12 May 2021
155-21

Approval report – Application A1207

Rebaudioside M as a Steviol Glycoside from *Saccharomyces cerevisiae*

Food Standards Australia New Zealand (FSANZ) has assessed an application made by Amyris Inc. to permit the use of the steviol glycoside, rebaudioside M, which is produced by fermentation from a genetically modified *Saccharomyces cerevisiae* expressing steviol glycoside biosynthesis pathway genes, as a general purpose sweetening agent.

On 21 October 2020 FSANZ sought submissions on a draft variation and published an associated report. FSANZ received four submissions.

FSANZ approved the draft variation on 28 April 2021 The Food Ministers' Meeting (formerly the Australia and New Zealand Ministerial Forum on Food Regulation) was notified of FSANZ's decision on 12 May 2021.

This Report is provided pursuant to paragraph 33(1)(b) of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act).

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Supporting document[1]

The following document which informed the assessment of this application is available on the FSANZ website:

SD1 Risk and technical assessment report (at Approval)

[1] https://www.foodstandards.gov.au/code/applications/Pages/A1207.aspx

Executive summary

Amyris Inc. (Amyris) applied for a variation to the Australia New Zealand Food Standards Code (the Code) to permit the use of rebaudioside M (Reb M) produced from fermentation by a genetically modified (GM) *Saccharomyces cerevisiae* (*S. cerevisiae*) strain, as a food additive general purpose sweetening agent (intense sweetener). Food Standards Australia New Zealand (FSANZ) assessed the application in accordance with the *Food Standards Australia New Zealand Act 1991* (FSANZ Act).

Reb M is one of various steviol glycosides already permitted as food additives in the Code. However, there was no permission for the Amyris Reb M, because of its specific production method. Amyris uses the microbial fermentation method for its Reb M, produced from *S. cerevisiae* expressing steviol glycoside biosynthesis pathway genes. This method is comparable to the recently permitted rebaudioside MD from application A1170 (see section S3—39 in the Code).

The Code permits the use of steviol glycosides, including Reb M, at maximum permitted levels (MPL) in a variety of food categories and at Good Manufacturing Practice (GMP) levels in tabletop sweeteners in Schedule 15. No changes to the current steviol glycosides permissions in the Code were requested, therefore no dietary exposure assessment was conducted.

An acceptable daily intake (ADI) of 0-4 mg/kg bodyweight for steviol glycosides, expressed as steviol, was established by FSANZ in 2008. This ADI was appropriate for Reb M produced from fermentation, as it is chemically the same as Reb M extracted traditionally from the leaves of *Stevia rebaudiana* Bertoni and would therefore follow the same metabolic pathway in humans. No new information was identified subsequent to FSANZ's previous assessments of steviol glycosides that raised concerns regarding their safety.

Amyris's Reb M meets the purity parameters of specifications in section S3—39 of the Code but not the specific method of production. These parameters are also consistent with international purity specifications for steviol glycosides. Its proposed technological purpose as an intense sweetener food additive matched that of permitted steviol glycoside preparations produced by the currently permitted methods.

Assessment of the host *S. cerevisiae* strain confirmed it was neither pathogenic nor toxigenic and had a long history of food use. Analysis of the production strain confirmed the presence and stability of the inserted DNA. The final product did not contain residual protein or DNA and did not give rise to any allergen concerns.

FSANZ assessed that Amyris's Reb M produced from *S. cerevisiae* expressing steviol glycoside biosynthesis pathway genes did not pose a risk to public health and safety. It is also permitted for use as a sweetener in Canada and the USA.

FSANZ considered that it was therefore appropriate to prepare a draft variation to amend the Code to permit the use of Amyris's Reb M as a food additive (intense sweetener) at current levels and in those food classes which currently permit steviol glycosides.

Following assessment and the preparation of a draft variation, FSANZ called for submissions regarding the draft variation on 21 October 2020. A total of four submissions were received, all of which FSANZ has had regard to. Three submissions were supportive. One submission opposed the draft variation. FSANZ considered and responded to the issues raised in the submission, some of which were out of scope. Section 2.1 of this report provides a summary of the submissions made and FSANZ's response to each.

For the reasons listed in this report, FSANZ decided to approve the draft variation as proposed following assessment.

The approved draft variation will amend Schedule 3 of the Code to permit the use of Reb M as a food additive (intense sweetener) in accordance with the Code's existing food additive permissions for steviol glycosides, provided that the Reb M complies with the specifications listed in subsection S3—39(3) of the Code.

1 Introduction

1.1 The Applicant

The applicant, Amyris Inc. (Amyris), is a manufacturer of food ingredients and provides food and non-food applications worldwide.

1.2 The application

Amyris's application, accepted on 23 July 2020, sought to change the Australia New Zealand Food Standards Code (the Code) to permit a purified steviol glycoside preparation produced by *Saccharomyces cerevisiae* (*S. cerevisiae*) expressing steviol glycoside biosynthesis pathway genes for use as an intense sweetener. This purified steviol glycoside product is primarily comprised of rebaudioside M (Reb M) and may contain a minor amount of other steviol glycosides. Steviol glycosides are food additives used as intense sweeteners. They are permitted for addition to a variety of foods within the Code. The current permissions for steviol glycosides allow for products extracted from the *Stevia rebaudiana* Bertoni plant either by hot water extraction or by bioconversion of the plant extract, as well as via fermentation process (like the production method for this application). Amyris uses a microbial fermentation method with a genetically modified yeast (*S. cerevisiae*) to manufacture Reb M. The steviol glycosides (Reb M and minor other steviol glycosides) are identical to those produced from the plant.

Amyris sought an amendment to Schedule 3 of the Code to allow permission for Amyris's Reb M.

No changes to the current steviol glycosides permissions in the Code were requested, therefore no dietary exposure assessment was conducted.

1.3 The current Code requirements

Australian and New Zealand food laws require food for sale to comply with the following requirements of the Code.

Paragraph 1.1.1—10(6)(a) provides that, unless expressly permitted by the Code, a food for sale cannot contain, as an ingredient or component, a substance that is used as a food additive. The Code also imposes identity and purity specifications with which Reb M and other steviol glycosides must comply.

The Code currently permits the use of steviol glycosides as food additives with the INS number 960. They are permitted in a wide range of food categories listed within the table to section S15—5 at maximum permitted levels (MPL) and at Good Manufacturing Practice (GMP) for tabletop sweeteners only.

However, the current specifications for identity and purity do not allow for Amyris's production method.

1.3.1 Food additives

Section 1.1.2—11 defines the expression 'used as a food additive'. Subsection 1.1.2—11(1) provides that a substance is 'used as a food additive' in relation to a food if both of the following conditions are met: the substance is added to the food to perform one or more technological functions listed in Schedule 14; and the substance is identified in subsection 1.1.2—11(2) – this includes (among other things) a substance identified in the table to

section S15—5 as a permitted food additive.

Section 1.3.1—3 details when substances are permitted to be used as food additives in food.

Schedule 14 lists the permitted technological purposes of food additives. The table in section S14—2 provides that use as an intense sweetener is a permitted purpose.

Schedule 15 lists the specific food additive permissions for different categories of foods in the table to section S15—5. 'Steviol glycosides' is listed in that table as a permitted food additive for various food categories.

Schedule 16 sets out the types of substances that may be used as food additives in any food at GMP levels. As 'steviol glycosides' is not such a food additive, it is not listed in Schedule 16.

Section 1.5.2—3 provides that permission for use as a food additive also constitutes the permission required by paragraph 1.1.1—10(6) for a food produced using gene technology.

1.3.2 Labelling

Paragraph 1.1.1—10(8) of the Code provides that food for sale must comply with all relevant labelling requirements imposed by the Code for that food.

The Code's labelling requirements which apply to foods for retail sale and to foods sold to a caterer are set out in Divisions 2 and 3 of Standard 1.2.1 respectively.

The Code requires the labels of most packaged food to contain a statement of ingredients. Subsection 1.2.4—7(1) requires food additives to be declared in the statement of ingredients by one of the following methods: if the food additive can be classified in accordance with Schedule 7—the relevant class name followed in brackets by the name or code number of the food additive specified in Schedule 8; or else, the name of the food additive specified in Schedule 8.

Schedule 7 lists the food additive class names that can be used in the statement of ingredients. Schedule 8 lists the names and code numbers of food additives that are to be used for labelling purposes.

Section 1.5.2—4 of Standard 1.5.2 outlines requirements for labelling of certain foods for sale that consist of, or have as an ingredient, food that is a genetically modified food. For labelling purposes, *genetically modified food* is defined in subsection 1.5.2—4(5) as a *food produced using gene technology* that contains novel DNA or novel protein or is listed in section S26—3.

1.3.3 Identity and purity requirements

Paragraph 1.1.1—15(1)(a) of the Code requires substances used as food additives to comply with any relevant identity and purity specifications listed in Schedule 3 of the Code.

Sections S3—31 and S3—32 of Schedule 3 provide specifications for Reb M and for steviol glycoside mixtures containing Reb M. These refer to primary source specifications for steviol glycosides contained within section S3—2, being either S3—2(1)(b) [the FAO[2] JECFA[3] Monograph, (JECFA 2017)], S3-2(1)(c) [the Food Chemicals Codex (FCC 2018)] or S3—2(1)(d) [European Commission Regulation No 231/2012 laying down specifications for food

[2] The Food and Agriculture Organization of the United Nations.
[3] The Joint FAO/World Health Organization (WHO) Expert Committee on Food Additives.

additives (EC 2012, EC 2016)]. Specifications for steviol glycosides from these primary sources, including Reb M, include a production method of extraction from the leaves of stevia (*S. rebaudiana* Bertoni).

Of most relevance to this application, Schedule 3 also contains section S3—39 which provides a specification for steviol glycosides produced via a fermentation process using microorganisms. This method of production is permitted to produce Reb MD, using a genetically modified *S. cerevisiae*, but it is a different strain to Amyris's yeast.

Section S3—35 of Schedule 3 also provides a specification for steviol glycosides prepared from the leaves of stevia (*S. rebaudiana* Bertoni) and a novel multi-step enzymatic pathway process. This method of production of steviol glycosides is different to the fermentation method of this application.

1.3.4 International Standards

Steviol glycosides are approved for use in a number of other jurisdictions, including the European Union, Canada, South and North Asia, Asia Pacific, United States of America (USA), Central/South America, the Middle East and Africa (PureCircle Stevia Institute, 2020). In the European Union, commercially available steviol glycoside products must comply with the specifications for steviol glycosides (INS number 960) adopted by the European Commission in 2012 and updated in 2016 (EC 2012, EC 2016).

1.3.4.1 JECFA

The 87th JECFA meeting in June 2019 established a framework for steviol glycosides building on JECFA's assessments and specifications at earlier meetings. The 87th meeting also prepared four steviol glycosides specification annexes, for the different production methods (JECFA 2020). These are:

- hot water extraction from the leaves of *Stevia rebaudiana* Bertoni (stevia) plant (Annex 1)
- fermentation using GM microorganisms (Annex 2)
- enzymatic modification (bioconversion) of the stevia plant extract using enzymes (Annex 3)
- glycosylation of stevia plant extracts using enzymes to add glucose units to steviol glycosides (Annex 4, tentative pending further information to finalise).

This meeting also confirmed that steviol glycosides prepared using any of these production methods, that comply with the specifications for the different production methods and purity requirements were considered equivalent in terms of safety and the earlier determined acceptable daily intake (ADI) applies (JECFA 2019a, JECFA 2019b).

It is important to note that the steviol glycosides specifications from the 87th JECFA meeting in 2019 have not yet been discussed by the Codex Committee on Food Additives (CCFA) or ultimately ratified by the Codex Alimentarius Committee (CAC) due to the cancelling of the CCFA 2020 meeting caused by the COVID-19 pandemic. Therefore these specifications are not yet part of the official JECFA Combined Compendium of Food Additive Specifications. The most current JECFA steviol glycosides monograph is monograph 20 from the 84th JECFA meeting in 2017.

Some earlier relevant JECFA meetings are the 84th meeting in 2017, where the Committee published JECFA Monograph 20 (JECFA 2017), superseding tentative specifications prepared at the 82nd JECFA meeting (2016) and published in FAO JECFA Monograph 19. An ADI of 0 - 4 mg/kg bodyweight (bw) (expressed as steviol) was established at the 69th

JECFA meeting (2008).

1.3.4.2 USA

Reb M has GRAS (Generally Recognized as Safe) status for a variety of food and beverage uses, and for different steviol glycosides producers in the USA. The US Food and Drug Administration (FDA) reviewed the self-assessed GRAS notification (GRN 812) describing the production of Amyris's Reb M produced in *S. cerevisiae* and responded on December 8, 2018 with a "no questions" letter regarding the GRAS status of Reb M. The FDA does not make its own assessment of such GRAS notifications.

1.3.4.3 Canada

Health Canada's Food Directorate completed a premarket safety assessment of the applicant's steviol glycoside and approved it as a sweetener in the same foods and the maximum levels as already permitted steviol glycosides. This approval was announced on 1st September 2020 through the Notice of Modification to the List of Permitted Sweeteners (NOM/ADM-0151) (Health Canada 2020a). The permission is within the List of permitted sweeteners, which is an updated list of that currently contained (but not updated) in the Canadian Food and Drug Regulations, Division 16 (Food Additives) Table IX (Food additives that may be used as sweeteners). This is item number S.1.2 in Table 9 (List of permitted sweeteners (Lists of permitted food additives)) available on the Health Canada website (Health Canada 2020b).

1.4 Reasons for accepting application

The Application was accepted for assessment because:

- it complied with the procedural requirements under subsection 22(2) of the FSANZ Act
- it related to a matter that warranted the variation of a food regulatory measure.

1.5 Procedure for assessment

The application was assessed under the General Procedure.

1.6 Decision

The draft variation as proposed following assessment was approved without change. The variation takes effect on gazettal. The approved draft variation is at Attachment A.

The related explanatory statement is at Attachment B. An explanatory statement is required to accompany an instrument if it is lodged on the Federal Register of Legislation.

2 Summary of the findings

2.1 Summary of issues raised in submissions

FSANZ sought public comments on the draft variation included in the call for submissions report between 21 October 2020 and 2 December 2020.

FSANZ received four submissions: one from a government agency, two from the food industry and one from a consumer advocacy group. Three submissions supported progression of the application while the consumer advocacy group opposed it. Issues raised in submissions have been addressed in Table 1 below.

Table 1: Summary of issues raised in submissions and FSANZ's response

Issue	Raised by	FSANZ response
FSANZ's literature review relied heavily on unpublished, industry supplied data from previous applications. This demonstrates a clear conflict of interest, given that industry supplied data is more likely to present favourable findings for industry. This should be considered both when weighing up the evidence for harm of the additive, but also of the benefit of the application.	Health Food Systems Australia	FSANZ takes a scientific weight-of-evidence approach when undertaking its risk assessments. FSANZ's literature review did not rely on unpublished, industry supplied data. In assessing this application, FSANZ conducted a new literature review to identify any new evidence that had not been previously considered. For that reason, the review focussed on literature published since FSANZ's last assessment of a steviol glycosides related application. The risk assessment for that assessment was based on the best available scientific evidence at that time. The review found few new papers that added to that best available scientific evidence. For that reason, the toxicological assessment for this application relied to a large part on assessments of previous applications. These assessments were almost entirely based on papers published in the peer-reviewed scientific literature. An affiliations search of authors of those papers also confirmed only 16% of papers used in the toxicological assessments came from industry sources. That is, the assessments of previous applications did not rely on 'unpublished, industry supplied data'. Nor did the assessment of this application.
In FSANZ's risk assessment, some information relevant to this section is Confidential Commercial Information (CCI). It would be beneficial to identify where in the risk assessment this has occurred, so that stakeholders can better review the documentation and provide opinions and advice on the application.	Health Food Systems Australia	FSANZ is prevented by the FSANZ Act and other Commonwealth laws from including in the published risk assessment any text that may disclose CCI.
Does using industrial methods of extraction and formulation of Reb M warrant a change in the labelling of this additive from 'natural' to 'artificial' – maintaining a 'natural' status for this additive seems misleading for consumers when trying to make considered consumption choices.	Health Food Systems Australia	The Code does not regulate claims made that certain food, including substances such as additives, are 'natural'. As outlined in section 2.5.2.3, such claims would be subject to other laws, such as consumer protection laws, in Australia and New Zealand that require that representations are not false, misleading or deceptive.
FSANZ is asked to clarify the requirements in regard to updating the INS numbering so that consumers may identify steviol glycosides derived from different	Health Food Systems Australia	Noted. This issue is addressed in section 2.3.1.1 of this report.

Issue	Raised by	FSANZ response
sources, in accordance with The Codex Alimentarius Code [Codex Alimentarius standards].		
The potential impact that increased intense sweeter consumption may have on taste preferences was not assessed by FSANZ. When sweetened food is consumed routinely, especially earlier in life, this flavour profile becomes familiar and acceptable, and ultimately can inform preferences for sweetened food. Overstimulation of sweet taste receptors may limit tolerance for more complex, less sweet tastes, such as fruits and vegetables.	Health Food Systems Australia	These issues (e.g. any potential to increase intense sweeter consumption, the impact of any such increase on consumer taste preferences and in turn on broader population consumption patterns) are outside the scope of this application. This application relates specifically to assessing the safety and technological purpose of a different method of production of one already permitted steviol glycoside or intense sweeter. No changes to the maximum permitted levels (MPL) or to permitted food classes were requested or will be made as part of this application (as noted in section 1.2 of this report). As such, the application will not result in steviol glycosides being used in a broader range of food products. Nor will it increase the permitted quantities of steviol glycosides in foods for which steviol glycosides is permitted to be used as a food additive.
There is a concern that consumers may exceed the ADI for steviol glycosides. FSANZ has stated that assuming an average body weight of 70 kg, a person would need to consume 1400 g/day of water-based beverages before exceeding the ADI for stevia. While consumption of 1.4L of a single type of water based beverage a day may be unlikely, the increasing adoption of stevia in many beverages (including dairy drinks, fruit juice and energy drinks) and commonly consumed products (including, yoghurts, confectionary and ice-cream) may increase the risk of consumers exceeding the ADI. For children, who need to consume only 830 g/day to exceed these limits, this is even more concerning.	Health Food Systems Australia	This issue is outside the scope of this application. The application only seeks permission for a new method of production of a steviol glycoside that is an already permitted intense sweetener. This application will not lead to a change in the current dietary exposure to steviol glycosides. No changes to the MPL or to permitted food classes were requested or will be made as part of this application. The information relied upon by the submitter appears taken from the recently conducted assessment for application A1149[4], which related to the use of steviol glycosides in fruit drinks. In that case, and unlike this application, permission for an extension of use of steviol glycosides was sought. As such, a dietary exposure assessment was undertaken for the purposes of assessing that application.
The consumption data used in FSANZ's dietary exposure assessments were collected almost a	Health Food Systems	For reasons stated above, this issue is out of scope.

[4] A1149 – Addition of steviol glycosides in fruit drinks https://www.foodstandards.gov.au/code/applications/Pages/A1149Addition-of-Steviol-Glycosides-in-Fruit-Drinks.aspx

Issue	Raised by	FSANZ response
decade prior. Evidence shows that intakes of intense sweeteners, and levels in the food supply, have increased over the last two decades globally. Therefore, more recent dietary exposure assessment data are needed to increase confidence in the risk assessment procedures.	Australia	FSANZ notes that the most recent dietary exposure assessment relating to steviol glycosides was completed in 2019 for Application A1149 and, as for all risk and dietary exposure assessments that FSANZ undertakes, it relied on the best scientific evidence available at that time.
The scope of public health investigated during FSANZ's risk assessment process was confined predominantly to toxicological considerations. The potential substitution of ultra-processed foods that have been reformulated with stevia for whole foods was not considered in this process, nor was the direct or indirect impacts on environmental sustainability. Another public health nutrition issue not addressed by FSANZ in their risk assessment is the potential for manufacturers to receive higher Health Star Ratings for their products when using intense sweeteners as a substitute for sugar. Intense sweeteners are not penalised in the current nutrient profiling criteria used to inform these ratings. Increasing intense sweetener permissions in the food supply, and the subsequent promotion of these products as healthy, could legitimise increased intakes of ultra-processed foods, and is an issue that warrants investigation and consideration moving forward.	Health Food Systems Australia	These concerns are outside the scope of this application. This application relates specifically to assessing the safety and technological purpose of a different method of production of one already permitted steviol glycoside or intense sweeter. No changes to the MPL or to permitted food classes for steviol glycosides will be made as a result of this application. FSANZ is not responsible for the operation of the Health Star Ratings system. The consideration of environmental impacts are also out of the scope of FSANZ's legislation.
Supported the application, with no issues raised	New Zealand Food Safety, Ministry for Primary Industries; AB Mauri; New Zealand Food & Grocery Council	Support was noted

2.2 Risk assessment

FSANZ assessed the public health and safety risks associated with Amyris's Reb M as a food additive (see SD1). The summary of this risk assessment is provided below.

The food technology assessment concluded that Reb M produced from Amyris's production strain of *S. cerevisiae* expressing steviol glycoside biosynthesis pathway genes meets the purity parameters of specifications in section S3—39, which sets out the specifications for steviol glycosides produced by fermentation but not the specific method of production. The purity parameters for Amyris's Reb M are also consistent with international purity specifications for steviol glycosides. Its technological purpose matches that of permitted steviol glycosides preparations produced by the currently permitted methods and meets the proposed purpose as an intense sweetener food additive.

FSANZ had assessed that the host *S. cerevisiae* strain is neither pathogenic nor toxigenic and has a long history of food use. Analysis of the production strain confirmed the presence and stability of the inserted DNA. The final product did not contain residual protein or DNA and did not give rise to any allergen concerns.

An ADI of 0-4 mg/kg bw for steviol glycosides, expressed as steviol, was established by FSANZ in 2008. This ADI was appropriate for Reb M produced from fermentation, as it is chemically the same as Reb M extracted traditionally from the leaves of *S. rebaudiana* Bertoni and would therefore follow the same metabolic pathway in humans. No new information had been identified subsequent to FSANZ's previous assessments that would raise concerns regarding the safety of steviol glycosides.

FSANZ has assessed that no potential public health and safety concerns had been identified with Amyris's Reb M produced from *S. cerevisiae* expressing steviol glycoside biosynthesis pathway genes.

2.3 Risk management

This application is very similar to an earlier application FSANZ assessed and approved - A1170 (FSANZ 2019a). Both applicants produced their steviol glycosides preparation via fermentation using a genetically modified *S. cerevisiae*. Therefore the risk management considerations were also very similar.

FSANZ's risk assessment concluded that Amyris's Reb M produced via its fermentation method using a genetically modified *S. cerevisiae* containing the genes for the production of rebaudiosides was safe and suitable for the proposed purpose of an intense sweetener. FSANZ considered that it was therefore appropriate to prepare a draft variation to amend the Code to permit Amyris's Reb M as a steviol glycosides preparation (as a food additive) at current levels and in those food classes which currently permit steviol glycosides.

FSANZ considered the Reb M is a food additive produced using gene technology i.e. 'derived or developed from an organism that has been modified using gene technology'. Paragraph 1.1.1—10(6)(g) requires that the presence as an ingredient or component in a food for sale of a food produced using gene technology must be expressly permitted by the Code. Section 1.5.2—3 provided that permission for use as a food additive also constitutes the permission required by paragraph 1.1.1—10(6)(g) (as noted in section 1.3.1).

Other risk management considerations relate to labelling requirements which are summarised in the sections below.

2.3.1 Labelling

2.3.1.1 Ingredient labelling

Under existing labelling requirements in the Code (unless the food is exempt from the requirement for a statement of ingredients), the Reb M preparation will require declaration as a food additive in the statement of ingredients on the label of foods. Steviol glycosides are required to be identified in the statement of ingredients using the food additive name 'steviol glycosides' or the International Numbering System (INS) code number 960 (as listed in Schedule 8).

As noted in previous reports[5], the Codex Committee on Food Additives (CCFA) has updated the INS numbers for steviol glycosides. These were subsequently adopted into the Class Names and International Numbering System for Food Additives (CXG 36-1989) by the Codex Alimentarius Commission (Codex 2019b). The new numbers distinguish between steviol glycosides produced from the plant (Steviol glycosides from *Stevia rebaudiana* Bertoni – INS 960a) and those produced by fermentation (INS 960b). Numbers have not been assigned however, for other methods of production such as enzymatic conversion. For various reasons, in particular because the INS listing has not been finalised for steviol glycosides produced by different methods of production, FSANZ decided not to include 960a and 960b in the Code when assessing earlier applications (A1170 (FSANZ 2019a) and A1183 (FSANZ 2020)).

FSANZ still considers that at this stage the most appropriate INS number for labelling of all steviol glycosides is 960. FSANZ will consider changes to this number in the Code in the future, but only if and when further finalised changes are made to the Codex INS list to incorporate numbers for a broader range of production methods. This would provide a more coordinated approach and efficient transition compared to an ad-hoc approach through various applications.

The FSANZ website has been updated to provide information on the new production methods for steviol glycosides[6]. Consumers wanting to know the source of any particular steviol glycosides in foods are advised that they may ask the manufacturer who should advise them accordingly.

2.3.1.2 Labelling as 'genetically modified'

As noted in section 2.3, the Reb M preparation is a *food produced using gene technology.* Standard 1.5.2 generally requires food produced using gene technology to be labelled as 'genetically modified' if it contains novel DNA or novel protein. As discussed in sections 2.5 and 3.1.5 of SD1, it is highly unlikely that novel protein or DNA will be present in the Reb M preparation. However, if Reb M is used as an ingredient in a food for retail sale or a food sold to a caterer and novel DNA or protein is present, the requirement to label Reb M as 'genetically modified' would apply in accordance with section 1.5.2—4 of the Code.

2.3.2 Risk management conclusion

FSANZ's risk management proposal was to permit the use of Amyris's Reb M produced by a GM yeast strain as a food additive. FSANZ's decision was based on risk assessment, risk management and the FSANZ Act considerations, including the cost benefit considerations

[5] applications A1170, A1172, A1176 and A1183 (FSANZ 2019a, FSANZ 2019b, FSANZ 2019c, FSANZ 2020 respectively)
[6] For more information please see the following FSANZ webpage:
https://www.foodstandards.gov.au/consumer/additives/Pages/Steviol-glycosides-(960)-(intense-sweetener).aspx

(detailed in section 2.5.1.1).

2.4 Risk communication

2.4.1 Consultation

Consultation is a key part of FSANZ's standards development process. FSANZ developed and applied a basic communication strategy to this application. The call for submissions was notified via the Food Standards Notification Circular, media release, FSANZ's social media tools and Food Standards News.

The process by which FSANZ considers standard development matters is open, accountable, consultative and transparent. Public submissions were called to obtain the views of interested parties on issues raised by the application and the impacts of regulatory options. FSANZ acknowledges the time taken by individuals and organisations to make submissions on this application.

The draft variation was considered for approval by the FSANZ Board having had regard to all submissions received from the call for submissions.

2.5 FSANZ Act assessment requirements

2.5.1 Section 29

2.5.1.1 Consideration of costs and benefits

The Office of Best Practice Regulation (OBPR) granted FSANZ a standing exemption from the requirement to develop a Regulatory Impact Statement for the approval of additional food additives (OBPR correspondence dated 24 November 2010, reference 12065). This standing exemption was provided as permitting additional food additives is a minor, deregulatory change and their use is voluntary. This standing exemption relates to the introduction of a food to the food supply that has been determined to be safe.

FSANZ however had given consideration to the costs and benefits that may arise from the proposed measure for the purposes of meeting FSANZ Act considerations. The FSANZ Act requires FSANZ to have regard to whether costs that would arise from the proposed measure outweigh the direct and indirect benefits to the community, government or industry that would arise from the proposed measure (paragraph 29(2)(a)).

The purpose of this consideration was to determine if the community, government, and industry as a whole is likely to benefit, on balance, from a move from the status quo. This analysis gave consideration to either approving or rejecting the application (retain the status quo). FSANZ remains of the view that no other realistic food regulatory measures exists.

The consideration of the costs and benefits in this section was not intended to be an exhaustive, quantitative economic analysis of the proposed measures and, in fact, most of the effects that were considered cannot easily be assigned a dollar value. Rather, the assessment sought to highlight the likely positives and negatives of moving away from the status quo by permitting the use of Reb M produced from fermentation as a food additive in certain foods.

Costs and benefits of permitting the use of Reb M produced by GM fermentation as an additive in certain foods

Consumers seeking products that have reduced sugar and/or energy content may benefit

from the use of Reb M (produced by GM fermentation of *S. cerevisiae*) as a food additive in certain foods.

In the USA, Amyris's Reb M has GRAS status for use as a table top sweetener and a general purpose non-nutritive sweetener in foods, and it is also permitted for similar purposes in Canada. Permission to use Amyris's Reb M as a food additive, will enable Australian and New Zealand food manufacturers to potentially access and use a product assessed as safe that is available to their overseas competitors. This may improve their capacity to compete in overseas markets. Use by industry is voluntary, therefore it will only be used where industry believe a net benefit exists for them above using existing intense sweeteners.

The Applicant was not requesting an extension for the use of steviol glycosides to additional food products, nor was it requesting an increase to the permitted quantities of steviol glycosides in permitted food products, but just a new method of production of an existing steviol glycoside. For this reason there are unlikely to be any additional costs for governments.

FSANZ had assessed that the direct and indirect benefits that would arise from permitting the use of Amyris's Reb M as a food additive will most likely outweigh the costs arising from that permission being granted.

2.5.1.2 Other measures

FSANZ considers that there are no other measures (whether available to FSANZ or not) that would be more cost-effective than a food regulatory measure developed or varied as a result of the application.

2.5.1.3 Any relevant New Zealand standards

The relevant Standards apply in both Australia and New Zealand. There are no relevant New Zealand only Standards.

2.5.1.4 Any other relevant matters

Other relevant matters are considered below.

2.5.2 Subsection 18(1)

FSANZ has also considered the three objectives in subsection 18(1) of the FSANZ Act during the assessment.

2.5.2.1 Protection of public health and safety

No potential public health and safety concerns associated with Amyris's Reb M were identified. For more detail, see SD1.

2.5.2.2 The provision of adequate information relating to food to enable consumers to make informed choices

The labelling requirements for the provision of information to consumers are discussed in section 2.3.1 above. FSANZ considered that those requirements would enable this objective to be satisfied.

2.5.2.3 The prevention of misleading or deceptive conduct

As explained above, Amyris's Reb M is not obtained from the stevia plant. FSANZ notes that steviol glycosides are sometimes marketed as stevia, a natural sweetener obtained from the leaves of the stevia plant, sometimes accompanied by leaf graphics. Any such marketing as well as claims such as 'natural' would be subject to consumer protection laws, fair trading laws and food laws in Australia and New Zealand that require that marketing and labels do not misinform consumers through false, misleading or deceptive representations.

2.5.3 Subsection 18(2) considerations

FSANZ has also had regard to:

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

FSANZ used the best available scientific evidence to conduct the risk assessment which is provided in SD1. The applicant submitted a dossier of scientific studies as part of its application. FSANZ also had regard to other technical information including scientific literature in assessing the application.

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

The specifications of Amyris's Reb M meet those established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 2017), the Food Chemicals Codex (FCC 2018) and the European Commission specifications for steviol glycosides (EC 2016).

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

Permission to use Amyris's Reb M as a food additive will enable Australian and New Zealand food manufacturers to access and use a product assessed as safe that is available to some overseas competitors. This will improve their capacity to compete in overseas markets. See discussion at section 2.5.1.1 above.

- **the promotion of fair trading in food**

FSANZ's assessment based on the best available scientific evidence is that Amyris's Reb M is safe for use as a food additive. It is permitted for use elsewhere. It is therefore appropriate that Australian and New Zealand food industries can also benefit by gaining permission to use Amyris's Reb M.

- **any written policy guidelines formulated by the Forum on Food Regulation[7]**

[7] From 21 February 2021 it is now called the 'Food Ministers' Meeting' following a decision by Ministers.

The Policy Guideline 'Addition to Food of Substances other than Vitamins and Minerals'[8] includes specific order policy principles for substances added to achieve a solely technological function, such as food additives. These specific order policy principles state that permission should be granted where:

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

FSANZ determined that permitting Amyris's Reb M from fermentation is consistent with these specific order policy principles.

3 References

EC (2012) COMMISSION REGULATION (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. Accessed 21 September 2020

EC (2016) COMMISSION REGULATION (EU) 2016/1814 of 13 October 2016 amending the Annex to Regulation (EU) No 231/2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards specifications for steviol glycosides (E 960). Accessed 21 September 2020

FCC (2018). Steviol Glycosides. In: Food Chemicals Codex, 11th edition. Rockville (MD): United States Pharmacopeial Convention, p1144.

FSANZ (2019a) Application A1170 Rebaudioside MD as a steviol glycoside from Saccharomyces cerevisiae. Food Standards Australia New Zealand, Canberra

FSANZ (2019b) Application A1172 Enzymatic production of rebaudioside D. Food Standards Australia New Zealand, Canberra

FSANZ (2019c) Application A1176 Enzymatic production of steviol glycosides. Food Standards Australia New Zealand, Canberra

FSANZ (2020) Application A1183 Enzymatic production of rebaudioside E. Food Standards Australia New Zealand

Health Canada (2020a) Notice of Modification to the List of Permitted Sweeteners to Enable the Use of Steviol Glycosides from Saccharomyces cerevisiae Y63348 in a Variety of Foods [NOM/ADM-0151] available at https://www.canada.ca/en/health-canada/services/food-nutrition/public-involvement-partnerships/notice-modification-list-permitted-sweeteners-steviol-glycosides.html. Accessed 16 March 2021

Health Canada (2020b), 9. List of Permitted Sweeteners (Lists of Permitted Food Additives), available at https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/lists-permitted/9-sweeteners.html. Accessed 15 March 2021

JECFA (2017). Steviol glycosides from Stevia *rebaudiana Bertoni* [New specifications prepared at the

[8] https://foodregulation.gov.au/internet/fr/publishing.nsf/Content/publication-Policy-Guideline-on-the-Addition-of-Substances-other-than-Vitamins-and-Minerals

84th JECFA, 2017), Superseding tentative specifications prepared at the 82nd JECFA (2016)]. In: *Compendium of Food Additive Specifications*. 84th Meeting, Rome, 6-15 June 2017 (FAO JECFA Monographs 20). Rome. pp. 50-69. http://www.fao.org/documents/card/en/c/4b06cdda-3e70-4c80-b7e5-56034601836b/ Accessed 21 September 2020

JECFA (2019a) Joint FAO/WHO Expert Committee on Food Additives, Eighty-seventh meeting, Rome, 4-13 June 2019. Summary and Conclusions. https://www.who.int/foodsafety/areas_work/chemical-risks/JECFA87_Summary_Report.pdf?ua=1 Accessed 21 September 2020

JECFA (2019b) World Health Organization & Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives: eighty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 1020. World Health Organization. https://apps.who.int/iris/handle/10665/330612. Accessed 21 September 2020

JECFA (2020) FAO and WHO. 2020. *Compendium of Food Additive Specifications. Joint FAO/WHO Expert Committee on Food Additives (JECFA), 87th Meeting June 2019.* Contains (Framework for) Steviol Glycosides, and four annexes. FAO JECFA Monographs 23. Rome. pp 62-84 http://www.fao.org/3/ca7513en/CA7513EN.pdf Accessed 21 September 2020.

PureCircle Stevia Institute 2020, Map Infographic Where in the World is Stevia Approved? https://www.purecirclesteviainstitute.com/resources/infographics/map-infographic Accessed 21 September 2020

Attachments

A. Approved draft variation to the Australia New Zealand Food Standards Code
B. Explanatory Statement

Attachment A – Approved draft variation to the Australia New Zealand Food Standards Code

Food Standards (Application A1207 – Rebaudioside M as Steviol Glycoside) Variation

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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 variation commences on the date specified in clause 3 of this variation.

Dated [To be completed by the Delegate]

[Insert name and title of Delegate]
Delegate of the Board of Food Standards Australia New Zealand

Note:

This variation will be published in the Commonwealth of Australia Gazette No. FSC XX on XX Month 20XX. This means that this date is the gazettal date for the purposes of clause 3 of the variation.

1 Name

This instrument is the *Food Standards (Application A1207 – Rebaudioside M as Steviol Glycoside) Variation*.

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

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

3 Commencement

The variation commences on the date of gazettal.

Schedule

[1] **Schedule 3** is varied by inserting in the table to subsection S3—39(2), in alphabetical order

Rebaudioside M	*Saccharomyces cerevisiae* strain Y63348 containing novel genes for the production of rebaudiosides

Attachment B – Explanatory Statement

1. Authority

Section 13 of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act) provides that the functions of Food Standards Australia New Zealand (the Authority) include the development of standards and variations of standards for inclusion in the Australia New Zealand Food Standards Code (the Code).

Division 1 of Part 3 of the FSANZ Act specifies that the Authority may accept applications for the development or variation of food regulatory measures, including standards. This Division also stipulates the procedure for considering an application for the development or variation of food regulatory measures.

The Authority accepted application A1207 which sought an amendment to the Code to permit the use of rebaudioside M (Reb M) produced from fermentation by a genetically modified *Saccharomyces cerevisiae* (*S. cerevisiae)* strain, as a food additive intense sweetener. The Authority considered the application in accordance with Division 1 of Part 3 and has approved a draft variation.

Following consideration by the Food Ministers' Meeting (formerly the Australia and New Zealand Ministerial Forum on Food Regulation)[9], section 92 of the FSANZ Act stipulates that the Authority must publish a notice about the standard or draft variation of a standard.

Section 94 of the FSANZ Act specifies that a standard, or a variation of a standard, in relation to which a notice is published under section 92 is a legislative instrument, but is not subject to parliamentary disallowance or sunsetting under the *Legislation Act 2003*.

2. Purpose

The Authority has approved a draft variation to the table to subsection S3—39(2) of the Code to permit Reb M to be used as a food additive (an intense sweetener) in accordance with the Code.

3. Documents incorporated by reference

The variations to food regulatory measures do not incorporate any documents by reference.

Existing provisions of the Code incorporate a document by reference that will prescribe identity and purity specifications for the food additive to be permitted by the draft variation. Section 1.1.1—15 of the Code requires substances used as food additives to comply with any relevant identity and purity specifications listed in Schedule 3 of the Code. Section S3—2 of Schedule 3 incorporates by reference the specifications listed in the Joint FAO/WHO Expert Committee on Food Additives (JECFA) Compendium of Food Additive Specifications (FAO/WHO 2017), the United States Pharmacopeial Convention (2018) Food Chemicals Codex (11th edition) and the Commission Regulation (EU) No 231/2012, specifications for food additives. These include specifications for this food additive.

4. Consultation

In accordance with the procedure in Division 1 of Part 3 of the FSANZ Act, the Authority's consideration of application A1207 included one round of public consultation following an assessment and the preparation of a draft variation and associated report. Submissions were

[9] The Forum name change took effect on 21 February 2021 following a decision by Ministers.

called for on 21 October 2020 for a six-week consultation period.

The Office of Best Practice Regulation (OBPR) granted the Authority a standing exemption from needing to develop a Regulatory Impact Statement for proposed variations of the Code to permit food additives (OBPR correspondence dated 24 November 2010 - reference 12065). This standing exemption was provided as permitting additional food additives (including new methods of manufacture of existing food additives) is likely to have only a minor impact on business and individuals. It is a minor, deregulatory change that allows for the introduction of a new version of a food additive to the food supply that has been determined to be safe. The use of the approved food additive is also voluntary.

5. Statement of compatibility with human rights

This instrument is exempt from the requirements for a statement of compatibility with human rights as it is a non-disallowable instrument under section 94 of the FSANZ Act.

6. Variation

Item 1 inserts a new entry into the table to subsection S3—39(2), which lists 'prescribed steviol glycosides' for the purposes of specifications in subsection S3—39(3).

The new entry is 'Rebaudioside M' derived from '*Saccharomyces cerevisiae* strain Y63348 containing novel genes for the production of rebaudiosides'. In other words, Reb M derived from this source will be a prescribed steviol glycoside and specifications in subsection S3—39(3) will apply to this Reb M.

The effect of this amendment will be to permit Reb M that is derived from this source, obtained by fermentation, and not from the leaves of the *Stevia rebaudiana* Bertoni plant, to be used as a food additive in accordance with the existing food additive permissions in the Code for steviol glycosides, provided that the Reb M complies with the specifications listed in subsection S3—39(3).