20 December 2019
[106-19]

Approval report – Application A1176

Enzymatic production of Steviol Glycosides

Food Standards Australia New Zealand (FSANZ) has assessed an application made by PureCircle Limited to seek approval for a new specification for steviol glycosides produced by an enzymatic conversion method using enzymes derived from genetically modified strains of *Escherichia coli*.

On 27 August 2019, FSANZ sought submissions on a draft variation and published an associated report. FSANZ received five submissions.

FSANZ approved the draft variation on 4 December 2019 The Australia and New Zealand Ministerial Forum on Food Regulation was notified of FSANZ's decision on 19 December 2019.

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

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

SD1 Risk assessment – Application A1176 – Enzymatic production of Steviol Glycosides

Executive summary

PureCircle Limited (PureCircle) has applied to amend the Australia New Zealand Food Standards Code (the Code) to permit an enzymatic conversion method to produce steviol glycoside preparations. The method uses three enzymes derived from genetically modified (GM) strains of *Escherichia coli* K-12, namely two UDP-glucosyltransferases and sucrose synthase. The resulting three different steviol glycoside preparations have a high content of rebaudioside (reb) M and/or reb D, or reb AM, subject to the starting material (reb A or stevioside respectively). The starting material is extracted from the *Stevia rebaudiana* Bertoni (stevia) leaves. Reb M, D and AM are known as 'minor' steviol glycosides as they are present in the stevia leaf at low levels compared to other 'major' steviol glycosides.

Steviol glycosides are currently permitted by the Code to be used in certain foods as food additives up to specified maximum permitted levels. They are used as an intense sweetener or flavour enhancer.

Substances used as food additives must comply with any relevant identity and purity specifications listed in Schedule 3 – Identity and Purity. Section S3—35 of Schedule 3 currently includes a specification for steviol glycosides prepared from the leaves of *Stevia rebaudiana* Bertoni which includes reb M and reb D produced by enzymatic conversion. The source of the enzymes used by PureCircle and one of the resulting steviol glycoside preparations (high in reb AM) are however, different to those already included in the specification.

The processing aids used in PureCircle's enzymatic conversion method are not currently permitted to be used by the Code.

FSANZ therefore carried out an assessment to determine whether there are any potential public health and safety concerns associated with PureCircle's steviol glycoside preparations produced using the specified enzyme processing aids. This risk assessment did not identify any health or safety concerns.

The enzymatic conversion method used by PureCircle is technologically justified in that it yields higher amounts of steviol glycosides that are present in stevia leaves in 'minor' amounts. PureCircle claims preparations containing these steviol glycosides have preferential taste characteristics compared to preparations containing major individual steviol glycosides alone.

A call for submissions and assessment report were released for consultation from 27 August to 8 October 2019. Five submissions were received in response; all of which were supportive of the draft variation.

Based on the information above and on other relevant considerations, FSANZ has approved a draft variation to the specification for steviol glycosides from *Stevia rebaudiana* Bertoni (S3—35) to include steviol glycosides (reb D, reb M and reb AM) produced from enzymatic conversion using specific enzymes derived from GM strains of *E. coli.*

Additionally, the sweetness potency of preparations of steviol glycosides with a high reb AM content was determined by PureCircle to be approximately 150 times sweeter than sucrose. This is less than that currently in the specification in S3—35, which is approximately 200-300 times sweeter than sucrose. The specification will therefore also be amended to refer to approximately 150-300 times sweeter than sucrose.

It was also considered appropriate to approve a draft variation to Schedule 18 – Processing aids permitting the use of the protein engineered enzymes UDP-glucosyltransferase and sucrose synthase, sourced from (GM) *E. coli* as processing aids for the production of reb D, reb M or reb AM.

The express permission for the enzymes' use as processing aids will also provide the required permission for their potential presence in the steviol glycoside preparations as a food produced using gene technology. The enzymes are food produced using gene technology for Code purposes as they are derived from 'an organism that has been modified using gene technology'.

These amendments would allow the use of PureCircle's steviol glycoside preparations in accordance with the Code's existing permissions and limits for steviol glycosides.

1 Introduction

1.1 The Applicant

PureCircle Limited (PureCircle) is a producer of high purity steviol glycoside ingredients for the global food and beverage industry. PureCircle has offices in the United States of America and in Malaysia.

1.2 The Application

PureCircle has applied to amend the Australia New Zealand Food Standards Code (the Code) to permit an enzymatic conversion process using specified enzymes to produce steviol glycoside preparations. The enzymes used are derived from GM strains of *Escherichia coli* K-12, namely UDP-glucosyltransferases and sucrose synthase.

The resulting steviol glycoside preparations have a high content of the minor rebaudiosides, rebaudiosides (reb) M and/or reb D, or reb AM, subject to the starting material (reb A or stevioside respectively). The starting material is extracted from the *Stevia rebaudiana* Bertoni (stevia) leaves. Reb M, D and AM are known as 'minor' steviol glycosides as they are present in the stevia leaf at low levels compared to other 'major' steviol glycosides.

Steviol glycosides are permitted for use by the Code in food as food additives. They are used by the food industry as an intense sweetener or flavour enhancer.

1.3 The current standards

1.3.1 Australia and New Zealand standards

Australian and New Zealand food laws require food for sale to comply with the following requirements of the Code, as relevant to this application.

1.3.1.1 Food additives

Subsection 1.1.1—10(6) provides that, unless expressly permitted by the Code, a food for sale cannot contain, as an ingredient or component: a substance 'used as a food additive'.

Section 1.3.1—3 details which substances are permitted to be used as a food additive for the purposes of the Code.

Schedules 15 and 16 list the specific food additive permissions for different categories of foods. For example, the permitted food additives for different food categories are listed in the table to section S15—5 and 'Steviol glycosides' is listed as a permitted food additive under item 11.4 ('Tabletop sweeteners') of that table.

Section 1.1.2—11 also provides that a substance is 'used as a food additive' if it is added to a food to perform one or more technological functions listed in Schedule 14 and is one of a number of substances listed in that section. These include a substance identified in the table to section S15—5 as a permitted food additive.

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.

1.3.1.2 Processing aids

Enzymes used in food processing and manufacturing are considered processing aids as although they may be present in the final food, they no longer provide a technological purpose in the final food.

Paragraph 1.1.1—10(6)(c) provides that a food for sale must not have, as an ingredient or a component, a substance that is used as a processing aid, unless expressly permitted.

Section 1.1.2—13 defines the expression 'used as a processing aid'. That definition imposes certain conditions on substances permitted by Standard 1.3.3 and Schedule 18 to be used as a processing aid, such that it does not perform a technological function in the final food for sale.

Standard 1.3.3 and Schedule 18 list the permitted processing aids. Enzymes of microbial origin permitted to be used as processing aids are listed in the table to subsection S18—4(5) or in the table to subsection S18—9(3) of Schedule 18, depending on whether a technological purpose has been specified.

1.3.1.3 Food produced using gene technology

Paragraph 1.1.1—10(6)(g) requires that the presence of a food produced using gene technology as an ingredient or component in a food for sale must be expressly permitted by the Code. Section 1.5.2—3 of the Code provides that permission for use as a food additive or processing aid also constitutes the permission required by paragraph 1.1.1—10(6)(g).

1.3.1.4 Identity and purity requirements

Paragraphs 1.1.1—15(1)(a) and (b) requires substances used as food additives and processing aids respectively, to comply with any relevant identity and purity specifications listed in Schedule 3.

Section S3—35 of Schedule 3 provides a specification for steviol glycosides prepared from the leaves of *Stevia rebaudiana* Bertoni.

1.3.1.5 Labelling

Paragraph 1.1.1—10(8) of the Code provides that the labelling of a 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 the purposes of the Code, *genetically modified food* (GM 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.

1.3.2 International standards

Steviol glycosides are approved for use in a number of other jurisdictions, including the European Union, Canada, United States of America (USA), South America, Asia, the Middle East and Africa (PureCircle Stevia Institute, 2018). FSANZ understands that the three steviol glycoside preparations produced using the specific enzymatic conversion method in this application are not approved in Canada or Europe, and in the USA there is a Generally Recognized as Safe (GRAS) notice for the steviol glycosides preparation with a high reb M content. Further detail for these countries, as well as standards developed by the international bodies JECFA and Codex Alimentarius is provided below.

1.3.2.1 Codex Alimentarius

Codex Alimentarius is an international body, incorporating the Food and Agriculture Organisation of the United Nations (FAO) and the World Health Organization (WHO), that sets international food standards. Codex Alimentarius has a General Standard for Food Additives (GSFA, CODEX STAN 192-1995) that contains provisions for food additives in various food categories (Codex 2018a). The GSFA contains permissions for the addition of steviol glycosides (as steviol equivalents) to a wide variety of food categories up to maximum permitted levels.

1.3.2.2 Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Monograph 20 includes a specification for steviol glycosides obtained from a hot water extraction from the leaves of *S. rebaudiana* Bertoni ('Steviol glycosides from *Stevia rebaudiana* Bertoni') (JECFA 2017). This specification does not apply to steviol glycosides produced by enzymatic conversion. The specification includes a mixture of any of the steviol glycosides extracted from the stevia leaf rather than an earlier defined list of steviol glycosides. The purity of steviol glycosides from *S. rebaudiana* Bertoni must be no less than 95% total steviol glycosides on the dried basis.

Although not directly related to this Application, it is of relevance to note that in the next Code Maintenance Proposal FSANZ will consider the need to omit the existing specifications S3—31 – Specification for rebaudioside M and S3—32 – Specification for steviol glycoside mixture including rebaudioside M as these are now covered by JECFA Monograph 20 which is referenced in S3—2. Additionally, FSANZ will consider the need to amend S3—35 to remove reference to steviol glycoside preparations obtained from the leaves of the *Stevia rebaudiana* Bertoni plant for the same reason.

The Joint FAO/WHO Expert Committee on Food Additives considered specifications for steviol glycosides at their 87th meeting in June 2019. A framework was adopted for developing specifications for steviol glycosides by four different methods of production, including Enzyme Modified Steviol Glycosides. This new specification is yet to be published (FAO/WHO 2019).

1.3.2.3 United States of America (USA)

In the USA there have been over 50 Generally Recognised as Safe (GRAS) notices relating to steviol glycosides submitted to the USA Food and Drug Administration (FDA) for review. In particular the FDA issued a 'no questions'[1] response to PureCircle's GRAS notice for steviol glycosides with a high reb M content produced by enzymatic conversion of reb A from stevia leaf extract (GRN 745). To date, excluding pending notifications, the US FDA has not raised any objections to the GRAS status of these steviol glycoside products for use as a sweetener in foods (USFDA 2019).

1.3.2.4 Canada

In Canada 'Steviol glycosides from *Stevia rebaudiana* Bertoni' are permitted in a variety of foods, provided they comply with the relevant international specifications for steviol glycosides (either JECFA or Food Chemicals Codex) and relevant conditions for use and requirements of the Food and Drug Act (Health Canada 2018).

1.3.2.5 European Union

Steviol glycoside preparations are permitted as food additives in a variety of different food categories (European Commission 2011) provided they comply with the European Commission specifications for steviol glycosides (European Commission 2016). The specification applies only to steviol glycosides preparations extracted from the leaves of the *S. rebaudiana* Bertoni plant.

1.4 Reasons for accepting Application

The Application was accepted for assessment because:

- it complied with the procedural requirements under subsection 22(2)
- 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 of the FSANZ Act.

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 27 August and 8 October 2019.

[1] 'No questions' response means the FDA does not question the basis for the notifier's GRAS conclusion (USFDA 2016).

FSANZ received five submissions[2]. All five submitters supported the draft variation. Two submitters raised issues which are addressed in Table 1 below.
One response was received after the call for submissions period had closed. This was also supportive of the draft variation however an issue raised in the response has been considered as a 'relevant matter' under section 29 of the FSANZ Act and is included in Table 1.

Table 1: Summary of issues

Issue	Raised by	FSANZ response
The departments note the previously raised concerns about FSANZ's decision to delay the use of a numbering system to distinguish steviol glycosides from different sources, and different technologies in the responses to Application A1172[3]. Codex Alimentarius has already adopted a classification system to distinguish steviol glycosides from fermentation through the INS number, 960b. The Codex's labelling approach enables the source identification of steviol glycosides and enforcement of any applicable consumer laws that might refer to 'natural' or leaf extracts. The departments recommend that FSANZ should more rapidly adopt this classification system to distinguish steviol glycosides and align with international approaches.	Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions	An INS (international numbering system) number for steviol glycosides produced by an enzymatic conversion process has not yet been incorporated into the Codex Alimentarius Guideline *International Numbering System for Food Additives (INS)*. FSANZ cannot include an INS number in the Code specifically for steviol glycosides produced via that method of production until the INS number is available. As noted in response to submitter comments in previous similar applications, FSANZ will consider changes to the INS names and numbers in the Code for different production methods of steviol glycosides in the future, if further changes are made to the INS list. Further information is in section 2.3.3.1 of this report.
In relation to the INS numbers for labelling purposes, NZFGC noted they had previously suggested that there be an administrative limit set after which the Code should be amended to reflect the novel production methods available at that time[4]. This would give assurance about future transparency in the food supply.	New Zealand Food and Grocery Council (NZFGC) (late comment)	As above. In addition, as noted in the A1170 Approval Report, FSANZ understands NZFGC's suggestion and desire to ensure transparency. However, FSANZ considers it is appropriate to wait until further consideration by Codex regarding steviol glycosides before considering making changes to the Code.
Note from the Call for Submissions that the use of enzymatic conversion methods for steviol glycosides are not approved in Canada or Europe. The consideration of international standards is important when assessing Applications of this type, and FSANZ should have included	Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions	It is common for different food additives to be approved (or not) in different jurisdictions. This is most often attributable to differences in: • local market needs • regulatory approval processes (legislation, policies and timeframes)

[2] These submissions are on the FSANZ website at A1176 – Enzymatic production of Steviol Glycosides.
[3] The Approval Report for Application A1172 is available at A1172 – Enzymatic production of Rebaudioside D.
[4] FSANZ notes this was suggested in response to Application A1170. The Approval Report for A1170 is available at A1170 – Rebaudioside MD as a Steviol Glycoside from Saccharomyces cerevisiae

Issue	Raised by	FSANZ response
information as to why these methods are not approved in those jurisdictions.		• when applications are submitted to national food authorities for assessment. By exception, FSANZ would explicitly discuss the absence of an approval in another country due to a 'ban' or the result of public health and safety concerns raised during a regulatory assessment. Enzymatic conversion is a newer method of production that has also not yet been incorporated into the JECFA specification (refer section 1.3.2) and FSANZ is simply ahead of some other countries in approving the use of steviol glycosides produced using that method.
The inclusion of steviol glycosides produced through this new method within the category of currently permitted foods was supported, as well as foods that will be permitted in the future. Omissions of permissions in any one non-alcoholic beverage class would need to be avoided.	New Zealand Beverage Council	Any consideration by FSANZ to amend the Code to provide permission for steviol glycosides to be added to additional food classes in the future would be subject to the standard pre-market assessment process undertaken by FSANZ.
It was noted that although the steviol glycosides produced by this method would not require labelling as 'genetically modified', 'GMO free' claims or claims of similar meaning on products using steviol glycosides produced by this method would be inappropriate.	New Zealand Beverage Council	The Code does not regulate 'GMO free' claims or claims of similar meaning. These types of representations are voluntary and are subject to fair trading laws and food acts in Australia and New Zealand, which prohibit representations about food that are, or are likely to be, false, misleading or deceptive.

2.2 Risk assessment

FSANZ carried out an assessment to determine whether there were any potential public health and safety concerns associated with PureCircle's steviol glycoside preparations produced using the specified enzyme processing aids.

The host strain for the enzyme processing aids, *E. coli* K-12, is not pathogenic or toxigenic and has a history of safe use for the production of food enzymes. Genes for three enzymes were introduced into *E. coli* K-12, generating three distinct production strains. Molecular characterisation of the production strains has confirmed the enzyme coding sequence is as expected and has not undergone any rearrangement, and the introduced DNA is stably inherited. The production strains have also been shown to be genetically stable.

Previous assessments of steviol glycosides by FSANZ and JECFA have confirmed that steviol glycosides share a metabolic pathway to steviol, which is then glucuronidated and excreted in the urine. The unpublished data presented in the current application confirm that reb AM, an isomer of reb D, is also metabolised to steviol.

Individual steviol glycosides produced using enzymes from GM *E. coli* are chemically equivalent to individual steviol glycoside extracted directly from leaves of *Stevia rebaudiana* Bertoni. Evidence has been provided that proteins used in production have been effectively removed and do not pose an allergenic hazard.

No new evidence of adverse effects of steviol glycosides has been identified that would justify changing the ADI of 0 to 4 mg/kg body weight, expressed as steviol, for steviol glycosides previously established by FSANZ. This is therefore appropriate for steviol glycosides produced by enzymatic conversion using enzymes produced by GM *E. coli* that are the subject of this application.

FSANZ is aware that a number of research papers have reported on possible links between consumption of intense sweeteners and unwanted metabolic effects resulting in weight gain, but considers that the current weight of evidence does not support a causal relationship. FSANZ will continue to monitor the emerging scientific literature in this area.

In conclusion, FSANZ's risk assessment did not identify any health or safety concerns associated with PureCircle's steviol glycosides preparations.

2.3 Risk management

2.3.1 Specification for steviol glycosides

The risk management options available to FSANZ, after assessment, were to reject the application or to prepare a draft variation to amend the Code to permit PureCircle's steviol glycosides D for use as a food additive at levels and in food classes currently permitted in the Code for steviol glycosides.

Based on the conclusion above, that there are no public health and safety concerns, and on supporting submitter comments and other considerations detailed in section 2.5, amendments to the specification for steviol glycosides from *Stevia rebaudiana* Bertoni (S3—35) to include steviol glycosides (reb D, reb M and reb AM) produced by an enzymatic conversion method using specific enzymes derived from GM strains of *E. coli* were appropriate. Amending the steviol glycosides specification ensures the steviol glycoside preparations that are the subject of this application have the same permissions for use as a food additive as other steviol glycoside preparations already included in specifications in the Code.

As the primary specification, i.e. the FAO JECFA Monographs 20 (2017), does not include the chemical name for reb AM, this has been included in the specification in S3—35.

According to the application, the sweetness potency of preparations of steviol glycosides with a high reb AM content was determined to be approximately 150 times sweeter than sucrose. This is less than that currently in the specification in S3—35, which is approximately 200-300 times sweeter than sucrose. The specification will therefore also be amended to refer to approximately 150-300 times sweeter than sucrose. As this allows for a reduction in sweetness, FSANZ does not anticipate any impact on steviol glycoside preparations currently required to comply with this specification.

2.3.2 Enzyme processing aids

It was also considered appropriate to amend Schedule 18 to permit the use of the protein engineered enzymes UDP-glucosyltransferase and sucrose synthase sourced from GM *E. coli* as processing aids. This is because it is possible (although highly unlikely) that the steviol glycoside preparations may contain traces of these enzyme processing aids and unless expressly permitted by the Code, a food for sale must not contain, as an ingredient or a component, a substance that was used as a processing aid or a food produced using gene technology. The enzymes are a food produced using gene technology for Code purposes as they are derived from 'an organism that has been modified using gene technology' (i.e. GM microorganisms). The draft variation includes the protein engineered enzymes UDP-glucosyltransferase and sucrose synthase sourced from GM *E. coli* in the table to subsection S18—9(3) because a technological purpose has been specified—the conversion of purified stevia leaf extract to produce reb D, reb M; and reb AM.

The express permission for the enzymes' use as processing aids will also provide the permission for their presence in the steviol glycosides preparations as a food produced using gene technology.

FSANZ's assessment is that the use of the enzymes as processing aids to manufacture the steviol glycoside preparations does not itself, make those preparations GM foods. As the preparations are not derived from an organism that has been modified using gene technology, FSANZ's determination is that these preparations are not of themselves a food produced using gene technology.

2.3.3 Labelling considerations

2.3.3.1 Ingredient labelling – steviol glycosides

Under existing labelling requirements in the Code (unless the food is exempt from the requirement for a statement of ingredients) the steviol glycosides would require declaration as a food additive in the statement of ingredients on the label of foods. These ingredient labelling requirements currently require steviol glycosides to be identified in the statement of ingredients using the food additive name 'Steviol glycosides' or the code number 960 (as listed in Schedule 8). As the proposed change to the Code is to the specification rather than approval of the steviol glycosides themselves as a food additive, the existing labelling requirements relating to steviol glycosides will apply.

The following information provides further detail in relation to concern from a submitter and the late comment as outlined in table 1 above about not updating the INS numbers in line with new numbers in the Class Names and International Number System for Food Additives.

The Codex Committee on Food Additives (CCFA) at its 50th Session (March 2018) updated the International Numbering System (INS) numbers for steviol glycosides, which were subsequently adopted into the Class Names and International Number System for Food Additives (CXG 36-1989) by the Codex Alimentarius Commission at its meeting in July 2018 (Codex 2018b). 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). As CCFA has not completed its work on the production method described in this application, a new INS number is not assigned at the present time.

When considering A1170, FSANZ decided not to include 960a and 960b in the Code at that stage for various reasons (as outlined in A1170 approval report). These reasons included the desire to provide a more coordinated approach and efficient transition for the labelling of steviol glycosides produced by all new novel methods of production compared to an unsystematic or ad-hoc approach for individual methods of production through various applications. This also maintains a level playing field for suppliers of steviol glycosides or for manufacturers of foods containing steviol glycosides produced using novel production methods, given INS numbers are not available for all methods.

For these reasons, FSANZ considers that the most appropriate INS number for labelling purposes, for all steviol glycosides at this stage, is 960. FSANZ will consider changes to this INS number in the future, if further changes are made to the INS list.

The FSANZ website has been updated to provide information on the new production methods. This advises consumers wanting to know the source of any particular steviol glycosides in foods that they can ask the manufacturer who should advise them accordingly.

2.3.3.2 Ingredient labelling – processing aids

In terms of the enzymes used as processing aids, paragraphs 1.2.4—3(2)(d) and (e) exempt processing aids from the requirement to be declared in the statement of ingredients. This exemption will apply to the processing aids approved in this application.

2.3.3.3 Labelling as 'genetically modified'

Section 1.5.2—4 requires certain foods for sale that consist of or have as an ingredient, food that is genetically modified to be labelled with the statement 'genetically modified'. The Code's labelling requirements imposed by section 1.5.2—4 apply to foods for retail sale and to foods sold to a caterer under subsection 1.2.1—8(1) and section 1.2.1—15 respectively.

FSANZ's assessment is that PureCircle's steviol glycoside preparations are not food produced using gene technology as they are not derived from an organism that has been modified using gene technology. This is in contrast to the enzyme processing aids used for their manufacture, which are food produced using gene technology for Code purposes. As such, the steviol glycoside preparations themselves that are the subject of this application do not require labelling as 'genetically modified'.

The enzymes used as processing aids to manufacture PureCircle's steviol glycoside preparations are highly unlikely to be present as an ingredient in food for sale which contains these preparations. Furthermore, it is understood that the steviol glycoside preparations themselves would not be sold for retail sale or to a caterer because they are highly concentrated intense sweeteners. As such, it is highly likely that the requirement to label the processing aids as 'genetically modified' would not apply to a food for sale that contains the steviol glycoside preparation(s) because the labelling requirements only apply to food that consists of, or has as an ingredient, a genetically modified food under section 1.5.2—4.

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 are 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. All comments are valued and contribute to the rigour of our assessment.

The draft variation was considered for approval by the FSANZ Board taking into account public comments 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 Regulation Impact Statement for the approval of additional processing aids or food additives (OBPR correspondence dated 24 November 2010, reference 12065). This standing exemption was provided as permitting additional processing aids or 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, has given consideration to the costs and benefits that may arise from the proposed measure for the purposes of meeting FSANZ Act requirements. 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 is 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 considers either the approval or rejection of the application (retain the status quo) to amend the Code to include the food additive, i.e. a new specification for steviol glycosides produced by an enzymatic conversion method using specific enzymes.

The consideration of the costs and benefits in this section is not intended to be an exhaustive, quantitative economic analysis of the proposed measure and, in fact, most of the effects that were considered cannot easily be assigned a dollar value. Rather, the assessment seeks to highlight the likely positives and negatives of moving away from the status quo by amending the Code as requested.

Costs and benefits of including a new specification for steviol glycosides produced by an enzymatic conversion method using specific enzymes

Steviol glycosides are used as intense sweeteners in reduced energy and no-added sugar products. The benefits provided are the ability to potentially more efficiently and effectively produce minor steviol glycosides, where minor steviol glycosides can have better taste attributes compared to other steviol glycosides (the results of taste tests).

Due to the voluntary nature of the permission, industry will only use the food additive (prepared using the specific enzyme processing aids) where they believe a net benefit exists. There are other methods available to industry to produce minor steviol glycosides. It is of benefit to industry to have additional choice available to them, especially where the food additive has preferential taste characteristics compared to preparations containing major individual steviol glycosides alone or is cheaper.

PureCircle may have an advantage over other intense sweetener manufacturing businesses from this voluntary permission. PureCircle acknowledges in its application that there is an exclusive capturable commercial benefit. The impact on other competing Australia-New Zealand manufacturers is unknown.

Food manufacturers that buy the food additive from PureCircle and down-stream retailers may reduce prices for the consumer in some existing products containing the food additive, where there are cost savings from using it.

There may also be greater substitution from products containing sugar or other sweeteners that have a less attractive taste, to generally better tasting minor steviol glycosides. That may increase the quality and choice of food products available to consumers.

The greater choice for consumers (highlighted above) may allow them to further maximise their utility by choosing a food or drink they may prefer. It may also result in some products becoming cheaper.

Permitting the food additive and associated enzyme processing aids may result in a small cost to government in terms of adding these to the current range of food additives and processing aids that are monitored for compliance.

Conclusions from cost benefit considerations

FSANZ's assessment is that the direct and indirect benefits that would arise from permitting the use of the food additive and enzyme processing aids most likely outweigh the associated costs.

2.5.1.2 Other measures

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 Standards and Schedules relevant to the draft variation apply in both Australia and New Zealand. There are no relevant New Zealand Standards.

2.5.1.4 Any other relevant matters

Other relevant matters are considered below.

2.5.2. Subsection 18(1)

FSANZ 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

FSANZ concluded that there are no public health and safety concerns associated with the use of the steviol glycosides preparations produced by an enzymatic conversion method using enzymes derived from genetically modified strains of *E. coli*. For further detail refer to section 2.2 above and SD1.

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

The generic labelling requirements will apply when these steviol glycoside preparations are added to food as an ingredient (see Section 2.3.3 above).

2.5.2.3 The prevention of misleading or deceptive conduct

No issues were identified with this application relevant to this objective.

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. PureCircle submitted a dossier of scientific studies as part of the application. Other technical information including scientific literature was also identified and used by FSANZ in assessing the application.

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

A number of international jurisdictions and standards permit the use of steviol glycosides in foods, the majority of which relate to steviol glycosides extracted directly from stevia leaves rather than enzymatic conversion. As outlined in section 1.3.2.2, JECFA recently adopted a framework for developing specifications for steviol glycosides by four different methods of production, including Enzyme Modified Steviol Glycosides.

As noted in Table 1 above, one submitter stated that FSANZ should have included in the Call for Submissions why the steviol glycoside preparations considered in this application are not currently approved in Canada or Europe. FSANZ notes that it is common for different food additives to be approved (or not) in different jurisdictions. Enzymatic conversion is a newer method of production that has also not yet been incorporated into the JECFA specification (refer section 1.3.2) and FSANZ is simply ahead of some other countries in approving the use of steviol glycosides produced using that method.

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

Permission to use these particular steviol glycoside preparations as food additives will provide additional choice to Australian and New Zealand food manufacturers, enabling access to an intense sweetener with preferential taste characteristics compared to preparations containing major individual steviol glycosides alone.

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

No issues were identified for this application relevant to this objective.

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

The Policy Guideline 'Addition to Food of Substances other than Vitamins and Minerals'[5] 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 has determined that the addition to food of steviol glycosides preparations that are the subject of this application would be consistent with these specific order policy principles.

3 References

Codex 2018a, General Standard for Food Additives, http://www.fao.org/gsfaonline/index.html;jsessionid=64CA5BB29D301405C4DD6FA3239EA22D Accessed 19 July 2019

Codex 2018b, CXG 36-1989, Class Names and the International Numbering System for Food Additives http://www.fao.org/fao-who-codexalimentarius/codex-texts/guidelines/en/ Accessed 22 July 2019

European Commission 2011, Commission Regulation (EU) No 1131/2011 of 11 November 2011 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council with regard to steviol glycosides. Available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1131&from=EN Accessed 22 July 2019

European Commission 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). Off J Eur Union 59(L278):37-41. Available at: https://publications.europa.eu/en/publication-detail/-/publication/ebcc38ed-91d5-11e6-8e27-01aa75ed71a1/language-en Accessed 22 July 2019

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

Health Canada 2018, 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 9 July 2019

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

JECFA (2017). Steviol glycosides from Stevia *rebaudiana Bertoni* [New specifications prepared at the 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, Italy: Food and Agriculture Organization of the United Nations (FAO) /Geneva, Switz.: World Health Organization (WHO), pp. 50-69. Available at: http://www.fao.org/documents/card/en/c/4b06cdda-3e70-4c80-b7e5-56034601836b/ Accessed 23 January 2019

PureCircle Stevia Institute 2018, Map Infographic Where in the World is Stevia Approved? https://www.purecirclesteviainstitute.com/resources/infographics/map-infographic Accessed 19 July 2019

USFDA (2016) About the GRAS Notification Program, October 2016. Accessed 1 August 2019.

USFDA (2019). GRAS Notices Inventory. Washington (DC): U.S. Food and Drug Administration (U.S. FDA). Available at: https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices Accessed 22 July 2019

Attachments

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

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

Food Standards (Application A1176 – Enzymatic production of Steviol Glycosides) 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 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 A1176 – Enzymatic Production of Steviol Glycosides) Variation.*

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

The Schedule varies Standards 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

[1.1] omitting subsection S3—35(1), substituting

(1) In this section:

prescribed rebaudiosides are:

(a) rebaudioside D;

(b) rebaudioside M; and

(c) rebaudioside AM.

rebaudioside AM means the steviol glycoside with the chemical name: 13-[(2-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]kaur-16-en-18-oic acid, 2-O-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-β-D-glucopyranosyl ester.

(1A) This specification relates to a steviol glycosides preparation obtained from the leaves of the *Stevia rebaudiana* Bertoni plant.

[1.2] omitting paragraph S3—35(2)(c), substituting

(c) by enzymatic conversion of purified stevia leaf extract to produce rebaudioside D using a protein engineered enzyme that:

(i) contains both UDP-glucosyltransferase (EC 2.4.1.17) and sucrose synthase (EC 2.4.1.13) components; and

(ii) is sourced from *Pichia pastoris* strain UGT-A;

(d) by enzymatic conversion of purified stevia leaf extract to produce one or more prescribed rebaudiosides using a combination of enzymes that contains:

(i) a UDP-glucosyltransferase from *Stevia rebaudiana* sourced from *Escherichia coli*; and

(ii) a UDP-glucosyltransferase from *Solanum lycopersicum* sourced from *Escherichia coli*; and

(iii) a sucrose synthase (EC 2.4.1.13) sourced from *Escherichia coli*.

[1.3] omitting paragraph S3—35(4)(a), substituting

(a) Description—white to light yellow powder, approximately 150 to 300 times sweeter than sucrose;

[2] **Schedule 18** is varied by

[2.1] inserting in the table to subsection S18—9(3), in alphabetical order

Sucrose synthase (EC 2.4.1.13) sourced from *Escherichia coli* K-12 containing the gene for sucrose synthase from *Arabidopsis thaliana*	For the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside D, rebaudioside M; and rebaudioside AM	GMP

[2.2] inserting in the table to subsection S18—9(3), in alphabetical order

Uridine diphosphate (UDP) glucosyltransferase sourced from *Escherichia coli* K-12 containing the UDP glucosyltransferase gene from *Solanum lycopersicum*	For the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside D, rebaudioside M; and rebaudioside AM	GMP

[2.3] inserting in the table to subsection S18—9(3), in alphabetical order

Uridine diphosphate (UDP) glucosyltransferase sourced from *Escherichia coli* K-12 containing the UDP glucosyltransferase gene from *Stevia rebaudiana*	For the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside D, rebaudioside M; and rebaudioside AM.	GMP

Attachment B – Draft 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 A1176 which seeks approval for a new specification for steviol glycosides produced by an enzymatic conversion method using enzymes derived from genetically modified strains of *Escherichia coli* (*E. coli*). The Authority considered the Application in accordance with Division 1 of Part 3 and has approved a draft variation to amend the Code.

Following consideration by the Australia and New Zealand Ministerial Forum on Food Regulation, section 92 of the FSANZ Act stipulates that the Authority must publish a notice about the 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 approved a draft variation to:

a. amend subsection S3—35(2) of the Code by including, in the specification for steviol glycosides from *Stevia rebaudiana* Bertoni, a reference to the enzymatic conversion method used to produce the following steviol glycosides: rebaudiosides D, M and AM, thereby permitting such steviol glycosides to be used as food additives in accordance with the existing permissions and limits for steviol glycosides in the Code; and
b. amend Schedule 18 of the Code to permit the use of the specific enzymes as processing aids in the production of rebaudiosides D, M and AM in accordance with Standard 1.3.3 of the Code.

3. Documents incorporated by reference

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

4. Consultation

In accordance with the procedure in Division 1 of Part 3 of the FSANZ Act, the Authority's consideration of Application A1176 included one round of public consultation following an assessment and the preparation of a draft variation and associated assessment summary. Submissions were called for on 27 August 2019 for a six-week consultation period.

A Regulation Impact Statement was not required because the approved variations to Schedules 3 and 18 are likely to have a minor impact on business and individuals (OBPR reference 12065).

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

6.1 Item [1.1]

Item [1.1] amends Schedule 3 of the Code by omitting subsection S3—35(1) and inserting, in its place, new subsections S3—35(1) and S3—35(1A).

New subsection S3—35(1) provides a definition of the terms 'prescribed rebaudiosides' and 'rebaudioside AM' for the purposes of section S3—35*, particularly* paragraph S3—5(2)(d) as provided by item [1.2] below.

New subsection S3—35(1A) simply restates the current section S3—35(1).

6.2 Item [1.2]

Item [1.2] adds a new paragraph (d) to subsection S3—35(2) of Schedule 3 of the Code.

The item does this by omitting paragraph S3—35(2)(c) and inserting in its place new paragraphs S3—35(2)(c) and (d).

Paragraph S3—35(2)(c) was inserted into the Code by the draft variation approved by FSANZ for Application A1172, which took effect prior to this draft variation approved for Application A1176.

Item [1.2] restates and does not amend paragraph S3—35(2)(c).

The new paragraph S3—35(2)(d) includes a reference to the enzymatic conversion of purified stevia leaf extract to produce rebaudiosides D, M and/or AM. The enzymatic conversion processes uses the following combination of enzymes:

- a uridine diphosphate (UDP) glucosyltransferase from *Stevia rebaudiana* sourced from *Escherichia coli*
- a UDP-glucosyltransferase from *Solanum lycopersicum* sourced from *Escherichia coli*
- a sucrose synthase (EC 2.4.1.13) sourced from *Escherichia coli.*

The effect of this amendment is to permit the following steviol glycosides: rebaudiosides D, M and/or AM, produced using this method, to be used as food additives in accordance with the existing food additive permissions in the Code for steviol glycosides.

6.3 Item [1.3]

Item [1.3] amends the requirement for steviol glycoside preparations obtained from the leaves of the *Stevia rebaudiana* Bertoni plant from 200 to 300 times sweeter than sucrose to 150 to 300 times sweeter than sucrose.

6.4 Item [2]

Item [2] amends Schedule 18 by inserting new entries into the table to subsection S18—9(3).

The effect of the new entries is to permit the use of specific enzymes as processing aids for the following technological purpose - the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside D, rebaudioside M; and rebaudioside AM. The permitted enzymes are:

- Sucrose synthase (EC 2.4.1.13) sourced from *Escherichia coli* K-12 containing the gene for sucrose synthase from *Arabidopsis thaliana*
- Uridine diphosphate (UDP) glucosyltransferase sourced from *Escherichia coli* K-12 containing the UDP glucosyltransferase gene from *Solanum lycopersicum*
- UDP glucosyltransferase sourced from *Escherichia coli* K-12 containing the UDP glucosyltransferase gene from *Stevia rebaudiana.*

The permissions include the condition that the maximum permitted amount used as a processing aid must be consistent with Good Manufacturing Practice (GMP) (as defined by section 1.1.2—2(3) of the Code).