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Supporting document

Risk and technical assessment – Application A1273
Steviol glycosides as a food additive in Food for special medical purposes

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Executive summary

This application from Nestlé Australia Limited and Nestlé New Zealand Limited (Nestlé) requested to amend the Australia New Zealand Food Standards Code (the Code) for the permission to add steviol glycosides to Food for Special Medical Purposes (FSMP) (category 13.5 in Schedule 15 of the Code), excluding products for infants under 12 months of age, at the proposed maximum permitted level of 330 mg/kg.

Steviol glycosides are currently permitted to be used as an intense sweetener in a number of foods. The permissions are listed in the table to section S15—5 of the Code. With the exception of tabletop sweeteners which are subject to Good Manufacturing Practice (GMP) use levels, all permissions for steviol glycosides are subject to numerical limits expressed as maximum permitted levels (MPLs).

The food technology assessment concluded that the use of steviol glycosides as a food additive in FSMP is consistent with its typical technological function as an intense sweetener. The evidence presented by the applicant provided adequate assurance that the use of steviol glycosides, is technologically justified and is effective in achieving its stated purpose. The category of FSMP that are formulated for a very low energy diet have a greater technological need for intense sweeteners than other FSMP.

FSANZ has previously assessed an extensive toxicological database on steviol glycosides, which has identified no safety concerns or a need to amend the ADI established by FSANZ in 2008 of 0-4 mg/kg bw for steviol glycosides, expressed as steviol equivalents. The applicant submitted a number of recent reviews on the toxicity of steviol glycosides which did not raise any concerns regarding the safety of steviol glycosides; nor provide any new toxicity information that has not previously been assessed by FSANZ. For this application FSANZ again determined there was no need to amend the established ADI.

FSANZ conducted dietary exposure assessments to estimate the level of chronic exposure to steviol glycosides (expressed as steviol equivalents) from manufactured very low energy foods produced for consumption as part of a very low energy diet (referred to as VLED in this report), and all other FSMP (referred to as ‘other FSMP’ in this report).

When used at the proposed maximum permitted level of 330 mg/kg, estimated dietary exposures from VLED (and other general purpose foods containing steviol glycosides) did not exceed the ADI, whereas estimated dietary exposures for adults, adolescents and

children from other FSMP when used as a sole source of nutrition exceeded the ADI. A lower maximum permitted level of steviol glycosides for other FSMP could result in exposures that do not exceed the ADI, if other FSMP are used as a sole source of nutrition. The highest use level of steviol glycosides (expressed as steviol equivalents) that would result in dietary exposures from other FSMP that do not exceed the ADI is 75 mg/kg.

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1 Introduction

Nestlé Australia Limited and Nestlé New Zealand Limited (Nestlé) applied to Food Standards Australia New Zealand (FSANZ) to amend the Australia New Zealand Food Standards Code (the Code) to permit the addition of the food additive steviol glycosides to Food for Special Medical Purposes (FSMP).

1.1 Objectives of the assessment

The objectives of this risk and technical assessment were to:

- determine whether the proposed purpose is a solely technological purpose and that steviol glycosides achieves its technological purpose as a food additive in the quantity and form proposed to be used
- evaluate potential public health and safety concerns that may arise from the use of this food additive, by considering:
  - any new data related to the safety and history of use of steviol glycosides
  - the dietary exposure assessment for steviol glycosides based on the proposed extension of use in FSMP.

2 Food technology assessment

When steviol glycosides are added to food as an intense sweetener, they are regulated as food additives.

FSANZ has previously completed food technology assessments for other applications relating to the use of steviol glycosides.[1] These assessments were consistent in concluding that steviol glycosides when used as a food additive in the form and quantity proposed, provide the technological purpose as an intense sweetener.

Steviol glycosides are a group of compounds naturally occurring in the *S. rebaudiana* Bertoni (stevia) plant. The major glycosides present in the extract of the leaves from the stevia plant are stevioside and rebaudioside A. The minor glycosides include rebaudioside M and rebaudioside D and about 40 other steviol glycosides (JECFA 2019).

All steviol glycosides share the same steviol backbone structure but have different sugar moieties attached, as conjugated glycosides. The sugar moieties include but are not limited to glucose, rhamnose, xylose, fructose, galactose and deoxyglucose, which can be attached in various combinations, quantity and orientation (FAO 2017).

Steviol glycosides are already permitted to be used as an intense sweetener in a number of foods. The permissions are listed in the table to section S15—5 of the Code. With the exception of tabletop sweeteners which are subject to Good Manufacturing Practice (GMP) use levels, all permissions for steviol glycosides are subject to numerical limits expressed as maximum permitted levels (MPLs).

2.1 Use of intense sweeteners in FSMP

The applicant has requested use of steviol glycosides as an intense sweetener in FSMP. The maximum permitted level requested is 330 mg/kg, excluding any use in FSMP for infants under 12 months of age.

[1] Refer to A1222 (FSANZ 2021b) and A1207 (FSANZ 2021c).

FSMP are permitted to contain a number of other intense sweeteners. Permissions for use are listed in the table to section S15—5 *Food category* 13.5 Food for special medical purposes. This list includes permission for '*Additives permitted at GMP'*. These are listed in Schedule 16 (S16). Several intense sweeteners are included in S16.

Thus, FSMP are already permitted to contain a number of intense sweeteners. Furthermore, the Code already permits steviol glycosides in a range of foods.

2.2 Technological purpose and function

The technological purpose of steviol glycosides as a food additive is that of an intense sweetener, which replaces the sweetness normally provided by sugars in food, without contributing significantly to their available energy. The technological purpose (sweetening foods) is well established as a solely technological purpose/function. Steviol glycosides are therefore appropriately regulated as food additives.

FMSP are specially formulated for the dietary management of individuals with certain diseases, disorders or medical conditions. FSMP are required when the dietary management of individuals cannot be easily or completely achieved with other dietary modification including the use of other special purpose foods. FSMP includes formulated dietary products that are intended for use as the sole source of nutrition, either consumed orally or through an enteral route (e.g. naso-gastric tube), as well as specialised supplementary formulated products.

Some FSMP are formulated for reduced energy diets, others products use intense sweeteners to reduce (or eliminate) the amount of sugar contained in FSMP. Intense sweeteners are therefore technologically justified for addition to such foods. FSMP that are formulated for use in VLED have a greater technological need for intense sweeteners than other FSMP. The technological need in other FSMP can be for improved palatability, as sweeteners mask the flavour of other added nutrients. As noted above, a number of permissions for the use of intense sweeteners in FSMP already exist.

Under the Code, intense sweeteners can only be added to food in an amount necessary to replace, either wholly or partially, the sweetness normally provided by sugars (refer to Section 1.3.1—5 of the Code).

The applicant provided a summary of steviol glycoside levels (expressed as steviol equivalents) used in the applicant's products sold in international jurisdictions.[2] This shows that internationally, steviol glycosides are already selected as the intense sweetener in some products, even though a number of alternative intense sweeteners are permitted. Manufacturers select a particular intense sweetener for a number of reasons, including palatability, ease of formulation, cost, consumer preferences, and whether regulatory permissions for intense sweeteners are in place. In the case of FSMP, many of the products are imported into Australia and New Zealand, due to their specialised nature.

General stability of steviol glycosides in products

JECFA concluded at its 68th meeting in 2007 that steviol glycosides are sufficiently thermally and hydrolytically stable for use in foods, including acidic beverages, under normal conditions of processing and storage (JECFA, 2007). Study results made available to JECFA for the 82nd meeting supported that the stability results can be extended to include steviol glycoside extract preparations containing higher levels of new glycosides added to the

[2] This was provided as commercial in confidence information

definition and appearing in commercial products, mainly rebaudioside D and rebaudioside M (FAO 2017). These publications therefore support the general stability of steviol glycosides. FSANZ has no reasons to question the stability of steviol glycosides for use in FSMP.

2.3 Identity and purity

Food additives permitted by section 1.3.1 and Schedule 15 must also meet any relevant identity and purity specifications set out in Schedule 3. Section S3—2 of Schedule 3 provides a list of specifications contained in primary sources.

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

Subsection S3—2(1) of Schedule 3 incorporates by reference the specifications listed in the Joint FAO/WHO Expert Committee on Food Additives (JECFA) Combined Compendium of Food Additive Specifications (FAO JECFA Monographs 26 (2021)), and the United States Pharmacopeial Convention (2022) Food chemicals codex (13th edition). These include specifications for steviol glycosides.

The applicant is not requesting a new source or type of steviol glycosides. Relevant identity and purity specifications are already incorporated by reference in Schedule 3 of the Code. Some steviol glycosides can be produced from the leaves of the stevia plant, but can also be produced by other methods, with no plant involved (such as fermentation from sugar to produce the steviol glycosides using genetically modified yeast). Such methods are included in the S3 specifications.

2.4 Food technology conclusion

FSANZ concludes that the use of steviol glycosides as a food additive in FSMP is consistent with its typical technological function as an intense sweetener.

There are already relevant identity and purity specifications for steviol glycosides in the Code.

FSANZ concludes that the evidence presented to support its proposed use provides adequate assurance that the use of steviol glycosides, is technologically justified and is effective in achieving its stated purpose. FSMP that are formulated for VLED have a greater technological need for intense sweeteners than other FSMP.

3 Safety assessment

3.1 Previous FSANZ assessments

FSANZ established an ADI for steviol glycosides of 0-4 mg/kg body weight/day expressed as steviol equivalents in 2008 under application A540 (FSANZ 2008). The ADI was derived by applying a 100-fold safety factor to the NOEL of 970 mg/kg bw/day (equivalent to 383 mg/kg bw/day steviol equivalents) based on a two-year rat study. There was no evidence of any non-neoplastic or neoplastic potential. The NOEL was based on effects on body weight and survival that are not considered adverse or indicative of toxicity, and are likely due to lower palatability of the diet containing stevioside. The NOEL on which the ADI is set is therefore conservative.

The FSANZ ADI is consistent with the ADI established by JECFA at the 69th meeting held in 2008, and published in 2009 (JECFA 2009). JECFA re-assessed steviol glycosides at the

82nd meeting in 2016 and confirmed the existing ADI (JECFA 2016). The assessments confirmed that steviol glycosides share a metabolic pathway to steviol. The ADI, expressed as steviol equivalents, is therefore appropriate for all steviol glycosides.

FSANZ updated the hazard assessment for steviol glycosides as a part of the following applications:

- A1222: Steviol glycosides from *Yarrowia lipolytica* (FSANZ 2021a)
- A1207: Rebaudioside M as a Steviol Glycoside from *Saccharomyces cerevisiae* (FSANZ 2021b)
- A1183: Enzymatic production of Rebaudioside E (FSANZ 2020)
- A1176: Enzymatic production of Steviol Glycosides (FSANZ 2019a)
- A1172: Enzymatic production of Rebaudioside D (FSANZ 2019b)
- A1149: Addition of Steviol Glycosides in Fruit Drinks (FSANZ 2019c)
- A1157: Enzymatic production of Rebaudioside M (FSANZ 2018)
- A1132: Broaden Definition of Steviol Glycosides (Intense Sweetener) (FSANZ 2017)
- A1108: Rebaudioside M as a Steviol Glycoside Intense Sweetener (FSANZ 2015)
- A1037: Steviol Glycosides: Increase in Permitted Use Levels (FSANZ 2011).

These assessments did not identify a need to change the ADI.

In 2023 FSANZ published a refined dietary exposure assessment for steviol glycosides for the Australian and New Zealand populations, based on the results of an analytical survey of steviol glycosides in a variety of foods (FSANZ 2023). A hazard assessment confirmed the ADI, and the estimated dietary exposures to steviol glycosides were well below the ADI for all population groups assessed. Furthermore, no public health and safety issues were identified as a result of the risk assessment.

3.2 Toxicity of steviol glycosides

3.2.1 Toxicity studies in laboratory animals

As covered in previous FSANZ assessments of steviol glycosides (see section 3.1) there is a substantial evidence base to show that steviol glycosides are hydrolysed to steviol in the large intestine or excreted unchanged in the faeces. Steviol is absorbed, glucuronidated and excreted as steviol glucuronide, primarily in the urine.

The applicant supplied a number of toxicity studies, all of which had previously been reviewed by FSANZ. FSANZ also conducted a literature search to capture scientific studies relevant to safety that have been published since A1222. No new toxicity studies of steviol glycosides were located.

3.2.2 Human tolerance studies

No new human studies were located by a literature search.

3.2.3 Human allergenic potential

In previous assessments, FSANZ concluded that there is no evidence that steviol glycosides are human allergens. No new evidence challenging that conclusion was found by a literature search.

3.2.4 Summary of the toxicity of steviol glycosides

FSANZ has previously assessed an extensive toxicological database on steviol glycosides, which has identified no safety concerns or a need to amend the ADI established by FSANZ in 2008 of 0-4 mg/kg bw for steviol glycosides, expressed as steviol equivalents.

The applicant submitted a number of recent reviews on the toxicity of steviol glycosides (Momtazi-Borojeni et al. 2017, Lea et al. 2021, Orellana-Paucer 2023, Li et al. 2023). These reviews did not raise any concerns regarding the safety of steviol glycosides; and did not review any new toxicity information that has not previously been assessed by FSANZ.

3.3 Assessments by other regulatory agencies

JECFA has considered steviol glycosides at a succession of meetings. JECFA established the ADI of 0-4 mg/kg at its 69th meeting (JECFA 2009). JECFA re-assessed steviol glycosides at the 82nd meeting in 2016 and confirmed the existing ADI (JECFA 2016). These assessments confirmed that steviol glycosides share a metabolic pathway to steviol. The ADI, expressed as steviol equivalents, is therefore appropriate for all steviol glycosides.

The 87th JECFA meeting in 2019 developed a framework for developing specifications for steviol glycosides, building on JECFA's earlier assessments and superseding the JECFA specification developed at the 84th JECFA meeting (JECFA 2019, JECFA 2020). Four steviol glycoside specification annexes were prepared for the different production methods (JECFA 2020). The ADI of 0-4 mg/kg body weight established at the 69th meeting of JECFA for steviol glycosides applies to steviol glycosides produced by the approved manufacturing technologies (JECFA 2020).

Health Canada has approved the use of steviol glycosides from *S. rebaudiana* Bertoni, *Saccharomyces cerevisae* CD15380, *S. cerevisae* CD15407, and *S. cerevisae* Y63348 (Health Canada 2019, 2020a, 2020b).

In 2020, EFSA published an opinion on an applicant-submitted proposal to amend the EU specifications for steviol glycosides. The applicant proposed expanding the definition of steviol glycoside to include all 60 steviol glycosides present in *S. rebaudiana* Bertoni and to include microbial safety limits (EFSA 2020).

The EFSA panel on Food Additives and Flavourings supported the proposed introduction of microbial safety limits and by considering the common metabolic fate of all steviol glycosides in the colon, agreed that a read-across approach to toxicological safety assessment was appropriate to support the safety of all 60 steviol glycosides. However, the EFSA panel noted that if the current steviol glycoside specifications were expanded to include all 60 steviol glycosides, this would change how product purity was calculated and thus products of lower quality than is currently accepted could be permitted into the European market (EFSA 2020).

In 2021, the same EFSA panel published an opinion on the safety of steviol glycoside preparations obtained by enzymatic bioconversion of highly purified stevioside and/or rebaudioside A stevia leaf extracts. No concern was identified from the new enzymatic bioconversion manufacturing process and the panel confirmed that the ADI of 0-4 mg/kg body weight/day, expressed as steviol equivalents, also applies to the steviol glycoside preparations obtained by enzymatic bioconversion (EFSA 2021).

There have been a number of GRAS notifications made to the US FDA concerning steviol glycosides, and to date the US FDA has responded with "No Questions" letters. However, these notifications and responses are not assessments by a regulatory agency.

3.4 Dietary Exposure Assessment

3.4.1 Purpose of dietary exposure assessment

The purpose of this dietary exposure assessment was to estimate exposure to steviol glycosides based on the proposed extension of use in FSMP.

FSANZ together with the Ministry for Primary Industries in New Zealand recently completed a review of all the intense sweeteners permitted for use in the Code, including a steviol glycoside risk assessment (FSANZ 2023). Data from this review are used in this assessment.

3.4.2 Approach to the dietary exposure assessment

Dietary exposure assessments at FSANZ are conducted using a tiered approach. The first assessment is conducted using the most conservative assumptions and the least amount of resources, with refinements made following this assessment if needed. A detailed discussion of the FSANZ methodology and approach to conducting dietary exposure assessments is set out in *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009).

Dietary exposure assessments require concentration data of the chemical of interest in foods, and consumption data of those foods usually collected through national nutrition surveys. Details of the steviol glycoside concentration data and food consumption data used in this dietary exposure assessment are outlined below.

The dietary exposure assessment was conducted to estimate the level of chronic exposure to steviol glycosides. Chronic dietary exposure estimates are used to represent the long term, usually life-long, dietary exposure for the population from the range of foods containing the chemical of interest. As noted in the application, FSMP are not consumed by the wider population and are consumed in the context of medical supervision either as a sole or partial source of nutrition. If consumed as a sole source of nutrition, it is unlikely that consumers would be consuming steviol glycosides from other dietary sources.

FSMP include both foods that are, and are not, very low energy foods. As consumption of FSMP that are very low energy foods is different to FSMP that are not very low energy foods, separate dietary exposure assessments were conducted for each FSMP type. For the purpose of this assessment, FSMP that are manufactured very low energy food products are referred to as VLED (Very Low Energy Diets) (and simply described as VLED hereafter), and FSMP that are not very low energy food products are referred to as other FSMP.

3.4.3 Other FSMP

3.4.3.1 Food consumption and steviol glycoside concentration used

The consumption of other FSMP, which in this case are formulated food products intended to be used under medical supervision, falls outside the scope of food consumption data available from the Australian or New Zealand National Nutrition Surveys (NNS). Therefore nationally representative consumption data for these products were not available. As noted in the application, FSMP may be developed to perform a wide range of medical functions. Therefore the composition and consumption amount of other FSMP will be different for each consumer.

Other FSMP may be consumed orally and/or used for enteral tube feeding. Recent American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines for the provision of nutrition support therapy in the adult critically ill patient recommend feeding between 12-25 kcal/kg bw/day in the first 7-10 days of an intensive care unit stay (Compher et al. 2022). If used for enteral feeding and assuming no refeeding syndrome risk, feeding 30 kcal/kg bw/day is likely to be adequate for an adult (Stroud et al. 2003). In a conservative approach, this higher energy intake is used for the dietary exposure assessment for adults.

The Australian and New Zealand Paediatric Critical Care Nutrition Support Guidelines recommend a minimum protein requirement of 1.5 g/kg bw/day for children up to 18 years of age (AuSPEN 2023). Online product information indicates the minimum protein content of several other FSMP suitable as a sole source of nutrition for children is 30 g/L[3]. These two variables (protein requirement and minimum protein content) were used in the dietary exposure assessment for children. The requirements for any person taking other FSMP may vary with medical and nutritional needs and is administered under medical supervision.

To estimate exposure, deterministic dietary exposure assessments were conducted for adults and children in a tiered approach assuming that other FSMP are consumed as a sole source of nutrition. The calculations used the energy and protein requirements and protein content information from above, the energy density of *milk, cow, fluid, regular fat (~3.5%)* from AUSNUT 2011-13 (FSANZ 2014), and the proposed maximum permitted level from the application (330 mg/kg as steviol equivalents).

Estimates of dietary exposure to steviol equivalents were expressed as mg/kg body weight/day to be consistent with the ADI.

3.4.3.2 Assumptions and limitations

The dietary exposure assessment was designed to calculate the most realistic estimate of dietary exposure to steviol glycosides as possible. However, where significant uncertainties in the data exist, conservative assumptions were generally used to ensure that the estimated dietary exposures are not an underestimation.

Assumptions made in the dietary exposure assessment included:

- other FSMP are a sole source of nutrition
- the density of all other FSMP is the same as regular fat cows' milk (1.03 g/mL)
- all other FSMP are a standard feed (1 kcal/mL)
- energy intake for adults is 30 kcal/kg bw/day
- the protein content of other FSMP is 30 g/L
- protein requirement for children up to 18 years is 1.5 g/kg bw/day
- all other FSMP contain steviol glycosides at the proposed maximum permitted level
- there are no other contributions to steviol glycoside exposure, for example through the use of dietary supplements or medicines, nor from general purpose foods containing steviol glycosides.

3.4.3.3 Results

All estimates of dietary exposure to steviol glycosides are expressed as steviol equivalents and compared to the ADI of 0-4 mg/kg bw. At the proposed maximum permitted level of steviol glycosides, estimated dietary exposure for adults is 10.2 mg/kg bw/day (250% of the ADI) and for children, is 17.0 mg/kg bw/day (430% of the ADI) (see Tables 1 and 2).

[3] https://www.nestlemedicalhub.com/products; https://www.abbottnutrition.com/product-guides

Table 1: Estimated dietary exposure to steviol glycosides for adults, expressed as steviol equivalents, from other FSMP

Energy intake (kcal/kg bw/day)*	Proposed steviol glycoside concentration (mg/kg)¥	Estimated steviol glycoside exposure (mg/kg bw/day) ¥	% ADI
30	330	10.2	250

**Stroud et al (2003).*
¥ as steviol equivalents.

Table 2: Estimated dietary exposure to steviol glycosides for children, expressed as steviol equivalents from other FSMP

Protein requirement (g/kg bw/day)*	Minimum protein content of FSMP (g/L)	Proposed steviol glycoside concentration (mg/kg)¥	Estimated steviol glycoside exposure (mg/kg bw/day)¥	% ADI
1.5	30	330	17.0	430

AuSPEN 2023.
¥ as steviol equivalents.

3.4.3.4 Maximum use concentration to not exceed the ADI

As a result of the exceedance of the ADI for both adults and children at the proposed maximum permitted level (330 mg/kg), an additional analysis was undertaken to determine the maximum amount of steviol glycosides (expressed as steviol equivalents) that could be added to other FSMP without exceeding the ADI. This was conducted using the assumptions and dietary exposures assessment inputs related to the estimation of dietary exposure for children as this resulted in the highest exceedance of the ADI. The highest concentration of steviol glycosides (expressed as steviol equivalents) that could be added to other FSMP before exceeding the ADI was calculated to be 75 mg/kg.

3.4.4 VLED

As described in the Nutrition assessment for A1230 (FSANZ 2023), VLED are used as a total diet replacement for the dietary management of overweight and obesity for a prescribed duration of typically no longer than twelve weeks. During the intensive phase of the program, daily consumption typically consists of three VLED (various product types), a minimum of 2 litres of water, two cups of low-starch vegetables, one teaspoon of vegetable oil and additional low joule beverages. Although the use of VLED is not recommended for pregnant, nursing, lactating women or use by infants, children, adolescents and elderly, all VLED consumers were included in the dietary exposure assessment. Consumption of VLED were also captured in the most recent Australian national nutrition survey (NNS), but not in the most recent New Zealand NNS. Australian consumers of VLED were from 12 years of age and above.

In a tiered approach, two methods were therefore used to estimate the dietary exposure to steviol glycosides from VLED:

- a deterministic dietary exposure assessment assuming total diet replacement with daily consumption of three serves of VLED, and two litres of low joule beverages containing

steviol glycosides at the mean concentration level from FSANZ's intense sweetener review (FSANZ 2023) (*VLED plus low joule beverages* scenario).
- A more refined semi-probabilistic assessment using food consumption data for VLEDs for individuals from the 2011-12 National Nutrition and Physical Activity Survey combined with estimated mean steviol glycoside exposures from FSANZ's intense sweetener review (FSANZ 2023) (*VLED plus all other foods* scenario). This assessment was undertaken using FSANZ's dietary modelling computer program Harvest.[4]

3.4.4.1 Food consumption data used

3.4.4.1.1 VLED plus low joule beverages scenario

A review of online product information determined the typical daily consumption of VLED during the intensive stage of the program to be three serves from a range of products available. Assuming 200 mL of water is added to 50 g of powder (shakes, soup or dessert), three serves provide 750 g VLED/day. In a conservative approach, for this scenario it was assumed that the recommended 2 litres of water included in the program was consumed as low joule beverages.

3.4.4.1.2 VLED plus all other foods scenario

The food consumption data used for the dietary exposure assessment for the *VLED plus all other foods* scenario was the 2011-12 Australian National Nutrition and Physical Activity Survey (2011-12 NNPAS). This was one 24-hour food recall survey of 12,153 Australians aged 2 years and above, with a second 24-hour recall undertaken for 64% of respondents (ABS 2015). Only those respondents who had two days of food consumption data (n=7,735) were used in this assessment. Two day average exposures were estimated which better reflect longer term estimates of dietary exposure and therefore are a better estimate of chronic dietary exposure.

Dietary exposure assessments based on food consumption data from national nutrition surveys provide the best estimation of actual consumption of a food and the resulting estimated dietary exposures for Australian and New Zealand populations. The design of these nutrition surveys and the key attributes, including survey limitations, are set out in *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009).

3.4.4.2 Concentration data used

The concentration data used in the dietary exposure assessment for VLED in both scenarios was the proposed maximum permitted level (330 mg/kg as steviol equivalents).

For the *VLED plus low joule beverages* scenario, the concentration of steviol glycosides in low joule beverages was taken from FSANZ's intense sweetener review. As part of this review an analytical survey for steviol glycosides was conducted and from this, the mean concentration of steviol glycosides (as steviol equivalents) in water based flavoured drinks sweetened with steviol glycosides was 21 mg/kg (FSANZ 2023).

[4] Harvest is FSANZ's custom-built dietary modelling program that replaced the previous program, DIAMOND, which does the same calculations just using a different software program.

3.4.4.3 Estimating steviol glycoside exposure

3.4.4.3.1 VLED plus low joule beverages scenario

To estimate exposure during the intensive phase of VLED consumption, a deterministic dietary exposure calculation was conducted assuming consumption of 750 g VLED at the proposed maximum permitted level, plus 2 litres of low joule beverages per day. The intensive phase is generally only recommended for adults up to the age of 65 years with a BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 with weight related co-morbidities. The mean body weight of all adults aged 18 to 65 years in the 2011-12 NNPAS who have a BMI ≥ 27 kg/m^2 is 92 kg. This body weight was used to compare estimated dietary exposure to the ADI of 0-4 mg/kg bw (steviol equivalents).

3.4.4.3.2 VLED plus all other foods scenario

Steviol glycosides dietary exposures from VLED were calculated for each individual consumer in the Australian national nutrition survey (2 years and above) using their individual consumption records. The Harvest program multiplied the specified concentrations of steviol glycosides for an individual food by the amount of the food that an individual has consumed in order to estimate the exposure to steviol glycosides from each food. Once this had been completed for all the foods specified to contain steviol glycosides, the total amount of steviol glycosides consumed from all foods was summed for each individual. For this application all foods relates to all VLEDs consumed by each respondent. Where results are expressed on a body weight basis, each individual's body weight was used. Mean and 90th percentile dietary exposures were then derived from the individuals' ranked exposures. Estimated dietary exposures for the population on a body weight basis were compared to the ADI for risk characterisation purposes.

A Harvest food additive model was the most appropriate for this dietary exposure assessment as nutrition survey foods are grouped as per the food classes in Schedule 15 of the Code and concentrations of steviol glycosides are assigned to those relevant classes.

Estimated exposures from VLED were then added to estimated mean dietary exposures from FSANZ's intense sweetener review (FSANZ 2023). Full details of the steviol glycoside risk assessment conducted as part of this review, including the scenarios, are available on the FSANZ website (https://www.foodstandards.gov.au/).

3.4.4.4 Assumptions and limitations

The dietary exposure assessment was designed to calculate the most realistic estimate of dietary exposure to steviol glycosides as possible. However, where significant uncertainties in the data exist, conservative assumptions were generally used to ensure that the estimated dietary exposure is not an underestimation.

Assumptions made in the dietary exposure assessment for the *VLED plus low joule beverages* scenario included:

- 3 serves of VLED/day = 750 g
- 2 litres of low joule beverages is consumed/day
- all low joule beverages have a steviol glycoside concentration of 21 mg/kg
- 1 litre = 1 kg
- the mean body weight of Australians and New Zealand adults aged 18-65 years, with a BMI ≥ 27 kg/m^2 is 92 kg
- there are no other contributions to steviol glycoside exposure, for example through the use of dietary supplements or medicines.

Assumptions made in the dietary exposure assessment for the *VLED plus all other foods* scenario included:

- VLED includes all survey foods specified as VLED, as well as meal replacement bars and meal replacement powders that are not further defined
- all VLED contains steviol glycosides at the proposed maximum permitted level
- where a food has a specified steviol glycoside concentration, this concentration is carried over to mixed foods where the food has been used as an ingredient e.g. VLED beverage made with milk
- there are no changes in steviol glycoside concentrations due to heating e.g. soups
- estimated exposure to steviol glycosides from all other foods is the same as from FSANZ's intense sweetener review (FSANZ 2023)
- consumption of VLED and all other foods containing steviol glycosides is the same in New Zealand as in Australia
- there are no other contributions to steviol glycoside exposure, for example through the use of dietary supplements or medicines.

In addition to the specific assumptions made in relation to this dietary intake assessment, there are a number of limitations associated with the nutrition surveys from which the food consumption data are used for the assessment. A discussion of these limitations is included in Section 6 of the *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2009).

3.4.4.5 Results

All estimates of dietary exposure to steviol glycosides are expressed as steviol equivalents and compared to the ADI of 0-4 mg/kg bw (as steviol equivalents).

For the *VLED plus low joule beverages* scenario the estimated dietary exposure for adults aged between 18 and 65 years is 3.1 mg/kg bw/day (80% of the ADI) (see Table 3). The exposure estimate derived from this scenario is conservative since it assumes that all VLED contain steviol glycosides at the proposed maximum permitted level, that 2 litres of water was consumed as low joule beverages containing steviol glycosides, and the consumer will continuously (over a lifetime) be exposed to steviol glycosides at these levels. As the intensive program is not recommended for more than twelve weeks and the 90th percentile consumption for a single day of water based beverages is 1125 g/day for Australians and 1170 g/day for New Zealand adults (FSANZ 2019c), this level of chronic dietary exposure is not likely to be the case in reality.

Table 3: Estimated steviol glycoside dietary exposure, expressed as steviol equivalents for the *VLED plus low joule beverages* scenario

	Value	Units
VLED consumption*	750	g/day
Steviol glycoside concentration in VLED¥	330	mg/kg
Low joule beverage consumption*	2000	g/day
Steviol glycoside concentration in water based flavoured drinks #	21	mg/kg
Mean body weight (18-65 years)^	92	kg
Estimated exposure from 3 serves VLED plus 2000 mL low joule drink	3.1	mg/kg bw/day
% of ADI	80	%

*****Assuming 3 x 250 g serves VLED/day*

¥ *Proposed maximum permitted level*

Concentration data from Intense sweetener review (FSANZ, 2023)

^BMI ≥ 27 kg/m^2

For the *VLED plus all other foods* scenario the estimated dietary exposures to steviol glycosides from VLED and all other foods were calculated for 'consumers' of steviol glycosides, that is only the respondents in the survey population that have been exposed to steviol glycosides as a result of consuming a food in which it is permitted to be used or has an assigned concentration.

The proportion of consumers is reported as the weighted[5] proportion of consumers to respondents. For the *VLED plus all other foods* scenario, the proportion of consumers to respondents is 1.3%.

For VLED alone, the mean and 90th percentile of estimated dietary exposures for Australian consumers is 0.7 mg/kg bw/day (15% of the ADI) and 1.5 mg/kg bw/day (35% of the ADI) respectively. For VLED plus all other foods, the mean and 90th percentile of estimated dietary exposures for Australian consumers ranges from 0.8-1.2 mg/kg bw/day (20-30% of the ADI) and from 1.6-2.0 mg/kg bw/day (40-50% of the ADI) respectively. Detailed results of the estimates of dietary exposure to steviol glycosides for VLED plus all other foods scenarios can be found in Table 4.

[5] Survey sample weighting factors are used to adjust the results of surveys to better reflect the results that would have been obtained if a truly representative sample from the population had been able to be obtained, and to make population based estimations of results.

Table 4: Estimated mean and 90th percentile dietary exposure to steviol glycosides, expressed as steviol equivalents, for the *VLED plus all other foods* scenario for Australian consumers^

	FSANZ Intense sweetener review scenario	Mean (mg/kg bw/day)	% ADI	90th percentile (mg/kg bw/day)	% ADI
Exposure from VLED only	NA	0.7	15	1.5	35
Exposure from VLED plus all other foods*	*Baseline* scenario	1.2	30	2.0	50
	Refined scenario	1.1	25	1.9	45
	Refined – Market uptake scenario	0.8	20	1.6	40

^ *Derived using the Australian 2011-12 NNPAS for all respondents aged 2 years and above (n=7735) (2 days average exposure).*
* *All other foods scenarios and exposures from FSANZ's intense sweetener review (FSANZ 2023).*
NA: not applicable.

4 Risk characterisation and Conclusion

FSANZ has previously assessed an extensive toxicological database on steviol glycosides, which has identified no safety concerns or a need to amend the ADI established by FSANZ in 2008 of 0-4 mg/kg bw for steviol glycosides, expressed as steviol equivalents. Following evaluation of recent toxicological review information provided by the applicant for this application, FSANZ again determined there was no need to amend the established ADI.

A dietary exposure assessment was conducted to estimate the level of chronic exposure to steviol glycosides (expressed as steviol equivalents) from other FSMP and VLED.

For other FSMP, at the proposed maximum permitted level estimated dietary exposures for adults and children exceeded the ADI. A predictive study of steviol glycoside dietary exposure in young Irish children aged 1-3 years with phenylketonuria and severe cows' milk allergy also showed exceedance of the ADI at mean and high exposures, when all FSMP (comprising 75% and 50% of the diet) and general purpose foods contained steviol glycosides at the MPL (330 mg/kg for FSMP) (O'Sullivan et al., 2018). FSANZ notes that although the applicant's actual use levels of steviol glycoside are lower than the proposed maximum permitted level, there is uncertainty about other products that could contain levels of steviol glycosides up to the proposed maximum permitted level. Considering that other FSMP could be used for a lifetime by an individual as a sole source of nutrition, there is the potential for exceedance of the ADI at the proposed maximum permitted level of 330 mg/kg. The highest use level of steviol glycoside (expressed as steviol equivalents) that would not result in dietary exposures from other FSMP exceeding the ADI is 75 mg/kg.

For VLED, two scenarios were considered - the *VLED plus low joule beverages* scenario and *VLED plus all food scenario*. In both scenarios, estimated dietary exposures were less than the ADI for the population groups assessed, assuming all VLED contained steviol glycosides at the proposed maximum permitted level.

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