GRAS ASSOCIATES, LLC

GRAS Notification

of

Purified Steviol Glycosides Primarily Composed of Rebaudioside A and Stevioside

Food Usage Conditions for General Recognition of Safety

on behalf of

Shandong Shengxiangyuan Biotechnology Co., Ltd.
Shandong, People's Republic of China

9/11/17

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FOREWORD

At the request of Shandong Shengxiangyuan Biotechnology Co., Ltd (hereinafter "Shandong"), GRAS Associates, LLC ("GA") has undertaken an independent safety evaluation of Shandong's purified steviol glycosides preparation (≥ 95% total steviol glycosides primarily composed of rebaudioside A and stevioside, with lesser amounts of rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside F, dulcoside A, rubusoside, and steviolbioside), referred to herein as SXY Stevia® Total Steviol Glycosides 95%. The purpose of the evaluation is to ascertain whether Shandong's conclusion that the intended food uses of purified steviol glycosides preparations as a non-nutritive sweetener as described in Part 3 are generally recognized as safe, i.e., GRAS, under the intended conditions of use. In addition, Shandong has asked that GRAS Associates act as agent for the submission of this GRAS notification.

Shandong based its GRAS assessment on a large body of information that addressed the safety/toxicity of purified steviol glycosides, history of use of purified steviol glycosides and similar compounds, and compositional details, specifications, and method of preparation of the subject ingredient.

Safety/toxicity studies performed with animals and human clinical trials were noted to have value. The composite safety/toxicity studies, in concert with dietary exposure information, ultimately provide the specific scientific foundation for the GRAS conclusion.

In addition to the product specifications, chemical properties, manufacturing, and safety-related information, Shandong also provided consumption/exposure information, along with other related documentation. This was augmented with an independent search of the scientific and regulatory literature extending through August 10, 2017. A GRAS assessment based primarily on the composite safety information, i.e., based on scientific procedures, was undertaken by Shandong followed by an Expert Panel review coordinated by GRAS Associates. Those references that were deemed pertinent to this review are listed in Part 7.

PART 1. SIGNED STATEMENTS AND CERTIFICATION

A. Basis of Exclusion from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36(c)(1)[1]

Shandong Shengxiangyuan Biotechnology Co., Ltd. (Shandong) has concluded that its purified steviol glycosides product (≥ 95% total steviol glycosides primarily composed of rebaudioside A and stevioside), referred to as purified steviol glycosides and SXY Stevia® Total Steviol Glycosides 95%, and which meet the specifications described below, is Generally Recognized As Safe (GRAS) in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act. This determination was made in concert with an appropriately convened panel of experts who are

[1] See 81 FR 54960, 17 August 2016. Accessible at: https://www.gpo.gov/fdsys/pkg/FR-2016-08-17/pdf/2016-19164.pdf (Accessed 4/15/17).

qualified by scientific training and experience. The GRAS determination is based on scientific procedures as described in the following sections. The evaluation accurately reflects the intended conditions of food use for the designated purified steviol glycosides preparations (≥ 95% total steviol glycosides primarily composed of rebaudioside A and stevioside).

Signed:

(b) (6)

Agent for Shandong

Steven Overgaard
President
GRAS Associates, LLC
27499 Riverview Center Blvd.
Suite 212
Bonita Springs, FL 34134

Date: 9/11/17

B. Name and Address of Responsible Party

Shandong Shengxiangyuan Biotechnology Co., Ltd.
Xizou Industrial Park
Qufu, Shandong
273100
People's Republic of China

As the Responsible Party, Shandong Shengxiangyuan Biotechnology Co., Ltd. ("Shandong") accepts responsibility for the GRAS conclusion that has been made for its SXY Stevia® Total Steviol Glycosides 95%, as described in the subject safety evaluation; consequently, the purified steviol glycosides preparations having acceptable steviol glycosides compositions that are primarily rebaudioside A and stevioside, with no less than 95% of the total of rebaudioside A, stevioside, rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside F, dulcoside A, rubusoside, and steviolbioside, which meet the conditions described herein, are not subject to premarket approval requirements for food ingredients.

C. Common Name and Identity of Notified Substance

The common name of the ingredient to be used on food labels is stevia extract or steviol glycosides.

D. Conditions of Intended Use in Food

Shandong's Purified Steviol Glycosides SXY Stevia® Total Steviol Glycosides 95% preparation is intended for use as a general-purpose sweetener in foods, excluding meat and poultry products and infant formulas, at levels determined by current good manufacturing practices.

E. Basis for GRAS Conclusion

Pursuant to 21 CFR 170.30(a) and (b), Shandong's SXY Stevia® Total Steviol Glycosides 95% has been concluded to be GRAS on the basis of scientific procedures as discussed in the detailed description provided below.

Purified steviol glycosides are not subject to premarket approval requirements of the FD&C Act based on Shandong's conclusion that the substance is GRAS under the conditions of its intended food use.

Shandong and GRAS Associates certify, to the best of our knowledge, that this GRAS notice is a complete, representative, and balanced assessment that includes all relevant information, both favorable and unfavorable, available and pertinent to the evaluation of safety and GRAS status of purified steviol glycosides.

F. Availability of Information

The data and information that serve as the basis for this GRAS Notice will be maintained at the offices of GRAS Associates, Bonita Springs, FL, and will be made available during customary business hours.

Shandong and GRAS Associates, LLC certify that no data or information contained herein are exempt from disclosure under the Freedom of Information Act (FOIA). No non-public, safety-related data were used by the Expert Panel to reach a GRAS conclusion.

PART 2. IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

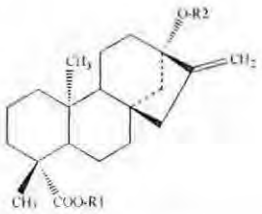
A. Chemical Identity of Ingredient

Purified steviol glycosides (≥ 95% total steviol glycosides) is the common or usual name of the non-nutritive sweetener derived from *Stevia rebaudiana* Bertoni that is the subject of this GRAS evaluation. The compositional features of the subject SXY Stevia® Total Steviol Glycosides 95%, composed primarily of rebaudioside A and stevioside, with lesser amounts of rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside F, dulcoside A, rubusoside, and steviolbioside, are described in more detail in Part 2.

In the scientific literature, steviol glycosides have been referred to as stevia, stevioside, steviol glycosides, and stevia glycoside. JECFA adopted the term "steviol glycosides" for the family of

steviol derivatives with sweetness properties that are derived from the stevia plant. Presently, the term "stevia" is used, more narrowly, to describe the plant or crude extracts of the plant, while rebaudioside A (Reb A) –like stevioside – is the common name for another one of the specific glycosides that is extracted from stevia leaves. Representative chemical structures of some of the various steviol glycosides that have been identified to date are presented in Figure 1.

Figure 1. Chemical Structures of Various Steviol Glycosides[a,b]



	Compound name	C.A.S. No.	R1	R2
1	Steviol	471-80-7	H	H
2	Steviolbioside	41093-60-1	H	β-Glc-β-Glc(2→1)
3	Stevioside	57817-89-7	β-Glc	β-Glc-β-Glc(2→1)
4	Rebaudioside A	58543-16-1	β-Glc	β-Glc-β-Glc(2→1) | β-Glc(3→1)
5	Rebaudioside B	58543-17-2	H	β-Glc-β-Glc(2→1) | β-Glc(3→1)
6	Rebaudioside C (dulcoside B)	63550-99-2	β-Glc	β-Glc-α-Rha(2→1) | β-Glc(3→1)
7	Rebaudioside D	63279-13-0	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1) | β-Glc(3→1)
8	Rebaudioside E	63279-14-1	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1)
9	Rebaudioside F	438045-89-7	β-Glc	β-Glc-β-Xyl(2→1) | β-Glc(3→1)
10	Rubusoside	63849-39-4	β-Glc	β-Glc
11	dulcoside A	64432-06-0	β-Glc	β-Glc-α-Rha(2→1)

[a] From FAO, 2007b.

[b] The indicated CAS No. for Rubusoside as reported in the cited reference is incorrect and should be 64849-39-4.

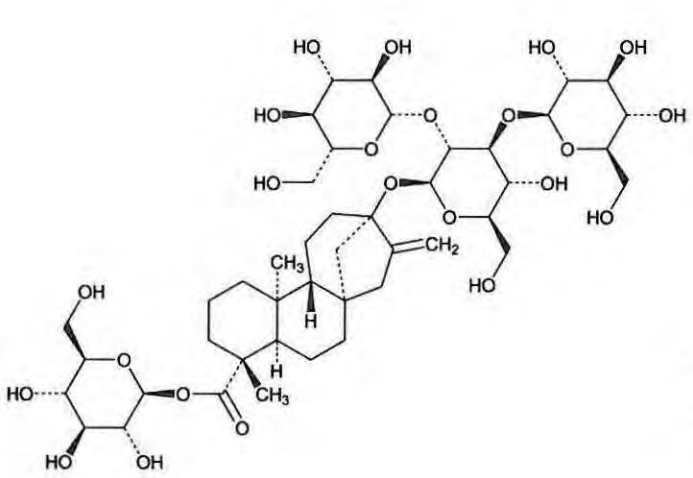
1. Chemical Structure of Purified Steviol Glycosides

The chemical identities and key chemical identifiers for the two major components of Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation are presented in Table 1, and the chemical structures of the two predominant steviol glycosides present are shown in Figure 2.

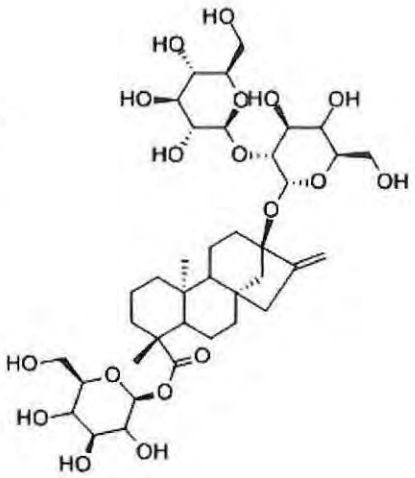
Table 1. Chemical Identity of Rebaudioside A and Stevioside

REBAUDIOSIDE A	
Common Name	Rebaudioside A
Chemical name	13-[(2-O-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-β-D- glucopyranosyl) oxy] kaur-16-en-18-oic acid, β-D- glucopyranosyl ester
Chemical formula	$C_{44}H_{70}O_{23}$
Formula weight	967.03 daltons
CAS Number	58543-16-1
STEVIOSIDE	
Common name	Stevioside
Chemical name	13-[2-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy] kaur-16-en-18-oic acid, β-D-glucopyranosyl ester
Chemical formula	$C_{38}H_{60}O_{18}$
Formula weight	804.88 daltons
CAS Number	57817-89-7

Figure 2. Chemical Structure of Rebaudioside A and Stevioside



Rebaudioside A



Stevioside

There are no known toxicants that have been identified in stevia.

A recent publication by Kumari et al. (2016) addressed the content and distribution of Total Phenolic Content (TPC), Total Flavonoid Content (TFC), and Total Antioxidant Capacity (TAC) of different portions of *Stevia rebaudiana*. TPC, TFC, and TAC were observed in all portions of the stevia plant, with the highest levels noted in the leaves; the relative TPC, TFC, and TAC amounts reflect the following order: leaf > flower > stem > branch > root. The higher levels in the leaves were attributed to an increased content of phenolics, flavonoids, and pigments in the stevia leaf. The authors also reported that TPC, TFC, and TAC amounts decreased with leaf maturity.

B. Manufacturing Processes

Shandong manufactures its purified steviol glycosides (≥ 95% total steviol glycosides) SXY Stevia® Total Steviol Glycosides 95% preparation from extracts derived from *Stevia rebaudiana* leaves using a fairly typical contemporary process that is used in the industry for the production of stevia-derived sweeteners manufactured under current Good Manufacturing Practices regulations (cGMP). In short, dry stevia leaves are steeped in water and then removed via filtration. The steviol glycosides are absorbed on resin and eluted with 60-70% ethanol prior to a number of purification steps. The resulting crude stevia extract serves as the raw material for Shandong's manufacturing process. A flow chart for the manufacturing process for the raw material stevia extract is provided in Figure 3.

An aqueous solution of food grade ethanol (88-90%) is added to a stevia extract consisting of ≥ 90% total steviol glycosides (≥ 50% rebaudioside A) at a ratio between 3:1 and 5:1 ethanol to stevia extract. The mixture is heated for 3-4 hours, with the temperature maintained between 70-80°C, with stirring every 5-10 minutes. The mixture is then allowed to rest for 3-4 hours for crystallization to occur. The crystallized steviol glycosides are washed with ethanol, and then separated by solid-liquid separation using a centrifuge. The finished purified steviol glycosides product is then dried, crushed into a powder, and packaged.

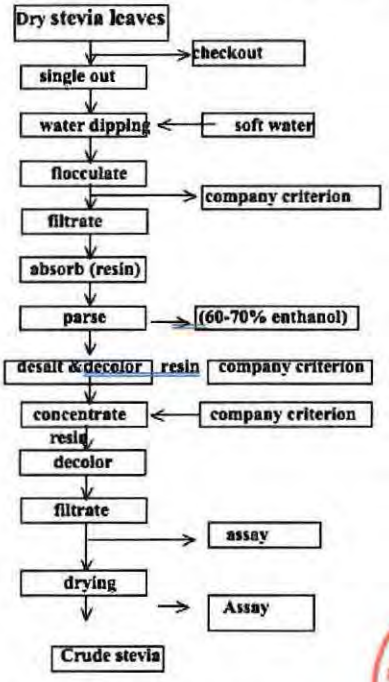
The manufacturing process is summarized in a flow chart provided in Figure 4.

The ethanol used in the purification process complies with Food Chemicals Codex (FCC) 10th Edition specifications. Specifications for ethanol and a certificate of analysis for a representative lot of the steviol glycoside extract raw material (≥ 90% total steviol glycosides) are provided in Appendix 1.

Figure 3. Flow Chart of Manufacturing Process for Shandong's Steviol Glycosides Extract Raw Material

Shandong Shengxiangyuan Biotechnology Co.,Ltd
山东圣香远生物科技有限公司
Adress: No.9,East haiguan Rd,qufu,jining,shandong province,chir
Tel:0086-537-4487369 Fax:0086-537-4400999

Flow Chart



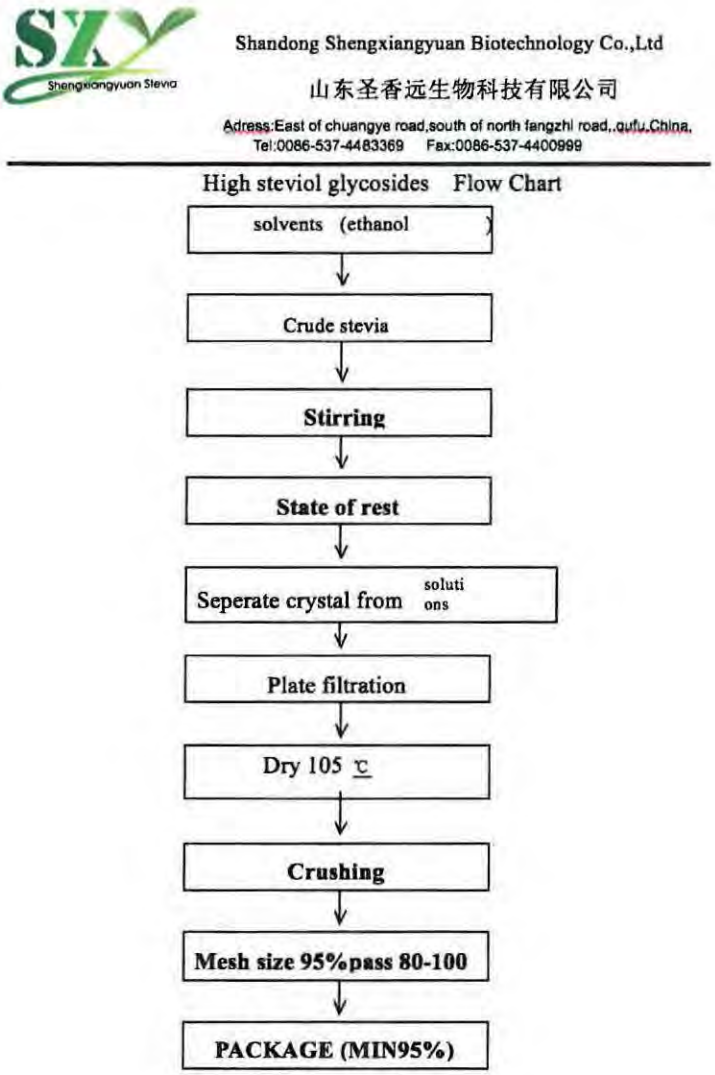
NAME OF SUPPLIER: Shandong Shengxiangyuan Biotechnology Co.,ltd

NAME OF PRODUCT: STEVIA EXTRACT

DATE. PLACE: Jan.22[illegible], 2016

PACKAGING STATEMENT – REV.1 22/01/2016

Figure 4. Flow Chart of Manufacturing Process for Shandong's SXY Stevia® Total Steviol Glycosides 95%



C. Product Specifications

1. JECFA Specifications for Steviol Glycosides

The composition of extracts of *Stevia rebaudiana* Bertoni depends upon the composition of the harvested leaves, which are, in turn, influenced by soil, climate, and the manufacturing process itself (FAO, 2007b).

In 2007, JECFA recommended that the method of assay should include a minimum requirement of 95% of the total of 7 specific steviol glycosides on a dried weight basis, and JECFA finalized food grade specifications at the 68th JECFA meeting with publication in the FAO JECFA Monograph 4

(FAO, 2007a). Stevioside and rebaudioside A (Reb A) are the major component glycosides of interest because of their sweetening property. The five other associated glycosides found in preparations of steviol glycosides accepted by the JECFA specifications with the 95% requirement are rebaudioside C (Reb C), dulcoside A, rubusoside, steviolbioside, and rebaudioside B (Reb B). These, however, are typically found at much lower levels than stevioside or rebaudioside A. JECFA updated the specifications for steviol glycosides in 2008 (FAO, 2008), and then again in 2010, when the specifications were expanded to include the original seven specific steviol glycosides plus rebaudioside D (Reb D) and rebaudioside F (Reb F) (FAO, 2010).Recently, rebaudioside M (Reb M) has garnered interest as an additional naturally-occurring sweet steviol glycoside.

JECFA describes steviol glycosides as a white to yellow powder, odorless to having a slight characteristic odor, and exhibiting a sweetness that is 200-300 times greater than sucrose. The ingredient must consist of a minimum of 95% of nine specific steviol glycosides. The steviol glycosides are freely soluble in water and ethanol, and the 1 in 100 solutions exhibit pH values between 4.5 and 7.0. The product should not have more than 1% ash, with no more than a 6% loss on drying at 105°C for 2 hours. Any residual methanol levels should not exceed 200 ppm, and ethanol residues should not exceed 5,000 ppm. Arsenic levels should not exceed 1 ppm as determined by the atomic absorption hydride technique. Lead levels should not exceed 1 ppm.

2. Specifications for Shandong's SXY Stevia® Total Steviol Glycosides 95% Purified Steviol Glycosides Preparations and Supporting Methods

Shandong has adopted product specifications for its SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation that meet or exceed JECFA recommendations, while also complying with Food Chemicals Codex (FCC, 2010) specifications for rebaudioside A as a consumable human food substance. The compositions of five lots of Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides are compared to the JECFA and FCC specifications in Table 2, and representative certificates of analysis for the five batches are presented in Appendix 2.

Table 2. Specifications for Shandong's SXY Stevia® Total Steviol Glycosides 95% Preparations

Physical & Chemical Parameters	JECFA[a] Specifications Steviol Glycosides	FCC[b] Specifications Rebaudioside A	Shandong Minimum Specifications for SXY Stevia® Total Steviol Glycosides 95%	Results of SXY Stevia® Total Steviol Glycosides 95%				
				Batch Number 20160913	Batch Number 20160916	Batch Number 20160914	Batch Number 20160917	Batch Number 20160918
Appearance Form	Powder	Crystal, granule or powder	Fine Powder	Fine Powder	Fine Powder	Fine Powder	Fine Powder	Fine Powder
Appearance Color	White to light Yellow	White to off-white	White	White	White	White	White	White
Sweetness Intensity	--	--	280-320	300	300	300	300	300
Solubility[c]	Freely soluble in water	Freely soluble in water: ethanol (50:50)	NS	Pass	Pass	Pass	Pass	Pass
Purity (HPLC Area) %	NS	≥ 95	≥ 95% Total Steviol Glycosides 50-70% Reb A 1.0-3.0% Reb B 2.0-5.0% Reb C 0.3-1.5% Reb D 0.5-1.5% Reb F 20.0-30.0% Stevioside 0.3-1.0% Dulcoside A 2.0-4.0% Rubusoside 0-1.0% Steviolbioside	95.52% Total Steviol Glycosides 61.18% Reb A 1.92% Reb B 2.44% Reb C 0.47% Reb D 0.66% Reb F 25.33% Stevioside 0.36% Dulcoside A 2.42% Rubusoside 0.74% Steviolbioside	95.32% Total Steviol Glycosides 61.16% Reb A 1.66% Reb B 1.87% Reb C 0.34% Reb D 0.59% Reb F 25.40% Stevioside 0.33% Dulcoside A 3.07% Rubusoside 0.91% Steviolbioside	95.57% Total Steviol Glycosides 63.60% Reb A 1.76% Reb B 1.89% Reb C 0.70% Reb D 0.57% Reb F 23.15% Stevioside 0.40% Dulcoside A 2.77% Rubusoside 0.73% Steviolbioside	95.70% Total Steviol Glycosides 62.58% Reb A 1.74% Reb B 1.82% Reb C 0.69% Reb D 0.56% Reb F 24.10% Stevioside 0.37% Dulcoside A 2.89% Rubusoside 0.94% Steviolbioside	95.88% Total Steviol Glycosides 62.63% Reb A 1.82% Reb B 2.01% Reb C 0.69% Reb D 0.62% Reb F 23.58% Stevioside 0.44% Dulcoside A 3.20% Rubusoside 0.89% Steviolbioside
Residual Ethanol	NMT 5,000 mg/kg	NMT 0.5%	≤ 5,000 mg/kg	583 mg/kg	397 mg/kg	502 mg/kg	503 mg/kg	501 mg/kg
Residual Methanol	NMT 200 mg/kg	NMT 0.02%	≤ 200 mg/kg	76 mg/kg	89 mg/kg	94 mg/kg	99 mg/kg	97 mg/kg
Loss on Drying (%)	NMT 6.0%	NMT 6.0%	≤ 4.00 %	3.10%	3.26%	3.07%	3.32%	3.41%
pH, 1% Solution	4.5-7.0	4.5-7.0	4.5-7.0	5.20	5.20	5.20	5.20	5.20
Total Ash (%)	NMT 1%	NMT 1%	≤ 0.1%	0.09%	0.08%	0.09%	0.09%	0.09%
Arsenic	NMT 1 mg/kg	NMT 1 mg/kg	≤ 0.1 mg/kg	Below detection limit	Below detection limit	Below detection limit	Below detection limit	Below detection limit
Lead	NMT 1 mg/kg	NMT 1 mg/kg	≤ 0.1 mg/kg	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg
Mercury	NS	NS	≤ 0.1 mg/kg	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg	0.05 mg/kg
Cadmium	NS	NS	≤ 0.1 mg/kg	Below detection limit	Below detection limit	Below detection limit	Below detection limit	Below detection limit

Total Plate Count (cfu/g, max)	NA	NA	≤ 1,000	<1,000	<1,000	<1,000	<1,000	<1,000
Yeast & Mold (cfu/g, max)	NA	NA	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella spp.	NA	NA	Negative	Negative	Negative	Negative	Negative	Negative
Staphylococcus aureus	NA	NA	Negative	Negative	Negative	Negative	Negative	Negative
***E. coli* (mpn/g)**	NA	NA	Negative	Negative	Negative	Negative	Negative	Negative

[a] Prepared at 73rd JECFA, 2010.
[b] Rebaudioside A monograph. Food Chemicals Codex (7th Ed.). (FCC, 2010).
[c] Shandong determined the solubility of its SXY Stevia® Total Steviol Glycosides 95% preparation following the method described in the 2015 Chinese Pharmacopoeia.
NS = not specified; NA = not applicable; NMT = not more than;

Shandong analyzes its SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation following the JECFA monograph for steviol glycosides (FAO, 2010). In addition to the presentation of key specifications found in Table 2 for comparison with generally accepted purity standards, certificates of analysis for five representative lots of SXY Stevia® Total Steviol Glycosides 95%, as well as solubility results, are provided in Appendix 2. The chromatograms for representative Shandong SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides are provided in Appendix 3. A test report for analysis of pesticide residues in a representative lot of purified steviol glycosides is located in Appendix 4. The collection of these reports demonstrates that the substance is well characterized and meets the established purity criteria.

D. Physical or Technical Effect

Shandong determined the relative sweetness of its SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation by organoleptic comparison to a 2% sucrose solution. The relative sweetness is reported for each lot of material on the Certificate of Analysis.

E. Stability

1. Stability Data on Steviol Glycosides

Steviol glycosides have been reported to be stable over the pH range 3-9 and can be heated at 100°C for 1 hour, but, at pH levels greater than 9, it rapidly decomposes (Kinghorn, 2002). At pH 10, steviolbioside would be the major decomposition product produced from stevioside by alkaline hydrolysis (Wood et al., 1955). Chang and Cook (1983) investigated the stability of pure stevioside and Reb A in carbonated phosphoric and citric acidified beverages. Some degradation of each sweetening component after 2 months of storage at 37°C was noted. However, no significant change at room temperature or below, following 5 months of storage of stevioside and 3 months of storage of Reb A, was observed. Exposure to one week of sunlight did not affect stevioside, but approximately 20% loss of rebaudioside A was detected. Heating at 60°C for 6 days resulted in 0-6% loss of rebaudioside A.

Merisant (2008) conducted stability testing on rebaudioside A (1) as a powder, (2) as a pure sweetener in solution, and (3) on both cola-type and citrus carbonated beverages. In these investigations, no degradation was detected when the powder was stored at 105˚C for 96 hours. It was concluded that the powder was stable when stored for 26 weeks at 40±2˚C with relative humidity of 75±5%. Both published and unpublished testing results from Merisant revealed that rebaudioside A in carbonated citric acid beverages and phosphoric acid beverages did not significantly degrade during prolonged storage at refrigeration, normal ambient, or elevated ambient temperatures. Minimal loss of rebaudioside A was detected after storage at 60˚C with considerable degradation noted after 13 hours at 100˚C for carbonated beverage solutions and pure sweetener solutions (Merisant, 2008).

Cargill (2008) also conducted extensive stability testing on rebaudioside A as a powder under various storage conditions and under a range of pH and temperatures. Additionally, Cargill also investigated rebaudioside A stability in several representative food matrices at room temperature and elevated temperatures. Stability profiles were created for table top sweetener applications, mock beverages including cola, root beer and lemon-lime, thermally processed beverages, yogurt, and white cake. The results of stability testing revealed some degradation products that had not been detected in bulk rebaudioside A. These degradation products were structurally related to the

steviol glycosides that are extracted from the leaves of *Stevia rebaudiana* Bertoni. All the degradation products were found to share the same steviol aglycone backbone structure as found in stevioside and rebaudioside A, but they differ by virtue of the glucose moieties present. The results of stability testing revealed that rebaudioside A is stable in various food matrices following several days or weeks of storage. The extent and rate of degradation is dependent on pH, temperature, and time. When placed in beverages, rebaudioside A is more stable in the pH range 4 to 6, and at temperatures from 5˚C to 25˚C (Cargill, 2008).

Photostability studies of the dry powder and mock beverages were performed to ascertain rebaudioside A behavior under defined conditions of fluorescent and near UV light exposure. Rebaudioside A was found to be photostable under the defined conditions of analysis (Clos et al., 2008).

In addition to the above described stability reports for purified rebaudioside A, in a GRAS notification by Sunwin and WILD Flavors (2010)---regarding purified steviol glycosides with rebaudioside A and stevioside as the principal components---stability was investigated using a 0.04% solution of Reb A 80% in acidic solutions between pH 2.81 and 4.18. In this study, the solutions were stored at 32°C for 4 weeks, and the Reb A content was determined at 1, 2, and 4 weeks. Reb A 80% was found to be very stable at pH 3.17 and above. At pH 2.81, after 4 weeks of storage under accelerated conditions, only a 7% loss of Reb A was noted. Sunwin and WILD Flavors also studied the stability of Reb A 80% in simulated beverages using 0.1% citric acid (pH 3.2). The solutions were pasteurized and stored for 8 weeks at 4°C and 32 °C, and little difference in sweetness perception was found under these conditions.

2. Stability Data for Shandong's SXY Stevia® Total Steviol Glycosides 95% Purified Steviol Glycosides Preparation

Shandong conducted a shelf-stability test study on its SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation. Over the course of 24 months, samples of one lot of each preparation were stored at 25°C ± 2°C at a relative humidity of 60% ± 10% for 0, 6, 12, 18, and 24 months. The stability samples were then tested for steviol glycosides, loss on drying, and microbial parameters. A summary of the shelf-stability results is presented in Table 3.

Table 3. SXY Stevia® Total Steviol Glycosides 95% Storage Stability Data

Batch Number 20140312				
Duration	**Assay[a]**	**Loss on Drying**	**Total Plate Count**	**Yeast & Mold**
t=0	95.92%	3.03%	< 1,000 cfu/g	Negative
6 months	95.87%	3.08%	< 1,000 cfu/g	Negative
12 months	95.51%	3.11%	< 1,000 cfu/g	Negative
18 months	95.48%	3.75%	< 1,000 cfu/g	Negative
24 months	95.43%	3.82%	< 1,000 cfu/g	Negative
Batch Number 20140313				
Duration	**Assay[a]**	**Loss on Drying**	**Total Plate Count**	**Yeast & Mold**
t=0	95.56%	3.16%	< 1,000 cfu/g	Negative
6 months	95.57%	3.21%	< 1,000 cfu/g	Negative
12 months	95.55%	3.25%	< 1,000 cfu/g	Negative
18 months	95.44%	3.32%	< 1,000 cfu/g	Negative
24 months	95.41%	3.94%	< 1,000 cfu/g	Negative
Batch Number 20140314				
Duration	**Assay[a]**	**Loss on Drying**	**Total Plate Count**	**Yeast & Mold**
t=0	95.64%	3.51%	< 1,000 cfu/g	Negative
6 months	95.64%	3.53%	< 1,000 cfu/g	Negative
12 months	95.59%	3.62%	< 1,000 cfu/g	Negative
18 months	95.58%	3.71%	< 1,000 cfu/g	Negative
24 months	95.55%	3.84%	< 1,000 cfu/g	Negative

[a] Reported as Total Steviol Glycosides as the sum of Reb A, Reb B, Reb C, Reb D, Reb F, stevioside, dulcoside A, rubusoside, and steviolbioside.

The stability data in the scientific literature for stevioside, the JECFA report, and the extensive stability testing for rebaudioside A as presented by Merisant, Cargill, and Sunwin & WILD Flavors, along with Shandong's stability testing results, support the position that Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation is well-suited for the intended food uses.

PART 3. DIETARY EXPOSURE

The subject SXY Stevia® Total Steviol Glycosides 95% is intended to be used as a table top sweetener and general purpose non-nutritive sweetener in various foods other than infant formulas and meat and poultry products. The intended use will be as a non-nutritive sweetener as defined in 21 CFR 170.3(o)(19).[2] The intended use levels will vary by actual food category, but the actual levels are self-limiting due to organoleptic factors and consumer taste considerations. However, the amounts of purified steviol glycosides preparations to be added to foods will not exceed the amounts reasonably required to accomplish its intended technical effect in foods as required by FDA regulation.[3]

A. Estimate of Dietary Exposure to the Substance

There have been many scholarly estimates of potential dietary intake replacement of sweeteners, including steviol glycosides, that have been published (FSANZ, 2008, WHO, 2003, Renwick, 2008) or submitted to FDA (Merisant, 2008). These are summarized in Appendix 5. In GRAS notification 301, a simplified estimate was proposed to, and accepted by, FDA based on the estimates of exposure in "sucrose equivalents" (Renwick, 2008) and the sweetness intensity of any particular sweetener (BioVittoria, 2009). As summarized in GRN 301, the 90th percentile consumer of a sweetener which is 100 times as sweet as sucrose when used as a total sugar replacement would be a maximum of 9.9 mg per kg bw per day for any population subgroup.

The estimated sweetness intensity for Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation ranges between 280 and 320-fold that of sucrose. Therefore, the highest 90th percentile consumption by any population subgroup of Shandong's SXY Stevia® Total Steviol Glycosides 95% purifed steviol glycosides preparation would consume approximately 3.54 mg per kg steviol glycosides bw per day. A weighted sum estimate was used to determine the steviol equivalency factor on a worst-case scenario basis. For example, Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides steviol equivalence factor was calculated from the molecular weight ratios of steviol to rebaudioside A, stevioside, and the remaining steviol glycosides, on a percent composition basis, as follows:

$$SteviolEquivalenceFactor = \left(\frac{MWSteviol}{MW\,RebA} * 0.50\right) + \left(\frac{MWSteviol}{MWStevioside} * 0.20\right) + \left(\frac{MWSteviol}{MW\,RebB} * 0.01\right) + etc.$$

[2] Non-nutritive sweeteners: Substances having less than 2 percent of the caloric value of sucrose per equivalent unit of sweetening capacity.
[3] See 21 CFR 182.1(b)(1).

Based on a weighted sum estimate for steviol equivalents,[4] the consumption would be less than 0.95 mg per kg bw per day on a steviol equivalents basis for any population group, on a worst-case scenario basis, for any of Shandong's purified steviol glycosides preparations. These calculations are summarized in Table 4.

Table 4. Daily Intake of Sweeteners (in Sucrose Equivalents) & Estimated Daily Intakes of SXY Stevia® Total Steviol Glycosides 95% Purified Steviol Glycosides

Population Group	Intakes of Sweeteners (mg sucrose/kg bw/day)[a]		Calculated Intake of SXY Stevia® Total Steviol Glycosides 95% (mg/kg bw/day)[b]		Calculated Intake of SXY Stevia® Total Steviol Glycosides 95% as Steviol Equivalents (mg/kg bw/day)[c]	
	Low	High	Low	High	Low	High
Healthy Population	255	675	0.91	2.41	0.24	0.65
Diabetic Adults	280	897	1.00	3.20	0.27	0.86
Healthy Children	425	990	1.52	3.54	0.41	0.95
Diabetic Children	672	908	2.40	3.24	0.64	0.87

[a] From Renwick, 2008. Renwick (2008)

[b] Calculated by dividing the sucrose intake by the minimum average relative sweetness value of 280 for Shandong's SXY Stevia® Total Steviol Glycosides 95%.

[c] Calculated based on the ratio of molecular weights of Reb A, stevioside, Reb B, Reb C, Reb D, Reb F, rubusoside, dulcoside A, and steviolbioside to steviol.

The values in Table 4 assume that Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation constitute the entire sweetener market, which makes these estimates extremely conservative since the likelihood of that occurrence is minimal. For the general healthy adult population, the estimated maximum intake of purified steviol glycosides is 2.41 mg per kg bw per day, or 0.65 mg per kg steviol equivalents. For healthy children, the estimated maximal intake is 3.54 mg per kg bw per day, or 0.95 mg per kg as steviol equivalents. In all population groups, the estimated daily intake of purified steviol glycosides, expressed as steviol equivalents, is well below the JECFA-established ADI of 4.0 mg per kg bw per day steviol equivalents.

[4] Calculated by Expert Panel as percent of molecular weight of steviol to molecular weight of rebaudioside A, stevioside, rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside F, rubusoside, dulcoside A, and steviolbioside, on a percent composition basis. Total steviol glycosides assumed to be 100%.

B. Estimated Dietary Exposure to Any Other Substance That is Expected to be Formed In or On Food

This section is not applicable to Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides product, which would be chemically stable under conditions of use.

C. Dietary Exposure to Contaminants or Byproducts

While a recent publication by Kumari et al. (2016) has demonstrated the presence of TPC, TFC, and TAC in *S. rebaudiana* leaf --- and the observed activity has been attributed to naturally-occurring phytochemicals such as phenolics, flavonoids, and pigments in the plant --- the study has minimal relevance with regard to the safety considerations of the highly purified stevia extract, of which ≥ 95% consists of the most familiar steviol glycosides. These contaminants, if present, are in low amounts and were likely similarly present in purified test materials that were used in the toxicology studies.

Furthermore, no concerns regarding dietary exposure to contaminants or byproducts have been raised by expert regulatory bodies, including the World Health Organization/Joint FAO/WHO Expert Committee on Food Additives (WHO/JECFA), European Food Safety Authority (EFSA), Food Standards Australia New Zealand (FSANZ), and FDA, since JECFA's first steviol glycosides review was performed in 2000 (WHO, 2000).

PART 4. SELF-LIMITING LEVELS OF USE

It has been well-documented in the published literature that the use of steviol glycosides is self-limiting due to organoleptic factors and consumer taste considerations (Kochikyan et al., 2006, Carakostas et al., 2008, Brandle et al., 1998, Prakash et al., 2008, Gupta et al., 2016, Gerwig et al., 2016). These organoleptic factors include bitterness and astringency, as well as a lingering metallic aftertaste (Gerwig et al., 2016).

PART 5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

A. Other Information on Dietary Exposure

1. History of Traditional Medicinal and Human Food Use

Stevia has been used as a traditional medicine and sweetener by native Guarani tribes for centuries (Esen, 2016, Gerwig et al., 2016, Brusick, 2008, Brandle et al., 1998).

For about 30 years, consumers in Japan and Brazil, where stevia has long been approved as a food additive, have been using stevia extracts as non-caloric sweeteners (Raintree, 2012). It was previously reported that 40% of the artificial sweetener market in Japan had been stevia based and that stevia is commonly used in processed foods in Japan (Lester, 1999). Use of steviol glycosides as a dietary supplement is presently permitted in the US, Canada, Australia, and New Zealand,

and as a natural health product in Canada. It has wide use in China and Japan in food and in dietary supplements. In 2005, it was estimated that sales of stevia in the US reached $45 million (Newsday, 2006).

More recent reports of consumption figures for stevia reveal pronounced increases in global consumption. Worldwide, Zenith International estimates stevia sales of 3,500 metric tons in 2010, which represents a 27% increase over 2009 figures. The market value is estimated to have increased to $285 million (Zenith, 2011). In 2013, worldwide sales of stevia was reported to reach 4,100 tons which represents a 6.5% increase over 2011 figures, and this corresponds to an overall market value of $304 million (Zenith, 2013).

In October 2014, Zenith International reported that worldwide stevia sales were on course to increase 14% to 4,670 tons, associated with a market value of $336 million. Furthermore, it has been projected that the total market for stevia in 2017 will be 7,150 tons with an associated market value of $578 million (Zenith, 2014).

More recently, NewHope360 reported that the global market for stevia in 2014 was $347 million, and that is expected to increase to $565.2 million by 2020. In addition, consumption is expected to increase from 2014 levels of 5,100.6 tons to 8,506.9 tons by 2020 (NewHope360, 2015).

Hawke (2003) reported that stevia is commonly used as a treatment for type 2 diabetes in South America. However, for its therapeutic effects, elevated doses in the range of 1 gram per person per day or more were reported to be necessary (Gregersen et al., 2004).

B. Summary of Regulatory History of SXY Stevia® Total Steviol Glycosides 95%

Stevia-derived sweeteners are permitted as food additives in South America and in several countries in Asia, including China, Japan, and Korea. In recent years, these sweeteners have received food usage approvals in Mexico, Australia, New Zealand, Switzerland, France, Peru, Uruguay, Colombia, Senegal, Russia, Malaysia, Turkey, Taiwan, Thailand, Israel, Canada, and Hong Kong (EFSA, 2010, Watson, 2010, Health Canada, 2012). In the US, steviol glycosides have been used as a dietary supplement since 1995 (Geuns, 2003).

1. U.S. Regulatory History

Based on available information from FDA's GRAS Notice Inventory website (FDA, 2017) as of August 10, 2017, FDA has issued 45 "no questions" letters on GRAS notices on rebaudioside A, rebaudioside D, rebaudioside M, or steviol glycosides, including those undergoing enzyme treatment. A summary of these filings is presented in Table 5.

Table 5. FDA's GRAS Notice Inventory on Rebaudioside & Steviol Glycosides Preparations[a,c]

Company	FDA GRAS Identifier	Material Identity	Intended Food Uses
1. Merisant	GRN 252	High-Purity Reb A ≥95%	Variety of food categories & table top sweetener
2. Cargill Inc.	GRN 253	High-Purity Reb A ≥97%	General-purpose sweetener, excluding meat & poultry products
3. McNeil Nutritionals LLC	GRN 275	Purified Steviol Glycosides – Reb A Principal Component	Table top sweetener
4. Blue California	GRN 278	High-Purity Reb A ≥97%	General-purpose & table top sweetener
5. Sweet Green Fields LLC	GRN 282	High-Purity Reb A ≥97%	General-purpose sweetener, excluding meat & poultry products
6. Wisdom Natural Brands	GRN 287	Purified Steviol Glycosides >95% - Reb A and Stevioside Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas
7. Sunwin USA LLC & WILD Flavors	GRN 303	High-Purity Reb A ≥95%/ ≥98%	General-purpose sweetener, excluding meat, poultry products & infant formulas
8. Sunwin USA LLC & WILD Flavors	GRN 304	Purified Steviol Glycosides >95% - Reb A and Stevioside Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas
9. Pyure Brands, LLC	GRN 318	High-Purity Reb A 95%/ 98%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
10. PureCircle USA Inc	GRN 323	Purified Steviol Glycosides – Reb A Principal Component	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
11. GLG Life Tech Ltd[c]	GRN 329	High-Purity Reb A ≥97%	General-purpose sweetener, excluding meat & poultry products
12. NOW Foods	GRN 337	Enzyme Modified Steviol Glycosides Preparation (EMSGP)	General-purpose sweetener in foods, excluding meat & poultry products, at levels determined by good manufacturing practices
13. GLG Life Tech Ltd[c]	GRN 348	High-Purity Stevioside ≥95%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
14. GLG Life Tech Ltd[c]	GRN 349	High-Purity Steviol Glycosides ≥97%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
15. Guilin Layn Natural Ingredients, Corp.	GRN 354	High-Purity Reb A ≥97%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
16. BrazTek International Inc.	GRN 365	Purified Reb A	General-purpose sweetener, excluding meat & poultry products
17. Sinochem Qingdao Co. Ltd.	GRN 367	High-Purity Steviol Glycosides ≥95%	General-purpose & table top sweetener, excluding meat, poultry products & infant formulas
18. Shanghai Freemen Americas LLC	GRN 369	Purified Reb A	General-purpose sweetener, excluding meat & poultry products

COMPANY	FDA GRAS IDENTIFIER	MATERIAL IDENTITY	INTENDED FOOD USES
19. Toyo Sugar Refining Co., Ltd. & Nippon Paper Chemicals Co., Ltd.	GRN 375	Enzyme Modified Steviol Glycosides	General-purpose sweetener in foods, excluding meat and poultry products, at levels determined by good manufacturing practices
20. GLG Life Tech Ltd[b]	GRN 380	Purified Reb A	General purpose & table top sweetener, excluding meat & poultry products
21. Chengdu Wagott Pharmaceutical	GRN 388	Purified Reb A	General purpose & table top sweetener, excluding meat & poultry products
22. Chengdu Wagott Pharmaceutical	GRN 389	Steviol Glycosides with Stevioside as the Principal Component	General purpose & table top sweetener, excluding meat & poultry products
23. Daepyung Co., Ltd.	GRN 393	Purified Reb A	General purpose & table top sweetener, excluding meat & poultry products
24. Daepyung Co., Ltd.	GRN 395	Steviol Glycosides with Reb A and Stevioside as the Principal Components	General purpose & table top sweetener, excluding meat & poultry products
25. MiniStar International, Inc.	GRN 418	Purified Reb A	General-purpose sweetener, excluding meat, poultry products & infant formulas.
26. Daepyung Co., Ltd.	GRN 448	Enzyme Modified Steviol Glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
27. Daepyung Co., Ltd.	GRN 452	Enzyme Modified Steviol Glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
28. PureCircle USA, Inc.	GRN 456	High-Purity Reb D ≥95%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
29. Almendra, Ltd.	GRN 461	High-Purity Reb A ≥97%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
30. Qufu Xiangzhou Stevia Products Co., Ltd.	GRN 467	High-Purity Reb A ≥98%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
31. PureCircle USA, Inc.	GRN 473	Purified Steviol Glycosides – Reb M (Reb X) Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
32. GLG Life Tech Corp.	GRN 493	High purity steviol glycosides ≥95%	General-purpose sweetener, excluding meat, poultry products.
33. GLG Life Tech Corp.	GRN 512	High purity Reb M ≥95%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
34. Almendra Limited	GRN 516	Steviol Glycosides with Reb A and Stevioside as the Principal Components	General-purpose sweetener, excluding meat, poultry products & infant formulas.

COMPANY	FDA GRAS IDENTIFIER	MATERIAL IDENTITY	INTENDED FOOD USES
35. GLG Life Tech Corp.	GRN 536	High purity Reb C and Steviol glycosides with Reb C as the Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
36. GLG Life Tech Corp.	GRN 548	High purity Reb D	General-purpose sweetener, excluding meat, poultry products & infant formulas.
37. Productora Alysa SpA	GRN 555	Steviol Glycosides with Reb A as the Principal Component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
38. PureCircle, Ltd.	GRN 607	Glucosylated steviol glycosides (minimum purity 80%)	Use as a flavoring agent and flavor modifier at levels ranging from 100 to 1,000 ppm
39. PureCircle, Ltd.	GRN 619	Steviol Glycosides ≥95%	General-purpose sweetener, excluding meat, poultry products & infant formulas.
40. Cargill, Inc.	GRN 626	Steviol glycosides (Reb M and Reb D) produced in *Saccharomyces cerevisiae*	General-purpose sweetener
41. DSM Nutritional Products, LLC.	GRN 632	Rebaudioside A from *Yarrowia lipolytica*	General-purpose sweetener, excluding meat, poultry products & infant formulas.
42. Hunan Huacheng Biotech Inc.	GRN 638	High purity steviol glycosides with Reb A as the principal component	General-purpose sweetener, excluding meat, poultry products & infant formulas.
43. GLG Life Tech Corporation	GRN 656	Enzyme-modified steviol glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
44. PureCircle USA	GRN 662	Glucosylated steviol glycosides	General-purpose sweetener, excluding meat, poultry products & infant formulas.
45. Blue California	GRN 667	Rebaudioside M	General-purpose sweetener, excluding meat, poultry products & infant formulas.

[a] This table was derived, in part, from (McQuate, 2011).

[b] The name of this company is now GLG Life Tech Corporation.

[c] GRN 702, submitted by Xinghua GL Stevia Co., Ltd., regarding purified steviol glycosides, was filed by FDA and is presently under review.

In addition, the Flavor and Extract Manufacturers Association (FEMA) has included several steviol glycosides preparations on their GRAS lists as shown in Table 6.

Table 6. FEMA GRAS Status for Steviol Glycoside Preparations

Steviol Glycosides Preparation	FEMA Number	Reference
Rebaudioside A	4601	(Smith et al., 2009)
Rebaudioside C; dulcoside B	4720	(Leffingwell, 2011)
Glucosyl steviol glycosides; enzymatically modified stevia extract	4728	(Leffingwell and Leffingwell, 2014, Marnett et al., 2013)
Stevioside	4763	(Leffingwell and Leffingwell, 2014, Marnett et al., 2013)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 60%	4771	(Marnett et al., 2013)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 80%	4772	(Marnett et al., 2013)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside C 30%	4796	(Cohen et al., 2015a, Cohen et al., 2015b)
Steviol glycoside extract, *Stevia rebaudiana*, Rebaudioside A 22%	4805	(Cohen et al., 2015a, Cohen et al., 2015b)
Steviol glycoside extract, *Stevia rebaudiana* Rebaudioside C 22%	4806	(Cohen et al., 2015a, Cohen et al., 2015b)

2. Canadian Regulatory History

On September 18, 2009, based on a review of the international regulation of *Stevia rebaudiana* and the clinical evidence for safety and efficacy, the Natural Health Products Directorate, Health Canada (2009) adopted the following guidelines for the use of *stevia* and steviol glycosides in Natural Health Products (NHPs) (Health Canada, 2009). The revised recommendation for the maximum limit for steviol glycosides in NHPs is in accordance with the full acceptable daily intake (ADI) of 4 mg steviol per kg bw established by JECFA (WHO, 2008).

On November 30, 2012, Health Canada published its final clearance for use of steviol glycosides as a sweetener in foods (Health Canada, 2012). In March 2014, Health Canada updated the List of Permitted Sweeteners (Lists of Permitted Food Additives) to include steviol glycosides in applications as a table-top sweetener and as an ingredient in a variety of foods, beverages, baked goods, meal replacement bars, condiments, and confectionary and gums (Health Canada, 2014). On January 15, 2016, Health Canada approved the use of Reb M for use as a high-intensity sweetener under the same conditions as the previously approved steviol glycosides (Health Canada, 2016).

Most recently, Health Canada's Food Directorate has updated its List of Permitted Sweeteners to allow for the use of steviol glycosides as a sweetener in 'unstandardized snack bars,' including granola bars, cereal bars, fiber bars, and protein isolate-based bars (Health Canada, 2017).

3. European Regulatory History

The Joint Expert Committee on Food Additives (JECFA) reviewed steviol glycosides at its 51st, 63rd, 68th and 73rd meetings. In 2000, JECFA published the original review on steviol glycosides (WHO, 2000). JECFA established a temporary ADI (acceptable daily intake) of 0-2 mg per kg (on a steviol basis) at its 63rd meeting (WHO, 2006). Additionally, JECFA finalized food grade specifications (FAO, 2007b), although they were subsequently updated in 2008 (FAO, 2008) and 2010 (FAO, 2010) (see below). At the 69th meeting, the temporary status of the ADI was removed, and the ADI was raised to 0-4 mg per kg bw per day (on a steviol basis) as a result of the JECFA review of more recently completed clinical studies with steviol glycosides (WHO, 2008). In 2009, JECFA published a final monograph addendum on steviol glycosides (WHO, 2009).

In early 2009, a number of parties, including the government of Australia and the Calorie Control Council, submitted a request to the Codex Committee on Food Additives in which it was proposed that the JECFA specifications for steviol glycosides should be modified to allow inclusion of rebaudioside D and rebaudioside F as specifically named acceptable glycosides that would be considered as part of the minimum 95% steviol glycosides composition (CCFA, 2009). This proposed modification was endorsed by the Codex Alimentarius Committee in July 2009; it was on the agenda for discussion at the JECFA Meeting in June, 2010 (FAO/WHO, 2009), and JECFA subsequently took final action in approving the modified steviol glycosides specifications to include rebaudioside D and rebaudioside F (FAO, 2010).

In 2008, Switzerland's Federal Office for Public Health approved the use of stevia as a sweetener citing the favorable actions of JECFA (Health, 2008). Subsequently, France published its approval for the food uses of rebaudioside A with a purity of 97% (AFSSA, 2009a, AFSSA, 2009b).

In light of JECFA's 2008 findings, and in response to a June 2008 request by the European Commission for European Food Safety Authority (EFSA) to deliver a scientific opinion on the safety of steviol glycosides as a sweetener for use in the food categories specified in the dossiers from three petitioners, EFSA reexamined the safety of steviol glycosides (EFSA, 2010). After considering all the data on stability, degradation products, metabolism and toxicology, the EFSA Panel established an ADI for steviol glycosides, expressed as steviol equivalents, of 4 mg per bw per day, which is similar to JECFA's determination.[5] In addition, on May 25, 2011, EFSA published a determination that the daily dietary intake for use of rebaudioside A as a flavoring substance in a variety of foods would be less than the ADI for steviol glycosides (EFSA, 2011a). In 2014, EFSA

[5] From a historical perspective, it is noted that the UK's Advisory Committee on Novel Foods and Processes for the Ministry of Agriculture, Fisheries and Food on September 24, 1998 rejected an application for use of steviol glycosides as a sweetener in herbal teas because "the applicant had not provided all of the information necessary to enable an assessment to be made" MAFF (1998) *Advisory Committee on Novel Foods and Processes for the Ministry of Agriculture, Fisheries and Food.* Available at: http://archive.food.gov.uk/maff/archive/food/novel/980924.htm (Accessed: June 30, 2014.). In 1999, the Scientific Committee on Food for the European Commission concluded that "there are no satisfactory data to support the safe use of these stevia plants and leaves" EuropeanCommission (1999a) 'Opinion on Stevia Rebaudiana Bertoni plants and leaves. Scientific Committee on Food (CS/NF/STEV/3 Final, 17 June 1999).'. In another opinion also dated June 17, 1999, the Committee also reiterated "its earlier opinion that stevioside is not acceptable as a sweetener on the presently available data" EuropeanCommission (1999b) 'Opinion on stevioside as a sweetener. Scientific Committee on Food (CS/ADD/EDUL/167Final, 17 June 1999)'.

evaluated extending the use of steviol glycosides as ingredients in food categories to include coffee, tea, and herbal and fruit infusions (assessed at 10 mg per L steviol glycosides). Exposure estimates were lower than those determined by the Panel in 2011 due to available data, and remained below the ADI of 4 mg per kg bw per day, with the exception of toddlers from one country at the 95th percentile exposure level of 4.3 mg per kg bw per day (EFSA, 2014). More recently, exposure estimates, based on maximum permitted levels (MPLs) and proposed use levels increased to 29 mg per L steviol glycosides, were found to have a "negligible" impact on dietary intake for all population groups, with the mean exposure estimate below the ADI of 4 mg per kg bw per day, with the exception of toddlers from one country at the 95th percentile exposure level of 4.3 mg per kg bw per day. The EFSA panel concluded that "dietary exposure to steviol glycosides (E 960) is similar to the exposure estimated in 2014 and therefore does not change the outcome of the safety assessment" (EFSA, 2015).

The appropriate European regulatory bodies, including the joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA), have now agreed that steviol glycosides are safe for all populations to consume and are a suitable sweetening option for diabetics. Effective December 2, 2011, the EU approved their use as food additives (EU, 2011). In March 2016, the EU approved the use of steviol glycosides in mustard (Michail, 2016).

Most recently, an amendment to the EU food additives regulation 231/2012, which became active on November 3, 2016, removed the previous requirement for stevia blends to contain at least 75% reb A or stevioside. In addition, the updated regulation ---(EU) 2016/1814---now permits the following steviol glycosides in stevia blends: stevioside, rebaudiosides A, B, C, D, E, F and M, steviolbioside, rubusoside, and dulcoside (Searby, 2016).

4. Asian Regulatory History

As of May 2010, the government of Hong Kong amended its food regulations to allow the use of steviol glycosides as a permitted sweetener in foods (Safety, 2010). This action followed in the aftermath of the detailed safety evaluation and favorable findings as reported by JECFA.

The international community continued to exhibit much interest in the food uses of steviol glycosides, with additional advances reported in early July 2011. The Codex Alimentarius Commission has adopted proposed maximum use levels for steviol glycosides in all major food and beverage categories, and this action was expected to favorably influence authorizations of stevia uses in India, Indonesia, Thailand, and the Philippines (FoodNavigator, 2011). An article published online by FoodNavigator (2013) states the following: "with approvals now in Vietnam, the Philippines, Malaysia, Singapore and Thailand, Indonesia is the only [Southeast Asian nation] where stevia hasn't been given the rubber stamp" (Whitehead, 2013). Furthermore, the International Alliance of Dietary/Food Supplement Associations (IADSA) reported that the Codex Alimentarius Commission agreed to adopt the use of steviol glycosides for addition to chewable food supplements as had been requested by IADSA (NewHope360, 2011).

The Food Safety and Standards Authority of India (FSSAI) convened on September 20, 2012, at which time they approved the use of steviol glycosides as a non-nutritive sweetener in a variety of foods. The FSSAI specified that: the steviol glycosides must meet the specifications and purity as established by JECFA; table top sweetener tablets may contain 7 mg of steviol equivalents per 100 mg carrier/filler, as well as established maximum use levels specific to 11 distinct food categories including dairy, beverage, and chewing gum applications (FSSAI, 2012).

Since December 10, 2012, over thirty registrations have been granted by FDA Philippines to stand-alone steviol glycosides sweeteners or foods containing steviol glycosides as ingredients, including: FR-104390, Steviten Light Brand Steviol Glycosides 95% Sweetener Powder; FR-109427, Del Monte Pineapple Chunks in Extra Light Syrup Reduced Calorie with Steviol Glycosides from Stevia; FR-101120, Diebetamil Zero Calorie Sweetener with Stevia (stick pack); and FR-102127, Sawayaka Stevia Sweetener (1 g sticks) (Philippines, 2014).

Steviol glycosides are also listed under INS number 960 in the Food Additives Permitted Under the Singapore Food Regulations document prepared by the Agri-Food & Veterinary Authority (AVA) of Singapore (AVA, 2014).

5. Other Regulatory History

In 2008, the Food Standards Australia New Zealand (FSANZ) completed its evaluation of an application for use of steviol glycosides in foods. FSANZ recommended that the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) amend the Australia New Zealand Food Standards Code to allow the use of steviol glycosides in food (FSANZ, 2008). In December 2010, FSANZ recommended accepting the increased usage levels as requested since no public health and safety issues were identified (FSANZ, 2010). Subsequently, FSANZ approved an increase in the maximum permitted level (MPL) of steviol glycosides (expressed as steviol equivalents) in ice cream, water based beverages, brewed soft drinks, formulated beverages, and flavored soy beverages up to 200 mg per kg, and in plain soy beverages up to 100 mg per kg (FSANZ, 2011). In a recent risk assessment, FSANZ concluded that the use of Reb M does not pose any "public health and safety issues" (FSANZ, 2015b). In addition, FSANZ proposed to add Reb M to the list of permitted steviol glycosides (FSANZ, 2015a). On January 14, 2016, Reb M was approved for use "as a food additive in accordance with the current permissions for steviol glycosides" (FSANZ, 2016a).

Most recently, FSANZ called for submissions on permitting all minor steviol glycosides extracted from stevia leaf to be included in the definition of steviol glycosides in the Food Standards Code, noting that "[no] evidence was found to suggest that the proposed changes pose any public health and safety concerns." The submission period ended on December 19, 2016 (FSANZ, 2016b). Subsequently, on February 8, 2017, FSANZ approved a draft variation of the definition of steviol glycosides to include all steviol glycosides present in the *Stevia rebaudiana* leaf (FSANZ, 2017).

On September 10, 2012, the South African Department of Health issued an amendment to labeling regulations indicating: "in the case of the sweetener steviol glycosides, it shall be described as 'Steviol Glycosides' or 'Steviol Extract.'" On the same date, steviol glycosides were added to the List of Permissible Sweeteners (RSADH, 2012b, RSADH, 2012a).

PART 6. NARRATIVE

The biological, toxicological, and clinical effects of stevia and steviol glycosides have been extensively reviewed (Carakostas et al., 2008, Geuns, 2003, Huxtable, 2002). Additionally---and as noted earlier---the national and international regulatory agencies have thoroughly reviewed the safety of stevia and its glycosides. Most notably, over the years, JECFA has evaluated purified steviol glycosides multiple times (WHO, 2000, WHO, 2006, WHO, 2007, WHO, 2008), and their findings have been summarized in Part 5.B.3. FSANZ (2008) also evaluated steviol glycosides for use in food. The JECFA reviews, as well as the other reviews completed before 2008, primarily focused on mixtures of steviol glycosides. These studies are summarized in Appendix 6.

Since the JECFA evaluation (WHO, 2008), over forty GRAS notifications for steviol glycosides or enzyme modified steviol glycosides have been submitted to FDA. In each case, FDA has agreed with the conclusions that steviol glycosides are GRAS based largely on the 0-4 mg per kg bw per day ADI on a steviol equivalence basis that was established by JECFA. A recent publication by Roberts et al. (2016) indicates that the ADI could be higher, as discussed further in Appendix 5. Among the GRAS notifications submitted to FDA, several assessed purified preparations of rebaudioside A, and they were supported by additional toxicology and clinical studies that are summarized in Appendix 8. To date, 45 of the submitted notifications have had "no questions" letters of response from FDA (see Table 5).

Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation contains not less than 95% steviol glycosides, and is composed of rebaudioside A, stevioside, rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside F, dulcoside A, rubusoside, and steviolbioside. Given the structural similarities with rebaudioside A, stevioside, and other steviol glycosides, and considering analogous metabolic pathways for all these substances, the safety data on stevia and its other components have a direct bearing on the present safety assessment for Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation. This is further supported by over a decade and a half of scientific studies on the safety of these substances, along with the fact that the major regulatory bodies view the results of toxicology studies on either stevioside or rebaudioside A as applicable to the safety assessment of all known steviol glycosides, since all are metabolized and excreted by similar pathways, with steviol being the common metabolite for each. The foundational safety of Reb A, other steviol glycosides and steviol has been summarized, with key studies detailed in Appendices 7-9.

Shandong has reviewed this safety information and has concluded that their SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation is generally recognized as safe for the proposed uses.

A. GRAS Criteria

FDA defines "safe" or "safety" as it applies to food ingredients as:

> "...reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[6]

Amplification is provided in that the conclusion of safety is to include probable consumption of the substance in question, the cumulative effect of the substance and appropriate safety factors. It is FDA's operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that:

> "...General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."
>
> "'Common knowledge' can be based on either "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958." [7]

FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following component elements:[8]

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as JECFA and the National Academy of Sciences.

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[6] See 21 CFR 170.3 (e)(i) and 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe (Accessed on 4/15/17).
[7] See 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe (Accessed on 4/15/17).
[8] See Footnote 1.

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

The apparent imprecision of the terms "appreciable," "at the time," and "reasonable certainty" demonstrates that the FDA recognizes the impossibility of providing absolute safety in this or any other area (Lu, 1988, Renwick, 1990, Rulis and Levitt, 2009).

As noted below, this safety assessment to ascertain GRAS status for high purity steviol glycosides for the specified food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

B. Expert Panel Findings on Safety of SXY Stevia® Total Steviol Glycosides 95%

Because of their sweetness characteristics, steviol glycosides have viable uses as a non-nutritive sweetener in foods.[9] Periodic reviews by JECFA over the years indicate the progression of knowledge on the toxicology of steviol glycosides. Several early safety-related studies on these compounds were performed on crude extracts of stevia. These studies also included multiple investigations with *in vivo* and *in vitro* models, which explored the biological activity of stevia extracts at high doses or high concentrations. These early investigations raised several concerns, including impairment of fertility, renal effects, interference with glucose metabolism, and inhibition of mitochondrial enzymes. In recent years, as more and more studies were performed on purified glycosides, the toxicology profile of steviol glycosides eventually proved to be rather unremarkable. A number of subchronic, chronic, and reproductive studies have been conducted in laboratory animals. These studies were well designed with appropriate dosing regimens and adequate numbers of animals to maximize the probability of detection of important effects. Notably, the initially reported concerns related to the effects of stevia leaves or crude extracts on fertility were refuted by the well-designed reproductive studies with purified steviol glycosides. All other concerns failed to manifest themselves at the doses employed in the long-term rat studies.

As discussed in Appendix 6 and elsewhere, at its 51st meeting, JECFA determined that there were adequate chronic studies in rats, particularly the study by Toyoda et al. (1997), to establish a temporary ADI of 0 - 2 mg per kg bw per day with an adequate margin of safety (Toyoda et al.,

[9] It has also been reported that steviol glycosides may have pharmacological properties, which can be used to treat certain disease conditions such as hypertension and type 2 diabetes. Chatsudthipong, V. and Muanprasat, C. (2009) 'Stevioside and related compounds: therapeutic benefits beyond sweetness', *Pharmacology & therapeutics*, 121(1), pp. 41-54., as well as others, have published reviews where they note that such therapeutic applications have not been firmly established as being due to steviol glycosides. The reviewers point out that the effects occur at higher doses than would be used for sweetening purposes. Furthermore, many effects noted in older studies may have been due to impurities in preparations that do not meet the contemporary purity specifications established by JECFA for use as a sweetener. If oral doses of steviol glycosides impart pharmacological effects, such effects would undoubtedly occur due to actions of the principal metabolite, steviol, but the pharmacological effects of steviol have not been comprehensively investigated. For more a more comprehensive discussion of this subject, see Section 7 of Appendix 9.

1997). The committee also critically reviewed the lack of carcinogenic response in well-conducted studies. These studies validated the Committee conclusion that the *in vitro* mutagenic activity of steviol did not present a risk of carcinogenic effects *in vivo* and, therefore, all common steviol glycosides that likely share the same basic metabolic and excretory pathway and that use high purity preparations of various steviol glycosides, are safe as a sugar substitute. Subsequently, the additional clinical data reviewed by JECFA allowed the Committee to establish a permanent ADI of 0 - 4 mg per kg bw per day (based on steviol equivalents). The GRAS Expert Panel critically reviewed the JECFA assessment and agrees with the calculation of the ADI for steviol glycosides.

Several published and unpublished studies (summarized in Appendix 8) on purified preparations of rebaudioside A showed an absence of toxicological effects in rats (Curry and Roberts, 2008, Nikiforov and Eapen, 2008) and dogs (Eapen, 2008) in subchronic studies, and an absence of reproductive (Curry et al., 2008, Sloter, 2008a) and developmental effects (Sloter, 2008b) in rats. Most notably, pharmacokinetic studies in rats (Roberts and Renwick, 2008) and humans (Wheeler et al., 2008) on purified rebaudioside A follow the same pathway of being degraded to steviol by intestinal bacteria with subsequent rapid glucosylation and elimination in urine and feces. The Panel concludes that these studies on rebaudioside A strengthen the argument that all steviol glycosides that follow the same metabolic pathway are safe at the JECFA established ADI.

The Panel has reviewed the findings from human clinical studies. The Panel noted that, regarding the clinical effects reported in humans, in order to corroborate the observations in these studies that these effects of steviol glycosides only occur in patients with either elevated blood glucose or blood pressure (or both), JECFA called for studies in individuals that are neither hypertensive nor diabetic (WHO, 2006). The supplemental data presented to JECFA and also published by Barriocanal et al. (2008) demonstrate the lack of pharmacological effects of steviol glycosides at 11 mg per kg bw per day in normal individuals, or approximately slightly more than 4 mg per kg bw on the basis of steviol equivalents (Barriocanal et al., 2008). Clinical studies on purified rebaudioside A showed an absence of effects on blood pressure (Maki et al., 2008a) and blood glucose levels (Maki et al., 2008b) at doses slightly higher than the exposures expected in food. The Panel concludes that there will be no effects on blood pressure and glucose metabolism in humans at the doses of steviol glycosides expected from its use in food as a non-nutritive sweetener.

Two previously published studies summarized in Appendix 7 raised a potential concern regarding the toxicological effects of steviol glycosides. In one study, DNA damage was seen in a variety of organs as assessed by Comet assay in rats given drinking water containing 4 mg per mL steviol glycosides for up to 45 days (Nunes et al., 2007a). Several experts in the field have since questioned the methodology used in this study (Geuns, 2007a, Williams, 2007, Brusick, 2008). The Panel has reviewed the cited publications, along with the responses made by the authors (Nunes et al., 2007c, Nunes et al., 2007b), and concurs with the challenges to the methodology utilized by Nunes et al. (2007a), thereby discounting the validity and importance of this study.

In another study with stevioside in rats, tartrate-resistant alkaline phosphatase (TRAP) levels were measured and found to be significantly decreased at doses as low as 15 mg per kg bw (Awney et al., 2011). TRAP is an enzyme that is expressed by bone-resorbing osteoclasts, inflammatory macrophages, and dendritic cells. This enzyme was not measured in any previous toxicology studies on steviol glycosides, nor has it been adequately vetted for application in toxicological studies. Critical reviews of this study by Carakostas (2012) and (Waddell, 2011) revealed a poor study design that included: insufficient numbers of animals; group-housing with the potential for stress-related changes; unreliable access to steviol *via* drinking water resulting in suspect dosing calculations in group-housed cages; no indication of fasting prior to blood collection (which affects many chemistry and hematological values); no urine collection; and no histopathological evaluations for confirmation of findings beyond the controls. Additionally, the report did not adequately describe mean or individual organ weight data, and it lacked comparison of study findings against laboratory historical control data.

Urban et al. (2013) examined the extensive genotoxicity database on steviol glycosides because some concern has been expressed in two relatively recent publications (Brahmachari et al., 2011, Tandel, 2011) in which the authors concluded that additional testing is necessary to adequately address the genotoxicity profile (Urban et al., 2013). The review aimed to address this matter by evaluating the specific genotoxicity studies of concern, while evaluating the adequacy of the database that includes more recent genotoxicity data not noted in these publications. The results of this literature review showed that the current database of *in vitro* and *in vivo* studies for steviol glycosides is robust and does not indicate that either stevioside or rebaudioside A are genotoxic. This finding, combined with a paucity of evidence for neoplasm development in rat bioassays, establishes the safety of all steviol glycosides with respect to their genotoxic/carcinogenic potential.

In addition, a recent paper by Shannon et al. (2016) raises a possible concern of endocrine disruption by steviol. The Panel has reviewed the publication and notes that the effects on progesterone production and on the action of progesterone (both antagonistic and agonistic) were observed *in vitro* in sperm cells. The Panel concludes that it is difficult to translate *in vitro* concentrations to local concentrations *in vivo* at receptors and that no adverse effects were observed in well-conducted reproductive toxicology studies. Therefore, this study does not alter the opinion of the Expert Panel that steviol glycosides preparations, with rebaudioside A and stevioside as the main components, are generally recognized as safe. A summary of this study is provided in Appendix 7.

The Expert Panel agrees with the safety conclusions of the 45 GRAS Expert Panels in the notifications for steviol glycosides previously submitted to FDA that resulted in "no questions" responses from FDA (as summarized in Table 5), JECFA (WHO, 2006, WHO, 2008), and Renwick (2008) that a sufficient number of good quality health and safety studies exist to support the determination that purified preparations of steviol glycosides, when added to food at levels up to full replacement of sucrose on a sweetness equivalency basis, meet FDA's definition of safe.

The Panel concludes that it is reasonable to apply the JECFA ADI of 4 mg per kg bw per day for steviol glycosides (expressed on a steviol basis) to Shandong's SXY Stevia® Total Steviol Glycosides 95%. Therefore, with the steviol equivalence values shown in Table 4, the Panel concludes that, for the general population, the estimated maximum daily intake of Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation is 3.54 mg per kg bw or 0.95 mg per kg expressed as steviol equivalents. Based upon these calculations, the intake of all of Shandong's SXY Stevia® Total Steviol Glycosides 95% safely aligns with the 4 mg per kg bw per day ADI expressed as steviol equivalents as determined by JECFA.

C. Common Knowledge Elements for GRAS Conclusions

The first common knowledge element for a GRAS conclusion requires that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing studies published in peer-reviewed scientific journals. The second common knowledge element for a GRAS conclusion requires that consensus exists within the broader scientific community.

1. Public Availability of Scientific Information

The majority of the studies reviewed on steviol glycosides and steviol have been published in the scientific literature as summarized in Appendices 7, 8, and 9. Most of the literature relied upon by JECFA has also been published---most importantly the chronic rat studies on steviol glycosides. JECFA did make limited use of unpublished studies, and they were summarized in the two JECFA monographs. Moreover, JECFA publicly releases the results of their safety reviews, and their meeting summaries and monographs are readily available on their website.

With regard to the safety documentation, the key pharmacokinetic data establish that steviol glycosides are not appreciably absorbed through the GI tract, *per se*; they are converted to steviol by bacteria normally present in the large intestine, and the steviol is absorbed but rapidly metabolized and excreted. It has been well-established experimentally from various published studies that the steviol glycosides molecules are not absorbed from the GI tract (Gardana et al., 2003, Koyama et al., 2003). The action of bacteria in the large intestine is directly supported by the published study that steviol glycosides can be converted to steviol in the large intestine by normal anaerobic GI flora as demonstrated by an *in vitro* study in fecal homogenates (Koyama et al., 2003, Renwick and Tarka, 2008). The ADI for steviol glycosides has been set largely based on a published chronic study in rats (Toyoda et al., 1997) and several published clinical studies that there are no pharmacological effects in humans at doses several fold higher than the ADI (Barriocanal et al., 2006, Barriocanal et al., 2008, Wheeler et al., 2008). Recently, Roberts et al. (2016) noted that the ADI could be higher than the 4 mg per kg bw per day figure (on a steviol equivalency basis) as established by JECFA based on evidence that glucuronidation of absorbed steviol is faster in humans than rats. The toxicity of the metabolite steviol has been well reviewed in the published literature (Geuns, 2003, WHO, 2006, Urban et al., 2013). In addition, there is a large, publicly available, collection of GRNs regarding steviol glycosides on FDA's website.

2. Scientific Consensus

The second common knowledge element for a GRAS conclusion requires that there must be a basis to conclude that consensus exists among qualified scientists about the safety of the substance for its intended use.

The Panel maintains that well-qualified scientists would conclude that Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation is not absorbed from the GI tract, *per se*. By virtue of fundamental principles of pharmacokinetics, the majority of scientists would support this determination, and they would likewise concur that the subject SXY Stevia® Total Steviol Glycosides 95% undergoes a conversion to steviol as is known to be the case with naturally occurring steviol glycosides.

A number of well-respected regulatory agencies, including JECFA, EFSA, FSANZ, the Switzerland Office of Public Health, and Health Canada, as well as numerous well-respected individual scientists, have indicated that steviol glycosides are safe for human consumption at doses in the range of the JECFA ADI (FAO, 2010, EFSA, 2010, FSANZ, 2008, Health, 2008, Health Canada, 2012, Xili et al., 1992, Toyoda et al., 1997, Geuns, 2003, Williams, 2007). We also note that, since December 2008, over forty GRAS notifications have been submitted to FDA for highly purified stevia-derived sweetener products, and FDA detailed reviews have consistently yielded "no questions" letters.

In summary, a compelling case can be made that scientific consensus exists regarding the safety of steviol glycosides when of sufficiently high purity. While the scientific conclusions are not unanimous regarding the safe human food uses of steviol glycosides, the Panel believes that a wide consensus does exist in the scientific community to support a GRAS conclusion as evidenced by several publications (Carakostas, 2012, Geuns, 2007a, Urban et al., 2013, Waddell, 2011, Williams, 2007, Brusick, 2008) that refute safety concerns expressed by a minority of scientists. Furthermore, FDA has reviewed 45 notifications regarding purified steviol glycosides preparations that yielded "no questions" letters, and these actions further support a scientific consensus of safety for steviol glycosides.

D. Conclusion

In consideration of the aggregate safety information available on naturally occurring steviol glycosides, Shandong and the designated Expert Panel[10] conclude that the purified steviol glycosides (≥ 95% total steviol glycosides) defined in the subject notification are safe for use as a general purpose non-nutritive sweetener in foods other than infant formulas and meat and poultry

[10] The detailed educational and professional credentials for two of the individuals serving on the Expert Panel can be found on the GRAS Associates website at www.gras-associates.com. Drs. Kraska and McQuate worked on GRAS and food additive safety issues within FDA's GRAS Review Branch earlier in their careers, and subsequently continued working within this area in the private sector. Dr. Emmel has substantial food safety experience in addressing steviol glycosides and other food ingredients. All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety and in participating in the deliberations of GRAS Expert Panels. Dr. Kraska served as Chair of the Panel.

products. The JECFA ADI for steviol glycosides of 4 mg per kg bw per day (as steviol equivalents) can be applied to Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation. Based on published dietary exposure data for other approved sweeteners and adjusting for relative sweetness intensity, intake was estimated for healthy non-diabetic children and adults, and diabetic children and adults with the following findings.

The worst-case estimated intakes of Shandong's SXY Stevia® Total Steviol Glycosides 95% for several population groups summarized in Table 4 are no greater than 0.95 mg per kg steviol equivalents per bw per day, which is well below the ADI of 4 mg per kg bw expressed as steviol equivalents as established by JECFA. The Panel finds that the dietary levels from anticipated food consumption will not exceed the ADI when purified steviol glycosides (≥95% total steviol glycosides) are used as a general non-nutritive sweetener.

The Panel also finds that the minimum ≥ 95% purity specification for Shandong's SXY Stevia® Total Steviol Glycosides 95% preparation is sufficient in view of the accepted JECFA specification for 95% purity for naturally occurring steviol glycosides. The Panel concludes that SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides (≥ 95% total steviol glycosides), as manufactured by Shandong, is an appropriate food grade ingredient and that adverse pharmacological effects are not likely to occur at this designated ADI level. Furthermore, even high consumers of steviol glycosides are not likely to exceed this specified ADI. Therefore, Shandong and the Expert Panel conclude that Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation (≥ 95% total steviol glycosides composed primarily of rebaudioside A and stevioside), when consumed in foods as described within this GRAS notification, is generally recognized as safe (GRAS) within the meaning of the Food, Drug, and Cosmetic Act.

Shandong's SXY Stevia® Total Steviol Glycosides 95% purified steviol glycosides preparation (≥ 95% total steviol glycosides composed primarily of rebaudioside A and stevioside), when produced in accordance with FDA Good Manufacturing Practices requirements and when meeting at a minimum the JECFA purity specifications for steviol glycosides and those specifications presented by Shandong in Table 2, is Generally Recognized As Safe when consumed as a non-nutritive sweetener within the JECFA ADI of 4 mg/kg bw/day. In order to remain within the designated ADI, it is important to observe good manufacturing practices principles in that the quantity of a substance added to food should not exceed the amount reasonably required to accomplish its intended technical effect.

This declaration has been made in accordance with FDA's standard for food ingredient safety, i.e., reasonable certainty of no harm under the intended conditions of use.

(b) (6)

Richard Kraska, Ph.D., DABT

Chair

(b) (6)

Robert S. McQuate, Ph.D.

(b) (6)

Katrina V. Emmel, Ph.D.

PART 7. LIST OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE.

A. List of Acronyms

ADI	Acceptable Daily Intake
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	area under the plasma-concentration time curve
AVA	Agri-Food & Veterinary Authority
BMI	Body Mass Index
BP	Blood pressure
bw	body weight
CAS	Chemical Abstract Service
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
cGMP	Current good manufacturing practices
C_{max}	Maximum (or peak) serum concentration of substance is observed
Co	Company
CSAF	Chemical-specific adjustment factor
DABT	Diplomat of the American Board of Toxicology
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FCC	Food Chemical Codex
FDA	Food and Drug Administration

FD&C	Federal Food, Drug, and Cosmetic Act
FEMA	Flavor and Extracts Manufacturing Association
FOIA	Freedom of Information Act
FSANZ	Food Standards Australia New Zealand
FSSAI	Food Safety and Standards Authority of India
g	gram
GA	GRAS Associates
GGT	gamma-glutamyltransferase
GI	Gastrointestinal
GMO(s)	genetically-modified organism(s)
gpt	guanine phosphoribosyltransferase
GPT	Glutamic-pyruvate transaminase
GRAS	Generally Recognized as Safe
GRN	GRAS Notification
HbA1c	glycated hemoglobin
HDL	High-density lipoprotein
Hg	Mercury
HPLC	High-Performance Liquid Chromatography
HR	Heart rate
IADSA	International Alliance of Dietary/Food Supplement Associations
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
L	Liter
LD_{50}	Lethal Dose, 50%
LDL	Low-density lipoprotein
LLC	Limited Liability Corporation

Ltd.	Limited
MAP	Mean arterial pressure
mg	milligram
min.	minimum
mL	milliliter
mm	millimeter
MPL	Maximum permitted level
MW	molecular weight
n	number
NA	Not applicable
NHANES	National Health and Nutrition Examination Survey
NHPs	Natural Health Products
NMT	Not more than
No.	Number
NOAEL	No Observed Adverse Effect Level
NOEL	No observed effect level
NS	Not Specified
PCV	Packed cell volume
Ph.D.	Doctor of Philosophy
PND	postnatal day
ppm	parts per million
RBC	Red blood cells
Reb A	Rebaudioside A
Reb B	Rebaudioside B
Reb C	Rebaudioside C
Reb D	Rebaudioside D

Reb F	Rebaudioside F
Reb M	Rebaudioside M
SBP	Systolic blood pressure
SCF	Scientific Committee for Food
t	Time
TAC	Total antioxidant capacity
tds	Total dissolved solids
TFC	Total flavonoid content
TK	Toxicokinetic
T_{max}	Time at which maximum (peak) plasma concentration (C_{max}) of substance is observed
TPC	Total phenolic content
TRAP	Tartrate-resistant alkaline phosphatase
μg	microgram
US	United States
UK	United Kingdom
VLDL	Very low density lipoprotein
WBC	White blood cells
WHO	World Health Organization

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C. Appendices

Appendix 1 Specifications and Certificates of Analysis for Production Processing Aids

Appendix 1.1 Ethanol Specification

Appendix 1.2 Stevia Extract (≥ 90% Total Steviol Glycosides) Certificates of Analysis

Appendix 1.1 Ethanol Specification

Sasma
Premium Alcohol Suppliers

PRODUCT SPECIFICATION

ORGANIC WHEAT ALCOHOL 96,0 % min. vol.(192 Proof)

Parameter(Unit)	Standard	Typical Result
Alcohol content at 20°C (%vol.)	Min.96,0%vol.	96,2 %vol.(192,4Proof)
Density at 20 °C (kg/liter)	Min. 0.8076	0.806
Appearance	Colorless, clear	Colorless, clear
Refractive index at 20°C	Method NGD C31: 1976	1,36
Maximum levels of residue		
Total carbonyl (Acetaldehyde, g/hl. AA)	Max. 0,5	0,1
Esters (Ethyl acetate, g/hl. AA)	Max. 1,3	0,1
Methanol (g/hl. AA)	Max. 30	0,2
Total Higher Alcohols (2-methyl-1-propanol. g/hl. AA)	Max. 0,5	0,1
Permanganate clearing time (minutes)	Min. 20	>25
Total Dry Residue (g/hl. AA)	Max. 1,5	0,2
Total acids (as Acetic acid g/hl. AA)	Max. 1,5	0,6
Volatile base containing nitrogen (g/hl. AA)	Max. 0.1	Pass
Furfural	Not Detectable	Pass

-AA: Content based on 100%vol. Ethanol.

Product Complies with EU regulation 110/2008, HACCP and ISO9001 principles.
Product is free from GMO's according to EU regulation1829/2003.
Product is free of allergenic compounds such as gluten or gluten residue.
Product is available with a Kosher certificate.(Please ask specifically)
Product is available with Organic (EU/USA) certificate. (Please ask specifically)

The Netherlands, April 09. 2014

An ISO 9001:2008 Certified Company by Lloyd's.
Heliumstraat 8 • 2718 SL Zoetermeer • The Netherlands
Phone:+ 31.79.3633064 • Fax +31.79.3633060
Email:sales@sasmabv.com • www.sasmabv.com