Doepker, C. L., & Wikoff, D. S. (2021). Lack of potential carcinogenicity for steviol glycosides-Systematic evaluation and integration of mechanistic data into the totality of evidence. *Food and Chemical Toxicology*, 150, 112045.

Clare, G. (2012). The in vitro mammalian chromosome aberration test. In Genetic Toxicology (pp. 69-91). Springer, New York, NY.

EFSA. (2021). EFSA Panel on Food Additives and Flavourings (FAF), Younes, M., Aquilina, G., Castle, L., Engel, K. H., Fowler, P., Frutos Fernandez, M. J., Furst, P., Gürtler, R., Gundert-Remy, U., Husøy, T., Manco, M., Mennes, W., Passamonti, S., Moldeus, P., Shah, R., Waalkens-Berendsen, I., Wölfle, D., Wright, M., Barat Baviera, J. M., Degen, G., Leblanc, J. C., Herman, L., Giarola, A., Aguilera, J., Vianello, G., & Castle, L. (2021). Safety evaluation of steviol glycoside preparations, including rebaudioside AM, obtained by enzymatic bioconversion of highly purified stevioside and/or rebaudioside A stevia leaf extracts. EFSA Journal, 19(8), e06691. Accessed in November, 2021. Available at: https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2021.6691

EFSA. (2010). EFSA Panel on Food Additives and Nutrient Sources (ANS); Scientific Opinion on safety of steviol glycosides for the proposed uses as a food additive (question no EFSA-Q-2007-071, EFSA-Q-2008-387, EFSA-Q-2008-401, adopted on 10 March 2010 by European Food Safety Authority). EFSA J 8(4):1537. [85 pp.]. doi:10.2903/j.efsa.2010.1537. Accessed in November, 2021. Available at: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1537/full

EFSA. (2018). Safety of the proposed amendment of the specifications of the food additive steviol glycosides (E 960). EFSA Journal, 16(3), e05236. Accessed in November, 2021. Available at: https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2018.5236

Fenech, M. (2000). The in vitro micronucleus technique. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 455(1-2), 81-95.

Fortune Business Insights, (2020). Food for Special Medical Purpose (FSMP) Market Size, Share and Global Trend by Type (Nutritionally Complete Foods, Nutritionally Complete Foods with A Disease, Nutritionally Incomplete Foods), By Form (Oral, Injectable, Others), By End User (Hospitals, Clinics, Ambulatory Surgical Centers, Homecare Settings), and Geography Forecast till 2021-2028. Accessed in November, 2021. Available online at: https://www.fortunebusinessinsights.com/industry-reports/food-for-special-medical-purpose-fsmp-market-100320

FSANZ. (2008). Final Assessment Report: Application A540: Steviol Glycosides as Intense Sweeteners. Canberra, Australia / Wellington, NZ: Foods Standards Australia New Zealand (FSANZ). Accessed in November, 2021. Available at: http://www.foodstandards.gov.au/code/applications/pages/applicationa540stevi3096.aspx

FSANZ. (2011). Final Assessment Report: Application A1037: Steviol Glycosides Increase in Permitted Use Levels. Canberra, Australia / Wellington, NZ: Foods Standards Australia New Zealand (FSANZ). Accessed in November, 2021. Available at: http://www.foodstandards.gov.au/code/applications/Pages/applicationa1037stev4605.aspx

FSANZ. (2015). Final Assessment Report: Application A1108: Rebaudioside M as a Steviol Glycoside Intense Sweetener. Canberra, Australia / Wellington, NZ: Foods Standards Australia New Zealand (FSANZ). Accessed in November, 2021. Available at: http://www.foodstandards.gov.au/code/applications/Pages/A1108- RebaudiosideM-SteviolGlycosideIntenseSweetener.aspx

FSANZ. (2017). Application A1132: Broaden Definition of Steviol Glycosides. Canberra, Australia / Wellington, NZ: Foods Standards Australia New Zealand (FSANZ). Accessed in November, 2021. Available at: http://www.foodstandards.gov.au/code/applications/Pages/A1132Definition-of-Steviol-Glycosides.aspx

FSANZ (2021). Application A1222: Steviol glycosides from *Yarrowia lipolytica*. Canberra, Australia / Wellington, NZ: Foods Standards Australia New Zealand (FSANZ). Accessed in February, 2023. Available at: https://www.foodstandards.gov.au/code/applications/Pages/A1222---Steviol-glycosides-from-Yarrowia-lipolytica.aspx

Global Market Monitor. (2020). Global Food for Special Medical Purpose (FSMP) Market Professional Research Report 2014-2026, Segmented by Players, Types, End-Users in Major 40 Countries or Regions. Accessed in November, 2021. Available online at: https://www.globalmarketmonitor.com/reports/590348-food-for-special-medical-purpose--fsmp--market-report.html

Gregersen, S., Jeppesen, P. B., Holst, J. J., & Hermansen, K. (2004). Antihyperglycemic effects of stevioside in type 2 diabetic subjects. Metabolism, 53(1), 73-76.

JECFA. (2005). Steviol glycosides. In: Evaluation of certain food additives. Sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 8-17, 2004, Geneva. Geneva: World Health Organization (WHO); 34-39, 138. (WHO Technical Report Series, no. 928. Accessed in November, 2021. Available at: http://apps.who.int/iris/bitstream/10665/43141/1/WHO TRS 928.pdf

JECFA. (2007). 3.1.9 Steviol glycosides. Evaluation of Certain Food Additives and Contaminants. Sixty-eighth Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 19-28, 2007, Geneva, Switz. (WHO Technical Report Series, no 947). Geneva, Switz.: World Health Organization (WHO), pp. 50-54, 206, 215. Accessed in November, 2021. Available at: http://apps.who.int/iris/bitstream/10665/43870/1/9789241209472 eng.pdf

JECFA. (2008). Steviol glycosides (addendum). In: Safety Evaluation of Certain Food Additives and Contaminants. Sixty-ninth Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 17-26-29, 2008, Geneva, Switz. (WHO Food Additives Series, vol 60). Rome, Italy: Food and Agriculture Organization of the United Nations (FAO) / Geneva, Switz.: World Health Organization (WHO), pp. 183219. Accessed in November, 2021. Available at: http://www.fao.org/documents/card/en/c/c1dfe308-c04e-444d-9885- e2b20ef6bb07/.

JECFA. (2010). Steviol glycosides [Prepared at the 73rd JECFA, 2010) and published in FAO JECFA Monographs 10, 2010)].

Jensen, T., Abdelmalek, M. F., Sullivan, S., Nadeau, K. J., Green, M., Roncal, C., Nakagawa, T., Kuwabara, M., Sato, Y., Kang, D.-H., Tolan, D. R., Sanchez-Lozada, L. G., Rosen, H. R., Lanaspa, M. A., Diehl, A. M., & Johnson, R. J. (2018). Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. Journal of Hepatology, 68(5), 1063-1075. https://doi.org/https://doi.org/10.1016/j.jhep.2018.01.019

Jeppesen, P. B., Gregersen, S., Rolfsen, S. E. D., Jepsen, M., Colombo, M., Agger, A., ... & Hermansen, K. (2003). Antihyperglycemic and blood pressure-reducing effects of stevioside in the diabetic Goto-Kakizaki rat. Metabolism, 52(3), 372-378.

Jeppesen, P. B., Gregersen, S., Poulsen, C. R., & Hermansen, K. (2000). Stevioside acts directly on pancreatic β cells to secrete insulin: Actions independent of cyclic adenosine monophosphate and adenosine triphosphate—sensitivie K+-channel activity. Metabolism, 49(2), 208-214.

Ji Li, Pradeep Thaker, Deshou Jiang, Qingrong Huang, Chi Tang Ho. Herb Stevia Rebaudiana's Functionalities, Safety, and Applications: A Review. Archives of Clinical and Biomedical Research 7 (2023): 64-85.

Kubica P, Namiesnik J, Wasick A (2015). Determination of eight artificial sweeteners and common Stevia rebaudiana glycosides in non-alcoholic and alcoholic beverages by reversed-phase liquid chromatography coupled with tandem mass spectrometry. Journal of Analytical and Bioanalytical Chemistry 407:1505-1512.

Lea, I. A., Chappell, G. A., & Wikoff, D. S. (2021). Overall lack of genotoxic activity among five common low-and no-calorie sweeteners: a contemporary review of the collective evidence. Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 503389.

Marković, I. S., Đarmati, Z. A., & Abramović, B. F. (2008). Chemical composition of leaf extracts of Stevia rebaudiana Bertoni grown experimentally in Vojvodina. Journal of the Serbian Chemical Society, 73(3), 283-297.

Nikiforov, A. I., Rihner, M. O., Eapen, A. K., & Thomas, J. A. (2013). Metabolism and toxicity studies supporting the safety of rebaudioside D. International journal of toxicology, 32(4), 261-273.

Nunes, A. P. M., Ferreira-Machado, S. C., Nunes, R. M., Dantas, F. J. S., De Mattos, J. C. P., & Caldeira-de-Araujo, A. (2007). Analysis of genotoxic potentiality of stevioside by comet assay. Food and chemical toxicology, 45(4), 662-666.

Orellana-Paucar, A. M. (2023). Steviol Glycosides from Stevia rebaudiana: An Updated Overview of Their Sweetening Activity, Pharmacological Properties, and Safety Aspects. *Molecules (Basel, Switzerland)*, *28*(3).

Pérez, E., González, C., Vaillant, F., & Lares, M. (2016). Stevia derivative and its potential uses in diabetic-directed foods. Review. Journal of Nutrients, 3(1), 1-20.

Rajab, R., Mohankumar, C., Murugan, K., Harish, M., & Mohanan, P. (2009). Purification and toxicity studies of stevioside from Stevia rebaudiana Bertoni. Toxicology International, 16(1), 49.

Roberts, A., Purkayastha, S., Bhusari, S., Pugh, G., Lynch, B., Rogerson, R., Crincoli, C., Eapen, A., Cuellar-Kingston, N., Kern, H., Coffee, M., Renwick, A., & Carakostas, M. (2016). Chemical-specific adjustment factors (inter-species toxicokinetics) to establish the ADI for steviol glycosides. Regulatory Toxicology and Pharmacology, 79, 91-102.

Rotimi, S. O., Rotimi, O. A., Adelani, I. B., Onuzulu, C., Obi, P., & Okungbaye, R. (2018). Stevioside modulates oxidative damage in the liver and kidney of high fat/low streptozocin diabetic rats. Heliyon, 4(5), e00640.

Simoens, C., Philippaert, K., Wuyts, C., Goscinny, S., Van Hoeck, E., Van Loco, J., Billen, J., de Hoon, J., Ampe, E., Vangoitsenhoven, R., Mertens, A., Vennekens, R., & Van der Schueren, B. (2022). Pharmacokinetics of Oral Rebaudioside A in Patients with Type 2 Diabetes Mellitus and Its Effects on Glucose Homeostasis: A Placebo-Controlled Crossover Trial. European Journal of Drug Metabolism and Pharmacokinetics. https://doi.org/10.1007/s13318-022-00792-7

Singh, S. D., & Rao, G. P. (2005). Stevia: The herbal sugar of 21 st century. Sugar tech, 7(1), 17-24.

Uçar, A., Yılmaz, S., Yılmaz, Ş., & Kılıç, M. S. (2018). A research on the genotoxicity of stevia in human lymphocytes. Drug and chemical toxicology, 41(2), 221-224.

Urban, J. D., Carakostas, M. C., & Brusick, D. J. (2013). Steviol glycoside safety: Is the genotoxicity database sufficient?. Food and Chemical Toxicology, 51, 386-390.

Williams, L. D., & Burdock, G. A. (2009). Genotoxicity studies on a high-purity rebaudioside A preparation. Food and Chemical Toxicology, 47(8), 1831-1836.

Yadav, S. K., & Guleria, P. (2012). Steviol glycosides from Stevia: biosynthesis pathway review and their application in foods and medicine. Critical reviews in food science and nutrition, 52(11), 988-998.

Yılmaz, Ş. G., Uçar, A., & Yılmaz, S. (2022). Do steviol glycosides affect the oxidative and genotoxicity parameters in BALB/c mice? Drug and Chemical Toxicology, 45(1), 464-469. https://doi.org/10.1080/01480545.2020.1716000