ORIGINAL SUBMISSION

NutraSource, Inc.
6309 Morning Dew Ct, Clarksville, MD 21029
(410)-531-3336 or (301) 875-6454

GRN 000647

April 1, 2016

Dr. Antonia Mattia
Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Subject: GRAS Notice for D-allulose

Dear Dr. Antonia Mattia:

On behalf of Samyang Corporation, we are submitting for FDA review a GRAS notification for D-allulose (or D-psicose). The attached documents contain the specific information that addresses the safe human food uses for the notified substance. We believe that this determination and notification are in compliance with proposed Sec. 170.36 of Part 21 of the Code of Federal Regulations as published in the Federal Register, Vol. 62, No. 74, FR 18937, April 17, 1997.

We enclose an original and two copies of this notification for your review. Please feel free to contact me if additional information or clarification is needed as you proceed with the review. We would appreciate your kind attention to this matter.

Sincerely,
(b) (6)

4/1/2016

Susan Cho, Ph.D.
Susanscho1@yahoo.com
Agent for Samyang Corporation

enclosure

#647

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE (GRAS) NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 02/29/2016
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000647	RECEIVED APR 6 2016 OFFICE OF FOOD ADDITIVE SAFETY
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835.

PART I – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3a. For New Submissions Only: Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: _____

3b. For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd)*: _____

PART II – INFORMATION ABOUT THE NOTIFIER

1a. Notifier	Name of Contact Person Dr. Chong-Jin Park		Position Team Manager	
	Company *(if applicable)* Samyang Corporation			
	Mailing Address *(number and street)* 730 Daedeok-daero, Yuseong-gu			
City Daejeon	State or Province Chung-chung nam do	Zip Code/Postal Code 34055	Country Korea	
Telephone Number +82-42-865-8344	Fax Number	E-Mail Address chongjin.park@samyang.com		
1b. Agent or Attorney *(if applicable)*	Name of Contact Person Susan S. Cho		Position Chief Science Officer	
	Company *(if applicable)* NutraSource, Inc.			
	Mailing Address *(number and street)* 6309 Morning Dew Ct.			
City Clarksville	State or Province MD	Zip Code/Postal Code 21029	Country USA	
Telephone Number +1-301-875-6454	Fax Number +1-410-531-3336	E-Mail Address susanscho1@yahoo.com		

000003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 02/29/2016
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835.

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3a. For New Submissions Only: Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd):* _____

3b. For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd):* _____

Name of Contact Person	Position
Dr. Chong-Jin Park	Team Manager
Company *(if applicable)*	
Samyang Corporation	
Mailing Address *(number and street)*	
730 Daedeok-daero, Yuseong-gu	

City	State or Province	Zip Code/Postal Code	Country
Daejeon	Chung-chung nam do	34055	Korea

Telephone Number	Fax Number	E-Mail Address
+82-42-865-8344		chongjin.park@samyang.com

Name of Contact Person	Position
Susan S. Cho	Chief Science Officer
Company *(if applicable)*	
NutraSource, Inc.	
Mailing Address *(number and street)*	
6309 Morning Dew Ct.	

City	State or Province	Zip Code/Postal Code	Country
Clarksville	MD	21029	USA

Telephone Number	Fax Number	E-Mail Address
+1-301-875-6454	+1-410-531-3336	susanscho1@yahoo.com

PART III – GENERAL ADMINISTRATIVE INFORMATION

1. Name of Substance

D-allulose (or D-psicose)

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☐ Electronic files on physical media with paper signature page

☒ Paper

If applicable give number and type of physical media

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

4. Does this submission incorporate any information in FDA's files by reference? *(Check one)*

☒ Yes *(Proceed to Item 5)* ☐ No *(Proceed to Item 6)*

5. The submission incorporates by reference information from a previous submission to FDA as indicated below *(Check all that apply)*

☒ a) GRAS Notice No. GRN 498

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for determination of GRAS status *(Check one)*

☒ Scientific Procedures *(21 CFR 170.30(b))* ☐ Experience based on common use in food *(21 CFR 170.30(c))*

7. Does the submission (including information that you are incorporating by reference) contain information that you view as trade secret or as confidential commercial or financial information?

☐ Yes *(Proceed to Item 8)*

☒ No *(Proceed to Part IV)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, see attached Designation of Confidential Information

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

PART IV – INTENDED USE OF THE NOTIFIED SUBSTANCE

1. Describe the intended use of the notified substance including the foods in which the substance will be used, the levels of use in such foods, the purpose for which the substance will be used, and any special population that will consume the substance *(e.g., when a substance would be an ingredient in infant formula, identify infants as a special population).*

Samyang Corp. proposes to use D-allulose as a sugar substitute and/or as a flavor modifier in food applications at use levels ranging from 0.5 to 100%. Intended applications include bakery products (bread, muffin, cake, and cookies - dietetic or low calorie; pastries); alcoholic beverages (reduced calories as a flavor enhancer); soft drinks (cola and pepper type - low or reduced calorie); fruit juice and fruit-flavored drinks (reduced- or low calorie); yogurt (low or reduced calorie); hard and soft candies (low or reduced calorie), chocolate (low or reduced calorie); chewing gums; coffee mix; sauce (low or reduced calorie); fat-based cream (used in modified fat/calorie cookies, cakes, pastries, and pie); sugar substitutes; nutrition bars (meal replacement bars, protein bars and energy bars); meal replacement shakes; and medical foods. Medical foods are defined as food formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary manage

2. Does the intended use of the notified substance include any use in meat, meat food product, poultry product, or egg product? *(Check one)*

☐ Yes ☒ No

PART V – IDENTITY

1. Information about the Identity of the Substance

	Name of Substance[1]	Registry Used (*CAS, EC*)	Registry No.[2]	Biological Source *(if applicable)*	Substance Category *(FOR FDA USE ONLY)*
1	D-allulose	551-68-8			
2	D-psicose	551-68-8			
3					

[1] Include chemical name or common name. Put synonyms *(whether chemical name, other scientific name, or common name)* for each respective item (1 - 3) in Item 3 of Part V *(synonyms)*

[2] Registry used e.g., CAS *(Chemical Abstracts Service)* and EC *(Refers to Enzyme Commission of the International Union of Biochemistry (IUB), now carried out by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB))*

2. Description

Provide additional information to identify the notified substance*(s)*, which may include chemical formula*(s)*, empirical formula*(s)*, structural formula*(s)*, quantitative composition, characteristic properties *(such as molecular weight(s)),* and general composition of the substance. For substances from biological sources, you should include scientific information sufficient to identify the source *(e.g., genus, species, variety, strain, part of a plant source (such as roots or leaves), and organ or tissue of an animal source)*, and include any known toxicants that could be in the source.

Chemical name is D-ribo-2-ketohexose
MW=180.16
Molecular formula: $C_6H_{12}O_6$
CAS Registry ID; 551-68-8

3. Synonyms

Provide as available or relevant:

1	D-psicose
2	Pseudo-fructose
3	

000006

PART VI – OTHER ELEMENTS IN YOUR GRAS NOTICE

(check list to help ensure your submission is complete – check all that apply)

- ☒ Any additional information about identity not covered in Part V of this form
- ☒ Method of Manufacture
- ☒ Specifications for food-grade material
- ☒ Information about dietary exposure
- ☐ Information about any self-limiting levels of use *(which may include a statement that the intended use of the notified substance is not-self-limiting)*
- ☐ Use in food before 1958 *(which may include a statement that there is no information about use of the notified substance in food prior to 1958)*
- ☒ Comprehensive discussion of the basis for the determination of GRAS status
- ☒ Bibliography

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☐ Yes ☒ No

Did you include this other information in the list of attachments?

☐ Yes ☐ No

PART VII – SIGNATURE

1. The undersigned is informing FDA that Samyang Corporation *(name of notifier)*

has concluded that the intended use*(s)* of D-allulose (or D-psicose) *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.

2. ☒ Samyang Corporation *(name of notifier)* agrees to make the data and information that are the basis for the determination of GRAS status available to FDA if FDA asks to see them.

Samyang Corporation *(name of notifier)* agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so.

730 Deadeok-daero, Yuseong-gu, Daejeon 34055, Korea *(address of notifier or other location)*

Samyang Corporation *(name of notifier)* agrees to send these data and information to FDA if FDA asks to do so.

OR

☐ The complete record that supports the determination of GRAS status is available to FDA in the submitted notice and in GRP No. ---------- *(GRAS Affirmation Petition No.)*

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
[redacted]	Susan S. Cho, Chief Science Officer, NutraSource, Inc	04/01/2016

PART VI – OTHER ELEMENTS IN YOUR GRAS NOTICE

(check list to help ensure your submission is complete – check all that apply)

- ☒ Any additional information about identity not covered in Part V of this form
- ☒ Method of Manufacture
- ☒ Specifications for food-grade material
- ☒ Information about dietary exposure
- ☐ Information about any self-limiting levels of use *(which may include a statement that the intended use of the notified substance is not-self-limiting)*
- ☐ Use in food before 1958 *(which may include a statement that there is no information about use of the notified substance in food prior to 1958)*
- ☒ Comprehensive discussion of the basis for the determination of GRAS status
- ☒ Bibliography

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☐ Yes ☒ No

Did you include this other information in the list of attachments?

☐ Yes ☐ No

1. The undersigned is informing FDA that Samyang Corporation *(name of notifier)*

has concluded that the intended use*(s)* of D-allulose (or D-psicose) *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.

2. ☒ Samyang Corporation *(name of notifier)* agrees to make the data and information that are the basis for the determination of GRAS status available to FDA if FDA asks to see them.

Samyang Corporation *(name of notifier)* agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so.

730 Deadeok-daero, Yuseong-gu, Daejeon 34055, Korea *(address of notifier or other location)*

Samyang Corporation *(name of notifier)* agrees to send these data and information to FDA if FDA asks to do so.

OR

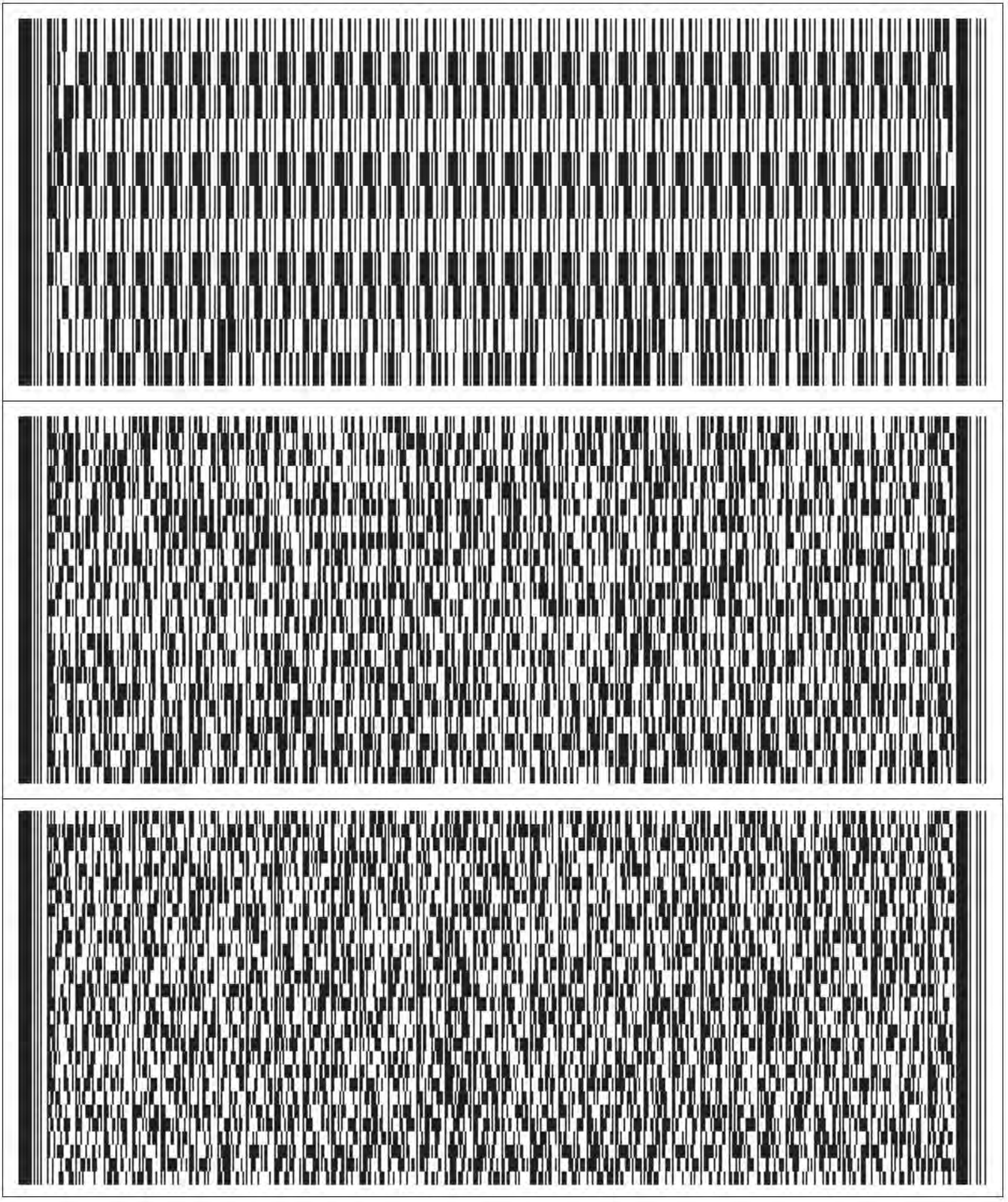
☐ The complete record that supports the determination of GRAS status is available to FDA in the submitted notice and in GRP No. ---------- *(GRAS Affirmation Petition No.)*

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
	Susan S. Cho, Chief Science Officer, NutraSource, Inc	04/01/2016

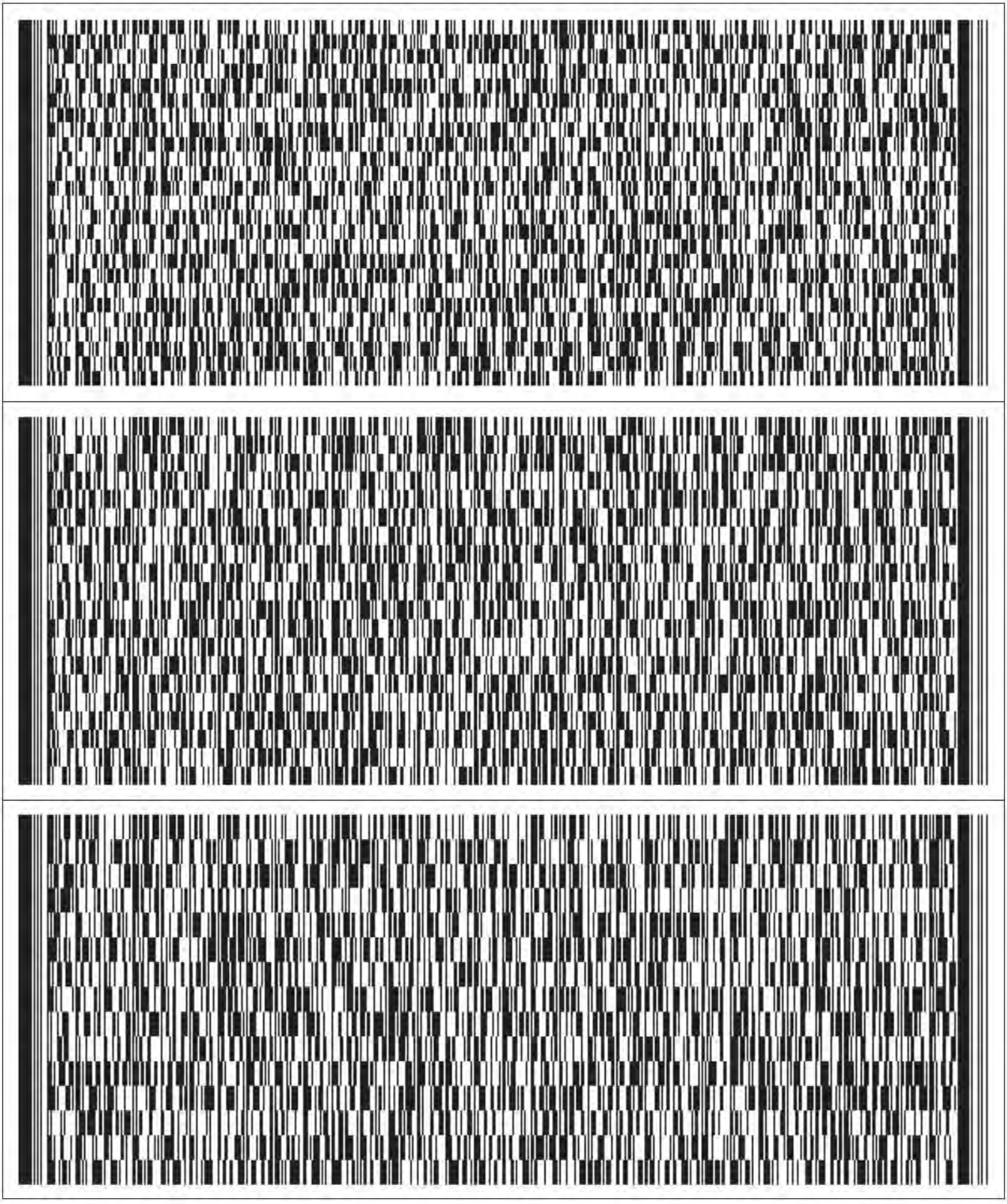
PART VIII – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

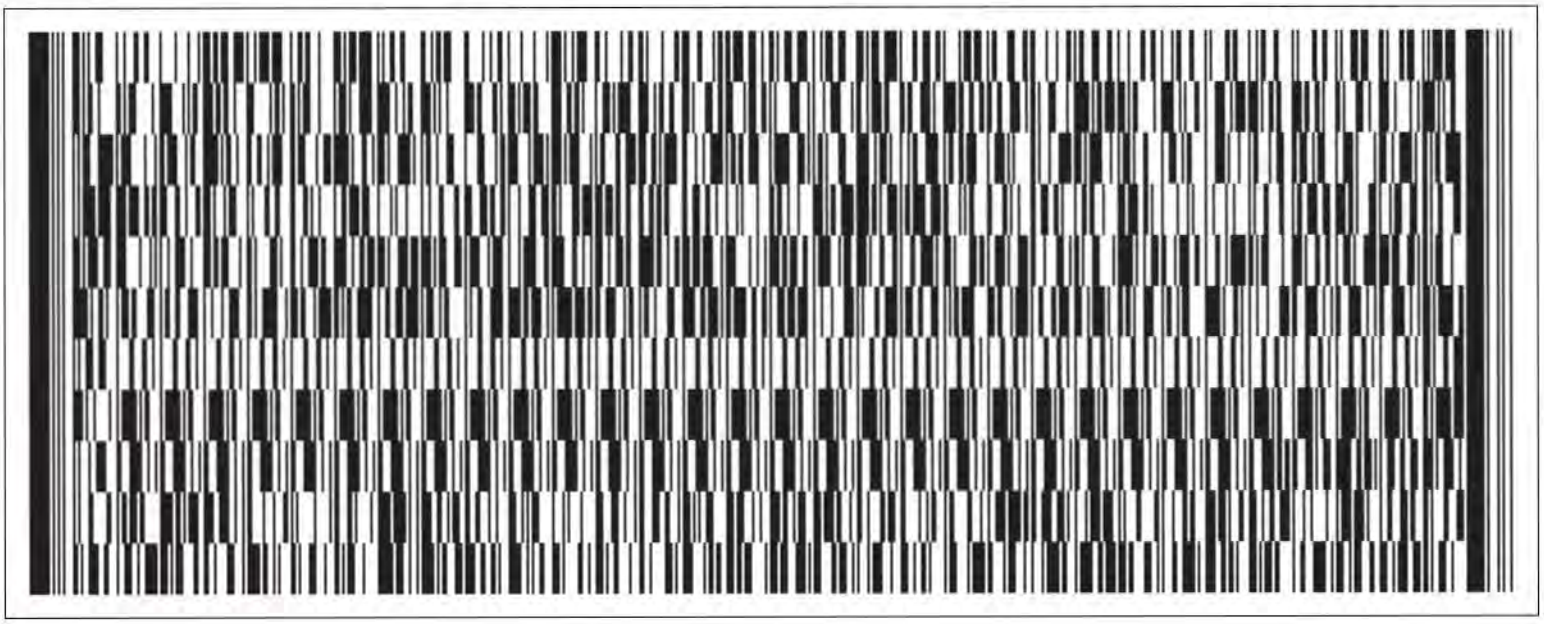
Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)



000010



000011



GRAS EXEMPTION CLAIM for D-Allulose (or D-psicose) Manufactured by Samyang Corporation

Prepared by: NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029
Tel: 410-531-3336
Susanscho1@yahoo.com

A. GRAS EXEMPTION CLAIM: D-Allulose (or D-psicose) - Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36.
Samyang Corporation (hereinafter referred to as Samyang Corp.) has determined that its D-allulose is Generally Recognized As Safe (GRAS). Consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act,* this determination is based on scientific procedures described in the following sections. Since these procedures specify the conditions of its intended use in food, the use of Samyang Corp.'s D-allulose is exempt from the requirement of premarket approval.

Signed
(b) (6)

4/1/2016

Susan Cho Date:
Agent for Samyang Corp.

B. Notifier's Name and Address
Contact person: Dr. Chong-Jin Park
Company name: Samyang Corp.
Address: 730, Deadeok-daero, Yuseong-gu Daejeon 34055, Korea
Telephone number : +82-42-865-8344
E Mail Address: Chongjin.park@samyang.com

C. Name of GRAS Substance
Common name is D-allulose (synonymous with D-psicose).

D. Product Description
D.1. Identity
Chemical name is D-ribo-2-ketohexose
MW=180.16
Molecular formula: $C_6H_{12}O_6$
CAS Registry ID; 551-68-8

GRAS EXEMPTION CLAIM for D-Allulose (or D-psicose) Manufactured by Samyang Corporation

Prepared by: NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029
Tel: 410-531-3336
Susanscho1@yahoo.com

A. GRAS EXEMPTION CLAIM: D-Allulose (or D-psicose) - Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36.

Samyang Corporation (hereinafter referred to as Samyang Corp.) has determined that its D-allulose is Generally Recognized As Safe (GRAS). Consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act,* this determination is based on scientific procedures described in the following sections. Since these procedures specify the conditions of its intended use in food, the use of Samyang Corp.'s D-allulose is exempt from the requirement of premarket approval.

Signed

Susan Cho Date:
Agent for Samyang Corp.

B. Notifier's Name and Address

Contact person: Dr. Chong-Jin Park
Company name: Samyang Corp.
Address: 730, Deadeok-daero, Yuseong-gu Daejeon 34055, Korea
Telephone number : +82-42-865-8344
E Mail Address: Chongjin.park@samyang.com

C. Name of GRAS Substance

Common name is D-allulose (synonymous with D-psicose).

D. Product Description

D.1. Identity

Chemical name is D-ribo-2-ketohexose
MW=180.16
Molecular formula: $C_6H_{12}O_6$
CAS Registry ID; 551-68-8

Chemical structure of D-allulose is shown in Figure 1.

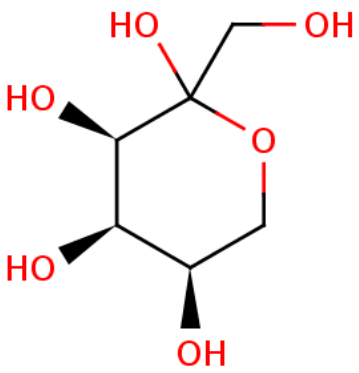


Figure 1. Chemical structure of A-allulose

D.2. Manufacturing Process

D-allulose is manufactured from fructose in aqueous solution by enzymatic epimerization in the presence of magnesium chloride. The enzyme used is an immobilized D-allulose-3-epimerase, which converts fructose to D-allulose.

1. The fructose syrup (≥75% solids concentration) is diluted with clean water (≥50% solids concentration) in a reception tank and then stored in a stock tank.
2. The neutralized fructose syrup is passed into an immobilized cell system (calcium alginate gel bead with recombinant *Corynebacterium glutamicum* [non-viable cell] harboring D-allulose 3-epimerase [DPE] from *Clostridium scindens*). The fructose then is converted to D-allulose at 50℃.
3. For decolorization and desalting, the D-allulose solution is mixed with active carbon in a stirred tank reactor. The liquid undergoes pressure filtration to clarify it, and it is treated through an ion exchange process (i.e., a cation column with strongly acidic cationic exchange resin; an anion column with intermediate basic anion exchange resin; and a mixed bed column that has a combination of both strongly-acidic and strongly basic resins) to remove any impurities (e.g., calcium, manganese, chloride, and other ionic components, including amino acids, peptides, and proteins).
4. Following ion exchange purification, the D-allulose solution is concentrated with an evaporator to produce syrup (D-allulose syrup, ≥20% on a dry weight basis).
5. This concentrated syrup is pumped into a separation chromatography system to separate D-allulose from other sugars (i.e., fructose).
6. Using an evaporator, the solution is concentrated to the final density of ≥65 ºBx to produce syrup (D-allulose syrup, ≥50% or ≥90% on a dry weight basis).
7. The final concentrated product is pumped into a batch continuous crystallizer.
8. The crystalline D-allulose is separated by basket centrifugation, washed by spraying distilled water, and finally dried in a rotary dryer.

<u>Quality assurance procedure:</u>

Samyang Corp. utilizes a Hazard Analysis and Critical Control Point (HACCP)-controlled manufacturing process and rigorously tests its final production batches to verify

adherence to quality control specifications. All processing aids used in the manufacturing process are food grades. D-allulose is manufactured under current Good Manufacturing Practices (cGMP) using common food industry materials and processes in accordance with the applicable parts of 21 CFR, part 110 of the Code of Federal Regulations. Process tanks and lines are cleaned with sodium hydroxide and hydrogen peroxide following standard procedures common to the dairy industry. The ion exchange resins used in the manufacturing process are food grade and comply with 21 CFR 173.25. A flow diagram of the manufacturing process is presented in Figure 2.

Safety of enzymes:

The enzyme is non-toxicological and non-pathogenic. An acute toxicity study showed that a single dose of 2 g/kg body weight (bw) did not cause any treatment-related abnormalities in Sprague-Dawley rats. The LD_{50} was determined to be far above 2 g/kg bw.

D.3. Typical Composition and Specifications

As shown in Tables 1-1 to 1-4, the only differences in specification are found in the concentrations of D-allulose and moisture. Specifications for microbial and heavy metal content are the same for powder and liquid forms.

Table 1-1. Specifications of Product 1 (D-allulose Syrup)

Composition	Specification	Analytical Method
Appearance	Clear yellow liquid	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥20	HPLC
Moisture, %, wt/wt	≤35	AOAC 941.14
Brix	≥65	Brix meter
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.5	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis

Table 1-2. Specifications of Product 2 (D-allulose Syrup)

Composition	Specification	Analytical Method
Appearance	Clear yellow liquid	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥50	HPLC
Moisture, %, wt/wt	≤35	AOAC 941.14

Brix	≥65	Brix meter
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.5	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis

Table 1-3. Specifications of Product 3 (D-allulose Syrup)

Composition	Specification	Analytical Method
Appearance	Clear yellow liquid	Visual
Odor	No-odor	
D-allulose*, %, wt/wt	≥90	HPLC
Moisture	≤35	AOAC 941.14
Brix	≥65	Brix meter
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.5	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis

Table 1-4. Specifications of Product 4 (Crystalline D-allulose, ≥98%)

Composition	Specification	Analytical Method
Appearance	Powder	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥98	HPLC
Moisture, %, wt/wt	≤2	AOAC 941.14
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.1	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14

Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis; CFU=colony forming unit.

E. Applicable Conditions for Use of the Notified Substance

E.1. Current Regulatory Status

The FDA has received two GRAS Notices related to food uses of D-allulose (GRN 400 submitted by CJ CheilJedang, Inc., 2011; GRN 498 submitted by Matsutani Chemical, 2014). In these GRAS notices, toxicity-related studies on D-allulose from the literature were presented that support the safety of use of D-allulose. The FDA did not question the acceptability and suitability of these studies to establish the safety of D-allulose for the proposed food uses. The FDA did not have questions on summary of safety, concluding that D-allulose intake up to 0.5 - 0.6 g/kg bw/day is safe. Table 2 summarizes previous GRAS notices for D-allulose.

Table 2. Summary of Previous GRAS Notices

GRN	Company	Intended use	EDI, 90th pctl for all users
400	CJ CehilJedang	As a sugar substitute in dietetic or low calorie bakery products, chewing gums, fat-based cream used in modified fat/calorie cookies, cakes and pastries, low calorie hard candies including pressed candy and mints, low calorie frozen dairy desserts, low calorie carbonated beverages, reduced and low calorie non-carbonated beverages, sugar substitutes, low calorie yogurt, medical foods, ready-to-eat cereals (<5% sugar), and coffee mix	28.5 g/person/day or 0.36 g/kg bw/day
498	Matsutani	As a sugar substitute in food applications at use levels ranging from 2 to 100%	24.8 g/person/day (0.33 g/kg bw/day
Present notice	Samyang Corp.	As a sugar substitute and/or as a flavor modifier in food applications at use levels ranging from 1 to 100%: selected (low or reduced calorie) bakery products, alcoholic beverages (as a flavor modifier), soft drinks, fruit juice and fruit-flavored drinks, yogurt, frozen dairy desserts, hard and soft candies, chocolate, chewing gums, coffee mix, sauce, fat-based cream, sugar substitutes, nutrition bars, meal replacement shakes, and medical foods.	36.0 g/person/day or 0.45 g/kg bw/day

Pctl=percentile.

The pertinent information is available as indicated below:
GRN 400: http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=400.
GRN 498: http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=498.

E.2. Intended Use Levels and Food Categories

As shown in Table 3, Samyang Corp. proposes to use D-allulose as a sugar substitute and/or as a flavor modifier in food applications at use levels ranging from 0.5 to 100%: selected (low or reduced calorie) bakery products, alcoholic beverages (as a flavor modifier), soft drinks, fruit juice and fruit-flavored drinks, yogurt, hard and soft candies, chocolate, chewing gums, coffee mix, sauce, and fat-based cream as well as sugar substitutes, nutrition bars, meal replacement shakes, and medical foods. Medical foods are defined as food formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Samyang Corp. does not intend to use D-allulose as a component of infant formula or in foods under the USDA's jurisdiction such as meat, poultry, and egg products.

Table 3. Intended Use and Maximum Use Levels of D-allulose, % (w/w)

Food category	Maximum use levels, % (w/w)
Baked products (bread, muffin, cake and cookies), dietetic or low calorie	10
Baked products (pastries)	0.5
Alcohol beverages, reduced calorie	2
Soft drinks, cola type, low or reduced calorie	3.75
Soft drinks, pepper type, low or reduced calorie	3.75
Fruit juice drinks, low or reduced calorie	1
Fruit flavored drinks, low or reduced calorie	3.75
Yogurt, low or reduced calorie	5
Hard candy, low or reduced calorie	70
Soft candy, low or reduced calorie	25
Chocolate, low or reduced calorie	30
Chewing gum	40
Coffee mix	30
Sauce, low or reduced calorie	5
Fat-based cream used in modified fat/calorie cookies, cakes, pastries, pie	10
Sugar substitutes	100
Nutrition bars (meal replacement bars, protein bars, and energy bars)	10
Meal replacement shakes, liquid	4
Medical foods	30

E.3. Estimated Dietary Intakes (EDIs) of D-allulose Under the Intended Food Uses

Based on the analysis of the most recent NHANES 2011-2012 (day 1 data), the proposed food uses would result in an EDI for users as follows: mean of 13.7 g/person/day or 0.17 g/kg bw/day and 90th percentile intake of 36.0 g/person/day or 0.45 g/kg bw/day for all users (Table 4). The results also reveal an average maximum exposure would occur in males greater than 20 years of age, with a 90th percentile value of 0.49 g/kg bw/day or 45.8 g/person/day. These EDIs are below the maximum tolerable intake levels of 0.5 - 0.6 g/kg bw/day (Ida, 2007). No age/gender groups exceeded maximum tolerable intake levels.

These estimates are highly optimistic since it is not likely that D-allulose will be used at maximum levels for all food categories under the intended uses. Also, food wastes should be considered. Overall, intended use will result in EDIs at levels significantly below those associated with any potential side effects.

Table 4. Maximum EDIs of D-allulose for All Users (assuming all the foods will be used at the maximum use levels)

Years	g/person/day				g/kg bw/day				Mean bw, kg
	Mean	SE	P 90	SE	Mean	SE	P 90	SE	
All gender									
1-99 y	13.7	0.69	36.0	2.60	0.17	0.01	0.45	0.02	77.0
1-6 y	3.1	0.25	7.6	0.90	0.18	0.02	0.40	0.09	19.1
7-12 y	3.8	0.56	12.1	2.18	0.10	0.01	0.26	0.03	41.6
13-19 y	9.0	2.19	19.4	15.1	0.13	0.03	0.36	0.01	67.4
20+ y	15.4	0.71	38.8	2.12	0.18	0.01	0.46	0.02	83.3
Males									
13-19 y	8.4	3.01	30.4	0.01	0.13	0.04	0.41	0.01	69.0
20+ y	18.2	1.36	45.8	3.80	0.20	0.02	0.52	0.04	90.4
Females									
13-19 y	9.7	2.47	18.8	0.01	0.14	0.03	0.33	0.01	65.5
20+ y	13.0	0.99	30.0	2.83	0.17	0.01	0.41	0.03	77.2

BW=body weight; P90=90th percentile; Based on NHANES 2011-2012.

E.4. Basis for the GRAS Determination

As noted above, the FDA has had no question on two GRAS Notices related to food uses of D-allulose. The FDA did not have questions on summary of safety concluding that D-allulose intake up to 0.5 - 0.6 g/kg bw/day is safe. Since the specifications for the liquid and powder forms of D-allulose are similar to those described in GRN 400 and 498, the metabolism and safety data and other pertinent information discussed in GRN 400 and 498 are applicable to the safety of D-allulose in this GRAS notice. The information is hereby incorporated by reference in these documents and will not be discussed in detail.

Since the FDA's review of GRNs 400 and 498 (GRN 400, FDA, 2012; GRN 498, FDA, 2014), five animal studies were published; one metabolism (Tsukamoto et al., 2014) and four efficacy studies (Hossaine et al., 2015; Itoh et al., 2015; Nagata et al., 2015; Ochiai et al., 2014). Findings from these studies were not inconsistent with the agency's prior decision.

The intended use of D-allulose has been determined to be safe though scientific procedures as set forth in 21 CFR 170.3(b), thus satisfying the so-called "technical" element of the GRAS determination. In addition, because this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called "common knowledge" element of a GRAS determination.

Common Knowledge Element of the GRAS Determination

D-allulose has been safely used as a food ingredient around the world for a decade. As a result, a number of comprehensive reviews of the safety of D-allulose have been published (Chung et al., 2012). In addition, the FDA has had no question on two GRAS Notices related to safety of D-allulose (GRN 400, FDA 2012; GRN 498, FDA, 2014).

Technical Element of the GRAS Determination (Safety Determination)

Numerous human and animal studies have reported benefits of D-allulose with no major adverse effects. Samyang Corp.'s D-allulose is manufactured under current Good Manufacturing Practices (cGMP) using common food industry materials and processes. Samyang Corp. uses a HACCP-controlled manufacturing process and rigorously tests its final production batches to verify adherence to quality control specifications. There is broad-based and widely disseminated knowledge concerning the chemistry of D-allulose. This GRAS determination is based on the data and information generally available and consented opinion about the safety of D-allulose. The literature indicates that D-allulose offers consumers benefits without adverse effects.

The following safety evaluation fully considers the composition, intake, nutritional, microbiological, and toxicological properties of D-allulose as well as appropriate corroborative data.

1. Analytical data from multiple lots indicate that D-allulose complies reliably with the established food-grade product specifications and meet all applicable purity standards.
2. Samyang Corp.'s D-allulose will be used as a sugar substitute and/or as a flavor modifier in reduced or low calorie food applications at use levels ranging from 0.5 to 100%: selected (low or reduced calorie) bakery products, alcoholic beverages (as a flavor modifier), soft drinks, fruit juice and fruit-flavored drinks, yogurt, hard and soft candies, chocolate, chewing gums, coffee mix, sauce, fat-based cream, sugar substitutes, nutrition bars, meal replacement shakes, and medical foods.
3. The LD_{50} value of D-allulose in rats, 15.8-16.3 g/kg bw (Matsuo et al., 2002), is comparable to that of fructose (14.7 g/kg bw). A chronic toxicity study in rats showed that D-allulose at a dose of 1,280 mg/kg bw/day, the maximum level tested, did not show adverse effects (Yagi and Matsuo, 2009). A 90 day subchronic toxicity study in rats reported the NOAEL for D-allulose as 3% of the diet, the highest level tested (Matsuo et al., 2012).
4. A human clinical study showed that the maximum tolerable levels in humans were 0.5 g/kg bw/day for males and 0.6 g/kg bw/day for females. The only side effect of non-digestible carbohydrates including D-allulose is gastrointestinal discomfort when ingested in large quantities. This type of symptom is usually transient and is not considered to be of toxicological significance even if such a symptom is associated with ingestion of large quantities (IOM, 2002).
5. The proposed food use results in exposure at levels below those associated with any adverse effects. The EDI estimates are based on the assumption that Samyang Corp.'s D-allulose will replace currently marketed D-allulose. Thus, cumulative exposures are not expected. In addition, the EDIs presented in this notice are highly optimistic estimates.

6. In the previous GRAS notices (GRN 400 and 498) to the FDA, the safety of D-allulose has been established in animal toxicity studies and mutagenicity studies, and is further supported by human clinical studies.
7. Additional animal studies published subsequent to the FDA GRAS notices (Hossain et al., 2015; Itoh et al., 2015; Nagata et al., 2015; Ochiai et al., 2014; Tsukamoto et al., 2014) continue to support the safety of D-allulose as a food ingredient.

Overall, there are no indications of significant adverse effects related to D-allulose in the publicly available literature. Therefore, not only is the proposed use of D-allulose safe within the terms of the Federal Food, Drug, and Cosmetic Act (meeting the standard of reasonable certainty of no harm), but because of this consensus among experts, it is also *Generally Recognized as Safe* (GRAS) according to Title 21 Code of Federal Regulations (21 CFR).

F. Availability of Information

The detailed data and information that serve as a basis for this GRAS determination will be provided to the U. S. FDA upon request, or are available for the FDA's review and copying during reasonable business hours at the offices of NutraSource, Inc. located at 6309 Morning Dew Ct., Clarksville, MD 21029, USA.

G. Basis of GRAS determination: Through scientific procedures.

References

Chung MY, Oh DK, Lee KW. Hypoglycemic health benefits of D-psicose. J Agric Food Chem. 2012;60:863-869.

FDA. 2012. GRN 400. D-psicose, filed by CJ CheilJedang.

FDA. 2014. GRN 498, D-allulose (synonymous with D-psicose), filed by Matsutani Chemical Industry.

Hossain A, Yamaguchi F, Hirose K, Matsunaga T, Sui L, Hirata Y, Noguchi C, Katagi A, Kamitori K, Dong Y, Tsukamoto I, Tokuda M. Rare sugar D-allulose prevents progression and development of diabetes in T2DM model Otsuka Long-Evans Tokushima Fatty rats. Drug Design Devel Ther. 2015;9:525-535.

Iida T, Kishimoto Y, Yoshikawa Y, Okuma K, Yagi K, Matsuo T, Izumori K. Estimation of maximum non-effective level of D-allulose in causing diarrhea in human subjects. J Advanced Food Ingred. 2007;10: 15-19.

Itoh K, Mizuno S, Hama S, Oshima W, Kawamata M, Hossain A, Ishihara Y, Tokuda M. Beneficial effects of supplementation of the rare sugar "D-allulose" against hepatic steatosis and severe obesity in Lep(ob)/Lep(ob) mice. J Food Sci. 2015;80:H1619-H626.

Matsuo T, Tanaka T, Hashiguchi M, Izumori K, Suzuki H. Effects of oral acute administration and subchronic feeding of several levels of D-psicose in rats. J Nutr Sci Vitaminol. 2002;48:512-516.

Matsuo T, Ishii R, Shirai Y. The 90-day oral toxicity of D-allulose in male Wistar rats. J Clin Biochem Nutr. 2012;50:158-161.

Nagata Y, Kanasaki A, Tamaru S, Tanaka K. d-D-allulose, an epimer of d-fructose, favorably alters lipid metabolism in Sprague-Dawley rats. J Agric Food Chem. 2015;63:3168-3176.

Ochiai M, Onishi K, Yamada T, Iida T, Matsuo T. D-alluloseincreases energy expenditure and decreases body fat accumulation in rats fed a high-sucrose diet. Int J Food Sci Nutr. 2014; 65:245-250.

Tsukamoto I, Hossain A, Yamaguchi F, Hirata Y, Dong Y, Kamitori K, Sui L, Nonaka M, Ueno M, Nishimoto K, Suda H, Morimoto K, Shimonishi T, Saito M, Song T, Konishi R, Tokuda M. Intestinal absorption, organ distribution, and urinary excretion of the rare sugar D-allulose. Drug Design Devel Ther. 2014;8:1955-1964.

Yagi K, Matsuo T. The study on long-term toxicity of D-allulose in rats. J Clin Biochem Nutr. 2009;45:271-277.

Appendix A. Animal Efficacy Studies Published since FDA's Last Review of D-allulose in 2014

Species	Dosage	Length	Primary endpoints	Reference
Young male Wistar rats	5% of high sucrose diet or control diet	8 weeks	Feed intake, wt. gain, clinical chemistry, energy expenditure, and body fat accumulation	Ochiai et al., 2014
Diabetic rats	5% of the diet	60 weeks	Body weight gain, glucose metabolism, inflammatory biomarkers, and abdominal fat deposition.	Hossain et al., 2015
Rat (SD)	3% of the diet	4 weeks	Lipid metabolism (serum and liver lipid levels, liver enzyme activity, and gene expression)	Nagata et al., 2015
Mice (ob/ob and wild type C57BL/6J)	0, 2.5 or 5% of the diet	15 weeks	Body and fat weights, liver weights and hepatic steatosis	Itoh et al., 2015

EXPERT PANEL STATEMENT

DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF D-ALLULOSE (D-PSICOSE) AS A FOOD INGREDIENT

Coordinated by: NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029
Tel: 410-531-3336
Susanscho1@yahoo.com

TABLE OF CONTENTS

I. INTRODUCTION	4
II. INFORMATION ABOUT THE IDENTITY OF THE NOTIFIED SUBSTANCE	4
II.A. Background	4
II.B. Standards of Identity	5
II.C. Common or Trade Name	5
II.D. Chemistry, Physicochemical Properties, and Structure	5
II.E. Manufacturing Process	5
II.F. Specifications	8
III. NATURAL OCCURRENCE AND EXPOSURE TO D-ALLULOSE	9
III.A. Food Sources of D-allulose	9
III.B. Intended Use	10
III.C. Current Consumer Intake Levels	11
III.D. Exposure Estimates under the Intended Use	11
IV. BASIS FOR GRAS DETERMINATION	11
IV.A. Current Regulatory Status	11
IV.B. Intended Technical Effects	12
IV.C. Review of Safety Data	12
IV.C.1. Metabolism	13
IV.C.2. Animal Toxicity Studies	13
IV.C.3. Animal Efficacy Studies Reporting No Adverse Effects of D-allulose	14
IV.C.4. Human Clinical Studies	17
V. SUMMARY	18
V.A. Common Knowledge Element of the GRAS Determination	18
V.B. Technical Element of the GRAS Determination (Safety Determination)	18
VI. GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR THE D-ALLULOSE (OR D-PSICOSE)	20
VII. DISCUSSION OF INFORMATION INCONSISTENT WITH GRAS DETERMINATION	21
VIII. REFERENCES	22
APPENDIX A. CERTIFICATE OF ANALYSIS	25

Tables

Table 1-1.	Specifications of Product 1 (D-allulose Syrup)	8
Table 1-2.	Specifications of Product 2 (D-allulose Syrup)	8
Table 1-3.	Specifications of Product 3 (D-allulose Syrup)	9
Table 1-4.	Specifications of Product 4 (Crystalline D-allulose, ≥98%)	9
Table 2.	Intended Use and Maximum Use Levels of D-allulose, % (w/w)	10
Table 3.	Daily Exposure Estimate of D-allulose for All Users	11
Table 4.	Summary of Previous GRAS Notices	12
Table 5.	Summary of Animal Toxicity Studies Referenced in GRNs 400 & 498	14
Table 6.	Animal Efficacy Studies Reporting No Adverse Effects of D-allulose	16
Table 7.	Human Clinical Studies Referenced in Previous GRNs	17

Figures

Figure 1.	Chemical Structure of D-allulose	5
Figure 2.	Flow Diagram of Manufacturing Process	7

I. INTRODUCTION

An independent panel of recognized experts (hereinafter referred to as the Expert Panel), qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was convened by NutraSource, Inc., at the request of Samyang Corp. to determine the Generally Recognized As Safe (GRAS) status of D-allulose as a food ingredient (21CFR 170.3 [o] [20] (as a sugar substitute or as a flavor modifier) in the following selected foods products at use levels ranging from 1 to 100%: Intended applications include selected (low or reduced calorie) bakery products, alcoholic beverages (as a flavor modifier), soft drinks, fruit juice and fruit-flavored drinks, yogurt, frozen dairy desserts, hard and soft candies, chocolate, chewing gums, coffee mix, sauce, fat-based cream, sugar substitutes, and medical foods. Samyang Corp. plans to introduce D-allulose for which FDA has had no question on GRAS notices (GRN 400 and 498).

The purpose of this dossier is to (1) Outline the identity and composition of D-allulose, (2) Estimate exposure under the intended conditions of use, (3) Document the literature pertaining to the safety, toxicity, and food uses of D-allulose, and (4) Assemble an independent expert panel of recognized experts to evaluate the data and information in this document to determine if the document is sufficient to establish GRAS status. The data and information summarized in this dossier demonstrate that the intended use of D-allulose, produced using current Good Manufacturing Practices (cGMP) and meeting food-grade specifications, is GRAS, based on scientific procedures, as described herein.

The Expert Panel members independently and critically evaluated materials submitted by Samyang Corp. and other information deemed appropriate or necessary. Following an independent, critical evaluation, the Expert Panel unanimously agreed to the decision described herein.

II. INFORMATION ABOUT THE IDENTITY OF THE NOTIFIED SUBSTANCE

II.A. Background

D-allulose is a monosaccharide, an epimer of D-fructose isomerized at C-3 (Karabinos, 1952). D-allulose has 70% of the sweetness of sucrose and has a higher solubility that makes it easy to use for food processing. Based on the results of the plot of breath hydrogen concentration vs. calories ingested, the energy value of D-allulose was predicted to be less than 0.2 kcal/g (Iida et al., 2010). Thus, it belongs to the non-digestible carbohydrate category. It is odorless, white or almost white, and non-hygroscopic. D-allulose is a naturally occurring monosaccharide present in small quantities in food products.

It has been reported that the addition of D-allulose to food products improve the gelling behavior and flavor while increasing the antioxidant property of the food products (Sun et al., 2006, 2007). Food products containing D-allulose maintain a high level of antioxidant effect over a long period of storage, which is able to delay the onset of lipid auto-oxidation and extend the food storage time (Sun et al., 2008). It gives proper sweetness, smooth texture, desirable mouthfeels and great self-stability to food products. Animal and human studies show that D-allulose improved glucose metabolism (Hossaine et al., 2012; Iida et al., 2008). Thus, D-allulose is expected to serve as a food ingredient with a low glycemic index.

II.B. Standards of Identity

In the notice, Samyang Corp. states its intention to use D-allulose in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

II.C. Common Name:

Common name is D-allulose, D-psicose, or pseudo-fructose.

II.D. Chemistry, Physicochemical Properties, and Structure

Chemical name is D-ribo-2-ketohexose
MW=180.16
Molecular formula: $C_6H_{12}O_6$
CAS Registry ID; 551-68-8

Chemical structure of D-allulose is shown in Figure 1.

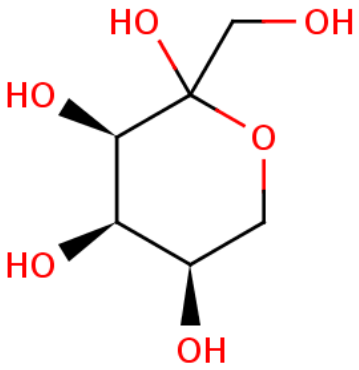


Figure 1. Chemical Structure of D-allulose

II.E. Manufacturing Process

D-allulose is manufactured from fructose in aqueous solution by enzymatic epimerization in the presence of magnesium chloride. The enzyme used is an immobilized D-allulose-3-epimerase, which converts fructose to D-allulose.

1. The fructose syrup (≥75% solids concentration) is diluted with clean water (>50% solids concentration) in a reception tank and then stored in a stock tank.
2. The neutralized fructose syrup is passed into an immobilized cell system (calcium alginate gel bead with recombinant *Corynebacterium glutamicum* [non-viable cell] harboring D-allulose 3-epimerase [DPE] from *Clostridium scindens*). The fructose then is converted to D-allulose at 50℃.
3. For decolorization and desalting, the D-allulose solution is mixed with active carbon in a stirred tank reactor. The liquid undergoes pressure filtration to clarify it, and it is treated through an ion exchange process (i.e., a cation column with strongly acidic cationic exchange resin; an anion column with intermediate basic anion exchange resin; and a

mixed bed column that has a combination of both strongly-acidic and strongly basic resins) to remove any impurities (e.g. calcium, manganese, chloride, and other ionic components, including amino acids, peptides, and proteins).

4. Following ion exchange purification, the D-allulose solution is concentrated with an evaporator to produce syrup (Product 1-Allulose syrup, ≥20% on a dry weight basis).
5. This concentrated syrup is pumped into a separation chromatography system to separate D-allulose from other sugars (i.e., fructose).
6. Using an evaporator, the solution is concentrated to the final density of ≥65 ºBx to produce syrup (Product 2 or 3- D-allulose syrup, ≥50% or ≥90% on a dry weight basis).
7. The final concentrated product is pumped into a batch continuous crystallizer.
8. The crystalline D-allulose (Product 4 - ≥98% D-allulose) is separated by basket centrifugation, washed by spraying distilled water, and finally dried in a rotary dryer.

Quality assurance procedure:

Samyang Corp.'s D-allulose is manufactured under current Good Manufacturing Practices (cGMP) using common food industry materials and processes. Samyang Corp. utilizes a Hazard Analysis and Critical Control Point (HACCP)-controlled manufacturing process and rigorously tests its final production batches to verify adherence to quality control specifications. All processing aids used in the manufacturing process are food grades. D-allulose is manufactured under current Good Manufacturing Practices (cGMP) using common food industry materials and processes in accordance with the applicable parts of 21 CFR, part 110 of the Code of Federal Regulations. Process tanks and lines are cleaned with sodium hydroxide and hydrogen peroxide following standard procedures common to the dairy industry. The ion exchange resins used in the manufacturing process are food grade and comply with 21 CFR 173.25. A flow diagram of the manufacturing process is presented in Figure 2.

Safety of enzymes:

The enzyme is non-toxicological and non-pathogenic. An acute toxicity study showed that a single dose of 2 g/kg body weight (bw) did not cause any treatment-related abnormalities in Sprague-Dawley rats. The LD_{50} was determined to be far above 2 g/kg bw.

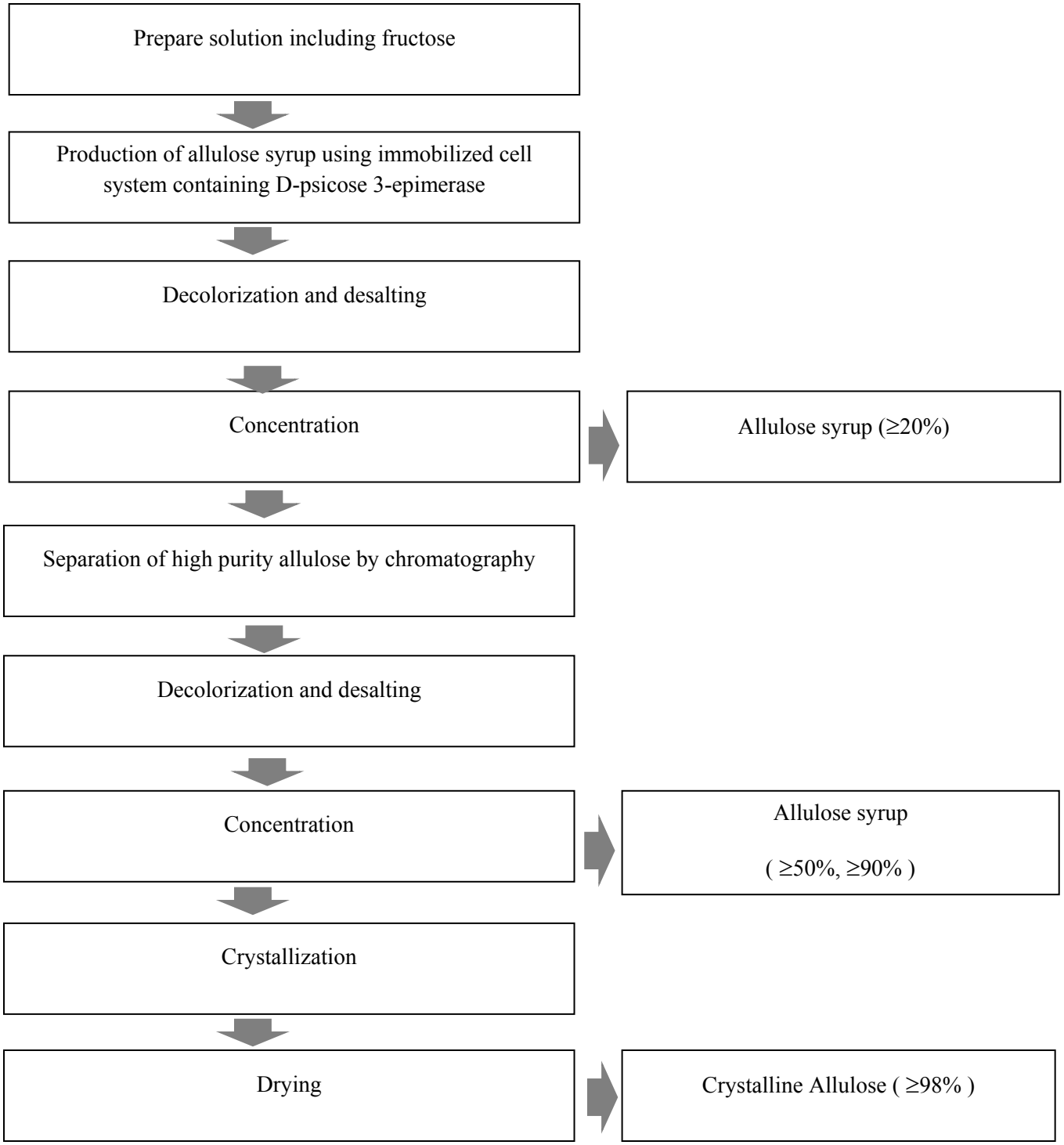


Figure 2. Flow Diagram of Manufacturing Process

II.F. Specifications

As shown in Tables 1-1 to 1-4, the only differences in specification are found in the concentrations of D-allulose and moisture. Specifications for microbial and heavy metal content are the same for powder and liquid forms.

Table 1-1. Specifications of Product 1 (D-allulose Syrup)

Composition	Specification	Analytical Method
Appearance	Clear yellow liquid	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥20	HPLC
Moisture, %, wt/wt	≤35	AOAC 941.14
Brix	≥65	Brix meter
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.5	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis

Table 1-2. Specifications of Product 2 (D-allulose Syrup)

Composition	Specification	Analytical Method
Appearance	Clear yellow liquid	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥50	HPLC
Moisture, %, wt/wt	≤35	AOAC 941.14
Brix	≥65	Brix meter
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.5	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis

Table 1-3. Specifications of Product 3 (D-allulose Syrup)

Composition	Specification	Analytical Method
Appearance	Clear yellow liquid	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥90	HPLC
Moisture	≤35	AOAC 941.14
Brix	≥65	Brix meter
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.5	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis

Table 1-4. Specifications of Product 4 (Crystalline D-allulose, ≥98%)

Composition	Specification	Analytical Method
Appearance	Powder	Visual
Odor	No odor	
D-allulose*, %, wt/wt	≥98	HPLC
Moisture, %, wt/wt	≤2	AOAC 941.14
pH	3.0 – 7.0	pH meter
Ash, %, wt/wt	≤0.1	AOAC 900.02
Pb, ppm	≤0.5	AOAC 2015.01
As, ppm	≤0.5	AOAC 2015.01
Cd, ppm	≤0.5	AOAC 2015.01
Total plate count, CFU/g	≤1,000	AOAC 2002.07
Coliforms	negative	AOAC 991.14
Salmonella	negative	AOAC 989.14
Staphylococcus aureus	negative	AOAC 987.09

*Dry wt. basis; CFU=colony forming unit.

III. NATURAL OCCURRENCE AND EXPOSURE TO D-ALLULOSE

III.A. Food Sources of D-allulose

D-allulose is a naturally occurring monosaccharide present in small quantities in natural products, particularly in sweets such as caramel sauce, maple syrup, brown sugar, processed cane and beet molasses, and wheat (Oshima et al., 2006).

III.B. Intended Use

Samyang Corp. proposes to use D-allulose as a sugar substitute and/or as a flavor modifier in food applications at use levels ranging from 0.5 to 100%. Intended applications include bakery products (bread, muffin, cake, and cookies - dietetic or low calorie; pastries); alcoholic beverages (reduced calories as a flavor enhancer); soft drinks (cola and pepper type - low or reduced calorie); fruit juice and fruit-flavored drinks (reduced- or low calorie); yogurt (low or reduced calorie); hard and soft candies (low or reduced calorie), chocolate (low or reduced calorie); chewing gums; coffee mix; sauce (low or reduced calorie); fat-based cream (used in modified fat/calorie cookies, cakes, pastries, and pie); sugar substitutes; nutrition bars (meal replacement bars, protein bars and energy bars); meal replacement shakes; and medical foods. Medical foods are defined as food formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Samyang Corp. does not intend to use D-allulose as a component of infant formula or in foods under the USDA's jurisdiction such as meat, poultry, and egg products.

Table 2. Intended Use and Maximum Use Levels of D-allulose, % (w/w)

Food category	Maximum use levels, % (w/w)
Baked products (bread, muffin, cake and cookies), dietetic or low calorie	10
Baked products (pastries)	0.5
Alcohol beverages, reduced calorie	2
Soft drinks, cola type, low or reduced calorie	3.75
Soft drinks, pepper type, low or reduced calorie	3.75
Fruit juice drinks, low or reduced calorie	1
Fruit flavored drinks, low or reduced calorie	3.75
Yogurt, low or reduced calorie	5
Hard candy, low or reduced calorie	70
Soft candy, low or reduced calorie	25
Chocolate, low or reduced calorie	30
Chewing gum	40
Coffee mix	30
Sauce, low or reduced calorie	5
Fat-based cream (used in modified fat/calorie cookies, cakes, pastries, pie)	10
Sugar substitutes	100
Nutrition bars (meal replacement bars, protein bars, and energy bars)	10
Meal replacement shakes, liquid	4
Medical foods	30

III.C. Current Consumer Intake Levels

Since the D-allulose level in each food is not listed in the USDA food composition tables and the National Health and Nutrition Examination Survey (NHANES) databases, the current exposure levels from food sources were not estimated.

III.D. Exposure Estimates Under the Intended Use

Based on the analysis of the most recent NHANES 2011-2012 (day 1 data), the proposed food uses would result in Estimated Daily Intakes (EDI) for users as follows: mean of 13.7 g/person/day or 0.17 g/kg bw/day and 90th percentile intake of 36.0 g/person/day or 0.45 g/kg bw/day for all users (Table 3). The results also reveal that an average maximum exposure would occur in males greater than 20 years of age, with a 90th percentile value of 0.49 g/kg bw/day or 45.8 g/person/day. These EDIs are below the maximum tolerable intake levels of 0.5 - 0.6 g/kg bw/day (Iida et al.,, 2007). No age/gender groups would exceed maximum tolerable intake levels.

These estimates are highly optimistic since it is not likely that D-allulose will be used at maximum levels for all food categories under the intended uses. Also, food wastes should be considered. Overall, intended use will result in EDIs at levels significantly below those associated with any potential side effects.

Table 3. Maximum EDIs of D-allulose for All Users (assuming all the foods will be used at the maximum use levels)

Years	g/person/day				g/kg bw/day				Mean bw, kg
	Mean	SE	P 90	SE	Mean	SE	P 90	SE	
All gender									
1-99 y	13.7	0.69	36.0	2.60	0.17	0.01	0.45	0.02	77.0
1-6 y	3.1	0.25	7.6	0.90	0.18	0.02	0.40	0.09	19.1
7-12 y	3.8	0.56	12.1	2.18	0.10	0.01	0.26	0.03	41.6
13-19 y	9.0	2.19	19.4	15.1	0.13	0.03	0.36	0.01	67.4
20+ y	15.4	0.71	38.8	2.12	0.18	0.01	0.46	0.02	83.3
Males									
13-19 y	8.4	3.01	30.4	0.01	0.13	0.04	0.41	0.01	69.0
20+ y	18.2	1.36	45.8	3.80	0.20	0.02	0.52	0.04	90.4
Females									
13-19 y	9.7	2.47	18.8	0.01	0.14	0.03	0.33	0.01	65.5
20+ y	13.0	0.99	30.0	2.83	0.17	0.01	0.41	0.03	77.2

BW=body weight; P90=90th percentile; Based on NHANES 2011-2012.

IV. BASIS FOR GRAS DETERMINATION

IV.A. Current Regulatory Status

The FDA has received two GRAS Notices related to food uses of D-allulose (GRN 400 submitted by CJ CheilJedang, Inc., 2011; GRN 498 submitted by Matsutani Chemical, 2014). In these GRAS notices, toxicity-related studies on D-allulose from the literature were presented that support the safety of use of D-allulose. The FDA did not question the acceptability and suitability of these studies to establish the safety of D-allulose for the proposed food uses. The FDA did not have questions on summary of safety, concluding that D-allulose intake up to 31-33 g/person/day is safe. Table 4 summarizes previous GRAS notices for D-allulose.

Table 4. Summary of Previous GRAS Notices

GRN	Company	Intended use	EDI, 90th pctl for all users
400	CJ CehilJedang	As a sugar substitute in dietetic or low calorie bakery products, chewing gums, fat-based cream used in modified fat/calorie cookies, cakes and pastries, low calorie hard candies including pressed candy and mints, low calorie frozen dairy desserts, low calorie carbonated beverages, reduced and low calorie non-carbonated beverages, sugar substitutes, low calorie yogurt, medical foods, ready-to-eat cereals (<5% sugar), and coffee mix.	28.5 g/person/day or 0.36 g/kg bw/day
498	Matsutani	As a sugar substitute in food applications at use levels ranging from 2 to 100%.	24.8 g/person/day (0.33 g/kg bw/day
Present notice	Samyang Corp.	As a sugar substitute and/or as a flavor modifier in food applications at use levels ranging from 0.5 to 100%: selected (low or reduced calorie) bakery products, alcoholic beverages (as a flavor modifier), soft drinks, fruit juice and fruit-flavored drinks, yogurt, hard and soft candies, chocolate, chewing gums, coffee mix, sauce, fat-based cream, sugar substitutes, nutrition bars, meal replacement shakes, and medical foods.	36.0 g/person/day or 0.45 g/kg bw/day

Pctl=percentile.

The pertinent information is available as indicated below:
GRN 400: http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=400.
GRN 498: http://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=498.

IV.B. Intended Technical Effects

D-allulose will be used as a food ingredient for low calorie and/or dietetic foods due to its technological properties (e.g., functions as a sweetener, humectant, and flavor modifier) and nutritional benefits (such as low calorie and glycemic control).

IV.C. Review of Safety Data

As noted above, the FDA has had no question on two GRAS Notices related to food uses of D-allulose. The FDA did not have questions on summary of safety concluding that D-allulose intake up to 0.5 - 0.6 g/kg bw/day is safe. Since the specifications for the liquid and powder forms of D-allulose are similar to those described in GRN 400 and 498, the metabolism and safety data and other pertinent information discussed in GRN 400 and 498 are applicable to the safety of D-allulose in this GRAS notice. The information is hereby incorporated by reference in these documents and will not be discussed in detail.

Since the FDA's review of GRNs 400 and 498 (GRN 400, FDA, 2012; GRN 498, FDA, 2014), five animal studies were published; one metabolism (Tsukamoto et al., 2014) and four efficacy studies (Hossaine et al., 2015; Itoh et al., 2015; Nagata et al., 2015; Ochiai et al., 2014). Findings from these studies were not inconsistent with the agency's prior decision.

IV.C.1. Metabolism

A study published since the FDA's decision of 2014 confirmed the previous findings that D-allulose was rapidly excreted through urine (Tsukamoto et al., 2014). Following oral administration, D-allulose is partly absorbed in the digestive tract and enters the bloodstream. The maximum blood concentration (48.5±15.6 μg/g) was observed at 1 hour. Excretion to urine was 20% within 1 hour and 33% within 2 hours (Tsukamoto et al., 2014). Accumulation in organs was detected only in the liver. Following intravenous administration, blood concentration was decreased with the half-life of 57 minutes, and the excretion to urine was up to almost 50% within 1 hour. Seven days after the single-dose oral administration, the remaining amounts in the whole body were less than 1%.

Previously reviewed studies reported that about 98% of intravenously administered D-allulose is excreted in the urine within 6 h (Whistler et al., 1974). When orally ingested, urinary excretion of unchanged D-allulose ranged from 11 to 25% (Matsuo et al., 2003). The data indicate that D-allulose absorbed in the small intestine may pass into the bloodstream and be excreted in the urine without being significantly metabolized (Matsuo et al., 2003). Unabsorbed D-allulose is fermented to short chain fatty acids (SCFA) by intestinal microflora in the colon (Noda and Oh, 1992) or is excreted in the feces (Matsuo et al., 2004).

IV.C.2. Animal Toxicity Studies

Since the FDA's last review of D-allulose in 2012-2014 (GRNs 400 and 498; U.S. FDA, 2012 and 2014), no new literature has been published. Previous reviews included the LD_{50} value of D-allulose in rats at 15.8-16.3 g/kg bw (Matsuo et al., 2002).

Subacute toxicity studies (up to 34 days) in rats showed that D-allulose concentration of up to 20% of the diet did not show adverse effects (Table 4; Matsuo et al., 2002).

A 90 day subchronic toxicity study reported the NOAEL for D-allulose as 3% of diet, the highest level tested (Matsuo et al., 2012). A 12-18 month chronic toxicity study showed that D-allulose at the dose of 3% D-allulose in the diet (or 1,280 mg/kg bw/day), the highest level tested, did not show adverse effects (Yagi and Matsuo, 2009).

In summary, D-allulose, like other monosaccharides, belongs to the group that has the lowest toxicity rating and is classified as an ordinary carbohydrate substance. Thus, the use of D-allulose in foods and beverages is not expected to pose a safety concern.

Table 5. Summary of Animal Toxicity Studies Referenced in GRNs 400 and 498

Species	Dosage	Duration	Primary endpoints and NOAEL	Reference
Male rat	8, 11, 14, 17, and 20 g/kg bw (D-allulosein water)	Single dose	Acute toxicity- LD_{50}, 16.3 g/kg bw	Matsuo et al., 2002
Young rat	10, 20, 30, and 40% in the diet	34 days	Feed intake, wt. gain, and organ wt.; NOAEL-up to 20% in the diet (corresponding to 10,000 mg/kg bw/day)	Matsuo et al., 2002
Male Wistar rats	3% in the diet	90 days	Feed intake, wt gain, organ wt., serum biochemistry, hematology, and histology; NOAEL- 3% in diet, the highest level tested	Matsuo et al., 2012
36 Male rats, Wistar	3% in the diet or 1,280 mg/kg bw/d (control, 3% sucrose)	12-18 months	Feed and energy intakes, wt. gain, organ wt., digestive tract size, serum biochemistry, hematology, and histology; NOAEL- 1,280 mg/kg bw/day, the highest level tested	Yagi and Matsuo, 2009

IV.C.3. Animal Efficacy Studies Reporting No Adverse Effects of D-allulose

Since the FDA's last review of D-allulose (GRNs 400 and 498; U.S. FDA, 2012 and 2014), four animal efficacy studies were published based on the repeat dose administration of D-allulose at high dietary concentrations for long durations (Table 6; Hossain et al., 2015; Itoh et al., 2015; Nagata et al., 2015; Ochiai et al., 2014). No studies reported results inconsistent with the FDA's prior reviews of 2012-2014. Although these studies were designed to investigate the efficacy of D-allulose on various health parameters, several safety related endpoints were obtained during the experiments. Therefore, these studies are reviewed below as additional supporting information.

Recent efficacy studies also showed that D-allulose at the level of up to 5% in the diet (corresponding to up to 2,500 mg/kg bw/day) did not cause any adverse effects on food efficiency, glucose metabolism, lipid metabolism, inflammatory biomarkers, body fat

accumulation, and/or histopatholgical parameters (Hossain et al., 2015; Itoh et al., 2015; Nagata et al., 2015; Ochiai et al., 2014).

Long-term administration (60 weeks) of D-allulose at a dose of 5% of diet prevented the commencement and progression of type 2 diabetes through the maintenance of blood glucose levels and the control of postprandial hyperglycemia with decreased levels of HbA_{1c} (by ~50%) in comparison to control rats (Hossaine et al., 2015). This improvement in glycemic control was accompanied by the maintenance of plasma insulin levels and the preservation of pancreatic β-cells with a significant reduction in inflammatory markers. In the control group, the glucose levels started to increase slowly from 25 weeks and then sharply until 60 weeks, whereas in the allulose group the glucose levels started to increase slightly from 45 weeks and remained constant until 60 weeks. By the end of 60 weeks, the fasting blood glucose concentrations in the psicose group were approximately 35% lower than that of the control group. Body fat accumulation, in particular adipose tissue, was lower (by ~25-30%) in the treatment group, with decreased infiltration of macrophages in the abdominal adipose tissue. No adverse effects of D-allulose were reported.

The study by Itoh et al. (2015) also reported anti-obesity effects of D-allulose (0, 2.5, or 5% of diet or 1,500-2,000 or 3,000-4,000 mg/kg bw/day) in inherited leptin-deficient ob/ob mice. Wild type C57BL/6J mice were used as an animal control (0% D-allulose). The results of this study showed that subchronic ingestion for 15 weeks significantly decreased body weights (by ~20%), liver weights (by ~6%), and total fat mass (by ~7%), including abdominal visceral fat (by ~5%) in the 5% allulose group. During the 15-week period, the total calorie intake of the 5% D-allulose treatment significantly decreased by 10% compared to that observed in both the control and 2.5% D-allulose groups. Furthermore, D-allulose improved hepatic steatosis as evaluated using hepatic histological evaluation and magnetic resonance imaging (MRI). In control mice, fat deposition produced a severely damaged liver histology presenting as remarkable ballooning degeneration. The ballooning degeneration and hepatic steatosis improved after the subchronic ingestion of D-allulose. The authors concluded that D-allulose may be useful as a supplement for preventing and improving obesity and obesity-related disorders. No adverse effects of D-allulose were reported.

In a study by Nagata et al. (2015), effects of D-allulose on lipid metabolism were evaluated. Rats were fed diets with or without 3% D-allulose for 4 weeks. In experiment 1, feeding D-allulose significantly decreased body weight by approximately 5%, but not food intake. Liver enzyme activities involved in lipogenesis were significantly lowered by the D-allulose diet, whereas gene expression of a transcriptional modulator of fatty acid oxidation was enhanced. Rats fed D-allulose had significantly lower serum insulin and leptin levels. In experiment 2, feeding the D-allulose diet resulted in significantly lower body weight (389±3 vs. 426±6 g, $p < 0.05$) and food intake (23.8±0.2 vs. 25.7±0.4 g/day, $p < 0.05$) compared to the control diet. Rats fed the D-allulose diet had significantly higher energy expenditure in the light period and fat oxidation in the dark period compared to rats fed the control diet, whereas carbohydrate oxidation was lower. The results indicate that the D-allulose diet decreased lipogenesis, increased fatty acid oxidation, and enhanced 24 h energy expenditure, leading to D-allulose's potential for weight management. No adverse effects of D-allulose were reported.

These studies confirmed the previous findings that D-allulose at the level of up to 5% in the diet did not cause treatment-related abnormalities on measured outcomes (Table 6; Baek et al., 2010; Chung et al., 2012a; Hossain et al., 2012; Matsuo et al., 2001a, 2001b; Matsuo and Izumori, 2004, 2006, 2009; Ochiai et al., 2013).

Several mechanisms of actions have been proposed to explain potential mechanisms of anti-obese and anti-hyperglycemic effects of D-allulose (Previous GRNs covered most of these aspects):

1) its zero-calorie effects and 70% relative sweetness of sucrose,
2) the inhibition of enzymatic activities for the digestion of polysaccharides, such as glucoamylase and maltase (Iida et al., 2008; Matsuo and Izumori, 2006),
3) inhibition of hepatic fatty acid synthatase (Matsuo et al., 2001a, 2001b),
4) the preservation of pancreas β-cells through the suppression of proinflammatory cytokines and reactive oxygen species production (Hossaine et al., 2015),
5) decreased absorption of sugars (Baek et al., 2010; Matsuo and Izumori, 2009),
6) enhanced insulin sensitivity (Hossaine et al., 2012; Iida et al., 2008) and/or
7) altered hepatic glucose metabolism via the translocation of glucokinase (Hossaine et al., 2011).

None of these animal efficacy studies reported adverse effects of D-allulose. For these 'pivotal' studies, the dose levels represent the maximum doses administered, rather than absolute safety endpoints.

Table 6. Animal Efficacy Studies Reporting No Adverse Effects of D-allulose

Species	Dosage	Length	Primary endpoints	Reference
Recent Animal Efficacy Studies				
Young male Wistar rats	5% of high sucrose diet or control diet	8 weeks	Feed intake, wt. gain, clinical chemistry, energy expenditure, and body fat accumulation	Ochiai et al., 2014
Diabetic rats	5% of diet	60 weeks	Body weight gain, glucose metabolism, inflammatory biomarkers, and abdominal fat deposition.	Hossain et al., 2015
Rat (SD)	3% of diet	4 weeks	Lipid metabolism (serum and liver lipid levels, liver enzyme activity, and gene expression)	Nagata et al., 2015
mice (ob/ob and wild type C57BL/6J)	0, 2.5 or 5% of diet	15 weeks	Body and fat weights, liver weights, and hepatic steatosis	Itoh et al., 2015
Studies Referenced in GRNs 400 and 498				
Rat, Sprague-Dawley	5% of high fat diet	8 weeks	Feed intake, wt. gain, liver wt., visceral fat mass, blood lipid profile	Chung et al., 2012a
Male Wistar rats	5% of high sucrose diet	8 weeks	Body weight, food intakes, organ wt., serum clinical chemistry,	Ochiai et al., 2013

	or high starch diet		liver triglycerides, carbohydrates and glycogen, and body fat	
Diabetic rats	5% of diet	13 weeks	Body weight, glucose metabolism, inflammatory biomarkers, and abdominal fat deposition.	Hossain et al., 2012
Male mice	0.2 g/kg BW/d	4 weeks	Glycemic responses, insulin release, and blood lipid profiles, 0.2 g/kg bw/day	Baek et al., 2010
24 Male rats, Wistar	5% in the high (25%) and low fat (5%) diets	16 weeks	Body weight, energy intake, body fat, organ wt., glucose tolerance, serum adipocytokine concentrations (adiponectin, tumor necrosis factor alpha, leptin), and liver glycogen and triglycerides.	Matsuo and Izumori, 2004
Male rat	5% in the diet	3 weeks	Body fat and lipid metabolism	Matsuo et al., 2001a
Male rat	5% in the diet	4 weeks	Body fat and lipid metabolism	Matsuo et al., 2001b
Male rat	5% in the diet	8 weeks	Body fat and glycemic responses	Matsuo and Izumori, 2006
Male rat	2,000 mg/kg bw	Single dose	Body fat and glycemic responses	Matsuo and Izumori, 2009

IV.C.4. Human Clinical Studies

Since the FDA's last review of D-allulose in 2014 (GRNs 400 and 498; U.S. FDA, 2012 and 2014), no new literature has been published. Several human clinical studies previously reviewed reported no adverse effects of D-allulose (Table 6; Hayashi et al., 2010; Iida et al., 2007, 2008, 2010). Like non-digestible oligosaccharides and fiber ingredients, the only side effect of D-allulose is gastrointestinal discomfort when ingested in large quantities. Even if gastrointestinal discomfort is noted when consumed in large quantities of D-allulose, it is not considered to be of toxicological significance since this type of symptom is usually transient and is often associated with ingestion of non-digestible carbohydrates including dietary fiber (IOM, 2002).

A clinical study showed that the maximum tolerable levels in humans were 0.5 g/kg bw/day for males and 0.6 g/kg bw/day for females, with the mean value of 0.55 g/kg bw/day. These dosages correspond to 33.3 g/day for a 67 kg Asian male and 31.0 g/day for a 52 kg Asian female (Iida et al., 2007). These dosages also correspond to 45 - 46 g/person/day for an average American adult aged 20 years or older.

Table 7. Human Clinical Studies Referenced in Previous GRNs

Dosage	Length	Results	Reference
Up to 0.9 g/kg BW/d	6 days	No gastrointestinal symptoms up to 0.5 - 0.6 g/kg bw/d	Iida et al., 2007
15 g/d (5 g in tea, three times a day)	12 weeks	Positive impact on glycemic responses; no adverse effects were noted.	Hayashi et al., 2010
7.5 g in beverage	Single dose	Positive impact on glycemic and insulinemic responses; no adverse effects were noted.	Iida et al., 2008
Up to 340 mg/kg bw in beverage	Single dose	Metabolism study; no adverse effects were noted.	Iida et al., 2010

V. SUMMARY

V.A. Common Knowledge Element of the GRAS Determination

D-allulose has been safely used as a food ingredient around the world for a decade. As a result, a number of comprehensive reviews of the safety of D-allulose have been published (Chung et al., 2012b). In addition, the FDA has had no question on two GRAS Notices related to safety of D-allulose (GRN 400, FDA 2012; GRN 498, FDA, 2014).

V.B. Technical Element of the GRAS Determination (Safety Determination)

Numerous human and animal studies have reported benefits of D-allulose with no major adverse effects. Samyang Corp.'s D-allulose is manufactured under cGMP using common food industry materials and processes. Samyang Corp. uses a HACCP-controlled manufacturing process and rigorously tests its final production batches to verify adherence to quality control specifications. There is broad-based and widely disseminated knowledge concerning the chemistry of D-allulose. This GRAS determination is based on the data and information generally available and consented opinion about the safety of D-allulose. The literature indicates that D-allulose offers consumers benefits without adverse effects.

The following safety evaluation fully considers the composition, intake, nutritional, microbiological, and toxicological properties of D-allulose as well as appropriate corroborative data.

1. Analytical data from multiple lots indicate that D-allulose complies reliably with the established food-grade product specifications and meet all applicable purity standards.
2. Samyang Corp.'s D-allulose will be used as a sugar substitute and/or as a flavor modifier in food applications at use levels ranging from 0.5 to 100%: selected (low or reduced calorie) bakery products, alcoholic beverages (as a flavor modifier), soft drinks, fruit juice and fruit-flavored drinks, yogurt, hard and soft candies, chocolate, chewing gums, coffee mix, sauce, fat-based cream, sugar substitutes, nutrition bars, meal replacement shakes, and medical foods.
3. The LD_{50} value of D-allulose in rats, 15.8-16.3 g/kg. A chronic toxicity study in rats showed that D-allulose at a dose of 1,280 mg/kg bw/day, the maximum level tested, did not show adverse effects. A 90 day subchronic toxicity study in rats reported the NOAEL for D-allulose as 3% of the diet, the highest level tested.

4. A human clinical study showed that the maximum tolerable levels in humans were 0.5 g/kg bw/day for males and 0.6 g/kg bw/day for females. The only side effect of non-digestible carbohydrates including D-allulose is gastrointestinal discomfort when ingested in large quantities. This type of symptom is usually transient and is not considered to be of toxicological significance (IOM, 2002).
5. The proposed food use results in exposure at levels below those associated with any adverse effects. The EDI estimates are based on the assumption that Samyang Corp.'s D-allulose will replace currently marketed D-allulose. Thus, cumulative exposures are not expected. In addition, the EDIs presented in this notice are highly optimistic estimates.
6. In the previous GRAS notices (GRN 400 and 498) to the FDA, the safety of D-allulose has been established in animal toxicity studies and mutagenicity studies, and is further supported by human clinical studies.
7. Additional animal studies published subsequent to the FDA GRAS notices continue to support the safety of D-allulose as a food ingredient.

Overall, there are no indications of significant adverse effects related to D-allulose in the publicly available literature. Therefore, not only is the proposed use of D-allulose safe within the terms of the Federal Food, Drug, and Cosmetic Act (meeting the standard of reasonable certainty of no harm), but because of this consensus among experts, it is also *Generally Recognized as Safe* (GRAS) according to Title 21 Code of Federal Regulations (21 CFR).

VI. GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR D-ALLULOSE (OR D-PSICOSE)

We, the undersigned expert panel members, Susan Cho, Ph.D., George Fahey, Ph.D., and Joanne Slavin, Ph.D., have critically evaluated the safety of D-allulose (D-psicose).

On behalf of Samyang Corp., we, the undersigned expert panel members, Susan S. Cho, Ph.D., George Fahey, Ph.D., and Joanne Slavin, Ph.D., have independently evaluated the materials summarized in this GRAS report. Based on a critical evaluation of the publicly available data summarized herein, the Expert Panel members, whose signatures appear below, have individually and collectively, concluded that D-allulose, produced consistent with current Good Manufacturing Practices and meeting the specifications described herein, is safe under its intended conditions of use (as a nutritional food ingredient).

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have concluded that D-allulose, when used as described in this dossier, is GRAS based on scientific procedures.

_____ _____

Susan Cho, Ph.D. Date
NutraSource, Inc., Clarksville, MD 21029

_____ _____

George C. Fahey, Jr, Ph.D. Date
Professor Emeritus, University of Illinois, Urbana, IL

_____ _____

Joanne Slavin, Ph.D., R.D. Date
Professor, University of Minnesota, St. Paul, MN

VI. GENERALLY RECOGNIZED AS SAFE DETERMINATION FOR D-ALLULOSE (OR D-PSICOSE)

We, the undersigned expert panel members, Susan Cho, Ph.D., George Fahey, Ph.D., and Joanne Slavin, Ph.D., have critically evaluated the safety of D-allulose (D-psicose).

On behalf of Samyang Corp., we, the undersigned expert panel members, Susan S. Cho, Ph.D., George Fahey, Ph.D., and Joanne Slavin, Ph.D., have independently evaluated the materials summarized in this GRAS report. Based on a critical evaluation of the publicly available data summarized herein, the Expert Panel members, whose signatures appear below, have individually and collectively, concluded that D-allulose, produced consistent with current Good Manufacturing Practices and meeting the specifications described herein, is safe under its intended conditions of use (as a nutritional food ingredient).

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have concluded that D-allulose, when used as described in this dossier, is GRAS based on scientific procedures.

(b) (6)

Susan Cho, Ph.D.
NutraSource, Inc., Clarksville, MD 21029

3-26-2016
Date

(b) (6)

George C. Fahey, Jr, Ph.D.
Professor Emeritus, University of Illinois, Urbana, IL

3-24-16
Date

(b) (6)

(b) (6)

Joanne Slavin, Ph.D., R.D.
Professor, University of Minnesota, St. Paul, MN

3-23-16
Date

VII. DISCUSSION OF INFORMATION INCONSISTENT WITH GRAS DETERMINATION

We are not aware of information that would be inconsistent with a finding that the proposed use of D-allulose preparations in foods and beverages, meeting appropriate specifications and used according to cGMP, is GRAS.

VIII. REFERENCES

Baek SH, Park SJ, Lee HG. D-psicose, a sweet monosaccharide, ameliorate hyperglycemia, and dyslipidemia in C57BL/6J db/db mice. J Food Sci. 2010;75:H49-53.

Chung YM, Hyun Lee J, Youl Kim D, Hwang SH, Hong YH, Kim SB, Jin Lee S, Hye Park C. Dietary D-allulose reduced visceral fat mass in high-fat diet-induced obese rats. J Food Sci. 2012a;77:H53-H58.

Chung MY, Oh DK, Lee KW. Hypoglycemic health benefits of D-psicose. J Agric Food Chem. 2012b;60(4):863-9.

FDA. 2012. GRN 400. D-psicose, filed by CJ CheilJedang.

FDA. 2014. GRN 498, D-allulose (synonymous with D-psicose), filed by Matsutani Chemical Industry.

Hayashi N, Iida T, Yamada T, Okuma K, Takehara I, Yamamoto T, Yamada K, Tokuda M. Study on the postprandial blood glucose suppression effect of D-allulose in borderline diabetes and the safety of long-term ingestion by normal human subjects. Biosci Biotechnol Biochem. 2010;74:510-519.

Hossain MA, Kitagaki S, Nakano D, Nishiyama A, Funamoto Y, Matsunaga T, Tsukamoto I, Yamaguchi F, Kamitori K, Dong Y, Hirata Y, Murao K, Toyoda Y, Tokuda M. Rare sugar D-psicose improves insulin sensitivity and glucose tolerance in type 2 diabetes Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biochem Biophys Res Commun. 2011;405:7-12.

Hossain A, Yamaguchi F, Matsunaga T, Hirata Y, Kamitori K, Dong Y, Sui L, Tsukamoto I, Ueno M, Tokuda M. Rare sugar D-allulose protects pancreas β-islets and thus improves insulin resistance in OLETF rats. Biochem Biophys Res Commun. 2012;425:717-723.

Hossain A, Yamaguchi F, Hirose K, Matsunaga T, Sui L, Hirata Y, Noguchi C, Katagi A, Kamitori K, Dong Y, Tsukamoto I, Tokuda M. Rare sugar D-allulose prevents progression and development of diabetes in T2DM model Otsuka Long-Evans Tokushima Fatty rats. Drug Design Devel Ther. 2015;9:525-535.

Iida T, Kishimoto Y, Yoshikawa Y, Okuma K, Yagi K, Matsuo T, Izumori K. Estimation of maximum non-effective level of D-allulose in causing diarrhea in human subjects. J Advanced Food Ingred. 2007;10: 15-19.

Iida T, Kishimoto Y, Yoshikawa Y, Hayashi N, Okuma K, Tohi M, Yagi K, Matsuo T, Izumori K. Acute D-allulose administration decreases the glycemic responses to an oral maltodextrin tolerance test in normal adults. J Nutr Sci Vitaminol. 2008;54:511-514.

Iida T, Hayashi N, Yamada T, Yoshikawa Y, Miyazato S, Kishimoto Y, Okuma K, Tokuda M, Izumori K. Failure of D-allulose absorbed in the small intestine to metabolize into energy and its low large intestinal fermentability in humans. Metabolism. 2010;59:206-214.

Institute of Medicine. 2002. Dietary Reference Intakes for energy, carbohydrates, fiber, fat, fatty acids, cholesterol, protein, and amino acids. National Academy Press, Washington, DC.

Itoh K, Mizuno S, Hama S, Oshima W, Kawamata M, Hossain A, Ishihara Y, Tokuda M. Beneficial effects of supplementation of the rare sugar "D-allulose" against hepatic steatosis and severe obesity in Lep(ob)/Lep(ob) mice. J Food Sci. 2015;80:H1619-1626.

Karabinos JV. D-allulose, sorbose and tagatose. Adv Carbohydr Chem. 1952;7:99-136.

Matsuo T,Baba Y, Hashiguchi M, Takeshita K, Izumori K, Suzuki H. Less body fat accumulation with D-psicose diet versus D-fructose diet. J Clin Biochem Nutr. 2001a;30:55-65.

Matsuo T, Baba Y, Hashiguchi M, Takeshita K, Izumori K, Suzuki H. Dietary D-psicose, a C-3 epimer of D-fructose, suppresses the activity of hepatic lipogenic enzymes in rats. Asia Pac J Clin Nutr. 2001b;10:233-237.

Matsuo T, Tanaka T, Hashiguchi M, Izumori K, Suzuki H. Effects of oral acute administration and subchronic feeding of several levels of D-psicose in rats. J Nutr Sci Vitaminol. 2002;48:512-516.

Matsuo T, Tanaka T, Hashiguchi M, Izumori K, Suzuki H. Metabolic effects of D-allulose in rats: Studies on fecal and urinary excretion and cecal fermentation. Asia Pac J Clin Nutr. 2003;12:225-231.

Matsuo T. Effects of supplemental D-psicose on glucose tolerance and serum adipocytokine levels in rats fed a high-fat diet or a low-fat diet. J. Oleo Sci. 2004;53:453-460.

Matsuo T, Izumori K. D-allulose inhibits intestinal α-glucosidase and suppresses glycemic response after carbohydrate ingestion in rats. Tech Bull Fac Agr., Kagawa Univ. 2006;58:27–32.

Matsuo T, Izumori K. D-Psicose inhibits intestinal alpha-glucosidase and suppresses the glycemic response after ingestion of carbohydrates in rats. J Clin Biochem Nutr. 2009;45:202-206.

Matsuo T, Ishii R, Shirai Y. The 90-day oral toxicity of D-allulose in male Wistar rats. J Clin Biochem Nutr. 2012;50:158-161.

Nagata Y, Kanasaki A, Tamaru S, Tanaka K. d-D-allulose, an epimer of d-fructose, favorably alters lipid metabolism in Sprague-Dawley rats. J Agric Food Chem. 2015;63:3168-3176.

Ochiai M, Nakanishi Y, Yamada T, Iida T, Matsuo T. Inhibition by dietary D-allulose of body fat accumulation in adult rats fed a high-sucrose diet. Biosci Biotechnol Biochem. 2013;77:1123-1126.

Ochiai M, Onishi K, Yamada T, Iida T, Matsuo T. D-allulose increases energy expenditure and decreases body fat accumulation in rats fed a high-sucrose diet. Int J Food Sci Nutr. 2014; 65:245-250.
Oshima H, Kimura I, Izumori K. D-allulose contents in various food products and its origin. Food Sci Technol Res. 2006;12:137-143.

Sun Y, Hayakawa S, Jiang H, Ogawa M, Izumori K. Rheological characteristics of heat-induced custard pudding gels with high antioxidative activity. Biosci Biotech Biochem. 2006;70:2859–2867.

Sun Y, Hayakawa S, Ogawa M, Izumori K. Antioxidant properties of custard pudding dessert containing rare hexose, D-allulose. Food Control. 2007;18:220–227.

Sun Y, Hayakawa S, Ogawa M, Fukada K, Izumori K. Influence of a rare sugar, D-allulose, on the physicochemical and functional properties of an aerated food system containing egg albumen. J Agric Food Chem. 2008;56:4789–4796.

Tsukamoto I, Hossain A, Yamaguchi F, Hirata Y, Dong Y, Kamitori K, Sui L, Nonaka M, Ueno M, Nishimoto K, Suda H, Morimoto K, Shimonishi T, Saito M, Song T, Konishi R, Tokuda M. Intestinal absorption, organ distribution, and urinary excretion of the rare sugar D-allulose. Drug Design Devel Ther. 2014;8:1955-1964.

Whistler RL, Singh PP, Lake WC. D-allulose metabolism in the rat. Carbohydr Res. 1974; 34: 200-202.

Yagi K, Matsuo T. The study on long-term toxicity of D-allulose in rats. J Clin Biochem Nutr. 2009;45:271-277.

APPENDIX A. CERTIFICATE OF ANALYSIS

1. Product 1. D-allulose syrup

Composition	Lot 1 (2015.08.08)	Lot 2 (2015.08.09)	Lot 3 (2015.08.20)	Analytical Method
Brix	75 Brix (%)			Brixmeter
pH	3.0 ~ 7.0			pH meter
D-Allulose*	24.63%	25.16%	25.04%	HPLC
Moisture	< 25%			AOAC941.14
Fructose or other sugars*	75.37%	74.84%	74.96%	HPLC
Total plate count	Negative	Negative	Negative	AOAC 2002.07
Salmonella	Negative	Negative	Negative	AOAC 989.14
Staphylococcus	Negative	Negative	Negative	AOAC 987.09
Coliforms	Negative	Negative	Negative	AOAC 991.14
Ash	0.00%	0.00%	0.00%	AOAC 900.02
Pb	0.0095 ppm	0.0048 ppm	0.0063 ppm	AOAC 2015.01
As	0.0071 ppm	0.0014 ppm	0.0024 ppm	AOAC 2015.01
Cd	0.0020 ppm	0.0011 ppm	0.0027 ppm	AOAC 2015.01

*Dry weight basis.

2. Product 2. D-allulose syrup

Composition	Lot 1 (2015.09.15)	Lot 2 (2015.09.30)	Lot 3 (2015.10.20)	Analytical Method
Brix	75 Brix (%)			Brixmeter
pH	3.0 ~ 7.0			pH meter
D-Allulose*	53.37%	53.22%	54.95%	HPLC
Moisture	< 25%			AOAC941.14
Fructose or other sugars*	46.63%	46.78%	45.05%	HPLC
Total plate count	Negative	Negative	Negative	AOAC 2002.07
Salmonella	Negative	Negative	Negative	AOAC 989.14
Staphylococcus	Negative	Negative	Negative	AOAC 987.09
Coliforms	Negative	Negative	Negative	AOAC 991.14
Ash	0.00%	0.00%	0.00%	AOAC 900.02
Pb	0.0040 ppm	0.0033 ppm	0.0074 ppm	AOAC 2015.01

D-Allulose (D-psicose)

As	0.0015 ppm	0.0015 ppm	0.0024 ppm	AOAC 2015.01
Cd	0.0038 ppm	0.0016 ppm	0.0013 ppm	AOAC 2015.01

*Dry weight basis.

3. Product 3. D-allulose syrup

Composition	Lot 1 (2015.09.15)	Lot 2 (2015.8.28)	Lot 3 (2015.10.06)	Analytical Method
Brix	75 Brix (%)			Brixmeter
pH	3.0 ~ 7.0			pH meter
D-Allulose*	95.90%	95.25%	96.19%	HPLC
Moisture	< 25%			AOAC 941.14
Fructose or other sugars*	4.10%	4.75%	3.81%	HPLC
Total plate count	Negative	Negative	Negative	AOAC 2002.07
Salmonella	Negative	Negative	Negative	AOAC 989.14
Staphylococcus	Negative	Negative	Negative	AOAC 987.09
Coliforms	Negative	Negative	Negative	AOAC 991.14
Ash	0.00%	0.00%	0.00%	AOAC 900.02
Pb	0.0024 ppm	0.0021 ppm	0.0028 ppm	AOAC 2015.01
As	0.0011 ppm	0.0006 ppm	0.0018 ppm	AOAC 2015.01
Cd	0.0022 ppm	0.0012 ppm	0.0014 ppm	AOAC 2015.01

*Dry weight basis.

4. Product 4-Crystalline **D-a**llulose, ≥98%

Composition	Lot 1 (2015.09.15)	Lot 2 (2015.9.30)	Lot 3 (2015.10.20)	Analysis Method
Moisture	0.15%	0.16%	0.14%	AOAC 941.14
D-Allulose*	99.44%	99.03%	99.43%	HPLC
Fructose or other sugars*	0.41%	0.81%	0.43%	HPLC
Total plate count	2.0×10^2	2.7×10^2	2.0×10^2	AOAC 2002.07
Salmonella	Negative	Negative	Negative	AOAC 989.14
Staphylococcus	Negative	Negative	Negative	AOAC 987.09
Coliforms	Negative	Negative	Negative	AOAC 991.14
Ash	0.00%	0.00%	0.00%	AOAC 900.02
Pb	0.0065 ppm	0.0054 ppm	0.0017 ppm	AOAC 2015.01

As	0.0027 ppm	0.0059 ppm	0.0062 ppm	AOAC 2015.01
Cd	0.0014 ppm	0.0016 ppm	0.0011 ppm	AOAC 2015.01

*Dry weight basis.

Pages 000053-000552 have been removed in accordance with copyright laws. The list of the references that have been removed are on page 000023 and pages 000047-000049.

SUBMISSION END