15 June 2023
246-23

Call for submissions – Application A1268

Steviol glycosides produced by bioconversion using new enzymes produced by GM *Escherichia coli*

Food Standards Australia New Zealand (FSANZ) has assessed an application made by Manus Bio Inc. to amend the Australia New Zealand Food Standards Code to permit three enzymes from genetically modified (GM) *Escherichia coli* strain K-12 as processing aids in the manufacture of steviol glycosides and has prepared a draft food regulatory measure. Pursuant to section 31 of the *Food Standards Australia New Zealand Act 1991* (FSANZ Act), FSANZ now calls for submissions to assist consideration of the draft food regulatory measure.

For information about making a submission, visit the FSANZ website at current calls for public comment and how to make a submission.

All submissions on applications and proposals will be published on our website. We will not publish material that we accept as confidential. In-confidence submissions may be subject to release under the provisions of the *Freedom of Information Act 1982*. Submissions will be published as soon as possible after the end of the submission period.

Under section 114 of the FSANZ Act, some information provided to FSANZ cannot be disclosed. More information about the disclosure of confidential commercial information is available on the FSANZ website at information for submitters.

For information on how FSANZ manages personal information when you make a submission, see FSANZ's Privacy Policy.

Submissions should be made in writing; be marked clearly with the word 'Submission.' You also need to include the correct application or proposal number and name. Electronic submissions can be made by emailing your submission to submissions@foodstandards.gov.au. FSANZ also accepts submissions in hard copy to our Australia and/or New Zealand offices.

There is no need to send a hard copy of your submission if you have submitted it by email or via the FSANZ website. FSANZ endeavours to formally acknowledge receipt of submissions within 3 business days.

DEADLINE FOR SUBMISSIONS: 6pm (Canberra time) 27 July 2023

Submissions received after this date will not be considered unless an extension had been given before the closing date. Extensions will only be granted due to extraordinary circumstances during the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.
Questions about making a submission or application and proposal processes can be sent to standards.management@foodstandards.gov.au.

Submissions in hard copy may be sent to the following addresses:

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Supporting document

The following document which informed the assessment of this application is available on the FSANZ website[1]:

SD1 Risk and technical assessment report

[1] https://www.foodstandards.gov.au/code/applications/Pages/A1268---Steviol-glycosides-produced-by-bioconversion-using-new-enzymes-produced-by-GM-Escherichia-coli.aspx

Executive summary

Manus Bio Inc. has applied to Food Standards Australia New Zealand (FSANZ) to amend the Australia New Zealand Food Standards Code (the Code) to permit the use of three new GM enzymes for the bioconversion production method of two steviol glycosides, rebaudiosides M and I. The protein engineered enzymes are:

- Uridine triphosphate (UTP)-glucose-1-phosphate uridylyltransferase (EC 2.7.7.9) produced by GM *Escherichia* coli K-12, expressing the gene for UTP-glucose-1-phosphate uridylyltransferase from *Bifidobacterium bifidum*
- Uridine diphosphate (UDP)-Glucosyltransferase produced by GM *Escherichia coli* K-12, expressing the gene for UDP-glucosyltransferase from *Oryza sativa* (rice)
- Sucrose synthase (EC 2.4.1.13) produced by GM *Escherichia coli* K-12, expressing the gene for sucrose synthase from *Glycine max* (soybean).

Both rebaudioside M and rebaudioside I are to be used as intense sweeteners in food and are already approved for that purpose in the Code.

FSANZ's risk assessment found the three enzymes are technologically justified for use as processing aids in the bioconversion production method of steviol glycosides.

No residual protein or DNA of the microorganisms and enzymes remains in the purified steviol glycosides and the purity complies with the relevant JECFA specifications for steviol glycosides.

The production organism *E. coli* strain K-12 has a long history of safe use. The derived strains which produce rebaudiosides M and I are neither pathogenic nor toxigenic and do not present a food safety risk. Analysis of the GM production strain confirmed the insertion and stability of the inserted genes.

The enzymes have a history of safe use for steviol glycoside production. For all three enzymes, the inserted genetic material is from a species with a long history of safe use. Recent bioinformatics searches were conducted by comparing the amino acid sequences of the three enzymes to those of known toxins and known allergens. No homologies of concern were identified in these searches.

Based on the reviewed data it was concluded that in the absence of any identifiable hazard, an Acceptable Daily Intake (ADI) 'not specified' is appropriate for all three enzymes.

The bioconversion production method of steviol glycosides is a well-known and assessed method that has permissions in international regulations, including Codex Alimentarius standards and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) framework for steviol glycosides specifications

Based on the risk assessment, FSANZ has prepared a draft variation to the Code which, if approved, would permit the use of the three enzymes as processing aids to produce the steviol glycosides rebaudioside M and rebaudioside I using the applicant's bioconversion production method in accordance with the Code.

FSANZ now seeks submissions to assist consideration of the draft variation.

1 Introduction

1.1 The Applicant

Manus Bio Inc. (Manus Bio) is a manufacturer of flavours, fragrances, food ingredients, cosmetics, vitamins, pharmaceuticals and agricultural chemicals. It uses fermentation technology to produce steviol glycosides, an intense sweetener food additive permitted to be added to various food products.

1.2 The application

Manus Bio has requested permission for the use of three new GM enzymes for the bioconversion production method of two steviol glycosides, rebaudiosides M and I, in the Australian New Zealand Food Standards Code (the Code). These enzymes are not currently permitted in the Code for such use.

The applicant's method of production is variously called bioconversion, biotransformation, enzymatic conversion or 'enzyme modified', with 'bioconversion' being used in this report.

JECFA has recently completed a framework for the specifications of steviol glycosides within monograph 26 (2021) of JECFA specifications (FAO and WHO 2021). This includes the four methods of production including annex 3 - Enzyme modified steviol glycosides - the method of production used for this application. The reason for the assessment of the enzymes is that they are either not listed within this JECFA specification or are derived from different sources to those listed.

Annex 3 of the JECFA framework for specifications of steviol glycosides contains the following definition of enzyme modified steviol glycosides: a process in which steviol glycosides that have been extracted from the leaves of *Stevia rebaudiana* Bertoni [*stevia* plant] undergo enzymatic conversion of major steviol glycosides to minor ones. In the applicant's case, the minor steviol glycosides are rebaudioside M and rebaudioside I.

FSANZ has already assessed a number of recent applications using the bioconversion method of manufacture - A1157, A1272, A1176 and A1183 (FSANZ 2018, FSANZ 2019a, FSANZ 2019b, FSANZ 2020 respectively) and the enzymes used for such manufacture are permitted in the Code. However, the specific enzymes proposed for the production of the applicant's steviol glycosides are not permitted in the Code.

1.3 The current standard

1.3.1 Australia and New Zealand standards

Australian and New Zealand food laws require food for sale to comply with relevant requirements in the Code. The requirements relevant to this application are summarised below.

1.3.1.1 Permitted use - 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 that substance's use as a processing aid is expressly permitted by the Code.

Section 1.1.2—13 provides that a substance 'used as a processing aid' in relation to a food is a substance used during the course of processing that meets all of the following conditions:

- it is used to perform a technological purpose during the course of processing
- it does not perform a technological purpose in the food for sale, and
- it is a substance listed in Schedule 18 or identified in section S16—2 as an additive permitted at GMP.

Standard 1.3.3 and Schedule 18 list the permitted processing aids. Enzymes of microbial origin listed in the table to subsection S18—4(5) are permitted for use as a processing aid to perform any technological purpose if the enzyme is derived from the corresponding source specified in the table. The table to subsection S18—9(3) lists those substances, including enzymes derived from particular sources, that are permitted to be used as processing aids for specific technological purposes in relation to:

- if a food is specified—that food; or
- if no food is specified—any food.

There are a number of enzymes listed within S18—9(3) permitted for the production of different steviol glycosides.

1.3.1.2 Permitted use - food additives

As noted, the application is to permit the use of the three enzymes that are used in the production of two steviol glycosides but not a permission for the steviol glycosides themselves. However, since the assessment does touch on the method of production of steviol glycosides which are food additives, it is relevant to provide some information on how steviol glycosides are regulated in 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.

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 with the International Numbering System (INS) number 960.

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. According to paragraph 1.5.2—3(b), permission in the Code for use as a food additive or processing aid also constitutes the permission required by paragraph 1.1.1—10(6)(g) if no novel DNA or novel protein from the substance remains present in the food.

1.3.1.4 Identity and purity requirements

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

Subsection S3—2(1) of Schedule 3 incorporates by reference primary source specifications listed in the following: Joint FAO/WHO Expert Committee on Food Additives (JECFA) Combined Compendium of Food Additive Specifications (FAO 2020), and the United States Pharmacopeial Convention (FCC 2020) Food chemicals codex (12th edition); and the Commission Regulation (EU) No 231/2012. These include general identity and purity specifications for enzyme preparations used in food processing; and food additives.

The current Proposal P1061 – Code Maintenance Proposal 2023 (FSANZ 2023) is updating the JECFA specifications to include monographs 25 and 26. As noted in section 1.2 of this report above, Monograph 26 includes the framework for steviol glycosides specifications. This includes annex 3 which is the form of manufacture Enzyme modified [bioconversion] steviol glycosides relevant to this application. The gazettal of P1061 is expected to occur before the final consideration of this application. The applicant's three enzymes are not currently permitted for such use in the Code therefore an application was still required.

Section S3—35 of Schedule 3 provides a specification for steviol glycosides produced by enzymatic conversion which is relevant to this application.

1.3.1.5 Labelling requirements

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

Standard 1.2.1 sets out the labelling requirements for food for sale.

Standard 1.2.4 generally requires packaged food to be labelled with 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 ways: if the food additive can be classified into a class of additives listed in Schedule 7—by referring to the relevant class name, followed in brackets by the name or code number of the food additive indicated in Schedule 8; otherwise—by referring to the name of the food additive as indicated 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.

Paragraphs 1.2.4—3(2)(d) and (e) exempt processing aids from the requirement to be declared in the statement of ingredients, unless other requirements apply.

Section 1.5.2—4 of the Code requires a food for sale that consists of a *genetically modified*

food[2] (GM food) or has a GM food as an ingredient to be labelled as 'genetically modified', unless an exemption applies. The statement 'genetically modified' must be made in conjunction with the name of the GM food. If the GM food is used as a processing aid, this statement may be included in the statement of ingredients. In these circumstances, the requirements imposed by section 1.5.2—4 apply foods for retail sale and to foods sold to a caterer in accordance with Standard 1.2.1.

1.3.2 International standards for processing aids

In developing food regulatory measures, Food Standards Australia New Zealand (FSANZ) must have regard to the promotion of consistency between domestic and international food standards. In terms of food safety, the relevant international standard setting body is the Codex Alimentarius Commission (Codex). There is no Codex Alimentarius 'general standard' for enzymes, however as noted above there are internationally recognised specifications for enzyme preparations established by JECFA and Food Chemicals Codex.

In addition, there is a Codex guideline, *Guidelines on Substances used as Processing Aids* (CAC/GL 75-2010), which sets out general principles for the safe use of substances used as processing aids, including that substances used as processing aids shall be used under conditions of GMP.

1.3.3 International standards for steviol glycosides

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 2021). 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).

1.3.3.1 Codex Alimentarius

Codex Alimentarius has a General Standard for Food Additives (GSFA, CXS 192-1995) that contains provisions for food additives in various food categories (Codex 2021a). 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. The GSFA includes four types of steviol glycosides, being:

- INS 960a - Steviol glycosides from Stevia rebaudiana Bertoni (Steviol glycosides from Stevia)
- INS 960b - Steviol glycosides fermentation
- INS 960c - Enzymatically produced steviol glycosides
- INS 960d - Glucosylated steviol glycosides

Codex also has a guideline CXG 36-1989, Class Names and the International Numbering System (INS) for Food Additives (Codex 2021b) which lists the Codex names and numbering (INS) of food additives. It includes the names and INS numbers listed above that have been updated in the GSFA but there is an earlier entry which has not yet been removed. The report of the 52nd meeting of the Codex Committee on Food Additives (CCFA) in September 2021 endorsed these new INS names and number for the four different methods of production which was then adopted by the Codex Alimentarius Committee at its 44th meeting in 2021 and added into the GSFA and CXG 36-1989.

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[2] Section 1.5.2—4(5) defines ***genetically modified food*** to mean a '*food produced using gene technology that
a) contains novel DNA or novel protein; or
b) is listed in Section S26—3 as subject to the condition that its labelling must comply with this section' (*that being section 1.5.2—4*).

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

The JECFA Monograph 26 (91st meeting of February 2021) includes a framework for steviol glycosides produced by four different methods. These are listed below with a short summary of the method of production:

Annex 1 ***Extraction from the leaves of*** **Stevia rebaudiana** ***Bertoni***
Annex 2 ***Steviol glycosides from fermentation***: a GM microorganism used to produce specific steviol glycosides
Annex 3 ***Enzyme modified steviol glycosides***: steviol glycosides extracted from the leaves (Annex 1) undergo bioconversion of major steviol glycosides to minor ones
Annex 4 ***Enzyme modified glycosylated steviol glycosides:*** steviol glycosides extracted from the leaves (Annex 1) undergo enzyme catalysed reactions to add glucose units to steviol glycosides.

1.3.3.3 USA

In the USA there have been over 50 GRAS notifications relating to steviol glycosides submitted to the USA Food and Drug Administration (FDA) for review. GRN No. 1010 relates to the same production method and preparation of rebaudioside M as this application. GRN No. 1010 was submitted by the applicant in August 2021 and the US FDA responded with 'no questions' to the GRAS status[3]. Therefore, the applicant's rebaudioside M is considered GRAS for use as a general-purpose sweetener in foods in the US (USFDA 2022).

1.3.3.4 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 2023).

1.3.3.5 European Union

Steviol glycosides 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 specifications have been updated so some do apply to steviol glycosides preparations produced by bioconversion.

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 *Food Standards Australia New Zealand Act 1991* (FSANZ Act)
- it related to a matter that warranted the variation of a food regulatory measure.

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

1.5 Procedure for assessment

The application is being assessed under the General Procedure.

2 Summary of the assessment

2.1 Risk assessment

The *E. coli* strain has been genetically modified to produce the following enzymes used in production of the steviol glycosides:

- Uridine triphosphate (UTP)-glucose-1-phosphate uridylyltransferase (EC 2.7.7.9) produced by GM *Escherichia* coli K-12, expressing the gene for UTP-glucose-1-phosphate uridylyltransferase from *Bifidobacterium bifidum*
- Uridine diphosphate (UDP)-Glucosyltransferase produced by GM *Escherichia coli* K-12, expressing the gene for UDP-glucosyltransferase from *Oryza sativa* (rice)
- Sucrose synthase (EC 2.4.1.13) produced by GM *Escherichia coli* K-12, expressing the gene for sucrose synthase from *Glycine max* (soybean).

The three enzymes are technologically justified for use in the production of steviol glycosides by the bioconversion method, consistent with the JECFA framework for steviol glycosides specification, and would function as processing aids for the purposes of the Code. The processing and purity steps undertaken ensure residual protein and residual DNA of microorganisms and enzymes is removed and not in the final purified steviol glycosides.

The production strains derived from *E. coli* strain K-12 to produce rebaudiosides M and I are neither pathogenic nor toxigenic and do not present a food safety risk. Analysis of the GM production strain confirmed the insertion and stability of the inserted genes.

The enzymes have a history of safe use for steviol glycoside production. The production organism has a long history of safe use as an enzyme production organism. For all three enzymes, the inserted genetic material is from a species with a long history of safe use either as a supplement (*Bifidobacterium bifidum*) or as a food (rice, soybean). Recent bioinformatics searches were conducted by comparing the amino acid sequences of the three enzymes to those of known toxins and known allergens. No homologies of concern were identified in these searches.

Based on the reviewed data it is concluded that in the absence of any identifiable hazard, an Acceptable Daily Intake (ADI) ‘not specified’ is appropriate for all three enzymes.

2.2 Risk management

The bioconversion production method of steviol glycosides is comparable to methods already considered and permitted by FSANZ (see A1157, A1172, A1176 and A1183).

The risk management options available to FSANZ, after assessment, were to either reject the application or to prepare a draft variation to amend the Code to permit the applicant's three enzymes as processing aids to produce rebaudioside M and rebaudioside I, using the bioconversion production method.

No public health and safety concerns were identified during the assessment of the three enzymes. The enzymes were found to be technologically justified for their use to produce the steviol glycosides, and as such are appropriately considered to be processing aids. Their use is also consistent with the JECFA framework for steviol glycoside specifications.

FSANZ's assessment is that the use of the GM-derived enzymes to manufacture the steviol glycosides does not make the steviol glycosides GM foods. This is because the steviol glycosides are not themselves derived from an organism that has been modified using gene technology. The processing and purification steps undertaken ensure any residual protein or residual DNA from the microorganisms and enzymes is removed and not in the final purified steviol glycosides.

Therefore, for reasons set out in this report, FSANZ considers it is appropriate to prepare a draft variation to amend the Code as proposed. The proposed amendments to the Code include listing the three enzymes as permitted processing aids within Schedule 18 for use in the production of the specific steviol glycosides.

In addition, amendments are proposed to be made to section S3—35 – Specifications for steviol glycosides produced by enzymatic conversion, which will list these new enzymes, if permitted.

2.2.1 Labelling

2.2.1.1 Ingredient labelling

Under existing labelling requirements in the Code (unless the food for sale is exempt from the requirement for a statement of ingredients) the steviol glycosides will require declaration as a food additive in the statement of ingredients on the label of foods to which the steviol glycosides have been added (see Section 1.3.1.5 above). These ingredient labelling requirements currently require steviol glycosides to be identified in the statement of ingredients using the prescribed class name 'sweetener' followed in brackets by either the food additive name 'steviol glycosides' or the International Numbering System (INS) code number 960 (as listed in Schedule 8).

As noted in Section 1.3.2.1, the CCFA updated the INS numbers for steviol glycosides. FSANZ is not applying the updated numbering system as part of the application. This is to allow a more coordinated approach and efficient transition for the labelling of all steviol glycosides in the Code instead of an ad-hoc approach through various applications. 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.

The FSANZ website provides information on the various production methods for steviol

glycosides[4]. 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.

In terms of the three enzymes used as processing aids, the generic exemption from listing processing aids in the statement of ingredients would apply (see Section 1.3.1.5 above).

2.2.1.2 Labelling as 'genetically modified'

FSANZ's assessment is that Manus Bio's steviol glycosides are not GM foods and therefore would not require labelling as 'genetically modified'. This is in contrast to the enzymes used as processing aids for their manufacture, which are GM foods. However as noted in Section 2.1 of this report, no residual protein or DNA of the microorganisms and enzymes would be present in the final purified steviol glycosides and therefore, would not be present in the food for sale. As such, the requirement to label the processing aids as 'genetically modified' would not apply to a food for sale that contains the steviol glycosides.

2.2.2 Risk management conclusion

The risk management conclusion is to prepare a draft variation permitting the use of three specific enzymes as processing aids in the production of the steviol glycosides, rebaudiosides M and I.

2.3 Risk communication

2.3.1 Consultation

Consultation is a key part of FSANZ's standards development process. FSANZ developed and applied a standard communication strategy to this application. All calls for submissions are notified via the Food Standards Notification Circular, media release, FSANZ's social media channels and Food Standards News.

The process by which FSANZ approaches standards development matters is open, accountable, consultative and transparent. Public submissions are called to obtain the views of interested parties on the written draft measure.

The draft variation will be considered for approval by the FSANZ Board taking into account all public comments received from this call for submissions.

2.3.2 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obliged to notify WTO members where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

This application is specifically to permit three enzymes as processing aids to produce rebaudiosides by the bioconversion production method. As noted in section 1.3.2.1 above, the relevant international standard setting body is the Codex Alimentarius Commission (Codex). There is no Codex Alimentarius 'general standard' for processing aids, however there are JECFA and Food Chemicals Codex general specifications. There are JECFA specifications for steviol glycosides produced by different production methods, including bioconversion. This method of production is well known and regulated, and the enzymes are very comparable to already permitted forms and the enzymes perform the same function as

[4] For more information please see the following FSANZ webpage: Steviol glycosides (960) (intense sweetener) (stevia)

those listed in the JECFA specification.

Therefore, a notification to the WTO under Australia's and New Zealand's obligations under the WTO Technical Barriers to Trade or Application of Sanitary and Phytosanitary Measures Agreement was not considered necessary.

2.4 FSANZ Act assessment requirements

When assessing this application and the subsequent development of a food regulatory measure, FSANZ has had regard to the following matters in section 29 of the FSANZ Act:

2.4.1 Section 29

2.4.1.1 Consideration of costs and benefits

The Office of Impact Analysis (OIA), formerly OBPR, granted FSANZ a standing exemption from the requirement to develop a Regulatory Impact Statement for applications relating to new processing aids and GM foods (OBPR correspondence dated 24 November 2010, reference 12065). This standing exemption was provided as permitting new processing aids and GM foods is deregulatory as their use will be voluntary if the application concerned is approved. This standing exception 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 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 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, where the status quo is rejecting the application. This analysis considers the costs and benefits of approving this Application.

FSANZ is of the view that no other realistic food regulatory measures exist, however information received may result in FSANZ arriving at a different outcome.

The consideration of the costs and benefits in this section is 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 seeks to highlight the potential positives and negatives of moving away from the status quo by permitting the proposed enzymes for the production of steviol glycosides, rebaudiosides M and I.

Costs and benefits of permitting the proposed new enzymes produced from GM Escherichia coli for the production of steviol glycosides .

Industry

The proposed new enzymes would be used as processing aids to produce certain food additives i.e. steviol glycosides which are low-calorie sweeteners for a range of foods. The specific steviol glycosides being rebaudiosides M and I. There are other methods of producing rebaudiosides M and I and other steviol glycosides. Industry may adopt this method for producing these rebaudiosides, using the proposed new enzymes as processing aids, if there was a net benefit for them. Benefits may include lower costs and higher efficiency of producing these rebaudiosides using this production method.

Consumers

Industry may pass some of any cost savings to consumers, where it is cheaper to produce these rebaudiosides using the new enzymes as processing aids.

Given the already wide permissions for use of steviol glycosides in foods, it is not currently clear whether or not approval of the draft variation would notably increase availability of lower calorie food products for consumers as claimed by the applicant. If the draft variation is approved, that would, however, be supportive of enabling the range of such food products to continue.

Government

Permitting the new enzymes may result in a small cost to government in terms of additions to the current range of enzymes 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 proposed use of the new enzymes as processing aids would most likely outweigh the associated costs. Information received, however, from this Call for Submissions, may result in FSANZ arriving at a different conclusion.

2.4.1.2 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.

2.4.1.3 Any relevant New Zealand standards

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

2.4.1.4 Any other relevant matters

Other relevant matters are considered below.

2.4.2 Subsection 18(1)

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

2.4.2.1 Protection of public health and safety

FSANZ identified no potential public health and safety concerns associated with the proposed use of the three enzymes as processing aids. See SD1 for more detail.

2.4.2.2 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 2.2.1 above.

2.4.2.3 The prevention of misleading or deceptive conduct

No issues have been identified with this application relevant to this objective.

2.4.3 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. This dossier, together with other technical and scientific information, was considered 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. As outlined in section 1.3.2.2, JECFA has adopted a framework for developing specifications for steviol glycosides by four different methods of production, including bioconversion. The applicant's method of production of the two rebaudiosides is consistent with Annex 3 of the JECFA framework along with the production method utilised in the USA.

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

Permission to use the applicant's three enzymes as processing aids to produce rebaudiosides M and I would 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 in section 2.4.1.1 above.

- **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 Ministerial 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 processing aids. These specific order policy principles state that permission should be granted where:

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

- 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 the proposed use of these enzymes is consistent with these specific order policy principles for 'Technological Function'. All other relevant requirements of the policy guideline are similarly met.

3 Draft variation

The draft variation to the Code is at Attachment A and is intended to take effect on gazettal.

A draft 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.

4 References

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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). Off J Eur Union 59(L278):37-41. Accessed 13 March 2023.

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FSANZ 2020, Application A1183, https://www.foodstandards.gov.au/code/applications/Pages/A1183.aspx

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PureCircle Stevia Institute 2023, Map Infographic Where in the World is Stevia Approved? Accessed 13

Attachments

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

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

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

Food Standards (Application A1268 – Steviol glycosides produced by bioconversion using new enzymes produced by GM *Escherichia coli*) 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 Delegate's name and position title]
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 A1268 – Steviol glycosides produced by bioconversion using new enzymes produced by GM* Escherichia coli*) 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

Schedule 3—Identity and purity

[1] Paragraphs S3—35(1) (definition of *prescribed rebaudiosides*)

Repeal the definition, substitute:

prescribed rebaudiosides are:

(a) rebaudioside AM; and

(b) rebaudioside D; and

(c) rebaudioside I; and

(d) rebaudioside M.

[2] Subparagraph S3—35(2)(c)

Repeal this paragraph, substitute:

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

(i) a sucrose synthase (EC 2.4.1.13) sourced from *Escherichia coli*; and

(ii) a UDP-glucosyltransferase from *Oryza sativa* sourced from *Escherichia coli*; and

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

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

(v) a UTP-glucose-1-phosphate uridylyltransferase (EC 2.7.7.9) sourced from *Escherichia coli*.

Schedule 18—Processing aids

[3] Subsection S18—9(3) (table)

Insert each of the following entries in alphabetical order:

Sucrose synthase, protein engineered variant, (EC 2.4.1.13) sourced from *Escherichia coli* K-12 containing the gene for sucrose synthase from *Glycine max*	For the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside I and rebaudioside M	GMP
Uridine diphosphate (UDP) glucosyltransferase, protein engineered variant, sourced from *Escherichia coli* K-12 containing the UDP glucosyltransferase gene from *Oryza sativa*	For the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside I and rebaudioside M	GMP

Uridine triphosphate (UTP)-glucose-1-phosphate uridylyltransferase, protein engineered variant, (EC 2.7.7.9) sourced from *Escherichia coli* K-12, expressing the gene for UTP-glucose-1-phosphate uridylyltransferase from *Bifidobacterium bifidum*	For the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside I and rebaudioside M	GMP

Attachment B – Draft Explanatory Statement

Food Standards Australia New Zealand Act 1991

Food Standards (Application A1268 – Steviol glycosides produced by bioconversion using new enzymes produced by GM* Escherichia coli*) Variation

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 A1268 which seeks to amend the Code to permit the use of three new protein-engineered enzymes sourced from genetically modified *Escherichia coli* as processing aids for the bioconversion of the steviol glycosides - rebaudiosides I and M. The Authority considered the Application in accordance with Division 1 of Part 3 and has prepared a draft variation - the *Food Standards (Application A1268 – Steviol glycosides produced by bioconversion using new enzymes produced by GM* Escherichia coli*) Variation*.

2. Variation will be a legislative instrument

If approved, the draft variation would be a legislative instrument for the purposes of the *Legislation Act 2003* (see section 94 of the FSANZ Act) and be publicly available on the Federal Register of Legislation (www.legislation.gov.au).

If approved, this instrument would not be subject to the disallowance or sunsetting provisions of the *Legislation Act 2003.* Subsections 44(1) and 54(1) of that Act provide that a legislative instrument is not disallowable or subject to sunsetting if the enabling legislation for the instrument (in this case, the FSANZ Act): (a) facilitates the establishment or operation of an intergovernmental scheme involving the Commonwealth and one or more States; and (b) authorises the instrument to be made for the purposes of the scheme. Regulation 11 of the *Legislation (Exemptions and other Matters) Regulation 2015* also exempts from sunsetting legislative instruments a primary purpose of which is to give effect to an international obligation of Australia.

The FSANZ Act gives effect to an intergovernmental agreement (the Food Regulation Agreement) and facilitates the establishment or operation of an intergovernmental scheme (national uniform food regulation). That Act also gives effect to Australia's obligations under an international agreement between Australia and New Zealand. For these purposes, the Act establishes the Authority to develop food standards for consideration and endorsement by the Food Ministers Meeting (FMM). The FMM is established under the Food Regulation Agreement and the international agreement between Australia and New Zealand, and consists of New Zealand, Commonwealth and State/Territory members. If endorsed by the FMM, the food standards on gazettal and registration are incorporated into and become part of Commonwealth, State and Territory and New Zealand food laws. These standards or instruments are then administered, applied and enforced by these jurisdictions' regulators as part of those food laws.

3. Purpose

The Authority has prepared a draft variation to permit three new protein-engineered enzymes sourced from genetically modified *Escherichia coli* as processing aids for bioconversion of the steviol glycosides - rebaudiosides I and M.

The draft variation proposes amendments to section S3—35 (Specification for steviol glycosides produced by enzymatic conversion) and the table to subsection S18—9(3) (permitted processing aids for various technological purposes) of the Code for the above purpose.

4. Documents incorporated by reference

The draft variation does not incorporate any documents by reference.

However, existing provisions of the Code incorporate documents by reference that would prescribe identity and purity specifications for the processing aids and food additives (the steviol glycosides rebaudiosides I and M produced by enzymatic conversion) to be permitted by the draft variation. Section 1.1.1—15 of the Code requires substances used as processing aids and food additives to comply with any relevant identity and purity specifications listed in Schedule 3 of the Code. Subsection S3—2(1) of Schedule 3 incorporates by reference primary source specifications listed in the following: Joint FAO/WHO Expert Committee on Food Additives (JECFA) Combined Compendium of Food Additive Specifications (FAO JECFA Monographs 23 (2019)); the United States Pharmacopeial Convention (2020) Food chemicals codex (12th edition); and the Commission Regulation (EU) No 231/2012. These include general specifications for the identity and purity parameters of food additives and enzyme preparations used as processing aids in the production of those additives.

5. Consultation

In accordance with the procedure in Division 1 of Part 3 of the FSANZ Act, the Authority's consideration of Application A1268 will include one round of public consultation following an assessment and the preparation of a draft variation and associated assessment summary. A call for submissions (including the draft variation) will be open for a six-week period.

The Office of Impact Analysis[6] granted the Authority a standing exemption from the requirement to develop a Regulatory Impact Statement for applications relating to permitting new processing aids and genetically modified foods (OBPR correspondence dated 24 November 2010, reference 12065). This standing exemption was provided as permitting new processing aids and genetically modified foods is deregulatory as their use will be voluntary if the application concerned is approved. This standing exemption relates to the introduction of a food to the food supply that has been determined to be safe.

6. Statement of compatibility with human rights

If approved, this instrument would be exempt from the requirements for a statement of compatibility with human rights as it is a non-disallowable instrument under section 44 of the *Legislation Act 2003*.

7. Variation

7.1 Item [1]

Item [1] of the Schedule to the draft variation amends section S3—35 of the Code which sets out the specifications for steviol glycosides produced by the enzymatic conversion [bioconversion] method of production.

Item [1] amends the definition of 'prescribed rebaudiosides' in subsection S3—35(1) by

[6] Formerly known as the Office of Best Practice Regulation (OBPR)

inserting a new paragraph S3—35(1)(d) to include rebaudioside I as a prescribed rebaudioside.

Item [2] repeals paragraph S3—35(2)(c) and is replaced with:

- a new entry for the enzyme UDP-glucosyltransferase from *Oryza sativa* sourced from *Escherichia coli*.
- the current subparagraph S3—35(2)(c)(iii) entry is renumbered to subparagraph S3—35(2)(c)(i).
- a new entry, as paragraph S3—35(c)(v), for the enzyme UTP-glucose-1-phosphate uridylyltransferase (EC 2.7.7.9) sourced from *Escherichia coli*.

7.2 Item [2]

Item [2] of the Schedule to the draft variation amends Schedule 18 by including three new enzymes into the table to subsection S18—9(3), which lists substances permitted to be used as processing aids for specific technological purposes.

The following protein-engineered enzymes would be listed in alphabetical order into column 1 of the table:

- 'Sucrose synthase, protein engineered variant, (EC 2.4.1.13) sourced from *Escherichia coli* K-12 containing the gene for sucrose synthase from *Glycine max*';
- 'Uridine diphosphate (UDP) glucosyltransferase, protein engineered variant, sourced from *Escherichia coli* K-12 containing the UDP glucosyltransferase gene from *Oryza sativa*'; and
- 'Uridine triphosphate (UTP)-glucose-1-phosphate uridylyltransferase, protein engineered variant, (EC 2.7.7.9) sourced from *Escherichia coli* K-12, expressing the gene for UTP-glucose-1-phosphate uridylyltransferase from *Bifidobacterium* bifidum'.

The specific technological purpose for each enzyme is prescribed in column 2 of the table for the corresponding enzyme i.e. 'for the conversion of purified stevia leaf extract to produce one or more of the following: rebaudioside M and rebaudioside I'.

The maximum permitted level (MPL) at which each enzyme may be present in food is prescribed in column 3 of the table for the corresponding enzyme i.e. the MPL must be consistent with Good Manufacturing Practice (as defined by subsection 1.1.2—2(3) of the Code).

If the draft variation is approved, the cumulative effect of the amendments in items [1] and [2] above would be to permit the use of a bioconversion method of producing the steviol glycosides - rebaudiosides I and M, which uses three new protein-engineered enzymes sourced from genetically modified *Escherichia coli* as processing aids, in accordance with the Code.