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September 7, 2021

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Dr.
College Park, MD 20740

Attention: Dr. Susan Carlson
Re: GRAS Notification – D-Allulose

Dear Dr. Carlson:

GRAS Associates, LLC, acting as the Agent for L&P Food Ingredient Co., Ltd ("L&P") (China), is submitting for FDA review Form 3667 and the enclosed CD, free of viruses, containing a GRAS Notification for D-Allulose. Along with L&P's determination of safety, an Expert Panel of qualified persons was assembled to assess the composite safety information of the subject substance with the intended use as ingredients in low-calorie or dietetic foods in a variety of applications as discussed in Part 3.A.2 of the GRAS dossier. The proposed uses do not include infant formulas or meat and poultry products. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the GRAS guidance document.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via telephone or email.

We look forward to your feedback.

Sincerely,

William J. Rowe

President
Agent for L&P
GRAS Associates, LLC
1810 Grand Park Ave, Suite 500
North Bethesda, MD 20852
wrowe@nutrasource.ca
Enclosure: GRAS Notification for L&P – D-Allulose

GRAS Notification

of

D-Allulose

Food Usage Conditions for General Recognition of Safety

on behalf of

L&P Food Ingredient Co., Ltd

Wengcheng Industrial Park, Wengchen Town, Wenyuan County, Shaoguan, Guangdong 512627, P.R. China

9/7/2021

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FOREWORD

L&P Food Ingredient Co., Ltd ("L&P") based our Generally Recognized as Safe (GRAS) assessment on D-allulose, also known as D-psicose, primarily on the composite safety information, i.e., scientific procedures with corroboration from history of use. The safety/toxicity of D-allulose, history of use of D-allulose and similar compounds, GRAS notifications submitted to FDA on D-allulose and D-psicose preparations, and compositional details, specifications, and method of preparation of the subject ingredient were reviewed. In addition, a search of the scientific and regulatory literature was conducted through May 2021, with particular attention paid to adverse reports, as well as those that supported conclusions of safety. Those references that were deemed pertinent to this review are listed in Part 7. The composite safety/toxicity studies, in concert with dietary exposure information, ultimately provide the specific scientific foundation for the GRAS conclusion.

At L&P's request, GRAS Associates, LLC ("GA") convened an Expert Panel to complete an independent safety evaluation of L&P's D-allulose preparation. The purpose of the evaluation is to ascertain whether L&P's conclusion that the intended food uses of D-allulose as described in Part 3 are generally recognized as safe, i.e., GRAS, under the intended conditions of use. In addition, L&P Food Ingredient Co., Ltd has asked GA to act as Agent for the submission of this GRAS Notification.

PART 1. SIGNED STATEMENT AND CERTIFICATION

A. Basis of Exclusion from the Requirement for Premarket Approval Pursuant to Subpart E of 21 CFR 170.301

L&P has concluded that our D-allulose preparations, referred to as D-allulose syrup and crystalline D-allulose, and which meet the specifications described herein, are 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 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 use for D-allulose preparations in foods.

Signed:

Agent for L&P Food Ingredient Co., Ltd

[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 4/7/18).

William J. Rowe
President
GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

Date: September 7, 2021

B. Name and Address of Responsible Party

L&P Food Ingredient Co., Ltd
Wengcheng Industrial Park
Wengchen Town, Wenyuan County
Shaoguan, Guangdong 512627
P.R. China

As the Responsible Party, L&P accepts the responsibility for the GRAS conclusion that has been made for its D-allulose preparations as described in the subject safety evaluation; consequently, D-allulose that meets the conditions described herein are not subject to the premarket approval requirements for food ingredients.

C. Common Name and Identity of Subject Ingredient

The common name of the ingredient to be used on food labels is “D-allulose.” D-allulose is commonly referred to as “D-psicose.”

D. Conditions of Intended Use in Food

D-allulose preparations are intended for use as ingredients in low-calorie or dietetic foods, excluding meat and poultry products and infant formulas.

E. Basis for GRAS Conclusion

Pursuant to 21 CFR 170.30(a) and (b), L&P’s D-allulose preparations have been concluded to be GRAS on the basis of scientific procedures as discussed in the detailed description provided below.

D-allulose is not subject to premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

L&P certifies, to the best of our knowledge, that this GRAS notice is a complete, representative, and balanced assessment that includes all relevant information available---both favorable and unfavorable---that is pertinent to the evaluation of safety and GRAS status of the subject D-allulose preparations. This safety evaluation also included a comprehensive relevant literature published through May 2021.

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

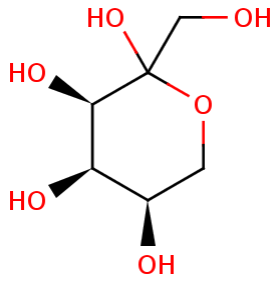
A. Chemical Identity of Ingredient

1. Chemistry of D-allulose

D-allulose is a ketohexose that is naturally available in small amounts from wheat, processed cane and beet molasses (Tsukamoto, 2014). D-allulose, also referred to as D-psicose, is naturally formed from fructose or fructose-containing foods such as fruit juice, fruit cereal, Worcestershire sauce, and Coke during the cooking process (Chung et al., 2012). It is approximately 70% as sweet as sucrose but has almost no calories (Sewalt et al., 2016).

D-allulose is an epimer of D-fructose isomerized at the C-3 position and is defined as a rare sugar (Hossain et al., 2011). The structure of D-allulose is shown in Figure 1.

Figure 1. Structure of D-allulose [a]



[a] Fig. 1 Adapted from GRN 693[2]

Common or Usual Name:	D-allulose
Chemical Name:	D-ribo-2 ketohexose; D-ribohexulose, (3*R*,4*R*,5*R*)-2-hydroxymethyl)oxane-2,3,4,5-tetrol
Synonyms:	D-psicose; allulose; psicose
CAS Number:	551-68-8
Molecular Formula:	$C_6H_{12}O_6$
Molecular Weight:	180.16 g per mole

There are no known toxicants that have been reported in D-allulose.

[2] Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=693 (Accessed 11/18/20).

2. Chemistry of the Bacterial Vector

L&P's manufacturing process for its D-allulose preparation uses D-allulose 3-epimerase to produce D-allulose from neutralized fructose syrup. The D-allulose 3-epimerase enzymes are produced by a gram-positive, nonpathogenic, and nontoxigenic strain of *Bacillus subtilis* 168 (Schallmey et al., 2004).

In 1999, FDA published a final rule in the Federal Register affirming that carbohydrase and protease enzyme preparations from *B. subtilis* are GRAS for use as direct food ingredients and that *B. subtilis* has a strong presumption of safety based on decades of use to produce a myriad of different human and animal food enzymes (Sewalt et al., 2016). Furthermore, the safety of enzymes produced by *B. subtilis* intended for use in the manufacturing of food ingredients has been evaluated in a number of GRAS Notices (GRNs) that received "no questions" responses from the FDA, as detailed in Table 1.

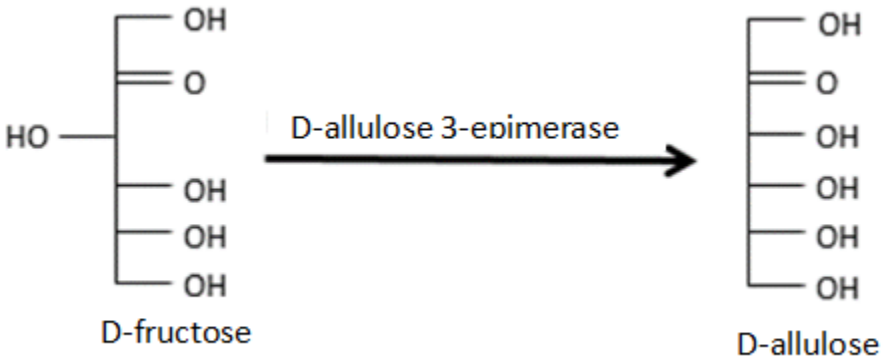
Table 1. *Bacillus subtilis*-Derived Enzyme Preparations Determined to be GRAS

GRN Number	Substance
20	Pullulanase derived from *Bacillus subtilis* carrying a gene encoding pullulanase from *Bacillus naganoensis*
114	Pectate lyase enzyme preparation from *Bacillus subtilis*
205	Pullulanase enzyme preparation from *Bacillus subtilis* expressing the pullulanase gene from *B. acidopullulyticus*
274	Branching glucosyltransferase enzyme preparation from *Bacillus subtilis* expressing a branching glycosyltransferase gene from *Rhodothermus obamensis*
406	1,4-α-glucan branching enzyme preparation form *Bacillus subtilis* strain 168 expressing the glucan branching enzyme gene from *Aquifex aeolicus* strain VF5
476	Asparaginase enzyme preparation produced by genetically modified *Bacillus subtilis*
579	Lactase from *Bifidobacterium bifidum* produced in *Bacillus subtilis*
592	β-glucanase from *Bacillus subtilis*
649	β-galactosidase enzyme preparation from *Bacillus circulans* produced in *Bacillus subtilis*
714	Subtilisin from *Bacillus amyloliquefaciens* produced in *Bacillus subtilis*
746	Maltogenic amylase from *Geobacillus stearothermophilus* produced in *Bacillus subtilis*
751	Maltogenic alpha-amylase from *Bacillus stearothermophilus* produced in *Bacillus subtilis*
861	Pullulanase from *Bacillus deramificans* produced in *Bacillus subtilis*

GRN – GRAS Notice

The genome for the *B. subtilis* strain 168 used in L&P's production process has been completely sequenced (Dedonder et al., 1977). The host strain of *B. subtilis* 168 carries D-allulose 3-epimerase genes and is not genetically modified and no modifications were made to enable the production of excess enzyme. A diagram of the conversion of fructose to D-allulose by D-allulose 3-epimerase is shown in Figure 2. There are no side products expected to be produced during the reaction.

Figure 2. Diagram of Conversion of Fructose to D-allulose



B. Manufacturing Process for D-allulose Syrup and Crystalline D-allulose

L&P's D-allulose is produced from neutralized fructose syrup by enzymatic epimerization. The use of bacteria to produce enzymes for the manufacture of D-allulose has been reported previously in GRAS Notices (GRNs) 400, 498, 693, and 828. The bacterial system utilized in L&P's manufacturing process is not novel; it uses the non-genetically modified organism, *Bacillus subtilis* 168, to produce D-allulose 3-epimerase activity, as discussed previously in Part 2.A.2. Table 2 compares the non-viable hosts and enzyme sources utilized in the manufacturing of D-allulose in L&P's manufacturing process with those described in GRNs 400, 498, 693, and 828.

Table 2. Enzyme Systems Utilized in the Production of D-allulose

GRN #	NON-VIABLE HOST	ENZYME SOURCE
L&P	*Bacillis subtilis 168*	*Bacillis subtilis 168*
400[3]	*Corynebacterium glutamicum*	*Agrobacterium tumefaciens*
498[4]	*Escherichia coli* (K12)	*Arthrobacter globiformis*

[3] Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=400 (Accessed November 10, 2020).
[4] Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=498 (Accessed November 10, 2020).

GRN #	NON-VIABLE HOST	ENZYME SOURCE
624[5]	*Escherichia coli* (K12)	*Arthrobacter globiformis*
693[6]	*Corynebacterium glutamicum*	*Clostridium scindens*
828[7]	*Microbacterium foliorum*	Not reported

L&P's manufacturing process is as follows:

1. Crystallized fructose (96 – 98% purity) is diluted with clean, food grade water in a reception tank, and the solution (≥50% solids) is mixed with $MgSO_4$/MgCl and sodium metabisulfite, then the pH is adjusted to 7.0-8.0 using sodium bicarbonate.
2. The solution is pumped at constant speed through an immobilized cell system (calcium alginate gel bead with non-GMO *B. subtilis* possessing D-allulose 3-epimerase activity). The fructose converts to D-allulose at 50°C.
3. The D-allulose solution then passes through a decolorization column packed with activated carbon.
4. For desalting, the solution undergoes treatment via an ion exchange process (i.e., a cation column with strongly acidic cation 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 ionic components such as calcium, manganese, chloride, amino acids, peptides, and proteins.
5. The desalted solution is pumped into a separation chromatography system to separate D-allulose from fructose and other sugars.
6. The purified solution is evaporated and concentrated to a density of ≥70° Brix to produce product 1 (D-allulose syrup, brix ≥70°).
7. The purified solution is then concentrated to a final density of ≥80° Brix.
8. The concentrated solution passes through a batch continuous crystallizer.
9. The crystalline D-allulose is centrifuged and washed by distilled water, then finally dried in a vacuum dryer to produce product 2 (crystalline D-allulose ≥98.5%).

L&P's D-allulose is produced using food grade materials in accordance with applicable US Federal Regulations and in accordance with FDA current Good Manufacturing Practices (CGMP). A manufacturing process flow chart for production of D-allulose is provided in Figure 3.

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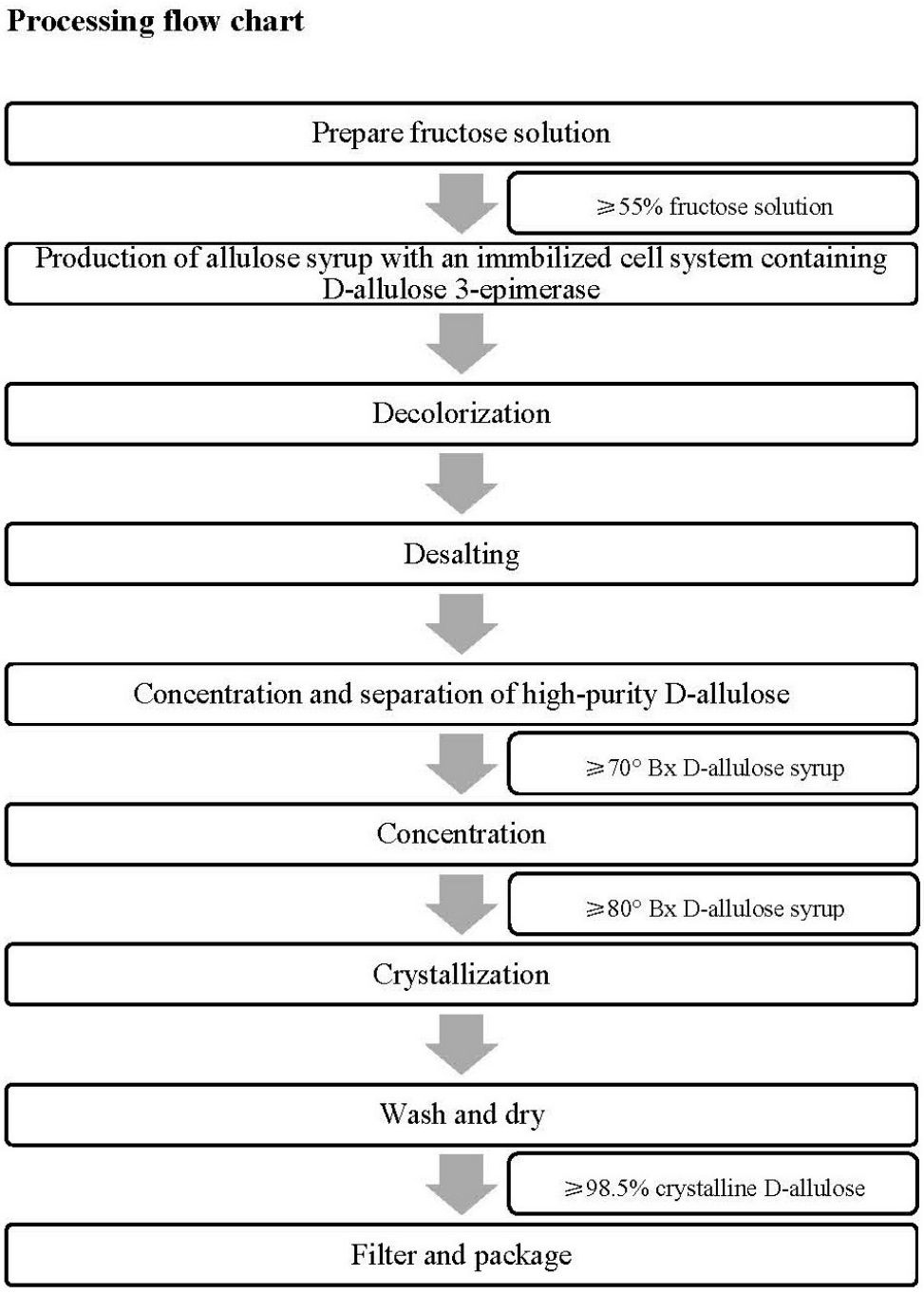
[5] Available at: https://wayback.archive-it.org/7993/20180123232657/https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/UCM505386.pdf (Accessed November 10, 2020).
[6] Available at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=693 (Accessed November 10, 2020).
[7] Available at: https://www.fda.gov/media/132576/download (Accessed November 10, 2020).

Figure 3. Manufacturing Process Flow Chart for D-allulose



C. Product Specifications

1. Specifications for D-allulose Syrup and Crystalline D-allulose

There are no established standardized specifications for D-allulose; therefore, L&P's D-allulose specifications were based upon the most recent accepted specifications for D-allulose, as detailed by Samyang Corporation in GRN 828 for their ≥90% D-allulose syrup and Samyang Corporation for their D-psicose (crystalline) in GRN 693, as shown in Table 3 and Table 4. Both GRN 693 and GRN 828 received a "no questions" response from FDA.

L&P's D-allulose material, both syrup and crystalline, are substantially equivalent to the materials described in GRN 693 and 828, respectively.

Table 3. Specifications for L&P's D-allulose Syrup as Compared to Samyang Corporations D-allulose Syrup

Physical and Chemical Parameters	L&P D-allulose Syrup		GRN 828[8] ≥90% D-allulose Syrup	
	Specification	Method	Specification	Method
Appearance	Pale yellow liquid, no obvious impurities	Visual	Clear yellow liquid	Visual
Odor	No odor	N/A	No Odor	N/A
Brix	≥71.0	Brix Meter	≥65	Brix Meter
D-Allulose (dry wt)	≥95.0%	HPLC	≥90.0%	HPLC
Fructose (%)	≤2.0%	HPLC	NR	NR
pH (of 40% aq)	3.0-7.0	pH meter	3.0-7.0	pH meter
Ash	≤0.5%	AOAC 900.02	≤0.5%	AOAC 900.02
Heavy Metals				
Lead	≤0.5 mg/kg	AOAC 2015.01	<0.5 ppm	AOAC 2015.01
Arsenic	≤0.5 mg/kg	AOAC 2015.01	<0.5 ppm	AOAC 2015.01
Cadmium	≤0.5 mg/kg	AOAC 2015.01	<0.5 ppm	AOAC 2015.01
Microbiological Limits				
Total Plate Count	≤1,000 CFU/g	AOAC 2002.07	≤1,000 CFU/g	AOAC 2002.07
Yeast and Molds	≤50 CFU/g	AOAC 997.02	Negative MPN/g	AOAC 997.02
Coliforms	≤0.43 MPN/g	AOAC 989.11	Negative CFU/g	AOAC 991.14
Staphylococcus aureus	Negative/25 g	AOAC 987.09	Negative CFU/25g	AOAC 987.09
Salmonella	Negative/25 g	AOAC 987.09	Negative CFU/25g	AOAC 989.14

AOAC – AOAC International, aq – aqueous; cfu – Colony Forming Unit; g – gram; HPLC – High Performance Liquid Chromatography; MPN – most probable number; mg/kg – milligrams per kilogram; N/A – Not applicable; NR – not reported; ppm – parts per million; wt/wt – weight/weight

[8] Available at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=828 (Accessed Dec 11, 2020).

Table 4. Specifications for L&P's D-allulose (Crystalline) as Compared to Samyang Corporation's D-allulose (Crystalline)

Physical and Chemical Parameters	L&P D-allulose (Crystalline)		GRN 693[a] D-allulose (crystalline)	
	Specification	Method	Specification	Method
Appearance	White Powder, no obvious impurities	Visual	Powder	Visual
Odor	No odor	N/A	No odor	N/A
D-Allulose (dry wt)	≥98.5%	HPLC	≥98%	HPLC
Fructose	≤1.5	HPLC	NR	NR
Moisture	≤1.0%	AOAC 941.14	≤2%	AOAC 941.14
pH (of 40% aq)	3.0-7.0	pH meter	3.0-7.0	pH meter
Ash, wt/wt	≤0.5%	AOAC 900.02	≤0.5%	AOAC 900.02
Heavy Metals				
Lead	≤0.5 mg/kg	AOAC 2015.01	≤0.5 ppm	AOAC 2015.01
Arsenic	≤0.5 mg/kg	AOAC 2015.01	≤0.5 ppm	AOAC 2015.01
Cadmium	≤0.5 mg/kg	AOAC 2015.01	≤0.5 ppm	AOAC 2015.01
Microbiological Limits				
Total Plate Count	≤1,000 CFU/g	AOAC 2002.07	≤1,000 CFU/g	AOAC 2002.07
Yeast and Molds (CFU/g)	≤50 CFU/g	AOAC 997.02	NR	NR
Coliforms	≤0.43 MPN/g	AOAC 989.11	Negative	AOAC 991.14
Staphylococcus aureus	Negative/25 g	AOAC 987.09	Negative	AOAC 987.09
Salmonella	Negative/25 g	AOAC 987.09	Negative	AOAC 989.14

[a] Available at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=693 (Accessed Nov 18, 2020).
AOAC – AOAC International, aq – aqueous; CFU – Colony Forming Unit; g – gram; HPLC – High Performance Liquid Chromatography; MPN – most probable number; mg/kg – milligrams per kilogram; N/A – Not applicable; NR – not reported; ppm – parts per million; wt/wt – weight/weight

2. Nutritional Profile for L&P's D-allulose

Table 5 below shows a typical nutritional profile for D-allulose. The Nutritional Analysis report is presented in Appendix 1.

Table 5. Typical Nutritional Profile for L&P's D-allulose

Component	Typical Analysis of D-allulose (Lot DA-P-18051501) / 100 g
Protein	<0.05 g
Total Fat	0.2 g
Cholesterol	Not detected
Carbohydrate	99.5 g
Insoluble Fiber	<0.05 g
Sodium	<0.3 g

g – grams

3. Batch Results for L&P's D-allulose and Supporting Methods

The compositions of four non-consecutive batches of D-allulose, as well as product specifications, are provided in Table 6 and Table 7. The collection of these reports demonstrates that the substance is well-characterized and meets the established purity criteria.

Table 6. Specifications and COAs of L&P's D-allulose (Syrup)

Physical and Chemical Parameters	L&P Specification	D-allulose Lot Results			
		DA-L-20092501	DA-L-20092401	DA-L-20101801	DA-L-20101501
Appearance	Pale yellow liquid, no obvious impurities	Pale yellow liquid, no obvious impurities	Pale yellow liquid, no obvious impurities	Pale yellow liquid, no obvious impurities	Pale yellow liquid, no obvious impurities
Odor	No odor	No odor	No odor	No odor	No odor
Brix (%)	≥71.0	72.3	71.8	71.9	72.5
D-allulose (dry weight) (%)	≥95.0	96.2	98.1	95.8	95.5
Fructose (%)	≤2.0	1.38	1.45	1.60	1.42
pH (of 40% aq)	3.0-7.0	4.7	4.3	4.5	4.6
Ash, wt/wt	≤0.5%	0.076	0.035	0.075	0.088
Heavy Metals					
Lead (mg/kg)	≤0.5	<0.01	<0.01	<0.01	<0.01
Arsenic (mg/kg)	≤0.5	<0.01	<0.01	<0.01	<0.01
Cadmium (mg/kg)	≤0.5	<0.01	<0.01	<0.01	<0.01
Microbiological Limits					
Total Plate Count (CFU/g)	≤1,000	Negative	Negative	Negative	5
Yeast and Molds (CFU/g)	≤50	Negative	Negative	Negative	5
Coliforms (MPN/g)	≤0.43	Negative	Negative	Negative	Negative
***Staphylococcus aureus* (per 25 g)**	Negative	Negative	Negative	Negative	Negative
***Salmonella* (per 25 g)**	Negative	Negative	Negative	Negative	Negative

aq – aqueous; CFU – Colony Forming Unit; g – gram; MPN – most probable number; mg/kg – milligrams per kilogram

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Table 7. Specifications and COAs of L&P's D-allulose (Crystalline)

Physical and Chemical Parameters	L&P Specification	D-allulose Lot Results			
		DA-P-20110801	DA-P-20102501	DA-P-20102201	DA-P-20111801
Appearance	White powder, no obvious impurities	White powder, no obvious impurities	White powder, no obvious impurities	White powder, no obvious impurities	White powder, no obvious impurities
Odor	No odor	No odor	No odor	No odor	No odor
D-allulose (dry weight) (%)	≥98.5	98.5	98.8	98.7	98.8
Fructose (%)	≤1.5	0.24	0.38	0.24	0.19
Moisture (%)	≤1.0	0.49	0.42	0.27	0.39
pH (of 40% aq)	3.0-7.0	4.0	4.2	4.6	4.5
Ash, wt/wt (%)	≤0.5	0.088	0.090	0.060	0.054
Heavy Metals					
Lead (mg/kg)	≤0.5	<0.01	<0.01	<0.01	<0.01
Arsenic (mg/kg)	≤0.5	<0.01	<0.01	<0.01	<0.01
Cadmium (mg/kg)	≤0.5	<0.01	<0.01	<0.01	<0.01
Microbiological Limits					
Total Plate Count (CFU/g)	≤1,000	Negative	Negative	Negative	Negative
Yeast and Molds (CFU/g)	≤50	Negative	Negative	Negative	Negative
Coliforms (MPN/g)	≤0.43	Negative	Negative	Negative	Negative
***Staphylococcus aureus* (per 25 g)**	Negative	Negative	Negative	Negative	Negative
***Salmonella* (per 25 g)**	Negative	Negative	Negative	Negative	Negative

aq – aqueous; CFU – Colony Forming Unit; g – gram; MPN – most probable number; mg/kg – milligrams per kilogram; wt/wt – weight/weight

D. Physical or Technical Effect

D-allulose will be added as an ingredient in low-calorie and/or dietetic foods to act as a sweetener, humectant, and flavor modifier.

1. Stability Data for D-allulose

Results of L&P's stability studies conducted on D-allulose syrup and crystalline D-allulose support the position that it is well-suited for the intended food uses, as no appreciable changes in stability were observed during the shelf life period of 240 days when samples were stored in airtight aluminum foil packaging at 35°C, as detailed in Table 8 and Table 10, and for up to 75 days in airtight aluminum foil packaging at 45°C, as detailed in Table 9 and Table 11. Given the documented stability data, the shelf life of L&P's D-allulose has been calculated to be 2 years

when preserved hermetically in aluminum foil packaging, away from light at room temperature (~25°C). The shelf life report and stability data for D-allulose can be found in Appendix 2.

Table 8. D-allulose Syrup Long-Term Storage Stability Data (35°C)[a]

Physical / Chemical Parameter Measured	Acceptance Criteria	DA-S-18020601 (35°C)		
		Day 0	Day 10[b]	Day 240
Form Condition	Liquid	Meets	Meets	Meets
Color	Pale yellow	Meets	Meets	Meets
Odor	No special odor	Meets	Meets	Meets
Content of D-Allulose (%)	≥70.0	71.10	71.00	71.20
Content of Fructose and Other Sugars (%)	≤2.0	1.40	1.50	1.30
pH	3.0 – 7.0	4.52	4.59	4.51
Bacteria Count (CFU/g)	Not detectable	Meets	Meets	Meets
***E. coli* (MPN/g)**	Not detectable	Meets	Meets	Meets
Mold/Yeast (CFU/g)	Not detectable	Meets	Meets	Meets

[a] Humidity was not recorded; the syrup was stored in a sealed container during the test
[b] Sample was checked every 10 days throughout the 240 day study at 35°C.
CFU – Colony Forming Units; g – grams; MPN – Most Probable Number

Table 9. D-allulose Syrup Long-Term Storage Stability Data (at 45°C)

Physical / Chemical Parameter Measured	Acceptance Criteria	DA-S-18020601 (45°C)		
		Day 0 (Day 5 for microbiological parameters)	Day 5[a] or 15 for microbiological parameters	Day 75
Form Condition	Liquid	Meets	Meets	Meets
Color	Pale yellow	Meets	Meets	Meets
Odor	No special odor	Meets	Meets	Unpleasant odor[b]
Content of D-Allulose (%)	≥70.0	71.10	71.00	71.00
Content of Fructose and Other Sugars (%)	≤2.0	1.50	1.40	1.50
pH	3.0 – 7.0	5.35	5.38	5.35
Bacteria Count (CFU/g)	Not detectable	Meets	Meets	Meets
***E. coli* (MPN/g)**	Not detectable	Meets	Meets	Meets
Mold/Yeast (CFU/g)	Not detectable	Meets	Meets	Meets

[a] Sample was checked every 5 days for sensory/physical/chemical indicators and every 10 days for microbiology indicators (starting on day 5).
[b] Considered stable up to day 75 at 45°C and was taken into account in the shelf-life calculations. Attributed to being heated for a long period of time.
CFU – Colony Forming Units; g – grams; MPN – Most Probable Number

Table 10. D-allulose (Crystalline) Long-Term Storage Stability Data (35°C)

Physical / Chemical Parameter Measured	Acceptance Criteria	DA-S-18020601 (35°C)		
		Day 0	Day 10[A]	Day 240
Form Condition	Powder	Meets	Meets	Meets
Color	White to light yellow	Meets	Meets	Meets
Odor	No special odor	Meets	Meets	Meets
Content of D-Allulose (%)	≥98.5	99.0	98.9	98.9
Content of Fructose and Other Sugars (%)	≤1.5	0.5	0.50	0.50
pH	3.0 – 7.0	5.36	5.36	5.42
Bacteria Count (cfu/g)	Not detectable	Meets	Meets	Meets
***E. coli* (MPN/g)**	Not detectable	Meets	Meets	Meets
Mold/Yeast (CFU/g)	Not detectable	Meets	Meets	Meets

[A] Sample was checked every 10 days throughout the 240 day study at 35°C.
CFU – Colony Forming Units; g – grams; MPN – Most Probable Number

Table 11. D-allulose (Crystalline) Long-Term Storage Stability Data (at 45°C)

Physical / Chemical Parameter Measured	Acceptance Criteria	DA-S-18020601 (45°C)		
		Day 0 (Day 5 for microbiological parameters)	Day 5[a] or 15 for microbiological parameters	Day 75
Form Condition	Liquid	Meets	Meets	Meets
Color	Pale yellow	Meets	Meets	Meets
Odor	No special odor	Meets	Meets	Unpleasant odor [b]
Content of D-Allulose (%)	≥70.0	98.90	99.10	98.90
Content of Fructose and Other Sugars (%)	≤2.0	0.60	0.40	0.60
pH	3.0 – 7.0	5.32	5.44	5.43
Bacteria Count (CFU/g)	Not detectable	Meets	Meets	Meets
***E. coli* (MPN/g)**	Not detectable	Meets	Meets	Meets
Mold/Yeast (CFU/g)	Not detectable	Meets	Meets	Meets

[a] Sample was checked every 5 days for sensory/physical/chemical indicators and every 10 days for microbiology indicators (starting on day 5).
[b] Considered stable up to day 75 at 45°C and was taken into account in the shelf-life calculations. Attributed to being heated for a long period of time.
CFU – Colony Forming Units; g – grams; MPN – Most Probable Number

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2. Stability Data from other GRAS Notifications

No stability data was presented in GRN 828, 693, 498, or 400 for comparison with the stability data for L&P's D-allulose.

PART 3. DIETARY EXPOSURE

A. Estimate of Dietary Exposure to the Substance

1. Estimated Background Intake of D-allulose from the Diet

D-allulose is obtained in the human diet as a naturally-occurring monosaccharide present in small quantities in numerous food products, including bakery products, sweets, and fruits (Oshima, 2006; FDA, 2017). The D-allulose content in certain foods is listed in Table 12. The mean and 90th percentile Estimated Daily Intakes (EDIs) of naturally occurring D-allulose reported in GRN 693 were 94.8 and 260.7 mg of D-allulose per person per day (FDA, 2017). It is unlikely that consumption patterns have changed significantly since the EDI was determined.

Table 12. D-allulose Content in Foods[a]

FOOD	MG D-ALLULOSE/100 G FOOD
BAKERY PRODUCTS	
Sponge Cake	11.0
Corn-snack	47.0
Rice cracker	27.3
Cookie	26.7
Brown sugar drop	76.5
Fried dough cake	95.6
Chocolate chip cookie	6.4
Cereal	2.2
SEASONINGS AND BEVERAGES	
Caramel sauce	83.0
Brown sugar	71.1
Meat sauce	15.8
Demiglace	16.3
Maple syrup	57.9
Ketchup	39.8
Worcestershire sauce	130.6
Coke	38.3
Coffee	0.5
Fruit juice	21.5
Tomato juice	2.4

Food	mg D-Allulose/100 g Food
Fruits	
Dried fig	29.6
Dried kiwi	9.4
Raisin	38.7
Canned peaches	1.5
Canned mandarin oranges	8.4
Canned cherries	2.0

[a] Adapted from Oshima (2006) and FDA (2017)

2. Estimated Dietary Intakes (EDIs) of D-allulose From Intended Use in Foods

L&P proposes to use our D-allulose in the same food products and at levels proportional to those outlined in GRN 400, GRN 498, GRN 693, and GRN 828. The EDI assessment for L&P's D-allulose is identical to the EDI assessment outlined in GRN 693, and it is expected that L&P's D-allulose would share the market and would not contribute to additional intake in excess of the EDIs determined in GRN 693. The proposed product categories and maximum use levels are identical to those outlined in GRN 400 and 693 for D-psicose and are summarized in Table 13.

Table 13. Proposed Food Applications of D-allulose and Maximum Levels of Use[a]

Food Category	Maximum Level (%)
Rolls, cake, pie, pastries, and cookies – diabetic or low calorie	10
Chewing gum	50
Fat-based cream used in modified fat/calorie cookies, cakes and pastries	10
Hard candies, low calorie (including pressed candy, mints)	70
Frozen dairy desserts (regular ice cream, soft serve, sorbet) – low calorie	5
Carbonated beverages – low calorie	2.1
Non-carbonated beverages - reduced and low calorie	2.1
Soft candies – low calorie (non-chocolate, plain chocolate, chocolate coated)	25
Sugar substitutes (carrier)	100
Yogurt (regular and frozen) – low calorie	5
Medical foods (as sweetener only)	15
Ready-to-eat cereals (<5% sugar)	10
Coffee mix	30

[a] GRN 693. Available at https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=693 (Accessed May 11, 2020).

The estimated daily intake of L&P's D-allulose is the same as that outlined in GRN 693, which was based on the EDI from two previous GRNs – 400 and 498. In GRN 693, Samyang Corporation reported an EDI for D-allulose that was slightly higher than the reported EDIs in

GRN 400 and 498. GRN 828 also reports intended use levels that are the same as those described in GRN 693.

The EDI estimation in GRN 693 was based on data from the National Health and Nutrition Examination Survey (NHANES) 2007 – 2010 survey. The estimation was completed assuming all foods would be used at the maximum use levels. The maximum EDIs on a gram per day and a gram per kg body weight (bw) per day basis for a range of populations are listed in Table 14 and Table 15, respectively. While newer NHANES survey data is available, it is not expected that intake levels have changed appreciably since the 2010 survey.

Table 14. Maximum EDIs of D-allulose Based on NHANES [2007-2010] Survey Data[a]

Population (years)	N-user	Per User (g/day)		Per Capita (g/day)	
		Mean	90th Percentile	Mean	90th Percentile
US 2+	13,455	11.0	30.0	8.6	24.8
Infants <2	536	0.8	2.6	1.7	4.1
Children 2-12	3,223	5.2	14.2	4.1	12.0
Adolescents 13-18	1,283	7.6	16.7	5.1	14.6
Males 19+	4,178	13.0	36.3	9.8	29.0
Females 19+	4,771	12.7	32.6	10.0	29.3

[a] From GRN 693. Available at https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=693 (Accessed May 11, 2020).
g – grams

Table 15. Maximum EDIs on a Per Kilogram Body Weight Basis of D-allulose Based on NHANES [2007-2010] Survey Data[a]

Population (years)	N-user	Per User (g/kg bw/day)		Per Capita (g/kg bw/day)	
		Mean	90th Percentile	Mean	90th Percentile
US 2+	13,455	0.16	0.42	0.12	0.35
Infants <2	536	0.08	0.24	0.15	0.42
Children 2-12	3,223	0.19	0.50	0.15	0.42
Adolescents 13-18	1,283	0.12	0.29	0.08	0.24
Males 19+	4,178	0.14	0.39	0.11	0.31
Females 19+	4,771	0.16	0.44	0.13	0.38

[a] From GRN 693 available at https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=693 (Accessed May 11, 2020).
bw – body weight; g – grams; kg – kilogram

In the population with the highest average consumption (>19-year-old males), the mean and 90th percentile estimated dietary intakes at the proposed maximum intended use levels of L&P's D-allulose would be 13.0 g per day and 36.3 g per day, respectively. The population with the

highest mean and 90th percentile consumption on a gram per kg bw per day basis are children between the ages of 2 and 12 years, with a mean and 90th percentile EDI of 0.19 and 0.50 g per kg bw per day, respectively.

It is unlikely that D-allulose will be used at the maximum levels in all food categories under the intended use and that a consumer would ingest products from all of these categories on a daily basis. While some individuals may consume full servings from all categories each day, that they would do so for 365 days per year is an overestimate for most users.

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

This section is not applicable to L&P's D-allulose, which would be chemically stable under the proposed conditions of use.

C. Dietary Exposure to Contaminants, Byproducts, and Bioactives

No concerns regarding dietary exposure to contaminants, byproducts, or bioactives have been raised by FDA upon review of previous GRAS Notices for D-allulose and D-psicose.

PART 4. SELF-LIMITING LEVELS OF USE

There are no known self-limiting levels of use associated with D-allulose, which is in agreement with the information presented in GRN 693.

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

The statutory basis for the conclusion of GRAS status of D-allulose in this document is not based on common use in food before 1958. The GRAS conclusion is based on scientific procedures.

PART 6. NARRATIVE

A. Other Information on Dietary Exposure

1. U.S. Regulatory History

A search of FDA's GRAS Notice Inventory website[9] using the search terms "D-allulose," "D-psicose," "allulose," and "psicose" identified a number of notices submitted to FDA. As of April 19, 2021, FDA has filed three GRAS notices relating to D-allulose or D-psicose, which have received "no questions" responses, as summarized in Table 16. In addition, three other GRAS

[9] GRAS Notice Inventory website. Available at: https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices (Accessed April 19, 2021).

notices were filed and subsequently ceased evaluation by FDA at the notifier's request: GRN 647 (D-psicose), GRN 755 (D-psicose), and GRN 893 (D-psicose), all due to submission issues.

FDA released a Guidance Document in October of 2020 titled "Guidance for Industry: The Declaration of Allulose and Calories from Allulose on Nutrition and Supplement Facts Labels"[10].

Table 16. Summary of D-allulose GRNs Listed in FDA's GRAS Notice Inventory[a]

Substance	GRN # / Closure Date	Intended Use	Use Rate	EDI, 90th Percentile for All Users	Company/ Reference
D-allulose	#400/2011	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, sugar substitutes, low calorie yogurt, medical foods, ready-to-eat cereals (<5% sugar) and coffee mix.	2-100% as a sugar substitute	28.5 g/person/day or 0.36 g/kg bw/day	CJ CheilJedang, Inc
Allulose/Psicose	#498/2014	As a sugar substitute in food applications	2-100% as a sugar substitute	24.8 g/person/day or 0.33 g/kg bw/day	Matsutani Chemical
D-allulose (D-psicose)	#693/2017	As a sugar substitute in food applications	2-100% as a sugar substitute	30 g/person/day or 0.42 g/kg bw/day	SamYang Corp.
D-psicose	#828/2020	For use as sugar substitute in bakery products; beverages (non-alcoholic), low calorie, reduced calorie, sugar-free; cereals, regular cereals, low calorie, reduced calorie, sugar-free; chewing gum; confections and frostings; frozen dairy desserts, low calorie, reduced calorie, sugar-free; yogurt and frozen yogurt, low calorie, reduced calorie, sugar-free; dressings for salads; gelatins, pudding and fillings, low calorie, reduced calorie,	2 – 100% (w/w) as a sugar substitute	30.0 g/person/day	SamYang Corp.

[10] Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-declaration-allulose-and-calories-allulose-nutrition-and-supplement-facts-labelsl (Accessed April 19, 2021).

SUBSTANCE	GRN # / CLOSURE DATE	INTENDED USE	USE RATE	EDI, 90TH PERCENTILE FOR ALL USERS	COMPANY/ REFERENCE
		sugar-free; hard candies, low calorie, reduced calorie, sugar-free; soft candies, low calorie, reduced calorie, sugar-free; jams and jellies; sugar; sugar substitutes; sweet sauces and syrups, low calorie, reduced calorie, sugar-free; fat-based cream			

[a] Includes only those that have received "no questions" responses
bw – body weight; EDI – Estimated Daily Intake; g – gram; kg – kilogram

2. European Regulatory History

The European Food Safety Authority (EFSA) has not reviewed D-allulose or D-psicose for health claims or for use as a dietary ingredient in foods; however, there are currently five applications filed for the approval of Allulose as a Novel Food Ingredient in the EU within the meaning of Article 10(1) of Regulation (EU) 2015/2283. No results were available as of November 2020[11].

D-Allulose 3-epimerase from *Arthrobacter globiformis* expressed in *Escherichia coli* is on the priority list of substances proposed for evaluation by the Joint Expert Committee on Food Additives (JECFA).

3. Danish Veterinary and Food Administration (DVFA)

No relevant information on D-allulose or D-psicose was found.

4. Spanish Agency for Food Safety and Nutrition (AESAN)

No relevant information on D-allulose or D-psicose was found.

5. Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM)

No relevant information on D-allulose or D-psicose was found.

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[11] Available from: https://ec.europa.eu/food/safety/novel_food/authorisations/summary-applications-and-notifications_en (Accessed May 3, 2021).

6. Canadian Regulatory History

Health Canada lists D-psicose in the Natural Health Products Ingredient Database as a non-medicinal ingredient on the New Ingredients list as of August 5, 2015.

7. Asian Regulatory History

Allulose has been commercialized in Japan since 2011 and, in February 2016, allulose was permitted as a Food for Specified Health Uses (FS/97/2016) under the Food Safety Commission of Japan (FSCJ)[12]. In 2018, the Ministry of Food and Drug Safety (MFDS) of Korea canceled the temporary requirements for D-allulose and registered it to the Korean Food Standards Codex[13].

8. Australia and New Zealand Regulatory History

No information on D-allulose or D-psicose was found in The Australia New Zealand Food Standards Code, "Substances That May Be Used as Food Additives."

B. Discussion of Safety of D-allulose

FDA has issued "no questions" responses to four GRAS notices related to D-allulose or D-psicose, as detailed in Table 16. The intended uses and intended use levels for L&P's D-allulose are identical to those found in the other four GRAS notices, specifically to those in GRN 693. Furthermore, L&P's D-allulose preparations, in crystalline and syrup forms, are substantially equivalent to Samyang Corporation's D-psicose (D-allulose) preparations described in GRNs 693 and 828, respectively.

A literature search covering the time period from 2017 to May 2021 was conducted in Pubmed, Google Scholar and Google, using the search terms "D-allulose", "allulose", "D-psicose", or "psicose". These searches identified one new study in rats (Kim et al., 2019) and one efficacy study (Ochiai et al., 2017). In addition, multiple new reports on human clinical trials were identified (Noronha et al., 2018; Tanaka, 2019; Tanaka, 2020). In addition, GRN 828 cites an unpublished acute toxicity study in male and female Sprague-Dawley rats (FDA, 2020). In this study, rats were given a single dose of D-allulose of either 0 or 5 g per kg bw and were then observed for 14 days. The authors concluded that the median lethal dose (LD_{50}) was higher than 5 g per kg bw, the highest dose tested, which does not alter the LD_{50} conclusion that was previously reported in the published literature.

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[12] Available from: https://www.fsc.go.jp/english/evaluationreports/newfoods_sphealth_e1.data/kya20130820300_203.pdf (Accessed April 19, 2021).

[13] Available from: https://mfds.go.kr/eng/brd/m_60/view.do?seq=73753 (Accessed April 19, 2021).

1. Absorption, Distribution, and Metabolism of D-allulose

No new studies were identified regarding metabolism of D-allulose other than those described in previous GRAS Notices; therefore, other than outlining a few key studies, the metabolism of D-allulose will not be discussed in detail herein.

A key study by Tsukamoto (2014), discussed in detail in GRN 693, confirms data from the earlier studies that following oral administration in laboratory rats, D-allulose is absorbed in the small intestine and then rapidly excreted in the urine. Radioactive D-psicose (100 mg per kg bw) was administered orally by gavage and intravenously to male Wistar rats (n=10) and concentrations in the blood, urine, liver, kidney, lung, thymus, spleen, heart, brain, skin, muscle, stomach, small intestine, cecum, large intestine and the gastrointestinal contents were subsequently determined at 10, 30, 60, and 120 minutes. Following oral dosing, D-psicose rapidly entered the bloodstream with the maximum concentration (48.5±15.6 µg per g) observed at one hour after dosing. Excretion in the urine was at 20% within one hour and at 33% within two hours. The liver was the only organ where accumulation was noted. At seven days after a single oral dose, the remaining amounts of D-psicose observed in the body were less than 1%. Following intravenous administration, blood concentration had a half-life of 57 minutes with the excretion in urine at almost 50% within one hour. As with oral administration, accumulation was only observed in the liver.

Matsuo (2003) conducted a study in which D-psicose was orally administered in a single dose of 5 mg per kg bw to 6-week-old male Wistar rats (n=58), and then urine and feces collected every 24 hours for a total of 72 hours. Animals had *ad libitum* access to food during the collection period. The urine and fecal samples were assayed by high performance liquid chromatography (HPLC). The level of D-psicose at 24 hours after a single dose in urine and feces was 11 – 15% and 8 – 13% of the initial dosage, respectively. D-psicose was not detected in urine or feces in any of the samples collected at 24 – 48 hours and 48 – 72 hours after dosing. In a second study, Matsuo (2003) evaluated the absorption of D-psicose from the gastrointestinal tract of 5-week-old male Wistar rats (n=18) following a single oral dose (5 mg per kg). Animals were fed a standard diet *ad libitum* for one week prior to dosing and then euthanized at 1, 3, and 7 hours post dose (n=6 per timepoint). Following euthanasia at each timepoint, blood was collected, and the serum extracted to evaluate D-psicose levels. Residual food in the stomach, small intestine and cecum was also collected at each timepoint and evaluated for D-psicose levels. D-psicose levels decreased rapidly in the blood at one hour after administration. In the stomach, D-psicose levels were higher at one hour (26 – 37% of initial dose) after dosing than at three hours (0.4 – 0.6% of initial dose) after dosing, while none was detected at seven hours after administration. In the small intestine, D-psicose levels were 6 – 10%, 2 – 3%, and 1 – 3% of the initial dose at 1, 3, and 7 hours, respectively. The D-psicose levels in the cecum at 1, 3, and 7 hours was 0%, 11 – 18%, and 10 – 19%, respectively. In an additional study by the same authors, twenty-six 3-week-old male Wistar rats were randomized into four groups and fed a basal diet until they were four weeks old (Matsuo, 2003). Rats were then fed a synthetic high carbohydrate diet that

contained 5% corn oil, 0, 10, 20, or 30% D-psicose, and 65, 55, 45, or 35% corn starch. Each group was given *ad libitum* access to the D-psicose containing diets and water for 34 days, after which the rats were fasted overnight and euthanized. The cecum was removed immediately, and residual food collected, cecal weight, surface area and cecal content weight was measured. Body weight gain, food intake and food efficiency were evaluated throughout the study and all decreased with increasing amounts of D-psicose in the diets. Cecal weight and surface area increased with increasing levels of D-psicose in the diet as did the short chain fatty acids (SCFA), and acetic, propionic and butyric acid. Cecal density did not differ between groups. The authors of these studies concluded that D-psicose is partly absorbable in the digestive tract and is excreted in the urine and feces, and that D-psicose is a fermentable saccharide as evidenced by the SCFAs produced in the cecum.

2. Acute, Subchronic, and Chronic Toxicity Studies

One new toxicity study was identified since FDA's review of D-allulose in GRN 693 in 2017 (FDA, 2017). An et al. (2019) conducted a 90-day repeat dose study in rats and determined that the NOAEL was 5,000 mg D-allulose per kg bw per day in male and female Sprague-Dawley rats. The LD_{50} of D-allulose was determined by Matsuo (2002) to be 16.3 g per kg bw. Matsuo (2002) also conducted a subchronic feeding study in rats with levels of D-psicose at 0, 10, 20, 30, and 40% D-psicose in the diet. Rats fed the 20%, 30%, and 40% diets had diarrhea for the first eight days and body weight gain was more suppressed by feeding the higher levels of D-psicose. Food intake and food efficiency were lower in the rats fed the higher D-psicose diets and carcass fat content and percentage of carcass fat decreased significantly with increasing D-psicose levels in the diet. The weights of the heart, spleen and abdominal adipose tissue were smaller in rats fed the higher concentrations but cecal weight increased with increasing D-psicose concentrations and cecal hypertrophy was observed in those fed 10 – 40% D-psicose. The mid and high dose group D-psicose consumption was determined to be 17 and 20 g per kg bw, respectively. The author concluded that diets extremely high in D-psicose, up to 20 g per kg bw, may be harmful to the intestinal tract.

Nishii et al. (2017) conducted a study in which healthy dogs were given 200 mg per kg bw per day of D-allulose orally for 12 weeks. Exposure to D-allulose did not cause any adverse clinical signs or changes in hematological and biochemical endpoints except for lipids. There was no adverse effect on body weight noted. No cumulative effects on glucose metabolism were reported. The authors concluded that long-term dosing with D-allulose caused no harmful effects in dogs.

Nishii et al. (2016) conducted a study in which healthy dogs were given a single acute oral dose of either a placebo or D-allulose at 1 or 4 g per kg. Some transient clinical signs were noted following the 4 g per kg dose and clinical pathology changes were noted in both D-allulose groups. The authors concluded that a single oral dose of D-allulose up to 4 g per kg bw did not show severe toxicity in dogs.

In a chronic study performed by Yagi and Matsuo (2009), male Wistar rats were exposed to a diet containing 3% D-psicose for 18 months. The authors concluded that no adverse effects were noted when rats were exposed to 3% D-psicose in the diet, equivalent to 1.28 g per kg bw per day, for up to 18 months.

Study details of the acute, subchronic, and chronic toxicity studies identified in GRN 693 and one additional study identified, are presented in Table 17.

L&P has reviewed these studies and concludes that, while adverse effects on the intestinal tract was noted in Matsuo (2002), the per body weight doses utilized in the study were much higher than those anticipated with L & P's intended use. The other studies reviewed show that oral D-allulose is well tolerated.

3. Reproductive/Developmental Studies

No reproductive or developmental studies were reviewed in the previous GRNs (GRN 400, 498, 693 and 828). One new study was found in the literature. Kim et al. (2019) conducted a study to assess the reproductive toxicity of D-allulose in rats (strain not specified). The females were continuously dosed from two weeks prior to mating until day 21 of lactation and males were dosed for the ten weeks prior to mating. Animals were exposed to either 0, 500, 1,000, or 2,000 mg D-allulose per kg bw per day. Animals were observed daily, and the males were euthanized when the mating period was completed. Females were allowed to give birth and rear their young until weaning at lactation day 21. All euthanized animals underwent a gross necropsy and special attention was given to the reproductive tissues. The ovaries, uterus, cervix, vagina, testes, epididymides, seminal vesicles, prostate, coagulating gland, and pituitary gland were all fixed, prepared for histopathological examination, and then evaluated. On the day of birth [postnatal day (PND) 0], the pups were examined, and the number of live and stillborn pups was recorded. The live pups were then sexed, weighed, and underwent an external examination. The pups were then examined daily on PND 4, 7, 14 and 21. On PND 4, litters were reduced to 4 males and 4 females when possible. Any deceased pups were evaluated for any structural or pathological findings. On PNDs 0, 3, 6, 9, 12, 15, 18, and 21, the body weights of the F_1 pups were taken and physical findings were assessed for one random male and female in each litter. On PND 2, the righting reflex of one random male and female pup from each litter was evaluated and if the pup failed to right itself after 2 minutes, the test was terminated. On PND 4, cliff avoidance was assessed, on PND 10, negative geotaxis was assessed, and then on PND 21, a rotarod test was performed.

There was no evidence of toxicity or mortality linked with treatment and there were no significant differences in the body weights in rats of any sex or at any time relative to the mating period. There were no treatment related effects on pregnancy rates, implantation, length of pregnancy, gender ratios, viability and lactation indexes, prenatal death rates, or the number of live young at birth. There were no treatment related changes identified at gross necropsy, with organ weights or with histopathological examination. The body weights of the F_1 pups from the treated parents

were slightly higher up to day 9 and at this point, these changes were no longer significant. The authors concluded that the No Observed Adverse Effect Level (NOAEL) for both the parental generation and the offspring was 2,000 mg per kg bw per day.

4. Genotoxicity/Mutagenicity Studies

No new studies were identified in the literature search in the time period since GRN 693 or GRN 828 were submitted to FDA. No genotoxicity or mutagenicity studies were reviewed in GRN 693 or GRN 828, but some studies were reviewed in GRN 400. The studies presented in GRN 400 included an Ames test, a micronucleus test, a chromosomal aberration test, and a study to evaluate the neuroprotective effects on 6-hydroxydopamine-induced apoptosis in catecholaminergic PC12 cells where D-psicose showed neuroprotective potential. No mutagenic potential for D-psicose was observed at levels up to 5,000 µg per plate in the Ames study and no significant increase in micronucleated polychromatic erythrocytes were noted at concentrations up to 2,000 mg per kg per day of D-psicose in a micronucleus test. In the chromosomal aberration test reported in GRN 400, D-psicose did not induce an increase in the number of chromosomal aberrations at a dosage of 1,800 µg per mL.

L&P has reviewed these studies and concludes that their product is substantively similar to the material from GRN 400 and that the results of the genotoxicity and mutagenicity studies detailed in previous GRNs are relevant to the safety conclusion of L&P's D-allulose product.

Table 17. Summary of Pre-Clinical Safety Studies for D-allulose

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
Study Design: *In vivo* **Study Length**: 14 days **Animals**: n = 20; male and female KM mice (n=10/sex) **Dose/Concentration:** 20 mL/kg/ 0.7 g/mL **Delivery/Vehicle:** gavage/distilled water **Frequency**: twice daily on day 1	**Outcome Measurements**: • Animals were observed daily for evidence of neuromuscular issues, breathing, heart rate, urination and feces, mucous membranes, skin, hair, eyes, and the urogenital system. • Animals were weighed on the day of dosing, day 7, and day 15. • On day 15, animals were euthanized, and a gross pathological examination was performed. **Results and Significance**: • No control group was included. • No mortalities were reported, and no obvious adverse clinical signs were seen in either sex. • Body weights increased during the study. • No gross pathological abnormalities were noted. • The LD_{50} was determined to be >28.0 g/kg bw for both sexes	L&P, Unpublished data, 2018
Study Design: *In vivo* **Study Length**: 90 days	**Outcome Measurements**: • OECD guideline 408 compliant • D-allulose was manufactured from an aqueous solution of fructose via enzymatic epimerization using a non-GMO *M. foliorum* SYG27B-MF.	An et al. (2019)

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
Animals: n = 32; male and female Sprague-Dawley (n=4/sex/group) **Dose/Concentration**: 0, 1,250, 2,500, 5,000 mg/kg bw **Delivery/Vehicle:** gavage/distilled water **Frequency**: daily	• Animals were observed once daily for clinical signs of toxicity, twice daily for mortality, and weighed on a weekly basis. The eyes of all animals in the study were examined prior to dosing and then again during the last week of dosing. • Food consumption was measured every 7 days for the first 13 weeks and then every 6 days, the average intake per day was calculated. • A complete urinalysis was performed on 5 rats per group after week 13 of dosing. • At the end of the dosing period, all animals were anesthetized, and blood collected for a complete blood count and a blood chemistry evaluation. Animals were then exsanguinated and underwent a complete gross necropsy. • Select organs and tissues were weighed and included the ovaries, adrenal glands, pituitary gland, prostate gland, testes, epididymides, spleen, kidneys, heart, lungs, brain and liver. The following tissues and organs were collected, fixed and prepared for histopathological examination: testes, epididymides, prostate gland, ovaries, uterus, vagina, urinary bladder, spleen, stomach, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, mesenteric lymph nodes, adrenal glands, kidneys, liver, femurs, submandibular lymph nodes, salivary glands, sternum, thymus, heart, lungs, aorta, spinal cord, tongue, trachea, esophagus, thyroid gland, eyes, Harderian gland, brain, pituitary gland and skin/mammary gland. • Blood was evaluated for white and red blood cell numbers, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, red cell distribution width, hemoglobin distribution width, reticulocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and large unstained cells. Serum was collected and evaluated for the following parameters: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, glucose, albumin, bilirubin, triglycerides, albumin/globulin ratio, inorganic phosphorus, electrolytes and calcium. Prothrombin time and activated partial thromboplastin time were also evaluated. **Results and Significance**: • No mortalities were reported, and no obvious adverse clinical signs were seen in either sex. • There was no significant difference in body weight between the treated and control animals except for the high dose males. The body weight significantly decreased by 11.9% as compared to controls. There were no differences in food consumption. • No D-allulose related changes in any of the hematology or clinical chemistry parameters were noted.	

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
	• No D-allulose related abnormalities were noted at gross necropsy or histopathological examination. Significant changes were observed in the absolute weight of the thymus in the males (decreased), and the liver and kidneys in females (increased). • The authors concluded that the NOAEL of D-allulose in both male and female rats was determined to be 5,000 mg per kg per day.	
Study Design: *In vivo* **Study Length**: One generation assessment **Animals**: n = 24 male and 48 female rats (strain not identified) (n=4/sex/group) **Dose/Concentration**: 0, 500, 1,000, 2,000 mg/kg bw **Delivery/Vehicle:** gavage/vehicle not specified. **Frequency**: daily	**Outcome Measurements**: • Study conducted in compliance with OECD 415. • Females were dosed continuously from 2 weeks prior to mating until day 21 of lactation and males were dosed for 10 weeks prior to mating. • D-allulose derived from a non-genetically modified *Microbacterium foilorum.* • Rats were allowed to give birth and rear the pups to day 21 of lactation. Normal maternal clinical signs were evaluated, and copulation, fertility and pregnancy indices were calculated. • All animals underwent a complete necropsy at the end of the study and the ovaries, uterus, cervix, vagina, testes, epididymides, seminal vesicles, prostate, coagulating gland, and pituitary gland were preserved for histopathological examination. Initially only the control and high dose tissues were examined. • Pups were examined on the day of parturition (post-natal day (PND 0) and the number of live and stillborn were recorded. Live pups were examined for sex, weight and external features. Pups were then monitored daily and the number of live/dead pups recorded on PNDs 4, 7, 14 and 21. On PNDs 0, 3, 6, 9, 12, 15, 18 and 21, body weights of the F1 animals were measured. • Behavior assessments were done in one random male and one random female from each litter. Righting reflex was measured on PND 2, cliff avoidance was assessed on PND 4 and on PND 10 the negative geotaxis was assessed. On PND 21 a rotarod test was conducted. **Results and Significance**: • No mortalities or direct toxicity was reported. • There were no changes in body weight or eating behavior and no alterations in precoital time, copulation index, fertility index in the males or pregnancy index in the males, between groups. • As compared to controls, there were no treatment related changes in pregnancy rates, implantation, pregnancy length, gender ratios, viability indexes, lactation indexes, prenatal death rates, or number of live young at time of birth. • No treatment related changes were noted in organ weights, necropsy findings or histopathological examination.	Kim et al. (2019)

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
	• In the F1 generation, the body weights of pups born to D-allulose treated parents were slightly higher for the first 9 days, as compared to controls, but after day 9 this was no longer apparent. The authors concluded that the NOAEL of D-allulose in both male and female rats and their offspring was determined to be 2,000 mg per kg per day.	
Study Design: *In vivo* **Study Length**: 144 hours for each dose **Animals**: n = 6 dogs (1 neutered male; 5 spayed females) **Dose/Concentration:** 1 and 4 g/kg bw **Delivery/Vehicle:** oral with plastic syringe/water **Frequency**: single dose/2 dosage levels each; Latin square design with 7 intervals of at least 7 days between	**Outcome Measurements**: • Blood samples collected before dosing and at 20 minutes, 40 minutes, 1, 2, 4, 8, 12, 24, 48, 96, and 144 hours after dosing. • Plasma concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol and triglyceride were determined at the 0, 4, 8, 12, 24, 48, 96, and 144-hour timepoints. • Plasma insulin concentrations were determined at 0, 20 minutes, 40 minutes, 1, and 2 hours after dosing. • Plasma concentrations of glucose, total calcium, inorganic phosphorus, sodium, potassium, and chlorine were determined at 0, 20 minutes, 40 minutes, 1, 2, 4, 8, 12, 24, 48, 96, and 144-hour timepoints. • Dogs were fed at 12 hours after dosing and then twice daily thereafter. **Results and Significance**: • One dog was vomiting shortly after dosing with 4 g/kg of D-allulose and was removed from the study. The remaining 5 animals in the group did not exhibit vomiting but did experience transient diarrhea between 2 and 24 hours after dosing. Two dogs exhibited transient nausea within 1 hour of dosing with 1 g/kg D-allulose. No other adverse clinical signs were noted, dogs were active and had good appetite throughout the rest of the study period. • Physiological Findings: Blood glucose concentrations decreased slightly at 2 hours after dosing of both 1 and 4 g/kg bw D-allulose. Plasma alkaline phosphatase activities showed were mildly increased in a dose dependent manner between 12 and 48 hours after D-allulose administration. Plasma inorganic phosphorus was mildly decreased, which was followed by a transient increase within 12 hours and the concentration at the 8-hour timepoint in the dogs that received 4 g/kg bw D-allulose was significantly higher when compared to the control dogs. There were no significant differences found in any other parameters between the dose rates. • The transient adverse gastrointestinal effects noted were not considered to be signs of serious toxicity but were assumed to be due to a rise in the enteric osmotic pressure caused by the administration of D-allulose. The authors did not consider the drop in blood glucose levels to be significant enough to be considered significant hypoglycemia. The authors noted that the increase in plasma ALP	FDA (2017); Nishii et al. (2016)

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
	activity was mild and transient without a significant rise in other hepatic enzymes and was therefore not considered a serious toxic effect. The pattern of change in the plasma inorganic phosphorus concentration was similar to normal diurnal patterns found in dogs but the authors concluded that the administration of D-allulose may mildly exaggerate the pattern in dogs but did not consider this a serious sign of toxicity. • The authors concluded that a single oral dose of D-allulose up to 4 g/kg bw did not show severe toxicity in dogs.	
Study Design: *In vivo* **Study Length**: 14 days **Animals**: n = 40 male Wistar rats (n=8/group); 4 weeks old **Dose/Concentration:** 8, 11, 14, 17, and 20 g/kg bw **Delivery/Vehicle:** gavage; water **Frequency**: once	**Outcome Measurements**: • Rats were observed daily for clinical signs and mortality. • Animals were fasted for 12 hours prior to dosing and for 4 hours after, then had *ad libitum* access to certified diet and water. • LD_{50} was calculated from the mortality using the Behrens-Karber method and Litchfield-Wilcoxon method **Results and Significance**: • All rats had diarrhea at 1-24 hours after dosing with D-psicose with the animals in the 17 and 20 g/kg bw groups becoming very weak. • Three rats in the 14 g/kg bw, three rats in the 17 g/kg bw, and all rats in the 20 g/kg bw group died in the first 48 hours following dosing. All rats that died in the 17 and 20 g/kg bw groups exhibited bleeding in the mucous layers of the stomach and small intestine. • No mortalities were noted after 48 hours and all surviving rats were normal after day 3 • The calculated LD_{50} was 16.3 g/kg bw and 15.8 g/kg bw by the Behrens-Karber and Litchfield-Wilcoxon methods, respectively.	Matsuo (2002); FDA (2017)
Study Design: *In vivo* **Study Length**: 34 days **Animals**: n = 30 male Wistar rats (n=7/group); 4 weeks old **Dose/Concentration:** 0, 10, 20, 30, and 40% **Delivery/Vehicle:** diet **Frequency**: daily in the diet	**Outcome Measurements**: • Body weight gain and food intake were recorded daily. • The number of rats with diarrhea were noted. • Following euthanasia on day 34, blood was collected, and the serum was analyzed for glucose and triacylglycerol. • The liver, heart, spleen, kidneys, cecum and intra-abdominal adipose tissues were removed immediately following euthanasia and weighed. • The remaining organs and tissues were removed, and the carcass stored at -20°C until analysis of carcass composition. • Total liver lipid and liver triacylglycerol were determined as well as carcass fat and protein. **Results and Significance**: • One rat in the 30% group and five rats in the 40% group died during the study. • Rats in the 20, 30, and 40% diet groups had diarrhea for the first 8 days.	Matsuo (2002); FDA (2017)

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
	• Body weight gain decreased as the level of D-psicose in the diet increased. A significant difference in weight gain was noted between the 0, 10, 20, and 30% D-psicose groups. • Food intake and food efficiency were lower in rats fed higher D-psicose levels. • Carcass fat content and percentage of carcass fat decreased significantly with increasing D-psicose levels in the diet. Carcass protein content decreased as the level of D-psicose in the diet increased; the level was significantly higher in the 0 and 10% groups as compared to the 20 and 30% groups. • The weights of heart, spleen and abdominal adipose tissue were decreased as the levels of D-psicose increased in the diet. Cecal weights increased as the level of D-psicose increased in the diet and cecal hypertrophy was observed in the rats fed diets with 10 – 40% D-psicose. • The authors concluded that feeding diets extremely high in D-psicose is harmful to the intestinal tract.	
Study Design: *In vivo* **Study Length**: 12 weeks **Animals**: n = 10 beagle dogs (1 neutered male + 4 spayed females/group) **Dose/Concentration:** 0.2 g/kg **Delivery/Vehicle:** oral/vehicle not specified **Frequency**: daily	**Outcome Measurements**: • Animals were fed a maintenance diet and had free access to water. • Control group received water rather than the D-allulose solution. • Food consumption, feces characteristics, activity and clinical signs were recorded daily. Body weight was measured at 0, 2, 4, 8, and 12 weeks. Blood samples were collected before the study started and during week 12 for complete blood counts and the following biochemical analyses: ALT, AST, ALP, total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol, triglyceride, total calcium, inorganic phosphorus, sodium, potassium, and chlorine concentrations. • An intravenous glucose tolerance test was conducted before the start of dosing and one day after the last D-allulose dose. A 50% glucose solution was injected intravenously at a rate of 0.5 g glucose/kg bw and blood samples collected at 0, 5, 10, 15, 30, and 60 minutes after for measurement of glucose and insulin concentrations. **Results and Significance**: • During the experimental period, all dogs had a normal appetite, normal feces, and were active with no adverse clinical signs. Body weights were stable in both groups and there was no significant difference between controls and experimental groups. • D-allulose administration did not cause clinical signs, body weight or changes in the hematological or biochemical levels, with the exception of significantly decreasing the total cholesterol. • Plasma glucose and insulin concentrations in the glucose tolerance test were not significantly different between groups. The authors concluded	Nishii et al. (2017)

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
	that this was evidence that D-allulose did not have cumulative effects on glucose metabolism in healthy dogs. • The authors concluded that long-term administration of D-allulose caused no harmful effects in healthy dogs.	
Study Design: *In vivo* **Study Length**: 90-days **Animals**: n = 20 male Wistar rats (n=10/group); 4 weeks old **Dose/Concentration:** 3% in the diet **Delivery/Vehicle:** diet **Frequency**: daily	**Outcome Measurements**: • Sucrose was used as a control. • Animals had free access to the control or D-psicose containing diets and water for 90-days. • At the end of the dosing period, animals were euthanized, and blood collected. The brain, heart, lungs, liver, pancreas, kidneys, adrenal glands, spleen, testicles, intra-abdominal adipose tissues and muscle tissues were removed. The stomach, small intestine, large intestine and cecum were also removed and weighed. Pieces of liver, kidneys and jejunum were placed in 10% neutral buffered formalin and examined histologically. The small and large intestine length, surface area and cecal content weight were measured. • The following hematological and clinical chemistry parameters were evaluated: white blood cell and red blood cell count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet, total protein, albumin/globulin ratio, albumin, globulin, AST, uric acid, blood urea nitrogen, creatine, calcium, iron, cholesterol, triglycerides, glucose and free fatty acid. **Results and Significance**: • Final body and tissue weights, food intake, and digestive tract size did not differ between control and D-psicose groups. • Actual D-psicose ingestion was 1.67 g/kg bw per day. • Mean liver and kidney weights were significantly higher in the D-psicose group as compared to the sucrose group. No other tissue weight differences were noted. • Total protein, albumin, white blood cell and red blood cell count, mean cell hemoglobin concentration, and platelet count were all significantly higher and the uric acid, mean cell volume and mean cell hemoglobin were significantly lower in the D-psicose group as compared to the sucrose group. These were not considered toxicologically significant. • No histological differences were noted between groups in the liver and kidneys. • The authors concluded that there were no adverse effects found following the consumption of a diet containing 3% D-psicose for 90 days	Matsuo (2012); FDA (2017)
Study Design: *In vivo* **Study Length**: 12-18 months	**Outcome Measurements**: • Control diet contained 3% sucrose (actual dose consumed was 1.22 g/kg bw per day) • Animals had *ad libitum* access to the diets and water.	Yagi and Matsuo (2009); FDA (2017)

STUDY SETUP AND DETAILS	PRE-CLINICAL STUDY DETAILS AND RESULTS	REFERENCE
Animals: n = 36 male Wistar rats (n=18/group); 4 weeks old **Dose/Concentration:** 1.28 g/kg bw per day; 3% in the diet **Delivery/Vehicle:** diet **Frequency**: daily	• Body weight and feed consumption was recorded during the study, but the frequency was not specified. • At the end of 12 months, 8 animals/group were fasted for 4.5 hours, anesthetized and blood was collected for hematological and clinical chemistry analysis. Samples were analyzed for platelet count, hemoglobin, erythrocyte count, leukocyte count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, glucose, insulin, triglycerides, free fatty acids, total cholesterol, AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin, creatinine, urea nitrogen, uric acid, albumin, total protein, ratio of albumin and globulin, lipid peroxide, calcium and iron. The remaining animals (10/group) underwent the same procedures at the end of 18 months. • The brain, heart, lungs, liver, pancreas, kidneys, adrenals, spleen, testicles, intra-abdominal adipose tissues and muscle tissues were quickly removed and weighed following exsanguination. Sections of the liver and kidney were placed in 10% neutral buffered formalin for histopathological examination. **Results and Significance**: • Final body weight, weight gain, and energy intake did not differ between the D-psicose and sucrose groups at the end of 12 months. Body weight and body weight gain and intra-abdominal adipose tissue weight was significantly reduced in the rats on the D-psicose containing diet as compared to those on the sucrose containing diet at 18 months. • No toxicologically significant differences were found in any of the hematological or clinical chemistry parameters evaluated. • Relative liver and kidney weights were significantly higher in the D-psicose group as compared to the sucrose group, but no gross pathological findings were evident which correlated with hypertrophy of the liver or kidney. No toxicologically significant histopathological lesions were noted in the liver or kidneys. • The authors concluded that no adverse effects were noted in the current study when rats were exposed to 3% D-psicose in the diet for up to 18 months	

bw – body weight; g – grams; kg – kilograms

5. Carcinogenicity

No carcinogenicity studies were reviewed in GRN 693 or 828, but three studies were reviewed in GRN 400 that demonstrated D-psicose is not carcinogenic. Furthermore, no new studies were identified in a literature search in the time period since GRN 693 and 828 were submitted to FDA.

6. *In vitro* Studies with D-allulose

No *in vitro* studies for D-allulose or D-psicose were found in the published literature and none were included in previous GRAS Notices submitted to FDA.

7. Animal Efficacy Studies with D-allulose

Since FDA's last review of D-allulose in 2017 in GRN 693, three additional efficacy studies with D-allulose were found. One study investigated and compared the anti-obesity effect of rare sugar syrup (D-allulose level was 5.62%) and a modified glucose syrup (D-allulose level was 12.83%) diet in a group of rats; however, the level of D-allulose in both syrups was low, so this study was of limited value with respect to safety and therefore not discussed further (Ochiai et al., 2017).

Studies by Choi et al. (2018) and Nishii et al. (2016) were found to be relevant, and study details for these studies as well as those discussed in the related D-allulose and D-psicose GRNs, in particular GRN 693, are presented in Table 18.

Table 18. Summary of Animal Efficacy Studies for D-allulose

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
Study Design: *In vivo* **Study Length**: 12 weeks **Animals**: n = 70; male C57BL/6J mice **Dose/Concentration:** 3% D-allulose in the diet **Delivery/Vehicle:** Diet **Frequency**: daily	**Outcome Measurements**: • Mice were fed a normal diet for 16 weeks and then a high-fat diet for 4 weeks to induce obesity. Following this, the mice were divided into seven groups (n=10/group) and fed the high fat diet with *Lactobacillus sakei* or *Leuconostoc kimchi* or 3% D-allulose with high fat diet or 3% allulose alone; high fat diet with D-allulose and *Lactobacillus sakei*, high fat diet with allulose and *Leuconostoc kimchi* and high fat diet with D-allulose, *Lactobacillus sakei* and *Leuconostoc kimchi*; all for 12 weeks. • Body weights were evaluated throughout the experimental period and used to determine the feed efficiency ratio throughout the experimental period. • At the end of 12 weeks, the animals were euthanized following a 16-hour fast, blood was collected, and the liver and adipose tissue were removed and stored for analysis. • Plasma triglycerides, total-cholesterol, high-density lipoprotein cholesterol, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels, plasma apolipoprotein AI and apolipoprotein B, plasma free fatty acid, plasma adipokines and cytokines were determined. • Hepatic lipid content including triglycerides, cholesterol and fatty acid contents, were determined. Hepatic lipid-regulating enzyme activities were also evaluated. The livers were examined histopathologically. **Results and Significance**: • The authors concluded that this study demonstrated that the symbiotic mixture with D-allulose was more effective in suppressing diet-induced obesity and its complications via the regulation of lipid metabolism than	Choi et al. (2018)

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
	either the probiotics or allulose alone. They suggest that this may mean the allulose acts as a prebiotic for the two probiotics tested. **Safety Measurements/Adverse Events Reported**: • No specific safety outcomes were reported in this study.	
Study Design: *In vivo* **Study Length**: 4 weeks **Animals**: n = 30; Sprague-Dawley rats (n=6/group) **Dose/Concentration:** 3% **Delivery/Vehicle:** diet **Frequency**: daily	**Outcome Measurements**: • Animals were fed either the control diet or a diet containing 3% of either D-allulose, D-tagatose, or D-sorbose for 4 weeks. Body weight and food intake were determined and used to calculate body weight gain and food efficiency ratio. • Animals were then euthanized without fasting and the following was collected: 1) liver and mesenteric, perirenal and epididymal adipose tissue, which was weighed and stored at -80°C prior to tissue lipid, enzyme or gene expression analysis; 2) the small intestine was collected, flushed with ice-cold saline and the jejunum and ileum were isolated, the jejunum was used for real-time quantitative polymerase chain reaction (PCR) analysis; 3) serum was collected to determine lipid levels; 4) feces was collected for 2 days prior to euthanasia and analyzed for lipid excretion **Results and Significance**: • No differences in body weight gain, food efficiency and liver weight were reported between groups. No difference in food intake was noted, which the authors concluded to mean there was no differences in caloric intake. • Hepatic lipogenic enzyme activity was lowered by D-allulose and D-sorbose but increased by D-tagatose. Fecal fatty acid excretions were not significantly decreased by D-allulose. There was a trend towards reduced adipose tissue weight observed in the rare sugars' groups. D-allulose tended to down-regulate the gene expression of cholesterol metabolism-related liver proteins. **Safety Measurements/Adverse Events Reported**: • No effects on body weight or food efficiency were noted. There was no reporting on any other safety measurements or any reports of mortalities. • The average feed intake in the D-allulose group was 24.5±0.88 g/day; therefore approximately 0.74 g of D-allulose was ingested/mouse/day.	Nagata et al. (2018)
Study Design: *In vivo* **Study Length**: 16 weeks **Animals**: n = 60; male C57BL/6J mice (n=10/group) **Dose/Concentration:** 5% in the diet	**Outcome Measurements**: • Groups included in the study were: control, high fat diet, 5% D-allulose, 5% erythritol, 5% D-glucose, and 5% D-fructose. The D-allulose, erythritol, D-glucose, and D-fructose were substituted for sucrose in the high fat diet to make the test diets. All animals were given isocaloric diets based on the energy intake of the D-allulose fed groups. • Food intake was recorded daily and body weights were collected every two weeks • Plasma, hepatic and fecal lipid profiles (triglycerides, high density lipoprotein cholesterol and total cholesterol) were determined on all animals at the end of the 16-week experimental period. • Plasma leptin, resistin and adiponectin were determined at the end of the experimental period. • The liver and epididymal white adipose tissue were collected from all animals at the end of the experimental period and fixed in 10% formalin for histopathological evaluation.	Sewalt et al. (2016)

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
	Results and Significance • Body weights and the fat-pad mass in the D-allulose group were lower than that in the control group with a decrease in plasma leptin and resistin concentrations. • D-allulose lowered plasma and hepatic lipids but elevated fecal lipids with a decrease in mRNA expression of CD36, ApoB48, and FATP4 in the small intestine • Both liver fatty acid synthase and β-oxidation were downgraded in the liver by D-allulose to the level of that in the normal group but in the epididymal white adipose tissue, fatty acid synthase was decreased while β-oxidation activity was enhanced. • The authors concluded that 5% dietary D-allulose led to the normalization of the metabolic status of diet-induced obesity by altering lipid-regulation enzyme activities and their gene expression levels as well as fecal lipids **Safety Measurements/Adverse Events Reported**: • No specific adverse events were reported.	
Study Design: *In vivo* **Study Length**: 8 weeks **Animals**: n = 31; male Wistar rats **Dose/Concentration:** 5% D-psicose in the diet **Delivery/Vehicle:** Diet **Frequency**: Daily	**Outcome Measurements**: • Base diet was a high sucrose diet; control diet had 5% added cellulose and the experimental diet had 5% added D-psicose (n=10). The cellulose group (n=21) was again divided into two groups: one fed the cellulose diet *ad libitum* (n=11) and a second group that was pair fed the cellulose + D-psicose diets (n=10). • Body weight and dietary intake were monitored daily. • Rats in both the cellulose-D-psicose and the D-psicose groups consumed equal amounts of the metabolizable energy during the experimental period. • Between weeks 5 and 7, energy expenditure was measured. • At the end of the experimental period, the rats were fasted for 4 hours, euthanized and blood was collected, and the serum harvested. Heart, liver, kidney, abdominal adipose tissues, brown adipose tissue and muscles were rapidly removed, weighed and stored at -80°C until analyzed. **Results and Significance**: • The resting energy expenditure during darkness and the lipoprotein lipase activity in the soleus muscle were significantly higher in the psicose group than in the cellulose + D-psicose group. • Serum levels of glucose, leptin and adiponectin were significantly lower in the D-psicose group as compared to the cellulose + D-psicose group. • The glucose-6-phosphate dehydrogenase activities in the liver and perirenal adipose tissue and body fat accumulation were significantly lower in the D-psicose group as compared to the cellulose + D-psicose group. • The authors concluded that the anti-obesity effects of D-psicose could be induced by suppressing lipogenic enzyme activity and by increasing energy expenditure in a high sucrose induced obese rat model. **Safety Measurements/Adverse Events Reported**: • No specific adverse events were reported.	Ochiai et al. (2014)

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
Study Design: *In vivo* **Study Length**: 4 weeks **Animals**: Experiment 1: n = 48 (n=24/group); Sprague-Dawley rats Experiment 2: n = 16 (n=8/group); Sprague-Dawley rats **Dose/Concentration:** 3% in the diet **Delivery/Vehicle:** diet **Frequency**: daily	**Outcome Measurements**: • Experiment 1: Rats were provided the diet *ad libitum* (D-psicose or control) for 4 weeks and then five to six animals were euthanized every 6 hours for 4 timepoints. Blood was collected and the liver, soleus muscle, and adipose tissue collected. Intrascapular brown adipose tissue was also collected for enzyme activity measurement. The small intestine was collected. Serum glucose and lipid levels, serum insulin and leptin levels, and the cholesterol, phospholipid and triglyceride levels in the liver were measured. The activity of lipid metabolism-related enzymes in the liver and brown adipose tissue were also measured. Gene expression of enzymes and proteins involved in lipid metabolism in the liver, jejunum soleus muscle and mesenteric adipose tissue was measured. • Experiment 2: Rats were fed the appropriate diet (3% D-psicose or control) for 4 weeks and then the 24-hour energy expenditure was measured. Rats were placed in a metabolic chamber and maintained on the appropriate diet. Energy expenditure and oxidation of carbohydrate and fat were measured over a 24-hour period. **Results and Significance**: • In the first experiment, rats fed D-psicose significantly lowered serum insulin and leptin levels as well as liver enzyme activity involved in lipogenesis. Gene expression of a transcriptional modulator of fatty acid oxidation was enhanced. • In the second experiment, rats fed the D-psicose diet had significantly lower body weights and food intake as compared to controls. The rats in the D-psicose group had significantly higher energy expenditure during the light period and fat oxidation in the dark period, as compared to controls and carbohydrate oxidation was lower. • The authors concluded that D-psicose decreased lipogenesis, increased fatty acid oxidation and enhanced 24-hour energy expenditure which could demonstrate a potential for weight management. **Safety Measurements/Adverse Events Reported**: • No specific safety endpoints were included in the study and no reports of adverse events were noted.	Nagata et al. (2015)
Study Design: *In vivo* **Study Length**: Single dose **Animals**: n = 7; dogs (one male; five females used in both experiments and one additional male for the oral administration study) **Dose/Concentration:** 0.2 g/kg bw **Delivery/Vehicle:** oral **Frequency**: once	**Outcome Measurements**: • The same dogs were used for all experiments with a minimum of a 1-week washout period between • Dogs were determined to be healthy prior to dosing. All dogs were fasted overnight with free access to water. • <u>Oral study:</u> Seven dogs were administered the 50% glucose solution at 2.0 g/kg bw and the 50% Maltose solution at 2.0 g/kg bw with oral D-allulose (0.2 g/kg bw) or the equivalent water dose. Blood samples were collected before dosing and at 30, 60, 90, and 120 minutes after dosing for determination of plasma glucose and insulin concentrations. • <u>Intravenous study:</u> The same dose rate was used as in the oral study. Six dogs were given an oral D-allulose solution (0.2 g/kg bw) or the equivalent volume of water 60 minutes before the intravenous administration of 50% glucose (0.5 g/kg bw). Blood samples were collected before dosing and at 5, 10, 15, 30, and 60 minutes after the glucose dose for the determination of plasma glucose and insulin concentrations.	Nishii et al. (2016)

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
	• Feeding study: Six dogs were fed a commercial maintenance dry food and given D-allulose (0.2 g/kg bw) or water. Blood samples were taken before feeding and at 1, 2, 3, 4, 6, and 8 hours after feeding for determination of glucose and insulin concentrations. **Results and Significance**: • Oral study: Oral dosing with glucose or maltose increased plasma glucose and insulin levels. Administration of D-allulose after dosing with glucose or maltose significantly diminished the rise in plasma glucose. The concentration of plasma insulin was significantly lower as well. The area under the curves (AUCs) for plasma glucose and insulin concentrations after oral dosing with glucose and maltose were significantly lower in the D-allulose group as compared to the water control group. • Intravenous study: The concentration of plasma glucose was lower at 5, 10, and 15 minutes after intravenous dosing with glucose when D-allulose was also given. There was no significant difference in the plasma insulin levels between the control and D-allulose groups. • Feeding study: After feeding, the level of plasma insulin increased while the level of plasma glucose did not fluctuate. Oral administration of D-allulose did not alter these parameters. **Safety Measurements/Adverse Events Reported**: • No specific safety outcomes were reported in this study.	
Study Design: *In vivo* **Study Length**: 60 weeks **Animals**: n = 20 (n=10/group); Otsuka Long-Evans Tokushima Fatty (OLETF) rats **Dose/Concentration:** 5% D-psicose **Delivery/Vehicle:** tap water **Frequency**: daily/*ad libitum*	**Outcome Measurements**: • Animals were divided into two groups: control receiving tap water only and treatment group receiving 5% D-psicose in the water. • Body weights were measured daily. • Food and water intake were determined for three consecutive days each week and the average rat/day intake was calculated. • Periodic fasting and postprandial blood glucose levels were measured; plasma was also collected. Rats were fasted for 12 hours for an oral glucose tolerance test. Additional blood was collected for plasma, which was tested for insulin, total cholesterol, triglycerides, and high- and low-density lipoproteins. • At the end of the experimental period, animals were fasted for 12 hours, anesthetized, blood collected, and organs/tissues removed. Abdominal fat was collected from the epididymal, retroperitoneal and mesenteric areas and weighed. Serum was analyzed for glutathione, IL-6, tissue necrosis factor alpha, leptin and adiponectin levels. Total fat mass, fat-free body mass and body mass index were estimated. To measure inflammatory profile, the pancreas and adipose tissues were fixed in formalin and prepared for histopathological evaluation. **Results and Significance**: • D-psicose prevented the start and progression of type II diabetes until week 60 by maintaining blood glucose levels, decreasing body weight gain and the control of postprandial hyperglycemia as compared to control rats. The improvement of glycemic control was accompanied by the maintenance of plasma insulin levels and preservation of pancreatic beta cells with a reduction in inflammatory markers. • Body fat accumulation was significantly lower in the treatment group.	Itoh et al. (2015)

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
	• The authors concluded that D-psicose could be beneficial in the prevention and control of obesity and hyperglycemia. **Safety Measurements/Adverse Events Reported**: • No specific safety endpoints were included in this study and no adverse effects were reported.	
Study Design: *In vivo* **Study Length**: 13 weeks **Animals**: n = 45 Otsuka Long-Evans Tokushima Fatty (OLETF) rats and non-diabetic Long-Evans Tokushima Otsua (LETO) as controls (n=15) **Dose/Concentration:** 5% D-psicose in water **Delivery/Vehicle:** drinking water **Frequency**: daily	**Outcome Measurements**: • Treated OLETF rats were fed with 5% D-psicose (n=15) or 5% D-glucose (n=15) supplemented drinking water, and only water (n=15) in the control for 13 weeks. Non-diabetic LETO rats, given water only, served as a counter control of OLETF. • Animals were allowed free access to water and food, and food intake for 3 consecutive days each week was measured to calculate the average of g/100 g body weight consumption and amount of water consumption was also calculated. • Multiple measurements of obesity, characterization of glucose metabolism and inflammatory profile were also evaluated. **Results and Significance**: • Consumption of D-psicose significantly attenuated progressive beta-islet fibrosis and preserved the islets. • D-psicose significantly reduced increase in body weight and abdominal fat deposition. The oral glucose tolerance test showed a reduced blood glucose level, which suggests the improvement of insulin resistance. • The authors concluded that the data suggested that D-psicose protected and preserved pancreatic beta-islets through the maintenance of hyperglycemia and the prevention of fat accumulation in OLETF rats. **Safety Measurements/Adverse Events Reported**: • No behavior changes were observed during the study, weight gain tended to be lower in the D-psicose treated group, and food intake was lower during the first weeks but was then not different from other groups.	Hossain et al. (2012)
Study Design: *In vivo* **Study Length**: 15 weeks **Animals**: n = not specified; mice – Lep^{ob}/Lep^{ob} and C57BL/6J wildtype **Dose/Concentration:** 0, 2.5, or 5% in the diet **Delivery/Vehicle:** diet **Frequency**: daily	**Outcome Measurements**: • This study was conducted to benefits of dietary supplementation of D-allulose in inherited leptin-deficient mice with severe obesity. • Animals were allowed free access to both food and water with intake measurements and body weights determined weekly. • Body composition was assessed *in vivo* and then mice were euthanized, the abdominal visceral fat and the liver and kidneys excised, and the wet weight was measured. • Hepatic steatosis and abdominal visceral fat were evaluated using magnetic resonance imaging (MRI). The liver was examined histologically for changes in hepatic steatosis. **Results and Significance**: • The subchronic ingestion in the *ob/ob* mice significantly decreased body and liver weights. The loss of body weight was linked with the reduction of total fat mass including abdominal visceral fat but not fat-free body mass, including muscle. In addition, ingestion of D-allulose improved hepatic steatosis in the *ob/ob*. • None of these parameters were influenced by ingestion of D-allulose in the wildtype mice.	Itoh et al. (2015)

STUDY SETUP AND DETAILS	ANIMAL EFFICACY STUDY DETAILS AND RESULTS	REFERENCE
	• The authors concluded that D-allulose may be useful as a supplement for preventing and improving obesity and obesity-related disorders. **Safety Measurements/Adverse Events Reported**: • No specific safety endpoints were included in this study and no adverse effects were reported.	

8. Human Studies and Experience with D-allulose

A number of human studies were reviewed in GRN 693 and 828. As discussed in GRN 693, Iida (2007) indicated that D-allulose is safe to ingest at 0.5 – 0.6 g per kg bw as a single dose, while a more recent gastrointestinal tolerance study by Han et al. (2018a) recommended that the maximum single dose of D-allulose should be 0.4 g per kg bw and the maximum total daily intake of D-allulose should be 0.9 g per kg bw. These recommendations were based on incidences of severe nausea, abdominal pain, headache, anorexia, and diarrheal symptoms when total daily intake of D-allulose was gradually increased to 1.0 g per kg bw. These symptoms of gastrointestinal discomfort are transient and generally not considered to be of toxicological significance. Key studies are presented in Table 19.

a. Reviews

Chung et al. (2012) conducted a review that summarized the properties, absorption, and excretion of D-psicose as well as its biological production, function, and safety. The authors concluded that D-psicose is relatively nontoxic and lowers glycemic responses following carbohydrate consumption.

b. Clinical Trials

Numerous clinical trials have been conducted on D-allulose for various health related endpoints. While these studies were not designed with safety related endpoints, these studies are summarized in Table 19 to outline the relevant study details in order to assess tolerability and safety. L&P has reviewed the data and agrees with the safety conclusions of these studies.

Table 19. Summary of Clinical Trials for D-allulose

STUDY SETUP AND DETAILS	HUMAN STUDY RESULTS, SIGNIFICANCE, SAFETY	REFERENCE
Study Design: Randomized, double-blinded, placebo-controlled **Study Length**: 52 weeks total; 48 weeks consumption and 4-week post	**Outcome Measurements**: • Inclusion criteria: (1) LDL-C levels of 120 – 159 mg/dL, and a fasting blood glucose concentration of 100-125 mg/dL or hemoglobin A1C of 6.0-6.5%; (2) a homeostasis model assessment of beyond 2.5 with high LDL-C levels; and (3) high LDL-C levels. Additional details and exclusion criteria were detailed in the publication.	Tanaka (2020)

STUDY SETUP AND DETAILS	HUMAN STUDY RESULTS, SIGNIFICANCE, SAFETY	REFERENCE
consumption observation period **Subjects**: n=90; males and females; aged 20-65 years **Dose, Delivery, and Frequency**: 0, 5, or 15 g D-allulose added to a sucralose sweetness adjusted drink	• On examination days, fasting morning urine and blood were collected, and physical measurements were taken. Routine blood biochemical marker analysis, hematological parameter measurements and urine analysis were performed at each examination timepoint. Additional endpoints were evaluated at various timepoints as detailed in the publication including the absolute risk of atherosclerotic cardiovascular disease (ASCVD) which was calculated and divided into three groups (low risk, moderate risk, and high risk). • Examinations were performed 4 weeks prior to the first day of consumption, on the first day of consumption, and then on week 8, 16, 24, 32, 40 and 48 after starting consumption. An oral glucose tolerance test was conducted on the first day of consumption and then 48 weeks after starting consumption. • The goal of the study was to evaluate the safety of D-allulose intake for 48 weeks and its effect on cholesterol metabolism in subjects with high LDL-C levels. **Results and Significance**: • Total cholesterol and LDL-C levels did not significantly change as compared to the placebo intake group. The ASCVD risks were evaluated using various risk factors and mechanistic perspectives, and none demonstrated an increase in ASCVD risks associated with D-allulose intake for 48 weeks. **Safety Measurements/Adverse Events Reported**: • No adverse treatment related events were reported and no increase in ASCVD risks was reported.	
Study Design: Open trial **Study Length**: 18 weeks total/12 weeks consumption **Subjects**: n=18; males and females; 12 with borderline diabetes and 6 with type 2 diabetes **Dose, Delivery, and Frequency**: 5 g D-allulose with meals, 3 times daily	**Outcome Measurements**: • General physical parameters included height, body weight, body mass index, body fat percentage, waist circumference, systolic blood pressure, diastolic blood pressure and pulse. Biochemical, hematological, and general urine analysis parameters were also evaluated. Living habits were also recorded. • The authors note that there are limitations with this study – small sample size and influencing factors could not be excluded because of study design (open study/no control group). **Results and Significance**: • D-allulose has the potential to suppress postprandial hyperglycemia and fat mass accumulation. **Safety Measurements/Adverse Events Reported**: • No adverse treatment related events were reported.	Tanaka (2019)
Study Design: randomized, multiple cross-over, double-blind, placebo-controlled	**Outcome Measurements**: • Plasma glucose incremental area under the curve	Noronha et al. (2018)

STUDY SETUP AND DETAILS	HUMAN STUDY RESULTS, SIGNIFICANCE, SAFETY	REFERENCE
acute feeding, equivalence trial **Study Length**: multiple-crossover – 1 week wash out **Subjects**: n=24; males and females with a body mass index (BMI) 18.5 - 35 kg/m^2 (66 ± 1.2 years); type II diabetes **Dose, Delivery, and Frequency**: Fructose or allulose (0, 5, or 10 g) added to a 75 g glucose drink	**Results and Significance**: • Allulose significantly reduced plasma glucose incremental area under the curve by 8% at 10 g dose with a linear dose response. **Safety Measurements/Adverse Events Reported**: No adverse treatment related events were reported.	
Study Design: randomized double-blind, placebo-controlled trial **Study Length**: 12 weeks **Subjects**: n=121 (n=48/group); males and females with a BMI ≥23 kg/m^2 (20-40 years) **Dose, Delivery, and Frequency**: low dose = 4 g/subject twice daily and high dose = 7 g/subject twice daily; given as a grapefruit flavored non-carbonated drink	**Outcome Measurements**: • Sucralose was included as the placebo control • Parameters for body composition, nutrient intake, computed tomography scan and plasma lipid profiles were assessed. **Results and Significance**: • There was no significant difference in nutrient intake, plasma lipid profiles, markers of liver and kidney function and major inflammation markers between groups. **Safety Measurements/Adverse Events Reported**: • No adverse events were reported.	Han et al. (2018b)
Study Design: non-randomized control trial **Study Length**: study 1: 11 weeks; study 2: 6 days **Subjects**: Experiment 1: n=30 healthy male (n=15) and female (n=15) subjects with a BMI of ≤23 kg/m^2 (21-30 yrs). Experiment 2: n=19 healthy male (n=10) and female (n=9) subjects **Dose, Delivery, and Frequency**: dose gradually increased in steps; given as	**Outcome Measurements**: • Two single-group open studies were done, with a separation of 7 days • Experiment 1: the dose gradually increased in steps of 0.1 g/kg bw, with a 1-week washout between doses, to a dose of 0.6 g/kg bw during week 11, to identify the maximum single dose for occasional ingestion. Each dose level was consumed once daily for 7 days • When the maximum dose for occasional consumption was identified in Experiment 1, Experiment 2 was conducted to determine the maximum total daily intake for regular ingestion. The subjects consumed increasing doses of D-allulose each day. • For both studies, the subjects were asked to record the incidence and magnitude of the gastrointestinal (GI) responses for the 24-hour period following the consumption of the test products.	Han et al. (2018a)

STUDY SETUP AND DETAILS	HUMAN STUDY RESULTS, SIGNIFICANCE, SAFETY	REFERENCE
a grape-flavored non-carbonated drink	**Results and Significance**: • In Experiment 1, no severe diarrhea or GI symptoms were noted until a dose of 0.4 g/kg. Severe symptoms of diarrhea were noted at 0.5 g/kg bw. • In Experiment 2, increasing the total daily D-allulose intake gradually to 1.0 g/kg bw for regular ingestion resulted in incidences of severe nausea, abdominal pain, headache, anorexia, and diarrhea. • The authors concluded that the maximum single dose and maximum total daily intake of D-allulose should be 0.4 g/kg bw and 0.9 g/kg bw, respectively. **Safety Measurements/Adverse Events Reported**: • GI effects were determined during these studies.	
Study Design: double-blind, randomized, controlled, acute feeding, equivalence trial **Study Length**: single doses **Subjects**: n=24; subjects with type 2 diabetes; male and female subjects (18-75 yrs) **Dose, Delivery, and Frequency**: single dose of 0, 5, or 10 g allulose with a washout period between	**Outcome Measurements**: • Each participant was randomly assigned six treatments separated by ≥1-week washouts. • Treatments included fructose or allulose at 0, 5, or 10 g added to a 75 g glucose solution. A standard oral glucose tolerance test protocol was followed with blood samples collected at -30, 0, 30, 60, 90, and 120 minutes. • The main outcome measured was the plasma glucose incremental area under the curve. **Safety Measurements/Adverse Events Reported**: • It was reported that most participants tolerated the treatments well and no specific reports of adverse effects with allulose.	Noronha et al. (2018) and Braunstein et al. (2018)
Study Design: randomized, single-blind crossover design with a 1-week washout period **Study Length**: acute **Subjects**: n=13 healthy male and female subjects (mean age 35.7±2.1 years) **Dose, Delivery, and Frequency**: 5 g D-allulose, once per subject	**Outcome Measurements**: • At 30 minutes after taking 5 grams of D-allulose or 10 mg aspartate without sugar as a control, the overnight-fasted subjects ingested a standardized meal. The energy metabolism was evaluated by a breath-by-breath method. Blood was collected during the experiment and biochemical parameters were analyzed. **Safety Measurements/Adverse Events Reported**: • No adverse effects were reported.	Kimura et al. (2017)
Study Design: randomized double-blind, placebo-controlled parallel-group **Study Length**: single dose **Subjects**: n=26 randomly assigned to two groups; healthy male and female	**Outcome Measurements**: • Meal-loading experiment, single meal with a one-week washout • Each subject was given tea with test or control substance (aspartame) and a standard meal, after the one week they were given another sample of tea with the same standard meal. They were not allowed to eat or drink anything else until the next day.	Hayashi et al. (2010)

STUDY SETUP AND DETAILS	HUMAN STUDY RESULTS, SIGNIFICANCE, SAFETY	REFERENCE
subjects with fasting blood glucose levels between 100 - 126 mg/dL **Dose, Delivery, and Frequency**: 5 g D-psicose in tea three times daily with a meal	• Fasting blood was collected within 1 hour prior to the meal and then blood was collected at 30, 60, 90, and 120 minutes after the meal. Blood glucose level and insulin level were evaluated. **Safety Measurements/Adverse Events Reported**: No specific safety outcomes were included but no adverse effects reported.	
Study Design: randomized double-blind, parallel group **Study Length**: 12 weeks **Subjects**: n=18 randomized to 2 groups; healthy male and female subjects with fasting blood glucose levels below 110 mg/dL **Dose, Delivery, and Frequency**: 5 g D-psicose in tea three times daily with a meal	**Outcome Measurements**: • The study involved a 2-week observation period before starting the treatment and a 4-week observation period after the 12-week treatment period. Each subject consumed 5 g of either D-psicose or aspartame three times daily for 12 weeks. • Fasting morning urine and blood were collected 2 weeks before treatment, on the first day of treatment, 2, 4, 8, and 12 weeks after start of the treatment and 4 weeks after completing the treatment. • Physical examinations (height, body weight, body mass index, body fat percentage, waist circumference, systolic blood pressure, diastolic blood pressure and pulse rate), blood sample analysis (total protein, albumin, albumin, globulin ratio, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactase dehydrogenase, gamma glutamyl transpeptidase, cholinesterase, creatine phosphokinase, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, remnant-like particle cholesterol, triglyceride, free fatty acid, phospholipids, urea nitrogen, uric acid, creatinine, sodium, potassium, chlorine, calcium, inorganic phosphate, magnesium, serum amylase, glucose, insulin, glycoalbumin, white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and platelets), urine analysis (protein, glucose, urobilinogen, specific gravity and occult blood) and interviews were conducted on each examination day. • Body weight and percentage of body fate were determined as well as body mass index two weeks prior to the experiment. **Results and Significance**: • No abnormal effects or clinical problems were noted by the continuous ingestion of 15 g D-psicose/day for 12 weeks. **Safety Measurements/Adverse Events Reported**: • Subjects were examined throughout the study and no adverse effects were reported.	Hayashi et al. (2010)
Study Design: Crossover **Study Length**: acute	**Outcome Measurements**: • Study 1: Six subjects participated, they ingested either starch hydrolysate, D-psicose, or water alone at intervals of at least 1 week.	Iida et al. (2010)

STUDY SETUP AND DETAILS	HUMAN STUDY RESULTS, SIGNIFICANCE, SAFETY	REFERENCE
Subjects: n=21 healthy male and female subjects **Dose:** Study 1: D-psicose 0.35 g/kg bw once (20 g per subject); Studies 2 and 3: 20, 10, or 5 g D-psicose per subject; Study 4: 15 g D-psicose per subject per day	Subjects consumed an evening meal the day before the study and then did not consume any food or drink other than water from then to the completion of measurements. Respiratory exchange was measured shortly after ingestion for 180 minutes. Urine was collected at the end of the measurement. • Studies 2 and 3: Fourteen subjects participated in these two studies; FOS was used as a positive control. Subjects ingested either 20, 10, or 5 g of D-psicose or fructooligosaccharides (FOS) and no ingestion was used as a negative control. Each measurement was randomly performed at intervals of at least one week. Standard meals were given during the study at 4 and 8 hours after test sample ingestion. End expiratory gas was collected at 1-hour intervals for 10 hours. Urine was collected for 48 hours. • Study 4: Eight subjects participated and ingested 5 g of D-psicose three times daily for 8 weeks. End-expiratory gas collection was done on the first and last day of ingestion where they ingested 15 g of D-psicose before collection. **Results and Significance**: • Based on the results of the plot of breath hydrogen concentration versus the calories ingested, the energy value of D-psicose was expected to be less than 1.6 kJ/g. Incremental D-psicose fermentability subsequent to an adaptation period was not observed. **Safety Measurements/Adverse Events Reported**: • No adverse effects were reported	
Study Design: crossover; 1-week washout **Study Length:** acute **Subjects**: n=20; healthy male and female subjects (20-39 years) with fasting plasma glucose of 100 mg/100 mL or less **Dose, Delivery, and Frequency**: 7.5 g D-psicose once	**Outcome Measurements**: • Subjects took one of five test beverages (7.5 g D-psicose alone, 75 g maltodextrin alone, 75 g maltodextrin with either 2.5, 5, or 7.5 g D-psicose with a 1-week washout period between. The order of intake was randomly assigned. • The subjects were fasted for 12 hours, blood was collected, and then the subjects consumed the test beverage. Blood was again collected at 30, 60, 90, and 120 minutes after intake. Plasma glucose was determined for each timepoint. **Safety Measurements/Adverse Events Reported**: • No specific safety measurements were included in the study, but no adverse effects were reported.	Iida (2008)

bw – body weight; g – grams; LDL-C – low density lipoprotein cholesterol

C. 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 conditions of its intended use."[14]

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 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 in food prior to January 1, 1958."[15]

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:[16]

- 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.

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

[14] 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 6/03/19).

[15] See 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe (Accessed on 6/03/19).

[16] See Footnote 3.

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 FDA recognizes the impossibility of providing absolute safety in this or any other area (Renwick, 1990; Rulis and Levitt, 2009; Lu, 1988).

As noted below, this safety assessment to ascertain GRAS status for L&P’s D-allulose for the specified food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

D. Expert Panel Findings on Safety of D-Allulose

An evaluation of the safety and GRAS status of the intended use of L&P’s D-allulose preparation has been conducted by an Expert Panel convened by GRAS Associates; the Panel consisted of Dr. Katrina Emmel, Dr. Kara Lewis and Dr. Jack Budny. The Expert Panel reviewed L&P’s dossier as well as other publicly available information available to them. The individuals who served as Expert Panelists are qualified to evaluate the safety of foods and food ingredients by merit of scientific training and experience.

The GRAS Expert Panel report and qualifications are provided in Appendix 3.

E. 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 relevant studies reviewed on D-allulose, including animal toxicology studies and human clinical trials, have been published in the scientific literature. In addition, four previous GRNs: GRN 400, 498, 693, and 828, are available on FDA’s GRAS Notice Inventory website and have received “no questions” responses from the Agency. This GRAS evaluation satisfies the first common knowledge element, as the scientific information that is the basis of the GRAS determination for D-allulose is publicly available with the exception of one single dose acute mouse study on L&P’s D-allulose, which is not considered a pivotal study for the determination of safety.

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. L&P intends for D-allulose to be used as an ingredient in low calorie and/or dietetic foods as a sweetener, humectant and flavor modifier with the same proposed food applications and maximum use levels as that detailed in GRN 693. The population with the highest average consumption is estimated to be the >19-year-old males, with a mean and 90th percentile EDI, when the maximum intended use levels are used, of 13.0 g per day and 36.3 g per day, respectively. Children between the ages of 2 and 12 years are estimated to be the population with the highest mean and 90th percentile consumption on a g per kg bw per day basis and are estimated to be 0.19 and 0.50 g per kg bw per day, respectively. These doses are likely overestimations and do not present a safety concern to humans. Furthermore, these estimates are identical to those presented in GRN 693.

Four GRNs listed on FDA's GRAS Notice Inventory website: GRN 400, 498, 693, and 828 for D-allulose, allulose/psicose, D-allulose (D-psicose), and D-psicose, respectively, have received "no questions" responses from FDA. Three additional GRNs for similar products were withdrawn by the notifiers. Health Canada lists D-psicose in the Natural Health Products Ingredient Database as a non-medicinal ingredient on the New Ingredients list as of August 2015. EFSA and a number of other regulatory authorities around the world have not reviewed D-allulose/D-psicose; however, there are currently two pending applications filed for the approval of Allulose as a Novel Food Ingredient in the EU within the meaning of Article 10(1) of Regulation (EU) 2015/2283. D-Allulose 3-epimerase from *Arthrobacter globiformis* expressed in *Escherichia coli* is on the priority list of substances proposed for evaluation by the Joint Expert Committee on Food Additives (JECFA).

The metabolism and safety of D-allulose has been well studied and multiple animal studies, including acute, subchronic and chronic studies, were reviewed. The LD_{50} for D-allulose was determined to be 16.3 g per kg in rats and a single oral dose up to 4 g per kg bw did not induce severe toxicity signs in dogs. In a 90-day repeat dose study conducted in rats and in accordance with OECD guideline 408, the NOAEL for D-allulose was determined to be 5,000 mg per kg bw per day (An et al., 2019). The reproductive toxicity of D-allulose in rats was evaluated in an OECD guideline 415 study and the NOAEL for both the parental generation and the F1 offspring was determined to be 2,000 mg per kg bw per day, the highest dose tested (Kim et al., 2019). In addition, multiple reviews and published studies in humans conclude that D-allulose is safe for human consumption. Chung et al. (2012) summarized the properties, absorption, and excretion of D-psicose as well as the potential benefits and safety and concluded that it is "relatively nontoxic". A study by Iida (2007) referenced in GRN 693, demonstrated that D-allulose is safe to ingest at 0.5 – 0.6 g per kg bw as a single dose, while a more recent study by Han et al. (2018a) recommended that the maximum single dose of D-allulose should be 0.4 g per kg bw and the maximum total daily intake of D-allulose should be 0.9 g per kg bw. These

levels are well above the expected mean and 90th percentile consumption of L&P's D-allulose at the intended use levels.

L&P maintains that well-qualified scientists would conclude that L&P's D-allulose is generally recognized as safe for use in food given the regulatory and safety data available and using well accepted toxicological principles.

F. Conclusion

L&P intends to add its D-allulose as an ingredient in low calorie and/or dietetic foods to act as a sweetener, humectant, and flavor modifier with the same proposed food applications and maximum use levels as those detailed in GRN 693. The population with the highest average consumption would have a mean and 90th percentile EDI, when the maximum intended use levels are used, of 13.0 g per day and 36.3 g per day, respectively. Children between the ages of 2 and 12 years are estimated to be the population with the highest mean and 90th percentile consumption on a g per kg bw per day basis and is estimated to be 0.19 and 0.50 g per kg bw per day, respectively. This dose does not present a safety concern to humans and is identical to the dose presented in GRN 693.

In consideration of the aggregate safety information available on D-allulose, L&P concludes that L&P's D-allulose, as defined in the subject notification, produced in accordance with FDA Current Good Manufacturing Practices, and when consumed in foods as described within this GRAS Notification, is safe for use in conventional foods.

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 as described in this dossier and, therefore, is generally recognized as safe (GRAS) within the meaning of the Food, Drug, and Cosmetic Act.

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

A. List of Acronyms and References

1. List of Acronyms

µg	Microgram
AESAN	Spanish Agency for Food Safety and Nutrition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AOAC	Association of Official Agricultural Chemists
aq	Aqueous
AST	Aspartate aminotransferase
bw	Body Weight
C	Celsius
CFR	Code of Federal Regulations
cfu	Colony Forming Unit
CGMP	Current Good Manufacturing Practice
COA	Certificate of Analysis
dL	Deciliter
DVFA	Danish Veterinary and Food Administration
EDI	Estimated daily intake
EFSA	European Food Safety Authority
EU	European Union
FD&C Act	Federal Food Drug and Cosmetics Act
FDA	Food and Drug Administration
FOS	Fructooligosaccharide
FSCJ	Food Safety Commission of Japan
g	Gram
GA	GRAS Associates
GI	Gastrointestinal
GRAS	Generally Recognized as Safe
GRN	GRAS Notification
HPLC	High-Performance Liquid Chromatography
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kJ	Kilojoules
LD_{50}	Median (50%) lethal dose
LETO	Long-Evans Tokushima Otsua
LLC	Limited Liability Corporation
mg/kg	Milligram per kilogram
mL	Milliliter
MPN	Most probable number
MRI	Magnetic resonance imaging
n	number
N/A	Not applicable/not reported
NHANES	National Health and Nutrition Examination Surveys
NR	Not reported
OLETF	Otsuka Long-Evans Tokushima Fatty
PCR	Polymerase chain reaction
ppm	Parts per million
SCFA	Short chain fatty acids
VKM	Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet)

wt/wt weight/weight

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B. Appendices

Appendix 1 Nutritional Analysis Report for D-Allulose

L&P Food Ingredient Co., Ltd.

Nutritional Analysis

I. General Information

Name	D-Allulose
Lot Number	DA-P-18051501
Manufacture Date	2018 May 15th
Test Date	2018 May 28th – 2018 Jun 8th
Storage Conditions	Cool, dry, damp-proof, avoid light
Manufacturer	L&P Food Ingredient Co., Ltd.
Test Executor	Quality Department of L&P Food Ingredient Co., Ltd.

II. Result

Parameter	Unit	Result	Analytical Method
Protein	g/100g	< 0.05	Kjeidahl
Total Fat	g/100g	0.2	Soxhlet Extraction
Cholesterol	mg/100g	Negative	Gas Chromatography
Carbohydrate	g/100g	99.5	By Different
Insoluble fiber	g/100g	< 0.05	Enzymatic Gravimetric
Sodium	mg/100g	< 3	AAS

Director of Quality Department:

Address: Wengcheng Industrial Park, Wengcheng Town, Wengyuan County, Shaoguan, Guangdong, P.R.China
Website: http://www.lpfoods-wy.com/ Tel: +86 (0751) 2882102

Appendix 2 Shelf Life Report and Calculations

Guangye L&P Food Ingredient Co., Ltd.

Shelf-life Report of D-Allulose

1. Basic Information

Sample Specification					
Name	D-Allulose				
Lot Number	DA-S-18020601				
Character	White to light yellow, powder				
Packaging	Aluminum foil, airtight				
Experiment Description					
Experiment Type	Accelerating Test				
Temperature (℃)	Experiment Period	Total Time (day)	Time Interval (day)	Indicator	Result
35	Mar 5, 2018 to Oct 31, 2018	240	10	Sensory, Physical and Chemical, Microbiology	Sample remained stable through the total experiment.
45	Mar 5, 2018 to May 19, 2018	75	5	Sensory, Physical and Chemical, Microbiology	Sample remained stable until the 75th day.

2. Shelf-life Calculation

Given:

Shelf-life under higher temperature: 75 days

Theoretical room temperature: 25 ℃

Q_{10} is the ratio of shelf-life under 2 temperatures which are 10 ℃ different from each other.

Calculations:

Hypothesizing shelf-life under temperature T is f_T

According to formula:

$$f_{T_1} = f_{T_2} \times Q_{10}^{\frac{\Delta T}{10}}$$

Where, $T_1 < T_2$. $\Delta T = T_2 - T_1$

The theoretical Q_{10} and shelf-life would be:

$$Q_{10} = \sqrt[\frac{\Delta T}{10}]{f_{T_1} \div f_{T_2}} = \sqrt[\frac{45-35}{10}]{f_{35} \div f_{45}} = 240 \div 75 = 3.2$$

$$f_{25} = f_{45} \times Q_{10}^{\frac{(45-25)}{10}} = 75 \times 3.2^2 = 768\ days = 25.6\ months \approx 2\text{years}$$

3. Conclusion

When preserved hermetically and away from light under room temperature, aluminum foil-packaged D-allulose theoretically has 2 years shelf-life.

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Guangye L&P Food Ingredient Co., Ltd.

D-Allulose Stability Experiment Record

Sample Lot Number: DA-S-18020601
Temperature: 35℃
Test Start Date: 2018.3.5

Checklist and Results

Inspection Date	Inspection Time	Time Interval (day)	Package Sealing	Sensory Index			Physical and Chemical Indicators			Microbiology Index		
				Form Condition	Color	Odor	Content of D-Allulose	Content of Fructose and Other Sugars	pH	Bacteria Count (cfu/g)	E. Coli (M PN/g)	Mold/Yeast (cfu/g)
Standard Criteria	-	-	Intact	Powder	White to light yellow	No special odor	≥ 98.5%	≤ 1.5%	3.0 - 7.0	Not detectable	Not detectable	Not detectable
2018.3.5	14:00	-	√	√	√	√	99.00%	0.50%	5.36	√	√	√
2018.3.15	14:00	10	√	√	√	√	98.90%	0.60%	5.42	√	√	√
2018.3.25	14:00	10	√	√	√	√	99.10%	0.40%	5.44	√	√	√
2018.4.4	14:00	10	√	√	√	√	98.90%	0.40%	5.38	√	√	√
2018.4.14	14:00	10	√	√	√	√	99.10%	0.60%	5.30	√	√	√
2018.4.24	14:00	10	√	√	√	√	98.90%	0.60%	5.43	√	√	√
2018.5.4	14:00	10	√	√	√	√	99.00%	0.50%	5.36	√	√	√
2018.5.14	14:00	10	√	√	√	√	99.00%	0.50%	5.41	√	√	√
2018.5.24	14:00	10	√	√	√	√	99.10%	0.40%	5.33	√	√	√
2018.6.3	14:00	10	√	√	√	√	98.90%	0.60%	5.39	√	√	√

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2018.6.13	14:00	10	√	√	√	√	99.00%	0.50%	5.30	√	√	√
2018.6.23	14:00	10	√	√	√	√	99.10%	0.40%	5.42	√	√	√
2018.7.3	14:00	10	√	√	√	√	99.10%	0.60%	5.33	√	√	√
2018.7.13	14:00	10	√	√	√	√	99.00%	0.50%	5.38	√	√	√
2018.7.23	14:00	10	√	√	√	√	99.00%	0.50%	5.29	√	√	√
2018.8.2	14:00	10	√	√	√	√	99.10%	0.40%	5.34	√	√	√
2018.8.12	14:00	10	√	√	√	√	99.00%	0.50%	5.37	√	√	√
2018.8.22	14:00	10	√	√	√	√	98.90%	0.40%	5.32	√	√	√
2018.9.1	14:00	10	√	√	√	√	99.10%	0.40%	5.40	√	√	√
2018.9.11	14:00	10	√	√	√	√	98.90%	0.60%	5.33	√	√	√
2018.9.21	14:00	10	√	√	√	√	99.00%	0.50%	5.31	√	√	√
2018.10.1	14:00	10	√	√	√	√	99.10%	0.40%	5.43	√	√	√
2018.10.11	14:00	10	√	√	√	√	99.00%	0.50%	5.38	√	√	√
2018.10.21	14:00	10	√	√	√	√	99.10%	0.60%	5.31	√	√	√
2018.10.31	14:00	10	√	√	√	√	98.90%	0.50%	5.42	√	√	√

*: All indicators were checked every 10 days.

Guangye L&P Food Ingredient Co., Ltd.

D-Allulose Stability Experiment Record

Sample Lot Number: DA-S-18020601
Temperature: 45℃
Test Start Date: 2018.3.5

Checklist and Results

Inspection Date	Inspection Time	Time Interval (day)	Package Sealing	Sensory Index			Physical and Chemical Index			Microbiology Index		
				Form Condition	Color	Odor	Content of D-Allulose	Content of Fructose and Other Sugars	pH	Bacteria Count (cfu/g)	E. Coli (M PN/g)	Mold/Yeast (cfu/g)
Standard Criteria	-	-	Intact	Powder	White to light yellow	No special odor	≥ 98.5%	≤ 1.5%	3.0 - 7.0	Not detectable	Not detectable	Not detectable
2018.3.5	14:00	---	√	√	√	√	98.90%	0.60%	5.32	-	-	-
2018.3.10	14:00	5	√	√	√	√	99.10%	0.40%	5.44	√	√	√
2018.3.15	14:00	5	√	√	√	√	98.90%	0.60%	5.36	-	-	-
2018.3.20	14:00	5	√	√	√	√	99.10%	0.40%	5.38	√	√	√
2018.3.25	14:00	5	√	√	√	√	98.90%	0.60%	5.43	-	-	-
2018.3.30	14:00	5	√	√	√	√	99.00%	0.50%	5.37	√	√	√
2018.4.4	14:00	5	√	√	√	√	99.00%	0.50%	5.33	-	-	-
2018.4.9	14:00	5	√	√	√	√	99.10%	0.40%	5.32	√	√	√
2018.4.14	14:00	5	√	√	√	√	98.90%	0.60%	5.35	-	-	-

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2018.4.19	14:00	5	√	√	√	√	99.10%	0.40%	5.43	√	√	√
2018.4.24	14:00	5	√	√	√	√	98.90%	0.60%	5.41	-	-	-
2018.4.29	14:00	5	√	√	√	√	99.00%	0.50%	5.39	√	√	√
2018.5.4	14:00	5	√	√	√	√	99.10%	0.40%	5.31	-	-	-
2018.5.9	14:00	5	√	√	√	√	99.00%	0.50%	5.34	√	√	√
2018.5.14	14:00	5	√	√	√	√	99.10%	0.40%	5.42	-	-	-
2018.5.19	14:00	5	√	√	√	unpleasant odor	98.90%	0.60%	5.43	√	√	√

*: Sensory and Physical and Chemical indicators were checked every 5 days, while Microbiology indicators were checked every 10 days.

Guangye L&P Food Ingredient Co., Ltd.

Shelf-life Report of D-Allulose (syrup)

1. Basic Information

Sample Specification					
Name	D-Allulose (syrup)				
Lot Number	DA-L-18021001				
Character	Pale yellow, liquid, no special odor				
Packaging	Transparent PETE bottle, sealed				
Experiment Description					
Experiment Type	Accelerating Test				
Temperature (℃)	Experiment Period	Total Time (day)	Time Interval (day)	Indicator	Result
35	Mar 5, 2018 to Oct 31, 2018	240	10	Sensory, Physical and Chemical, Microbiology	Sample remained stable through the total experiment.
45	Mar 5, 2018 to May 19, 2018	75	5	Sensory, Physical and Chemical, Microbiology	Sample remained stable until the 75th day.

2. Shelf-life Calculation

Given:

Shelf-life under higher temperature: 75 days

Theoretical room temperature: 25 ℃

Q_{10} is the ratio of shelf-life under 2 temperatures which are 10 ℃ different from each other.

Calculations:

Hypothesizing shelf-life under temperature T is f_T

According to formula:

$$f_{T_1} = f_{T_2} \times Q_{10}^{\frac{\Delta T}{10}}$$

Where, $T_1 < T_2$. $\Delta T = T_2 - T_1$

The theoretical Q_{10} and shelf-life would be:

$$Q_{10} = \sqrt[\frac{\Delta T}{10}]{f_{T_1} \div f_{T_2}} = \sqrt[\frac{45-35}{10}]{f_{35} \div f_{45}} = 240 \div 75 = 3.2$$

$$f_{25} = f_{45} \times Q_{10}^{\frac{(45-25)}{10}} = 75 \times 3.2^2 = 768\ days = 25.6\ months \approx 2\text{years}$$

3. Conclusion

When preserved hermetically and away from light under room temperature, D-allulose syrup in sealed PETE bottle theoretically has 2 years shelf-life.

Guangye L&P Food Ingredient Co., Ltd.

D-Allulose (syrup) Stability Experiment Record

Sample Lot Number: DA-L-18021001
Temperature: 35℃
Test Start Date: 2018.3.5

Checklist and Results

Inspection Date	Inspection Time	Time Interval (day)	Package Sealing	Sensory Index			Physical and Chemical Indicators			Microbiology Index		
				Form Condition	Color	Odor	Content of D-Allulose	Content of Fructose and Other Sugars	pH	Bacteria Count (cfu/g)	E. Coli (M PN/g)	Mold/Yeast (cfu/g)
Standard Criteria	-	-	Intact	Liquid	Pale yellow	No special odor	≥ 70.0%	≤ 2.0%	3.0 - 7.0	Not detectable	Not detectable	Not detectable
2018.3.5	14:00	---	√	√	√	√	71.10%	1.40%	4.52	√	√	√
2018.3.15	14:00	10	√	√	√	√	71.00%	1.50%	4.59	√	√	√
2018.3.25	14:00	10	√	√	√	√	71.20%	1.40%	4.49	√	√	√
2018.4.4	14:00	10	√	√	√	√	71.10%	1.30%	4.44	√	√	√
2018.4.14	14:00	10	√	√	√	√	71.20%	1.50%	4.52	√	√	√
2018.4.24	14:00	10	√	√	√	√	71.00%	1.30%	4.58	√	√	√
2018.5.4	14:00	10	√	√	√	√	71.10%	1.40%	4.46	√	√	√
2018.5.14	14:00	10	√	√	√	√	71.10%	1.40%	4.51	√	√	√
2018.5.24	14:00	10	√	√	√	√	71.20%	1.30%	4.43	√	√	√
2018.6.3	14:00	10	√	√	√	√	71.00%	1.50%	4.47	√	√	√

2018.6.13	14:00	10	√	√	√	√	71.20%	1.30%	4.55	√	√	√
2018.6.23	14:00	10	√	√	√	√	71.10%	1.40%	4.50	√	√	√
2018.7.3	14:00	10	√	√	√	√	71.20%	1.50%	4.48	√	√	√
2018.7.13	14:00	10	√	√	√	√	71.00%	1.40%	4.56	√	√	√
2018.7.23	14:00	10	√	√	√	√	71.10%	1.40%	4.49	√	√	√
2018.8.2	14:00	10	√	√	√	√	71.10%	1.30%	4.52	√	√	√
2018.8.12	14:00	10	√	√	√	√	71.20%	1.40%	4.57	√	√	√
2018.8.22	14:00	10	√	√	√	√	71.00%	1.30%	4.56	√	√	√
2018.9.1	14:00	10	√	√	√	√	71.20%	1.50%	4.51	√	√	√
2018.9.11	14:00	10	√	√	√	√	71.10%	1.50%	4.47	√	√	√
2018.9.21	14:00	10	√	√	√	√	71.20%	1.40%	4.53	√	√	√
2018.10.1	14:00	10	√	√	√	√	71.00%	1.30%	4.52	√	√	√
2018.10.11	14:00	10	√	√	√	√	71.10%	1.40%	4.48	√	√	√
2018.10.21	14:00	10	√	√	√	√	71.20%	1.30%	4.45	√	√	√
2018.10.31	14:00	10	√	√	√	√	71.20%	1.30%	4.51	√	√	√

*: All indicators were checked every 10 days.

Guangye L&P Food Ingredient Co., Ltd.

D-Allulose (syrup) Stability Experiment Record

Sample Lot Number: DA-L-18021001
Temperature: 45℃
Test Start Date: 2018.3.5

Checklist and Results

Inspection Date	Inspection Time	Time Interval (day)	Package Sealing	Sensory Index			Physical and Chemical Index			Microbiology Index		
				Form Condition	Color	Odor	Content of D-Allulose	Content of Fructose and Other Sugars	pH	Bacteria Count (cfu/g)	E. Coli (M PN/g)	Mold/Yeast (cfu/g)
Standard Criteria	-	-	Intact	Liquid	Pale yellow	No special odor	≥70.0%	≤2.0%	3.0 - 7.0	Not detectable	Not detectable	Not detectable
2018.3.5	14:00	---	√	√	√	√	71.10%	1.50%	5.35	-	-	-
2018.3.10	14:00	5	√	√	√	√	71.00%	1.40%	5.38	√	√	√
2018.3.15	14:00	5	√	√	√	√	71.20%	1.40%	5.42	-	-	-
2018.3.20	14:00	5	√	√	√	√	71.00%	1.30%	5.37	√	√	√
2018.3.25	14:00	5	√	√	√	√	71.20%	1.50%	5.32	-	-	-
2018.3.30	14:00	5	√	√	√	√	71.10%	1.50%	5.42	√	√	√
2018.4.4	14:00	5	√	√	√	√	71.10%	1.30%	5.35	-	-	-
2018.4.9	14:00	5	√	√	√	√	71.20%	1.40%	5.36	√	√	√
2018.4.14	14:00	5	√	√	√	√	71.00%	1.30%	5.35	-	-	-

2018.4.19	14:00	5	√	√	√	√	71.20%	1.50%	5.41	√	√	√
2018.4.24	14:00	5	√	√	√	√	71.10%	1.50%	5.40	-	-	-
2018.4.29	14:00	5	√	√	√	√	71.00%	1.30%	5.37	√	√	√
2018.5.4	14:00	5	√	√	√	√	71.10%	1.50%	5.42	-	-	-
2018.5.9	14:00	5	√	√	√	√	71.20%	1.50%	5.39	√	√	√
2018.5.14	14:00	5	√	√	√	√	71.10%	1.40%	5.44	-	-	-
2018.5.19	14:00	5	√	√	√	unpleasant odor	71.00%	1.50%	5.35	√	√	√

*: Sensory and Physical and Chemical indicators were checked every 5 days, while Microbiology indicators were checked every 10 days.

Appendix 3 GRAS Associates Expert Panel Report

GRAS ASSOCIATES, LLC

11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF THE PROPOSED USES OF WENGYUAN GUANGYE L&P FOOD INGREDIENT CO., LTD'S D-ALLULOSE

May 10, 2021

Foreword

An independent panel of experts ("Expert Panel") was convened by GRAS Associates, LLC on behalf of their client, Wengyuan Guangye L&P Food Ingredient Co., Ltd ("L&P"), a subsidiary of Guangye L&P Food Ingredient Co., Ltd., to evaluate the safety and Generally Recognized as Safe (GRAS) status of L&P's proposed uses of D-allulose syrup and D-allulose (crystalline) preparations in conventional foods. The members of this Expert Panel† are qualified to serve in this capacity by their scientific training and experience in the safety of food and food ingredients.

Discussion

A significant amount of safety information related to the consumption of D-allulose is generally available, and has been discussed in Part 6 of L&P's D-allulose GRAS dossier. First, there is a history of safe consumption of D-allulose when used as an ingredient in food products in the US, Japan, and Korea. Second, a number of experimental studies have investigated the safety of D-allulose. The composite evidence from historical safe consumption and experimental studies demonstrates the safety of D-allulose preparations for human food consumption.

The majority of studies reviewed on D-allulose (syn. D-psicose) have been discussed in detail in previous GRAS Notices (GRNs) that received "no questions" letters from FDA: GRN 400, GRN 498, GRN 693, and GRN 828.

With regard to the safety documentation, the key pharmacokinetic data presented by Tsukamoto (2014) establish that D-allulose is absorbed in the small intestine and then rapidly excreted in the urine. The liver was noted to be the only organ with D-allulose accumulation following oral and intravenous administration. No pathology linked to liver concentration has been reported. Rapid excretion of D-allulose was confirmed by Matsuo (2003), who concluded that D-allulose is partially absorbed in the digestive tract and rapidly excreted in the urine and feces. In addition, the presence of short chain fatty acids in the cecum indicate that D-allulose is a fermentable saccharide.

† Dr. Emmel, Chair of the Expert Panel, is a chemist with substantial food safety experience in addressing steviol glycosides and other food ingredients. Dr. Lewis is a biologist with more than 10 years of experience preparing GRAS dossiers. Dr. Budny is a toxicologist with over 50 years of experience in human health risk assessments for a wide variety of product types and usages, and ,specifically in this instance, in food, nutrition, nutraceuticals, and artificial sweeteners. All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety and in participating in deliberations of GRAS Expert Panels.

The median lethal dose (LD_{50}) of D-allulose was determined to be 16.3 g per kg body weight (bw) in rats (Matsuo, 2002). A 90-day repeat dose study conducted by An et al. (2019) in male and female Sprague-Dawley rats determined the No Observed Adverse Effect Level (NOAEL) for D-allulose to be 5,000 mg per kg bw per day. Previous studies by Yagi and Matsuo (2009) and Matsuo et al. (2012) determined the NOAEL of D-allulose to be 3% of the diet (equivalent to 1,280 mg D-allulose per kg bw day) in male Wistar rats.

D-allulose was not observed to cause any adverse effects in healthy dogs when administered as a single dose at 1 or 4 g per kg or administered at 200 mg per kg bw per day for 12 weeks (Nishii et al., 2016, 2017).

Kim et al. (2019) investigated the reproductive toxicity of D-allulose in an unspecified strain of rats. No treatment-linked toxicity, mortality, or adverse effects on reproduction were observed. The authors determined the NOAEL to be 2,000 mg per kg bw per day for the parental and offspring generations.

Genotoxicity and mutagenicity studies reviewed in GRN 400 indicate that D-allulose is not mutagenic at levels of up to 5,000 μg per plate in an Ames study, no significant increase in micronucleated polychromatic erythrocytes was noted at levels of up to 2,000 mg per kg per day in a micronucleus test, and no significant increase in the number of chromosomal aberrations was observed at 1,800 μg per mL.

Numerous studies did not detect any adverse effects in humans with doses as much as 15 g total intake for as many as 48 weeks. Products with as much as 30.0 g per person per day allulose have been in commercial commerce for as many as four years without any causal connections to adverse health effects. Furthermore, Han et al. (2018) recently recommended a maximum single dose of 0.4 g per kg bw D-allulose and a maximum total daily intake of 0.9 g per kg bw of D-allulose, as transient gastrointestinal discomfort, including severe nausea, abdominal pain, headache, anorexia, and diarrhea, is reported when total daily intake approaches 1.0 g per kg bw.

L&P states in their GRAS dossier that their D-allulose preparation is intended to be used as a sweetener, humectant, and flavor modifier in the same food products and at proportional use levels to those presented in GRNs 400, 498, 693, and 828. L&P notes that their estimated daily intake (EDI) assessment for their D-allulose is identical to the EDI assessment detailed in GRN 693 and duplicated in GRN 828. L&P notes that their D-allulose is expected to share the current market and would not contribute to additional intake in excess of the EDIs determined in GRN 693 and that the assessment remains valid as the consumption patterns are unlikely to have change significantly since the EDI was determined using data from the 2007-2010 National Health and Nutrition Examination Survey (NHANES). FDA issued “no questions” letters in response to GRN 693 and GRN 828.

The GRAS Associates Expert Panel convened on behalf of L&P reviewed the proposed uses for D-allulose as an ingredient in low-calorie or dietetic foods. The highest 90th percentile per person per day consumption by any population subgroup of D-allulose, based upon the proposed maximum intended use levels, was calculated to be 36.3 g per day for >19-year-old males, which

is equivalent to 0.39 mg per kg bw per day. The highest 90th percentile consumption by any population subgroup on a gram per kg bw per day basis is 0.50 g per kg bw per day for children ages 2 to 12 years. The mean EDIs for >19-year-old males and children ages 2 to 12 years are 0.14 and 0.19 g per kg bw per day, respectively.

The EDIs are well below the maximum single dose and total daily intake levels recommended by Han et al. (2018). In addition, the Expert Panel agrees with L&P's assessment that it is unlikely that D-allulose will be used at the maximum levels in all food categories and that a consumer would ingest products from all categories on a daily basis. Therefore, D-allulose preparations are expected to be safe within established allowable limits.

L&P's states that their D-allulose is manufactured with raw materials and processing aids that comply with applicable US federal regulations and are of appropriate purity for food manufacturing purposes. Supporting documentation for these claims were not included in the dossier. The Expert Panel notes that only D-allulose derived from materials that meet US federal regulations are GRAS.

L&P's manufacturing process utilizes D-allulose 3-epimerase produced by *Bacillus subtilis* 168 to produce D-allulose from neutralized fructose syrup. *B. subtilis* 168 is a Gram-positive, nonpathogenic, and nontoxigenic strain of bacteria that has a long history of safe use in food manufacturing applications. L&P states that the *B. subtilis* 168 strain used is not genetically modified and has not been modified to produce D-allulose 3-epimerase in excess. The Expert Panel notes that L&P uses a calcium alginate gel bead immobilized cell system for the enzymatic-conversion process; therefore, there is little chance for the presence of enzyme or *B. subtilis* 168 in the finished product.

L&P states that D-allulose is manufactured under Current Good Manufacturing Practices (CGMP) and it has been demonstrated that their preparations consistently yield reproducible product results, as detailed in Tables 6 and 7 of the GRAS dossier. The specifications for D-allulose are consistent with industry-established parameters and values, and are appropriate and sufficient for an ingredient intended for human consumption. Furthermore, the specifications for L&P's D-allulose syrup and D-allulose (crystalline) are substantially equivalent to those described in GRNs 693 and 828, respectively, which received "no questions" letters from FDA.

Conclusion

In summary, sufficient qualitative and quantitative scientific evidence in the composite is available to support the safety-in-use of L&P's D-allulose preparations given the following conditions:

- L&P's D-allulose preparations continue to meet the designated specifications;
- The proposed uses and use levels of L&P's D-allulose remain unchanged; and
- L&P's D-allulose preparations are produced in accordance with Current Good Manufacturing Practices (CGMPs) using raw materials and processing aids that comply with applicable US federal regulations and are of appropriate purity for food manufacturing purposes.

The Expert Panel critically reviewed the data provided by L&P for their D-allulose preparations, as well as publicly available published information obtained from peer-reviewed journals and other safety assessments prepared by other Expert Panels and well-respected international regulatory bodies.

The ingestion of L&P's D-allulose preparations from the intended uses results in intakes that are expected to be safe within the limits of established historical use and published safety studies. The Expert Panel notes that the per body weight doses in the Matsuo (2002) study are significantly higher than those anticipated from L&P's intended uses and use levels for their D-allulose preparation.

The Expert Panel unanimously concluded that the proposed uses of L&P's D-allulose preparations, manufactured under GMP standards using raw materials and processing aids in compliance with applicable US federal regulations and as described in Part 2.b. of L&P's GRAS dossier , and declared within the subject assessment meets the FDA definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein, and L&P's D-allulose syrup and D-allulose (crystalline) preparations are generally recognized as safe (GRAS).

John A. Budny, MBA, Ph.D. Kara Lewis, Ph.D. Katrina V. Emmel, Ph.D.
Panel Chair

References

An, M., Lee, J., Park, Y. C., Park, C. and Kim, H. J. (2019) '90-Day repeated oral toxicity test of D-allulose produced from Microbacterium foliorum', Regul Toxicol Pharmacol, pp. 104485.

Han, Y., Choi, B. R., Kim, S. Y., Kim, S. B., Kim, Y. H., Kwon, E. Y. and Choi, M. S. (2018) 'Gastrointestinal Tolerance of D-Allulose in Healthy and Young Adults. A Non-Randomized Controlled Trial', Nutrients, 10(12).

Kim, H., Park, C., Sa, S., Case, I., Li, C., Gao, Y., Wang, H. and Tian, J. (2019) 'A study of D-allulose-associated reproductive toxicity in rats', Food Chem Toxicol, 131, pp. 110548.

Matsuo, T., Ishii, R., Shirai, Y. (2012) 'The 90-day oral toxicity of d-psicose in male Wistar rats', J Clin Biochem Nutr, 50(2), pp. 158-61.

Matsuo, T., Tanaka, T., Hashiguchi, M., Izumori, K., Suzuki, H. (2002) 'Effects of Oral Acute Administration and Subchronic Feeding of Several Levels of D-Psicose in Rats', J Nutr Sci Vitaminol (Tokyo), 48, pp. 512-516.

Matsuo, T., Tanaka, T., Hashiguchi, M., Izumori, K., Suzuki, H. (2003) 'Metabolic effects of D-psicose in rats: studies on faecal and urinary excretion and caecal fermentation', Asia Pacific J Clin Nutr, 12(2), pp. 225-231.

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Nishii, N., Takashima, S., Kobatake, Y., Tokuda, M. and Kitagawa, H. (2017) 'The long-term safety of D-allulose administration in healthy dogs', J Vet Med Sci, 79(11), pp. 1780-1784.

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. (2014) 'Intestinal absorption, organ distribution, and urinary excretion of the rare sugar D-psicose', Drug Design, Development and Therapy, 8, pp. 1955-1964.

Yagi, K. and Matsuo, T. (2009) 'The study on long-term toxicity of d-psicose in rats', J Clin Biochem Nutr, 45(3), pp. 271-7.

END

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE (Subpart E of Part 170)

Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022
(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,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – 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)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: _____

4 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)*: _____

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Sanyong Wang	Chairman of the Board, Guangye L&P Food Ingred

Organization *(if applicable)*: L&P Food Ingredient Co., Ltd

Mailing Address *(number and street)*: Wengcheng Industrial Park

City	State or Province	Zip Code/Postal Code	Country
Wengchen Town, Wenyuan County	Shaoguan, Guangdong	512627	China

Telephone Number	Fax Number	E-Mail Address
+86 20 84215975		

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position or Title
William Rowe	President

Organization *(if applicable)*: GRAS Associates, LLC

Mailing Address *(number and street)*: 11810 Grand Park Avenue Suite 500

City	State or Province	Zip Code/Postal Code	Country
North Bethesda	Maryland	20852	United States of America

Telephone Number	Fax Number	E-Mail Address
519-341-3667	1-888-531-3466	wrowe@nutrasource.com

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

D-allulose (also known as D-psicose)

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

☐ Electronic Submission Gateway

☒ Electronic files on physical media

☐ 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 CFSAN's files? *(Check one)*

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

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

☐ a) GRAS Notice No. GRN _____

☐ 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 conclusions of GRAS status *(Check one)*

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

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8) and 170.250(d) and (e))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

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, 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

SECTION D – INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

D-allulose (also known as D-psicose) is intended for use as an ingredient in low-calorie or dietetic foods in a variety of applications as discussed in Part 3.A.2 of the GRAS dossier. The proposed uses do not include infant formulas or meat and poultry products.

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☒ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☐ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete – PART 1 is addressed in other sections of this form)

☒ PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).

☒ PART 3 of a GRAS notice: Dietary exposure (170.235).

☒ PART 4 of a GRAS notice: Self-limiting levels of use (170.240).

☒ PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).

☒ PART 6 of a GRAS notice: Narrative (170.250).

☒ PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

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

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that Sanyong Wang
(name of notifier)

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

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. Sanyong Wang agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; 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; agrees to send these data and information to FDA if FDA asks to do so.
(name of notifier)

Wengcheng Industrial Park, Wengchen Town, Wenyuan County, Shaoguan, Guangdong 512627, P.R. China
(address of notifier or other location)

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
Amy Mozingo Digitally signed by Amy Mozingo Date: 2021.09.08 14:14:35 -04'00'	Amy Mozingo on behalf of William J. Rowe, President	09/08/2021

SECTION G – 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)
	Appendices 1-3 in the body of the dossier.	

Viebrock, Lauren

From: Amy Mozingo <amozingo@gras-associates.com>
Sent: Tuesday, June 7, 2022 12:06 PM
To: Viebrock, Lauren
Cc: William J. Rowe
Subject: RE: [EXTERNAL] RE: Acknowledgement of filing of GRAS Notice No. GRN 001029
Attachments: GRN 001029_Supplement_Updated Intake Analysis_07June2022.pdf

Dear Lauren,
Please find attached an updated intake analysis supplement to GRN 001029.
Best Regards,
Amy
Amy Mozingo, MS
VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
O: 301-461-8929| C: 772-532-3454

LinkedIn | Twitter | Blog

From: Amy Mozingo
Sent: Tuesday, May 24, 2022 3:47 PM
To: 'Viebrock, Lauren' <Lauren.Viebrock@fda.hhs.gov>
Cc: William J. Rowe <wrowe@nutrasource.ca>
Subject: RE: [EXTERNAL] RE: Acknowledgement of filing of GRAS Notice No. GRN 001029

Hi Lauren,
Thank you very much and we will return on the intake analysis within 10-days.
Regards
Amy

Amy Mozingo, MS

VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
O: 301-461-8929| C: 772-532-3454

LinkedIn | Twitter | Blog

From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Sent: Tuesday, May 24, 2022 3:43 PM
To: Amy Mozingo <amozingo@gras-associates.com>
Cc: William J. Rowe <wrowe@nutrasource.ca>
Subject: RE: [EXTERNAL] RE: Acknowledgement of filing of GRAS Notice No. GRN 001029

Hi Amy,

Thank you for the correct email address. We understand the previous emails were not received and can accommodate an extension for the response to our question. Thanks.

Best,
Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 301-796-7454
lauren.viebrock@fda.hhs.gov

From: Amy Mozingo <amozingo@gras-associates.com>
Sent: Tuesday, May 24, 2022 3:36 PM
To: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>

Cc: William J. Rowe <wrowe@nutrasource.ca>
Subject: [EXTERNAL] RE: Acknowledgement of filing of GRAS Notice No. GRN 001029

Hi Lauren,
Will Rowe's email is wrowe@nutrasource.ca not .com. Therefore we did not receive this filing letter.
Apologies if the incorrect email was included into the notice paperwork.
Thank you for providing this as well as the question posed in your email of May 5th requesting a 10 business day turnaround on the question related to the request for an updated intake analysis. We respectfully request an extension as we just are now aware of this request.
Regards,
Amy

Amy Mozingo, MS
VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
O: 301-461-8929| C: 772-532-3454

LinkedIn | Twitter | Blog

From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Sent: Tuesday, May 24, 2022 2:04 PM
To: Amy Mozingo <amozingo@gras-associates.com>
Subject: FW: Acknowledgement of filing of GRAS Notice No. GRN 001029

From: Viebrock, Lauren
Sent: Tuesday, March 8, 2022 3:22 PM
To: WRowe@nutrasource.com
Subject: Acknowledgement of filing of GRAS Notice No. GRN 001029

Dear Mr. Rowe,

Attached to this email, please find the acknowledgement letter for filing of the GRAS notice you submitted to our office, which has been designated as GRAS Notice No. GRN 001029.

Please let me know if you have any questions.

Regards,
Lauren VieBrock

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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GRN 001029- Supplement- Updated Estimated Daily Intake Estimates

Introduction

This supplement to GRAS Notice No. 001029 provides updated estimated daily intakes of allulose among the U.S. population from the proposed uses as described in GRN 001029.

Methods

The dietary exposure distributions were calculated using the Creme Food Safety® model[i], a scientific cloud-based software service designed and developed to calculate dietary intakes of foods, chemicals, and nutrients in populations of consumers. This is achieved by linking food consumption data from the What We Eat In America (WWEIA) portion of the National Health and Nutrition Examination Survey (NHANES) to the appropriate food composition and chemical occurrence data using a number of validated and published models, available upon request from Crème Global (https://www.cremeglobal.com/). Calculations for this intake analysis were completed using deterministic (single points) input data. Output calculation types include daily average intakes, acute exposures, as well as population statistics such as mean, percentiles, standard errors, and confidence intervals. Results are output for "Consumers Only" (i.e., consumers of the food / substance of interest), and Total Population (consumers and non-consumers). Results of the exposure assessment are given in absolute terms (mg/day) as well as relative to the consumer's body weight (mg/kg bw/day). The per unit of bodyweight exposure is calculated on a subject level using the bodyweight recorded by the NHANES data.[1]

The most recent NHANES dataset (2017-2018) was utilized to perform the intake analysis and results and food codes utilized in the analysis are provided herein.

Estimated Daily Intake (EDI) of D-Allulose from the Background Diet

The GRN 001029 submission noted that the mean and 90th percentile Estimated Daily Intakes (EDIs) of naturally occurring D-allulose reported in GRN 693 were 94.8 and 260.7 mg of D-allulose per person per day, respectively and noted that it was unlikely that consumption patterns have changed significantly since the EDI was determined. To update the estimated intake of allulose from the background diet, the same scenario as used in GRN 693 is used with updated reference amounts customarily consumed to better estimate the US intake patterns. Based on Oshima (2006), the estimated allulose from natural sources was calculated using a fictitious average daily diet of foods that include naturally occurring D-allulose, including breakfast cereal, fruit juice, caramel sauce, Bolognese pasta sauce, a can of soda, sauces on a hamburger, and canned fruit salad for dessert. The allulose per 100 g serving identified in

[1] A note on Creme Food Safety® model: The system supports both deterministic (single points) input data and probabilistic input data. Probabilistic data can be represented by parametric or empirical distributions, integrated in the analysis using Monte Carlo simulations. If the type of modelling used is probabilistic, it means the input data may be represented as probability distributions when required (rather than using point estimates only) and the simulation process uses conditional distribution sampling. When using probabilistic modelling and a population-based approach, the output from the model – the systemic exposure results – are themselves a distribution. In the Creme Food Data Science ® model, standard errors of statistics are calculated using a resampling technique called bootstrapping. For example, a mean value can be estimated from the collected sample data which is assumed to be representative of the total population. Using the bootstrap method allows a distribution of the mean values to be generated and used to assess the accuracy of the estimated statistic (in this case, the mean value). This is performed by sampling with replacement from the data set in question several times, generating a number of different estimates of each statistic. The standard error of the mean is then the standard deviation of the mean values obtained from the large number of bootstrap samples.

Oshima 2006 was used to calculate the allulose per reference amount customarily consumed for each of the food categories identified in the average daily diet. The calculations are shown in **Table *1***.

Table 1. Estimated Potential Daily Intake of D-Allulose from Natural Occurrence/Background Diet

Food	RACC (ml or g)	Allulose (mg) per 100 g Food	Allulose Total (mg)
Fruit cereal	40	2.2	0.88
Fruit Juice	240	21.5	51.6
Caramel sauce	30	83	24.9
Meat sauce	125	15.8	19.75
Coke	360	38.3	137.88
Worchestershire	5	130.6	6.53
Ketchup	15	39.8	5.97
Canned fruit	100	14.9	14.9
TOTAL			**262.41**

This estimated intake of 262.41 mg of allulose from natural sources, is comparable to the Oshima estimate of 206 mg and the 90th percentile estimate in GRN 693 of 260.7 mg/person/day. GRN 693 used the food categories identified in Oshima and calculated intake based on NHANES intake data. The food codes used for this analysis were not reported.

Estimated Daily Intakes (EDIs) of D-Allulose from Intended Use in Foods

The results are reported by for all ages (1+ years) and subpopulations by gender for the following age groups: children 1-5 years, children 6-11 years, adolescents 12-18 years and adults 19+ years. **Table 2** below provides a summary of the estimated daily intake of allulose from the proposed uses in grams per day and **Table 3** provides the estimated daily intake in a grams/kg body weight (bw)/day basis.

All intakes are in grams and N equals the number of individuals reporting eating the foods and the “Percentage” is the percent of the population the “N” represents. “Per capita” intake refers to the estimated intake averaged over all individuals surveyed, regardless of whether they consumed food products the ingredient is intended to be added. from the selected food codes in one of the two days of the survey. Individuals were considered “consumers” if they reported consumption of one or more food products on either Day 1 or Day 2 of the survey.

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Table 2. Summary of the Estimated Daily Intake of D-Allulose (Grams) from All Foods (2017-2018)

		Per Capita Intake		Consumer-only Intake			
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	1.47	4.22	137	44.8	2.96	5.74
Children (1-5 years)	Male	1.59	5.26	135	42.5	3.38	6.26
Children (6-11 years)	Female	1.56	4.51	145	41.2	3.33	6.36
Children (6-11 years)	Male	1.49	5.03	102	31.0	4.83	10.53
Teenage (12-18 years)	Female	1.59	6.39	100	25.2	5.19	9.55
Teenage (12-18 years)	Male	1.26	5.10	92	23.2	4.79	8.35
Adults (19+ years)	Female	3.47	9.54	900	40.6	7.87	17.25
Adults (19+ years)	Male	4.10	12.63	731	36.1	10.52	23.14
All ages	Total Population	3.20	8.80	2367	35.7	7.96	17.64

Table 3. Summary of the Estimated Daily Intake of D-Allulose (Grams/Kg bw/Day) From All Foods (2017-2018)

		Per Capita Intake		Consumer-only Intake			
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.09	0.24	137	44.8	0.19	0.42
Children (1-5 years)	Male	0.10	0.36	135	42.5	0.22	0.50
Children (6-11 years)	Female	0.05	0.15	145	41.2	0.11	0.26
Children (6-11 years)	Male	0.04	0.16	102	31.0	0.14	0.29
Teenage (12-18 years)	Female	0.03	0.10	100	25.2	0.08	0.13
Teenage (12-18 years)	Male	0.02	0.08	92	23.2	0.08	0.17
Adults (19+ years)	Female	0.05	0.12	900	40.6	0.11	0.24
Adults (19+ years)	Male	0.04	0.13	731	36.1	0.11	0.22
All ages	Total Population	0.05	0.13	2367	35.7	0.11	0.24

Considering the highest daily intake “Consumer Only” scenario from these calculations, the “All ages” group consumes 7.96 and 17.64 g/day at the mean and 90th percentile, respectively. The consumer with the highest daily intake is adult males with 10.52 and 23.14 grams/day at the mean and 90th percentile, respectively. The consumer with the highest daily intake on a body weight basis is male children (1-5 years) with a mean and 90^{h} percentile intake of 0.22 and 0.50 g/kg bw.

The GRN 001029 original submission declares that the proposed food uses of the D-allulose is in the same food products and at levels proportional to those outlined in GRN 400, GRN 498, GRN 693 and GRN 828 and that the EDI assessment would be identical to the EDI assessment

in GRN 693. This statement is incorrect as the proposed food applications for L&P's D-allulose excludes some of the foods that are included in the previous GRNs. The EDI for L&P's D-allulose are lower than those reported in GRN 498, likely due to the intended use for GRN 001029 does not include several categories that GRN 498 included (e.g. Frostings, salad dressings, jams & jellies, sweet sauces & syrups, cooked cereals and high sugar ready-to-eat cereals) and the food codes selected for Confections & Frostings in GRN 498 include cakes, cookies and brownies that were not denoted as "lite" or "diet." GRN 498 also included raw sugar, and this updated intake assessment only includes sugar substitutes because it is not anticipated that D-allulose will replace use of raw sugar. It is not anticipated that D-allulose would fully replace other sugar substitutes; however, all these food codes are included in the analysis to provide for a conservative approach.

Similarly, the EDI is also lower than that estimated in GRN 693 which stated "the same food products and levels proportional to those mentioned in GRN 498 and GRN 400" were utilized for the intake calculations; however, the food codes are not included in the notification so this could not be analyzed.

All the proposed uses for L&P's D-allulose are included in the GRNs 400, 498, 693 and 828 and there are no additional uses proposed for L&Ps D-allulose. It is anticipated that L&Ps D-allulose would be substitutive for other D-allulose and will not be additive. The EDI from the proposed use of L&P's D-allulose is conservative in that the analysis assumes that the consumer will partake in consuming all foods containing D-allulose on a daily basis.

Cumulative Estimated Daily Intakes (CEDI) of D-Allulose from Intended Use and Background Diet

The background intake estimate, based on a scenario in which an individual would consume all foods in one day containing naturally occurring D-allulose, is 262.41 mg per day. Using the highest daily intake (adult males, consumer only, 90th percentile) from the proposed use from the NHANES calculations (23.14 g/day), the CEDI is 23.4 g/day.

Food Codes and Proposed Use Utilized for Intake Calculation

Food codes that most appropriately matched the intended use were selected. **Table 4** provides the food codes from the NHANES 2017 – 2018 survey utilized to calculate the estimated daily intake. The food codes selected for the intake calculation included foods that would serve as the best match for the intended use and those foods within a category noted as "diet", "low calorie", "sugar free", "light" and "reduced fat or sugar" were selected. Although reduced sugar is not specified for "light" or "low fat", these codes were selected to serve as a proxy for reduced sugar varieties.

Table 4. Food Codes (2017-2018 NHANES) Used for Estimated Daily Intake Analysis

Food Code	Main Food Description
Bakery[1] - Cakes and pies, Doughnuts, sweet rolls, pastries, Cookies and brownies, Cream cheese, sour cream, whipped cream, Rolls and buns	
53104300	Cake, carrot, diet
53105500	Cake, chocolate, with icing, diet
53108220	Snack cake, chocolate, with icing or filling, reduced fat and calories
53109220	Snack cake, not chocolate, with icing or filling, reduced fat and calories
53123500	Cake, shortcake, with whipped topping and fruit, diet
51161030	Roll, sweet, with fruit, frosted, diet
53260030	Cookie, chocolate chip, sugar free
53260200	Cookie, oatmeal, sugar free
53260300	Cookie, sandwich, sugar free
53260400	Cookie, sugar or plain, sugar free
53260500	Cookie, sugar wafer, sugar free
53260600	Cookie, peanut butter, sugar free
12220280	Whipped topping, sugar free
51154510	Roll, diet
Coffee[2] - Not included in a food category, Coffee, Cream and cream substitutes	
92192030	Coffee, mocha, instant, pre-lightened and pre-sweetened with low calorie sweetener, not reconstituted
92192040	Coffee, mocha, instant, decaffeinated, pre-lightened and pre-sweetend with low calorie sweetener, not reconstituted
92193020	Coffee, instant, pre-lightened and pre-sweetened with low calorie sweetener, not reconstituted
92193025	Coffee, instant, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener, not reconstituted
92121030	Coffee, mocha, instant, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92121040	Coffee, instant, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92121041	Coffee, instant, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92121050	Coffee, mocha, instant, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92130005	Coffee, pre-lightened and pre-sweetened with low calorie sweetener
92130006	Coffee, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener
92130030	Coffee, pre-sweetened with low calorie sweetener
92130031	Coffee, decaffeinated, pre-sweetened with low calorie sweetener
12210280	Coffee creamer, liquid, fat free, sugar free, flavored
12210505	Coffee creamer,powder, sugar free, flavored
12210310	Coffee creamer, liquid, sugar free, flavored
Ice cream and frozen dairy desserts[3]	
13130100	Light ice cream, NFS
13130300	Light ice cream, vanilla
13130310	Light ice cream, chocolate
13135000	Light ice cream sandwich, vanilla

Food Code	Main Food Description
13135010	Light ice cream sandwich, chocolate
13140000	Light ice cream bar, vanilla
13140100	Light ice cream bar, vanilla, chocolate coated
13140115	Light ice cream bar, chocolate
13140710	Creamsicle, light
13142100	Light ice cream cone, vanilla, prepackaged
13142110	Light ice cream cone, chocolate, prepackaged
13161600	Fudgesicle, light
11459990	Frozen yogurt, NFS
11460000	Frozen yogurt, vanilla
11460100	Frozen yogurt, chocolate
11460500	Frozen yogurt, soft serve, vanilla
11460510	Frozen yogurt, soft serve, chocolate
11461200	Frozen yogurt sandwich
11461210	Frozen yogurt bar, vanilla
11461220	Frozen yogurt bar, chocolate
11461250	Frozen yogurt cone, chocolate
11461260	Frozen yogurt cone, vanilla
11461300	Frozen yogurt cone, vanilla, waffle cone
11461320	Frozen yogurt cone, chocolate, waffle cone
Yogurt[4] - Yogurt, Greek, Yogurt, regular	
11411410	Yogurt, Greek, low fat milk, plain
11411420	Yogurt, Greek, nonfat milk, plain
11434010	Yogurt, Greek, low fat milk, fruit
11434020	Yogurt, Greek, nonfat milk, fruit
11435020	Yogurt, Greek, low fat milk, flavors other than fruit
11435030	Yogurt, Greek, nonfat milk, flavors other than fruit
11411200	Yogurt, low fat milk, plain
11411300	Yogurt, nonfat milk, plain
11432000	Yogurt, low fat milk, fruit
11433000	Yogurt, nonfat milk, fruit
11434200	Yogurt, low fat milk, flavors other than fruit
11434300	Yogurt, nonfat milk, flavors other than fruit
Sugar substitutes	
91106010	Sugar substitute and sugar blend
91107000	Sugar substitute, sucralose, powder
91108000	Sugar substitute, stevia, powder
91108010	Sugar substitute, stevia, liquid
91108020	Sugar substitute, monk fruit, powder
91200000	Sugar substitute, powder, NFS
91200005	Sugar substitute, liquid, NFS

Food Code	Main Food Description
91200040	Sugar substitute, saccharin, powder
91200110	Sugar substitute, saccharin, liquid
91201010	Sugar substitute, aspartame, powder
Non-carbonated Beverages[5] - Diet sport and energy drinks, Other diet drinks, Tea, Flavored or carbonated water, Fruit drinks	
95322200	Sports drink, low calorie (Gatorade G2)
95322500	Sports drink, low calorie (Powerade Zero)
95323000	Sports drink, low calorie
92900200	Fruit flavored drink, powdered, not reconstituted, diet
92513010	Slush frozen drink, no sugar added
92550400	Vegetable and fruit juice drink, with high vitamin C, diet
92550610	Fruit flavored drink, with high vitamin C, diet
92550620	Fruit flavored drink, diet
92552000	Fruit flavored drink, with high vitamin C, powdered, reconstituted, diet
92552010	Fruit flavored drink, powdered, reconstituted, diet
92305090	Tea, iced, instant, black, pre-sweetened with low calorie sweetener
92305110	Tea, iced, instant, black, decaffeinated, pre-sweetened with low calorie sweetener
92305920	Tea, iced, instant, green, pre-sweetened with low calorie sweetener
92307510	Iced Tea / Lemonade juice drink, light
92307520	Iced Tea / Lemonade juice drink, diet
92308010	Tea, iced, brewed, black, pre-sweetened with low calorie sweetener
92308040	Tea, iced, brewed, black, decaffeinated, pre-sweetened with low calorie sweetener
92308510	Tea, iced, brewed, green, pre-sweetened with low calorie sweetener
92308540	Tea, iced, brewed, green, decaffeinated, pre-sweetened with low calorie sweetener
92309020	Tea, iced, bottled, black, diet
92309030	Tea, iced, bottled, black, decaffeinated, diet
92309510	Tea, iced, bottled, green, diet
94100200	Water, bottled, sweetened, with low calorie sweetener
92550030	Fruit juice drink, with high vitamin C, light
92550035	Fruit juice drink, light
92550040	Fruit juice drink, diet
92550110	Cranberry juice drink, with high vitamin C, light
92550200	Grape juice drink, light
92550350	Orange juice beverage, 40-50% juice, light
92550360	Apple juice beverage, 40-50% juice, light
92550370	Lemonade, fruit juice drink, light
92550380	Pomegranate juice beverage, 40-50% juice, light
92550405	Vegetable and fruit juice drink, with high vitamin C, light
92552020	Fruit juice drink, reduced sugar (Sunny D)
Carbonated Beverages[6] - Diet soft drinks, Liquor and cocktails, Soft drinks, Diet sport and energy drinks	
92400100	Soft drink, NFS, diet

Food Code	Main Food Description
92410320	Soft drink, cola, diet
92410350	Soft drink, cola, decaffeinated, diet
92410370	Soft drink, pepper type, diet
92410400	Soft drink, pepper type, decaffeinated, diet
92410420	Soft drink, cream soda, diet
92410520	Soft drink, fruit flavored, diet, caffeine free
92410560	Soft drink, fruit flavored, caffeine containing, diet
92410620	Soft drink, ginger ale, diet
92410720	Soft drink, root beer, diet
92410820	Soft drink, chocolate flavored, diet
92411610	Soft drink, cola, fruit or vanilla flavored, diet
92411620	Soft drink, cola, chocolate flavored, diet
95312400	Energy drink, low calorie (Monster)
95312410	Energy drink, sugar free (Monster)
95312500	Energy drink, sugar free (Mountain Dew AMP)
95312550	Energy drink, sugar free (No Fear)
95312555	Energy drink, sugar-free (NOS)
95312600	Energy drink, sugar-free (Red Bull)
95312700	Energy drink, sugar free (Rockstar)
95312800	Energy drink, sugar free (Vault)
95313200	Energy drink, sugar free
92410250	Carbonated water, sweetened, with low-calorie or no-calorie sweetener
93301183	Whiskey and diet cola
93301191	Rum and diet cola
93301215	Vodka and diet cola
92410315	Soft drink, cola, reduced sugar
Candy and Gum[7] - Candy containing chocolate, Candy not containing chocolate	
91770030	Dietetic or low calorie candy, chocolate covered
91770000	Dietetic or low calorie candy, NFS
91770010	Dietetic or low calorie gumdrops
91770020	Dietetic or low calorie hard candy
91770050	Dietetic or low calorie mints
91802000	Chewing gum, sugar free
91703080	Caramel, all flavors, sugar free
Cereals[8] - Ready-to-eat cereal, lower sugar (=<21.2g/100g), Ready-to-eat cereal, higher sugar (>21.2g/100g)	
57000100	Cereal, oat, NFS
57101000	Cereal (Kellogg's All-Bran)
57103000	Cereal (Post Alpha-Bits)
57106050	Cereal (Post Great Grains Banana Nut Crunch)
57123000	Cereal (General Mills Cheerios)

Food Code	Main Food Description
57132000	Cereal (General Mills Chex Corn)
57134000	Cereal, corn flakes
57135000	Cereal (Kellogg's Corn Flakes)
57137000	Cereal, corn puffs
57148000	Cereal (Kellogg's Crispix)
57151000	Cereal, crispy rice
57206700	Cereal (General Mills Fiber One)
57206710	Cereal (General Mills Fiber One Honey Clusters)
57207000	Cereal, bran flakes
57208000	Cereal (Kellogg's All-Bran Complete Wheat Flakes)
57209000	Cereal (Post Bran Flakes)
57214000	Cereal (Kellogg's Frosted Mini-Wheats)
57228000	Granola, homemade
57230000	Cereal (Post Grape-Nuts)
57237100	Cereal (Post Honey Bunches of Oats Honey Roasted)
57237200	Cereal (Post Honey Bunches of Oats with Vanilla Bunches)
57237300	Cereal (Post Honey Bunches of Oats with Almonds)
57241200	Cereal (Post Shredded Wheat Honey Nut)
57301500	Cereal (Kashi 7 Whole Grain Puffs)
57301505	Cereal (Kashi Autumn Wheat)
57301510	Cereal (Kashi GOLEAN)
57301530	Cereal (Kashi Heart to Heart Honey Toasted Oat)
57303100	Cereal (General Mills Kix)
57303105	Cereal (General Mills Honey Kix)
57304100	Cereal (Quaker Life)
57305160	Cereal (Malt-O-Meal Blueberry Muffin Tops)
57306700	Cereal (Malt-O-Meal Toasted Oat Cereal)
57308400	Cereal (General Mills Cheerios Multigrain)
57321900	Cereal (Nature's Path Organic Flax Plus)
57326000	Cereal (Barbara's Puffins)
57327450	Cereal (Quaker Toasted Oat Bran)
57327500	Cereal (Quaker Oatmeal Squares)
57336000	Cereal (General Mills Chex Rice)
57337000	Cereal, rice flakes
57339000	Cereal (Kellogg's Rice Krispies)
57340000	Cereal, puffed rice
57344000	Cereal (Kellogg's Special K)
57401100	Cereal, toasted oat
57408100	Cereal (Uncle Sam)
57411000	Cereal (General Mills Chex Wheat)
57416000	Cereal, puffed wheat, plain

Food Code	Main Food Description
57417000	Cereal (Post Shredded Wheat)
57418000	Cereal (General Mills Wheaties)
57125010	Cereal (General Mills 25% Less Sugar Cinnamon Toast Crunch)

[1] Food codes indicating "sugar free" or "diet" were chosen from these categories. Codes indicating "Fat Free" only were excluded because it does not imply low sugar.
[2] Food codes indicating "sugar free" or "low calorie sweetener". Codes indicating only "Fat Free" were not chosen because they do not imply low sugar.
[3] Food codes indicating "reduced fat or sugar" or "sugar free". No food codes for "lite" or "low calorie" frozen yogurt therefore all frozen yogurt codes were included.
[4] Food codes indicating "Light". Although reduced sugar is not specified, these codes serve as a proxy for reduced sugar varieties.
[5] Chose codes from the specified categories that indicated "sugar free" or "reduced sugar" or "diet". Mixes and syrups intended for use with milk or milk substitutes were not included as these are not part of the intended use.
[6] Chose codes from the following categories that indicated "sugar free" or "reduced sugar" or "diet". Alcoholic beverage food codes included because of the diet cola mixer.
[7] Chose codes from the selected categories that said "sugar free" or "low calorie" or "dietetic".
[8] Used all "lower sugar" food codes as a proxy for reduced sugar varieties and included a food code indicating "reduced sugar" from the "Higher sugar" category.

The intended uses and use levels in percent of the finished food in the various food categories utilized in the intake calculations are provided in **Table 5**. The intended use in soft candies is up to 25%; however, the soft candies were grouped with hard candies and chewing gum, therefore the highest value (70%) was utilized for the intake estimates. Food codes for fat-based cream subject to standards of identity were not included in the intake analysis. The intended use is in fat-based cream for use in modified fat/calorie cookies, cakes and pastries. The intended maximum use level is 10% of the finished food in the cream products and the dietetic/low calorie rolls, cake, pie, pastries and cookies therefore, the assumption is that the use of D-allulose in fat-based cream added to these foods is captured in the consumption of the finished food product.

Table 5. D-Allulose Intended Use Levels Utilized in the Estimated Daily Intake Analysis

Intended Food Use Category	Use Level (% in Finished Food)
Cakes and pies	10
Doughnuts, sweet rolls, pastries	10
Cookies and brownies	10
Cream cheese, sour cream, whipped cream	10
Rolls and buns	10
Not included in a food category	30
Coffee	30
Cream and cream substitutes	30
Ice cream and frozen dairy desserts	5
Yogurt, Greek	5
Yogurt, regular	5
Sugar substitutes	100

Intended Food Use Category	Use Level (% in Finished Food)
Diet sport and energy drinks	2.1
Other diet drinks	2.1
Tea	2.1
Flavored or carbonated water	2.1
Fruit drinks	2.1
Diet soft drinks	2.1
Liquor and cocktails	2.1
Soft drinks	2.1
Candy containing chocolate	70
Candy not containing chocolate	70
Ready-to-eat cereal, lower sugar (=<21.2g/100g)	10
Ready-to-eat cereal, higher sugar (>21.2g/100g)	10

Summary tables of the daily consumption of the various food categories in grams and in grams/kg bw/day are provided in Tables 6-25.

Table 6. Summary of Daily Consumption of All Foods (Grams)

		Per Capita Intake		Consumer-only Intake			
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	35.33	104.74	137	44.8	71.32	126.94
Children (1-5 years)	Male	33.75	99.27	135	42.5	71.85	170.72
Children (6-11 years)	Female	34.28	96.40	145	41.2	73.35	157.91
Children (6-11 years)	Male	47.88	120.00	102	31.0	154.82	343.67
Teenage (12-18 years)	Female	40.01	150.00	100	25.2	130.60	280.78
Teenage (12-18 years)	Male	35.95	120.00	92	23.2	136.27	323.33
Adults (19+ years)	Female	104.06	300.00	900	40.6	236.27	559.46
Adults (19+ years)	Male	141.04	364.08	731	36.1	361.64	988.31
All ages	Total Population	100.91	273.03	2367	35.7	251.34	660.00

Table 7. Summary of Consumption of All Foods Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	2.18	6.07	137	44.8	4.40	9.00
Children (1-5 years)	Male	2.17	7.10	135	42.5	4.62	10.49
Children (6-11 years)	Female	1.13	3.56	145	41.2	2.42	5.48
Children (6-11 years)	Male	1.29	3.69	102	31.0	4.18	10.08
Teenage (12-18 years)	Female	0.62	2.20	100	25.2	2.03	5.01
Teenage (12-18 years)	Male	0.60	1.73	92	23.2	2.27	6.04
Adults (19+ years)	Female	1.37	3.88	900	40.6	3.10	7.22
Adults (19+ years)	Male	1.41	4.05	731	36.1	3.62	8.99
All ages	Total Population	1.34	3.89	2367	35.7	3.33	8.28

Table 8. Summary of Daily Consumption of Bakery (Grams)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.12	0.00	4	1.3	15.44	20.00
Children (1-5 years)	Male	0.15	0.00	4	1.3	20.18	30.00
Children (6-11 years)	Female	0.12	0.00	4	1.1	24.55	40.00
Children (6-11 years)	Male	0.03	0.00	3	0.9	8.85	10.00
Teenage (12-18 years)	Female	0.05	0.00	1	0.3	30.00	30.00
Teenage (12-18 years)	Male	0.33	0.00	4	1.0	22.77	29.11
Adults (19+ years)	Female	0.13	0.00	10	0.5	47.15	119.20
Adults (19+ years)	Male	0.28	0.00	18	0.9	37.40	60.00
All ages	Total Population	0.19	0.00	49	0.7	34.29	64.85

Table 9. Summary of Daily Consumption of Bakery Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.01	0.00	4	1.3	1.05	1.35
Children (1-5 years)	Male	0.01	0.00	4	1.3	1.57	2.08
Children (6-11 years)	Female	0.00	0.00	4	1.1	0.67	1.23
Children (6-11 years)	Male	0.00	0.00	3	0.9	0.29	0.42
Teenage (12-18 years)	Female	0.00	0.00	1	0.3	0.48	0.48
Teenage (12-18 years)	Male	0.01	0.00	4	1.0	0.59	0.60
Adults (19+ years)	Female	0.00	0.00	10	0.5	0.70	1.59
Adults (19+ years)	Male	0.00	0.00	18	0.9	0.45	0.80
All ages	Total Population	0.00	0.00	49	0.7	0.60	1.42

Table 10. Summary of Daily Consumption of Coffee (Grams)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.00	0.00	1	0.3	0.25	0.25
Children (1-5 years)	Male	0.00	0.00	0	0.0	0.00	0.00
Children (6-11 years)	Female	0.16	0.00	1	0.3	60.00	60.00
Children (6-11 years)	Male	0.01	0.00	1	0.3	1.00	1.00
Teenage (12-18 years)	Female	0.00	0.00	0	0.0	0.00	0.00
Teenage (12-18 years)	Male	0.22	0.00	2	0.5	74.77	97.50
Adults (19+ years)	Female	1.44	0.00	98	4.4	42.04	133.74
Adults (19+ years)	Male	0.84	0.00	70	3.5	36.52	120.27
All ages	Total Population	0.89	0.00	173	2.6	39.84	120.00

Table 11. Summary of Consumption of Coffee Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.00	0.00	1	0.3	0.02	0.02
Children (1-5 years)	Male	0.00	0.00	0	0.0	0.00	0.00
Children (6-11 years)	Female	0.00	0.00	1	0.3	1.76	1.76
Children (6-11 years)	Male	0.00	0.00	1	0.3	0.03	0.03
Teenage (12-18 years)	Female	0.00	0.00	0	0.0	0.00	0.00
Teenage (12-18 years)	Male	0.01	0.00	2	0.5	1.87	2.46
Adults (19+ years)	Female	0.02	0.00	98	4.4	0.63	1.97
Adults (19+ years)	Male	0.01	0.00	70	3.5	0.47	1.84
All ages	Total Population	0.01	0.00	173	2.6	0.58	1.87

Table 12. Summary of Daily Consumption of Frozen Dairy (Grams)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.86	0.00	3	1.0	40.11	43.75
Children (1-5 years)	Male	0.33	0.00	4	1.3	30.31	67.50
Children (6-11 years)	Female	1.20	0.00	10	2.8	50.01	92.92
Children (6-11 years)	Male	1.49	0.00	8	2.4	55.33	85.78
Teenage (12-18 years)	Female	4.20	0.00	11	2.8	122.24	289.85
Teenage (12-18 years)	Male	2.15	0.00	9	2.3	93.76	160.00
Adults (19+ years)	Female	2.41	0.00	49	2.2	77.60	127.50
Adults (19+ years)	Male	1.77	0.00	52	2.6	76.01	118.43
All ages	Total Population	2.02	0.00	146	2.2	76.99	127.50

Table 13. Summary of Consumption of Frozen Dairy Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.05	0.00	3	1.0	2.39	2.88
Children (1-5 years)	Male	0.02	0.00	4	1.3	1.54	2.90
Children (6-11 years)	Female	0.04	0.00	10	2.8	1.57	3.84
Children (6-11 years)	Male	0.05	0.00	8	2.4	1.89	2.53
Teenage (12-18 years)	Female	0.07	0.00	11	2.8	2.15	5.81
Teenage (12-18 years)	Male	0.03	0.00	9	2.3	1.43	2.54
Adults (19+ years)	Female	0.03	0.00	49	2.2	1.08	1.68
Adults (19+ years)	Male	0.02	0.00	52	2.6	0.89	1.31
All ages	Total Population	0.03	0.00	146	2.2	1.18	2.49

Table 14. Summary of Daily Consumption of Yogurt (Grams)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	15.45	56.70	60	19.6	78.10	122.50
Children (1-5 years)	Male	16.78	75.00	57	17.9	73.87	122.70
Children (6-11 years)	Female	14.81	61.78	49	13.9	72.64	127.77
Children (6-11 years)	Male	8.85	32.00	31	9.4	69.47	125.32
Teenage (12-18 years)	Female	6.64	0.00	20	5.0	101.14	154.75
Teenage (12-18 years)	Male	1.67	0.00	9	2.3	96.68	151.48
Adults (19+ years)	Female	9.71	0.00	192	8.7	97.01	176.66
Adults (19+ years)	Male	6.82	0.00	95	4.7	108.52	187.05
All ages	Total Population	8.58	0.00	519	7.8	93.41	170.00

Table 15. Summary of Daily Consumption of Yogurt Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.97	2.87	60	19.6	4.89	9.17
Children (1-5 years)	Male	1.11	4.37	57	17.9	4.88	9.17
Children (6-11 years)	Female	0.52	1.77	49	13.9	2.56	5.48
Children (6-11 years)	Male	0.28	0.95	31	9.4	2.21	3.82
Teenage (12-18 years)	Female	0.11	0.00	20	5.0	1.70	2.37
Teenage (12-18 years)	Male	0.03	0.00	9	2.3	1.48	2.63
Adults (19+ years)	Female	0.14	0.00	192	8.7	1.35	2.37
Adults (19+ years)	Male	0.08	0.00	95	4.7	1.31	2.44
All ages	Total Population	0.19	0.00	519	7.8	2.02	3.89

Table 16. Summary of Daily Consumption of Sugar Substitutes

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.00	0.00	1	0.3	0.50	0.50
Children (1-5 years)	Male	0.00	0.00	1	0.3	0.50	0.50
Children (6-11 years)	Female	0.04	0.00	4	0.6	2.25	3.00
Children (6-11 years)	Male	0.00	0.00	0	0.0	0.00	0.00
Teenage (12-18 years)	Female	0.24	0.13	4	1.0	2.35	6.00
Teenage (12-18 years)	Male	0.18	0.00	0	0.0	2.18	4.00
Adults (19+ years)	Female	0.01	0.00	229	10.3	0.48	0.65
Adults (19+ years)	Male	0.00	0.00	206	10.2	0.00	0.00
All ages	Total Population	0.16	0.00	443	6.7	2.26	4.50

Table 17. Summary of Consumption of Sugar Substitutes Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.00	0.00	1	0.3	0.03	0.03
Children (1-5 years)	Male	0.00	0.00	1	0.3	0.04	0.04
Children (6-11 years)	Female	0.00	0.00	4	0.6	0.05	0.07
Children (6-11 years)	Male	0.00	0.00	0	0.0	0.00	0.00
Teenage (12-18 years)	Female	0.00	0.00	4	1.0	0.03	0.07
Teenage (12-18 years)	Male	0.00	0.00	0	0.0	0.02	0.04
Adults (19+ years)	Female	0.00	0.00	229	10.3	0.02	0.02
Adults (19+ years)	Male	0.00	0.00	206	10.2	0.00	0.00
All ages	Total Population	0.00	0.00	443	6.7	0.03	0.06

Table 18. Summary of Daily Consumption of Non-carbonated Beverages (Grams or ML)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	14.74	60.99	25	8.2	117.16	248.52
Children (1-5 years)	Male	11.51	0.00	23	7.2	128.99	370.86
Children (6-11 years)	Female	11.19	0.00	30	8.5	121.64	221.46
Children (6-11 years)	Male	27.78	0.00	20	6.1	352.86	590.99
Teenage (12-18 years)	Female	7.36	0.00	20	5.0	171.77	258.52
Teenage (12-18 years)	Male	12.15	0.00	20	5.1	178.51	297.20
Adults (19+ years)	Female	33.80	0.00	154	7.0	376.02	764.31
Adults (19+ years)	Male	41.57	0.00	114	5.6	571.60	1047.82
All ages	Total Population	31.62	0.00	409	6.2	394.39	917.03

Table 19. Summary of Daily Consumption of Non-carbonated Beverages Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.89	3.94	25	8.2	7.08	11.51
Children (1-5 years)	Male	0.70	0.00	23	7.2	7.83	18.73
Children (6-11 years)	Female	0.36	0.00	30	8.5	3.91	8.18
Children (6-11 years)	Male	0.66	0.00	20	6.1	8.38	14.07
Teenage (12-18 years)	Female	0.10	0.00	20	5.0	2.44	4.00
Teenage (12-18 years)	Male	0.24	0.00	20	5.1	3.46	7.92
Adults (19+ years)	Female	0.46	0.00	154	7.0	5.17	10.39
Adults (19+ years)	Male	0.41	0.00	114	5.6	5.71	10.94
All ages	Total Population	0.44	0.00	409	6.2	5.47	10.90

Table 20. Summary of Daily Consumption of Carbonated Beverages (Grams or ML)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	1.24	0.00	5	1.6	62.64	116.81
Children (1-5 years)	Male	0.41	0.00	4	1.3	31.81	97.24
Children (6-11 years)	Female	2.88	0.00	7	2.0	182.69	319.94
Children (6-11 years)	Male	7.55	0.00	13	4.0	277.73	529.91
Teenage (12-18 years)	Female	17.01	0.00	17	4.3	223.17	411.67
Teenage (12-18 years)	Male	15.58	0.00	17	4.3	252.94	692.53
Adults (19+ years)	Female	53.23	133.96	230	10.4	412.97	900.00
Adults (19+ years)	Male	84.89	240.00	236	11.7	595.00	1117.19
All ages	Total Population	53.66	113.64	529	8.0	481.34	988.59

Table 21. Summary of Consumption of Carbonated Beverages Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.06	0.00	5	1.6	3.26	6.38
Children (1-5 years)	Male	0.03	0.00	4	1.3	2.15	6.89
Children (6-11 years)	Female	0.08	0.00	7	2.0	5.06	7.44
Children (6-11 years)	Male	0.22	0.00	13	4.0	8.04	15.13
Teenage (12-18 years)	Female	0.26	0.00	17	4.3	3.35	4.81
Teenage (12-18 years)	Male	0.23	0.00	17	4.3	3.73	8.87
Adults (19+ years)	Female	0.66	1.75	230	10.4	5.15	11.49
Adults (19+ years)	Male	0.82	2.74	236	11.7	5.77	10.58
All ages	Total Population	0.60	1.39	529	8.0	5.35	10.76

Table 22. Summary of Daily Consumption of Candy and Gum (Grams)

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.01	0.00	4	1.3	1.00	1.00
Children (1-5 years)	Male	0.02	0.00	3	0.9	1.32	2.82
Children (6-11 years)	Female	0.01	0.00	3	0.9	1.15	1.94
Children (6-11 years)	Male	0.02	0.00	2	0.6	1.80	2.00
Teenage (12-18 years)	Female	0.03	0.00	5	1.3	2.67	3.50
Teenage (12-18 years)	Male	0.01	0.00	6	1.5	1.47	2.96
Adults (19+ years)	Female	0.07	0.00	38	1.7	2.65	6.00
Adults (19+ years)	Male	0.15	0.00	28	1.4	7.57	20.73
All ages	Total Population	0.08	0.00	89	1.3	4.29	12.32

Table 23. Summary of Consumption of Candy and Gum Grams/Kg (Body Weight)/Day

		Per Capita Intake			Consumer-only Intake		
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.00	0.00	4	1.3	0.05	0.06
Children (1-5 years)	Male	0.00	0.00	3	0.9	0.08	0.17
Children (6-11 years)	Female	0.00	0.00	3	0.9	0.04	0.04
Children (6-11 years)	Male	0.00	0.00	2	0.6	0.06	0.06
Teenage (12-18 years)	Female	0.00	0.00	5	1.3	0.05	0.07
Teenage (12-18 years)	Male	0.00	0.00	6	1.5	0.02	0.05
Adults (19+ years)	Female	0.00	0.00	38	1.7	0.04	0.08
Adults (19+ years)	Male	0.00	0.00	28	1.4	0.09	0.24
All ages	Total Population	0.00	0.00	89	1.3	0.06	0.19

Table 24. Summary of Daily Consumption of Cereal (Grams)

		Per Capita Intake		Consumer-only Intake			
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	2.91	12.90	61	19.9	15.53	29.60
Children (1-5 years)	Male	4.55	21.00	72	22.6	18.02	32.25
Children (6-11 years)	Female	3.90	15.21	62	17.6	23.24	44.08
Children (6-11 years)	Male	2.16	0.00	41	12.5	22.02	42.62
Teenage (12-18 years)	Female	4.68	19.58	37	9.3	38.11	75.52
Teenage (12-18 years)	Male	3.83	11.60	36	9.1	36.41	79.51
Adults (19+ years)	Female	3.04	10.50	240	10.8	28.06	49.43
Adults (19+ years)	Male	4.53	17.68	241	11.9	34.28	64.05
All ages	Total Population	3.70	13.81	807	12.2	29.47	56.67

Table 25. Summary of Consumption of Cereal Grams/Kg (Body Weight)/Day

		Per Capita Intake		Consumer-only Intake			
Age Group	Gender	Mean	90th	N	Percentage	Mean	90th
Children (1-5 years)	Female	0.20	0.85	61	19.9	1.05	1.93
Children (1-5 years)	Male	0.31	1.39	72	22.6	1.22	1.82
Children (6-11 years)	Female	0.12	0.43	62	17.6	0.73	1.25
Children (6-11 years)	Male	0.08	0.00	41	12.5	0.82	1.66
Teenage (12-18 years)	Female	0.08	0.32	37	9.3	0.62	1.16
Teenage (12-18 years)	Male	0.06	0.15	36	9.1	0.58	1.12
Adults (19+ years)	Female	0.04	0.13	240	10.8	0.39	0.79
Adults (19+ years)	Male	0.05	0.18	241	11.9	0.39	0.78
All ages	Total Population	0.07	0.21	807	12.2	0.52	1.10

References:

Oshima, H., Kimura, I., Izumori, K. (2006) 'Psicose Contents in Various Food Products and its Origin', *Food Sci Technol Res,* 12(2), pp. 137-143.

Viebrock, Lauren

From: Amy Mozingo <amozingo@gras-associates.com>
Sent: Monday, October 17, 2022 4:08 PM
To: Viebrock, Lauren
Cc: William J. Rowe; Margitta Dziwenka
Subject: [EXTERNAL] RE: GRN 001029 Questions
Attachments: FDA Questions_Response Ltr GRN 1029_17Oct2022.pdf; Attachment_Chemistry Q1_Test Report_Sulfur Dioxide.pdf; Attachment_Chemistry_Q5_Analytical Statement.pdf; Attachment_Chemistry_Q3_Other sugars_CONFIDENTIAL.pdf; Attachment_Chemistry_Q4 _Specifications (1).pdf

Dear Dr. Viebrock,
Attached you will find a response to the questions for GRN 001029 along with the attachments referenced in the response letter. Please let me know if there are any further clarifications required.
Best Regards,
Amy

Amy Mozingo, MS
VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
O: 301-461-8929| C: 772-532-3454

LinkedIn | Twitter | Blog

From: Amy Mozingo
Sent: Monday, October 3, 2022 1:56 PM

To: 'Viebrock, Lauren' <Lauren.Viebrock@fda.hhs.gov>; William J. Rowe <wrowe@nutrasource.ca>
Subject: RE: GRN 001029 Questions

Dear Dr. Viebrock,
We are confirming receipt and will respond within the requested 10-business days (by October 17, 2022).
Best Regards
Amy

Amy Mozingo, MS
VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
O: 301-461-8929| C: 772-532-3454

LinkedIn | Twitter | Blog

From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Sent: Monday, October 3, 2022 1:41 PM
To: Amy Mozingo <amozingo@gras-associates.com>; William J. Rowe <wrowe@nutrasource.ca>
Subject: GRN 001029 Questions

Dear Mr. Rowe,

During our review of GRAS Notice No. 0001029, we noted questions that need to be addressed. Please find the questions attached to this email.

We respectfully request a response within **10 business days**. If you are unable to complete the response within that time frame, please contact me to discuss further options.

If you have questions or need further clarification, please feel free to contact me. Thank you in advance for your attention to our comments.

Regards,
Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

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October 17, 2022

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Petition Review
5001 Campus Drive
College Park, MD 20740-3835

Attention: Dr. Lauren Viebrock
Re: GRN 001029—Response to Questions Posed in an Email Dated October 3, 2022

Dear Dr. Viebrock:

Per your request, GRAS Associates, LLC, acting as the agent for L&P Food Ingredient Co., Ltd., is providing responses to FDA's requests for additional clarification as denoted in your email dated October 3rd.

Chemistry:

1. *Please provide a narrative for the rationale of the use of sodium metabisulphite in the fructose solution (p. 9) and describe its residual breakdown (sulfur dioxide) in the final products. For the administrative record, please provide the correct chemical formula for magnesium chloride on p. 9.*

Response:
Sodium metabisulphite is used as an antioxidant and preservative in the fructose solution. In the manufacturing process, it is removed by ion exchange resin. There is no residue in the final product. Please find a third party test report as Attachment_Chemistry Q1_Test Report Sulfur Dioxide.
For the administrative record, the chemical formula on page 9 should be $MgCl_2$.

2. *Please clarify the discrepancy on the concentration of fructose solution and state whether it is a ≥50% (p. 9) or ≥55% (p. 10).*

Response:
The concentration of the fructose solution is ≥*55%.*

3. *The manufacturing section of the notice states that D-allulose is separated from fructose and "other sugars" (p.9). Please clarify what the "other sugars" are, whether they are present in the final ingredient and if yes, in what quantities.*

Response: "Other sugars" refer to some mono and disaccharides from the raw material fructose. The Business Confidential HPLC analysis is provided as Attachment_Chemistry_Q3_Other Sugars.

4. *We note that the proposed specification limits for heavy metals are ≤ 0.5 mg/kg, while the levels of heavy metals in each of the four batches are reported to be < 0.01 mg/kg (Tables 6-7, pp. 13-14). We request that the notifier consider lowering the specification limits for heavy metals to reflect the results of batch analyses and to be as low as possible.*

Response:
L&P Food Ingredient Co., Ltd. (L&P) agrees to lower the specifications for the heavy metals to ≤0.1 mg/kg. Revised specification sheets are included as Attachment_Chemistry_Q4_Specifications.

5. *Please provide a statement that all analytical methods used for batch analyses of the specification parameters are validated for their respective purpose.*

Response:
A signed statement that all analytical methods used for batch analysis are validated for their respective purpose is provided as Attachement_Chemistry_Q5_Analytical Statement.

Toxicology:

1. *A recent review by Daniel et al., 2021 states, "Safety concerns were raised about allulose consumption based on reports suggesting that allulose may represent a substrate for potentially harmful bacteria [Blin et al., 2017]. Allulose consumption may thereby confer a growth advantage for these bacteria and enhance the incidence and/or severity of an infection [Martin et al., 2018]." Additionally, a 2020 opinion by the German Federal Institute for Risk Assessment (BfR)2 noted, "scientific clarification is still needed as to the extent to which regular consumption of unusual quantities of D-allulose thus far, as a novel food, increases the concentration of this sugar in certain areas of the human body, has an unwanted influence on the occurrence and characteristics of Klebsiella spp. in the human intestinal flora and/or changes the infectiousness of virulent Klebsiella ssp. (esp. K. pneumoniae). We note that none of these published studies or the BfR scientific opinion are considered in the notice. Please provide a detailed safety narrative that discusses why these do not present a safety concern for the consumption of D-allulose.*

Response: The publication by Martin (2018) discusses the characterization of the function of the sugar utilization locus which is associated with infection and represented by specific genes. The authors conducted *in vitro* studies and note that "*it is **possible** that the presence of D-psicose **could** enhance intestinal K. pneumoniae colonization, although this has not been investigated*". The Blin et al. (2017) publication also reports on the hypothetical/potential concerns regarding the ability of *Klebsiella spp.* to utilize psicose as a substrate but fail to show evidence that this is a concern for the general population consuming D-allulose/D-psicose in conventional foods. The publication by Daniel et al. (2021) also poses only a general question if "*a high dietary intake of allulose may cause an undesirable growth advantage for potentially harmful bacteria at mucosal sites …*" but does not give sufficient evidence that there is a real safety concern. The 2020 review by German Federal Institute for Risk Assessment (BfR) discusses the potential for D-allulose to pose a health risk because it may selectively "*favor the growth of bacterial in the species Klebsiella…., within the human body*", however they conclude that this may be "*considered as a possibly emerging risk*".

The relevance of these findings to ingestion of D-allulose by the general population in conventional foods is not evident from these publications and these findings do not indicate that there is a safety

concern from the ingestion of D-allulose/D-psicose in conventional foods. While this may be an area of current research, there is no definitive evidence in the published literature that the utilization of D-psicose by virulent *Klebsiella spp.* poses a safety concern in humans. NIH notes that "*Klebsiella is a type of bacteria commonly found in nature. In humans, the bacteria are often present in parts of the digestive tract where they do not generally cause problems.*"[1] Daniel et al. (2021) notes that the overall intestinal absorption of allulose has been estimated and may be approximately 70% of the ingested dose which is in agreement with the findings of Iida et al. (2010) who report that the majority of D-psicose would be absorbed in the small intestine and only about 20% would pass into the large intestine. Iida et al. (2010) also states that the small amount of D-psicose that does reach the large intestine is not readily fermented by the bacteria typically present. Based on these findings, there is no indication that D-allulose would be readily available as an energy source for proliferation of *Klebsiella spp*. in the human gut.

D-allulose/D-psicose has a ten year long history of safe consumption and there is broad consensus by experts that it is safe for its intended use. As of October 2022, FDA has filed numerous GRAS notices with a number receiving "no questions" responses and in the available information on FDA's GRAS Notice Inventory website for D-allulose/D-psicose submissions, there is no indication that FDA has raised concerns regarding the safety of D-allulose/D-psicose under its intended use.

2. *Table 13 (page 18) includes an intended use for D-allulose as a sweetener in medical foods. Please clarify the specific population intended to consume these medical foods and why consumption of D-allulose by a potentially sensitive subpopulation is not expected to be a safety concern*.

Response:
L&P withdraws the intended use in medical foods.

3. *Tables 14 and 15 (page 19) report the estimated daily intake of D-allulose for infants less than 2 years. However, we note that there is no accompanying safety narrative that addresses the safe consumption of D-allulose in this sensitive subpopulation, especially for infants less than 12 months. Please provide a narrative that explains why consumption of D-allulose is not expected to be a safety concern when consumed by infants (< 12 months) and toddlers (1-3 years).*

Response:
The intended use of D-allulose is not in foods specifically targeted to infant and young children.

A further analysis was performed on intake of D-allulose for children ages 5 and under to refine the intake by age. The age groups were refined to <1 years; 1-3 years; and 4-5 years. The summary data for mean and 90th percentile intake for both per capita and consumer-only intakes can be found in Table 1 (total D-allulose intake) and Table 2 (D-allulose intake on a per kg bw basis).

[1] Available at Klebsiella infection - About the Disease - Genetic and Rare Diseases Information Center (nih.gov). Accessed October 16, 2022

Table 1. Summary of the Estimated Daily Intake of D-Allulose (Grams) from All Foods (2017-2018)

		Per Capita Intake			Consumer-only Intake		
Age Group	**Gender**	**Mean**	**90th**	**N**	**Percentage**	**Mean**	**90th**
<1 year	Males & Females	0.15	0.00	25	8.3	1.70	4.84
1-3 years	Males & Females	1.54	5.28	187	45.1	3.14	6.20
4-5 years	Males & Females	1.52	4.48	85	40.7	3.25	6.37

Table 2. Summary of the Estimated Daily Intake of D-Allulose (Grams/Kg bw/Day) From All Foods (2017-2018)

		Per Capita Intake		Consumer-only Intake			
Age Group	**Gender**	**Mean**	**90th**	**N**	**Percentage**	**Mean**	**90th**
<1 year	Males & Females	0.02	0.00	25	8.3	0.19	0.49
1-3 years	Males & Females	0.11	0.41	187	45.1	0.23	0.49
4-5 years	Males & Females	0.08	0.23	85	40.7	0.17	0.34

The total number of infants <1 year of age that were consumers of any of the selected food codes, was 25 (8.3% of the total surveyed group) for a total estimated intake of 1.7 g per day (0.19 g/kg bw/day). The most commonly consumed food category was cereal (17 consumers) followed by yogurt (6 consumers). These estimates using the most recent NHANES data, are similar to the intake reported in GRNs 693 and 828 (FDA, 2017; FDA, 2020) which reported per capita intake of infants <2 years to be 4.1 grams per day based on the intended use. The intake estimates for the intake of L&P's D-allulose from the intended use assume that all foods in consumed contain the D-allulose, which is an unlikely scenario. While it is likely that infants would consume cereal specific for the age group, and products containing D-allulose are not intended for infants and will not be marketed for infants, a small number of infants may consume food products containing D-allulose.

The total number of toddlers and children ages 1-3 years that were consumers of any of the selected food codes, was 187 (45.1% of the total surveyed group) for a total estimated intake of 3.14 g/day (0.23 g/kg bw/day). The most commonly consumed food category was cereal (96 consumers) followed by yogurt (76 consumers) and non-carbonated beverages (30 consumers). This indicates that although products containing D-allulose are not intended for toddlers and children and will not be marketed for toddlers and children, the representative food codes include items such as low-sugar cereals and yogurt that are consumed by toddlers and children.

The total number of children ages 4-5 years that were consumers of any of the selected food codes, was 85 (40.7% of the total surveyed group) for a total estimated intake of 3.25 g/day (0.17 g/kg bw/day). The most commonly consumed food category was yogurt (41 consumers) followed by cereal (37 consumers) and non-carbonated beverages (18 consumers). This indicates that although products containing D-allulose are not intended for children and will not be marketed for children, the representative food codes include items such as low-sugar cereals and yogurt that are consumed by children.

• • •

The intake estimates for the intake of D-allulose from the intended use assume that all foods consumed contain the D-allulose, which is an unlikely scenario. L&P intends to add its D-allulose as an ingredient in low calorie and/or dietetic foods, which are foods that are not typically consumed by infants and young children.

The metabolism of D-allulose by infants and young children is not expected to differ from adults and the majority of D-allulose will be excreted in the urine. The intended food uses of L&P's D-allulose do not differ from previous GRNs receiving no questions and will serve as a substitute for other D-allulose products on the market and will not increase the potential intake by infants and young children. While D-allulose is not added to foods specifically targeted to infants and young children, D-allulose has been in the food supply over the last ten years and has likely been consumed by infants and young children. Therefore under the intended uses for L&P's D-allulose there is no indication that intake of D-allulose by children would be a safety concern.

4. *We note that the 90-day repeated dose toxicity study by An et al., 2019 is discussed on page 25 and in Table 17 (pages 27-29). However, the narrative does not fully explain or rebut potentially adverse findings as reported in the notice (i.e., the 11.9% decrease in the body weight of the high-dose males; decreased absolute thymus weight (males); increased absolute weight of the liver and kidneys (females)). Given that L&P notes that the An et al., 2019 study was identified since FDA's review of D-allulose in GRN 000693, please provide a more detailed discussion of this study and the significant findings. For the administrative record, please also clarify if the notifier agrees with the conclusions of the study authors and the NOAEL value of 5,000mg/kg bw/d.*

Response: An et al. (2019) conducted a study which evaluated the subchronic toxicity of D-allulose in male and female Sprague Dawley rats in a 90-day repeat dose study. In this study, the doses ranged up to 5,000 mg/kg bw/day and included a concurrent control group. The endpoints included in the study were standard endpoints included in subchronic toxicity studies. The authors report that there was a 11.9% decrease in the body weight of the high dose males. It is important to evaluate a change in body weight together with all other results as well as reviewing the physiological effects of the test material in order to conclude if the change in body weight is an adverse or non-adverse change. D-allulose has been shown to have anti-obesity activity and a reduction in body weight was not unexpected given the findings reported by others (Ochiai et al., 2013; Matsuo, 2002). L&P agrees with the authors that the decrease in body weight reported in the high dose males was treatment related but was a non-adverse change. The decrease in the absolute weight of the thymus in the high dose males was not seen when the relative thymus weight was calculated and compared to control males. In addition, histopathological evaluation of the thymus showed no microscopic abnormalities. A significant decrease in absolute and relative thymus weights was not reported in the females. Given these findings, L&P agrees with the authors that the decrease in absolute thymus weights in the high dose males was a non-adverse change. A significant increase in absolute and relative liver weights were reported in the high dose females and a significant increase in the relative liver weight was reported in the high dose males. There were no significant correlating changes found in the related serum biochemistry values in the females and the significant changes reported in the males were within historical control ranges. In addition, no microscopic changes were reported in the liver for the

males or the females during histopathological examination. L & P agrees with the authors that the increased liver weights may be treatment related but were non-adverse. A significant increase in the relative weight of both kidneys in the males and a significant increase in the absolute and relative weights of both kidneys in the females was reported. No correlating changes were reported in the serum biochemistry or urinalysis parameters indicating that there were no functional concerns with the kidneys and there were no abnormal histopathological findings. L&P agrees with the authors that these changes were either not treatment related and/or not adverse in nature. The authors of the publication determined that the NOAEL for D-allulose was 5,000 mg/kg bw/day. The authors did not include evaluation of thyroid hormones which would have added value to their conclusions, but this does not preclude the determination of a NOAEL and L&P agrees with the NOAEL under the conditions of the reported study.

5. *On page 25, there is discussion of the results of the Matsuo et al., 2002 toxicity study and states, "The mid and high dose group of D-psicose consumption was determined to be 17 and 20 g per kg bw, respectively. The author concluded that diets extremely high in D-psicose, up to 20 g per kg bw, may be harmful to the intestinal tract." Since the doses given in the Matsuo et al., 2002 study are reported as a percent in the diet for the subchronic feeding study, it is unclear to which experiment (i.e., Experiment 1: Oral acute administration of several levels of D-psicose or Experiment 2: Subchronic feeding of several levels of D-psicose) this sentence is referring. Please clarify if this sentence refers to "Experiment 1" or "Experiment 2" as reported in Matsuo et al., 2002. If this statement refers to the subchronic feeding study, please explain how the mid-and high doses were determined to be 17 g/kg bw/d and 20 g/kg bw/d, respectively.*

Response: The sentence *"The mid and high dose group D-psicose consumption was determined to be 17 and 20 g per kg bw, respectively"* was included in error and is not relevant to the Matsuo et al., 2002 reference and should be disregarded.

6. *Please clarify how the Nishii et al., 2017 study supports the safety of D-allulose considering that the reported dose (0.2 g/kg bw/d) is below the highest 90th percentile EDI (i.e., 0.5 g/kg bw/d) described in the notice.*

Response: This reference provides information regarding the exposure of healthy male and female dogs to D-allulose for 12 weeks at a dose of 0.2 g/kg bw and included a placebo control group. There are some limitations to this study (small group size, only a single dose level, etc.), however it provides supportive safety information for D-allulose even though the dose used in the study and the design of the study do not allow for the determination of an acceptable daily intake in humans. This study was included in the submission to ensure completeness of the submission.

7. *Page 27 includes the statement "L&P has reviewed these studies and concludes that their product is substantively similar to the material from GRN 400 and that the results of the genotoxicity and mutagenicity studies detailed in previous GRNs are relevant to the safety conclusion of L&P's D-allulose product." Please provide a comparison of the composition of the subject of GRN 000400 to L&P's D-allulose to substantiate this statement.*

Response: The specifications for L&P's D-allulose crystalline and syrup are compared with the specifications for CJ Cheijedang, Inc.'s D-allulose crystalline material, as described in GRN 400, in Table 3 below. L&P's crystalline D-allulose has the same minimum D-allulose requirement of not less

than 98.5% allulose (by weight) and both the L&P crystalline and syrup meet or exceed the maximum heavy metal and microbial specifications for D-allulose as presented in GRN 400, with exception of the *Coliform* limit.

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Table 3. L&P D-allulose Specification Comparison to GRN 400 D-allulose Crystalline

Physical and Chemical Parameters	L&P D-allulose (Crystalline)	L&P D-allulose (Syrup)		GRN 400[1] D-allulose (Crystalline)	
	Specification	Specification	Method	Specification	Method
Appearance	White powder, no obvious impurities	Pale yellow liquid, no obvious impurities	Visual	White crystal	NS
Odor	No odor	No odor	N/A	NS	NS
D-Allulose (dry wt)	≥98.5%	≥95.0%	HPLC	>98.5% (wt/wt)	NS
Fructose	≤1.5 %	≤2.0 %	HPLC	<1% (fructose and other sugars) (wt/wt)	NS
Moisture	≤1.0%	N/A	AOAC 941.14	<1% (wt/wt)	NS
pH (of 40% aq)	3.0-7.0	3.0-7.0	pH meter	NS	NS
Ash, wt/wt	≤0.5%	≤0.5%	AOAC 900.02	<0.1% (wt/wt)	NS
Heavy Metals	NS	NS	NS	<1.0 ppm	NS
Lead	≤0.1 mg/kg	≤0.1 mg/kg	AOAC 2015.01	<0.5 ppm	NS
Arsenic	≤0.1 mg/kg	≤0.1 mg/kg	AOAC 2015.01	<1.0 ppm	NS
Cadmium	≤0.1 mg/kg	≤0.1 mg/kg	AOAC 2015.01	NS	NS

Total Plate Count	≤1,000 CFU/g	≤1,000 CFU/g	AOAC 2002.07	<10,000 CFU/g	NS
Yeast and Molds	≤50 CFU/g	≤50 CFU/g	AOAC 997.02	NS	NS
Coliforms	≤0.43 MPN/g	≤0.43 MPN/g	AOAC 989.11	Negative	NS
Staphylococcus aureus	Negative/25 g	Negative/25 g	AOAC 987.09	Negative	NS
Salmonella	Negative/25 g	Negative/25 g	AOAC 987.09	Negative	NS

AOAC – AOAC International, aq – aqueous; CFU – Colony Forming Unit; g – gram; HPLC – High Performance Liquid Chromatography; MPN – most probable number; mg/kg – milligrams per kilogram; N/A – Not applicable; NS – not specified; ppm – parts per million; wt/wt – weight/weight

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If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via email.

Sincerely,

Amy Mozingo, MS
Vice President US Nutra Regulatory Sciences
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References

An, M., Lee, J., Park, Y.-C., Park, C. and Kim, H.-J. (2019) '90-Day repeated oral toxcity test of D-allulose produced from *Microbacterium foliorum*', *Regulatory Toxicology and Pharmacology*, 109.

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ATTACHMENTS

Attachment_Chemistry Q1_Test Report Sulfur Dioxide
Attachment_Chemistry_Q3_Other Sugars (BUSINESS CONFIDENTIAL)
Attachment_Chemistry_Q4_Specifications
Attachement_Chemistry_Q5_Analytical Statement

中广测

检 测 报 告

报 告 编 号：**F201617538b**

委 托 单 位：广东省食品工业研究所有限公司

联 络 信 息：广州市番禺区南村镇金新大道303号

检 测 类 型：☑送检 ☐抽样

收 样 日 期：2020-12-24

批准：　　签发日期：2020-12-31

广东省测试分析研究所（中国广州分析测试中心）

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中广测

检 测 报 告

样品名称：D-阿洛酮糖　　报告编号：F201617538b

样品批号：DP200921　　检测日期：2020-12-24 至 2020-12-31

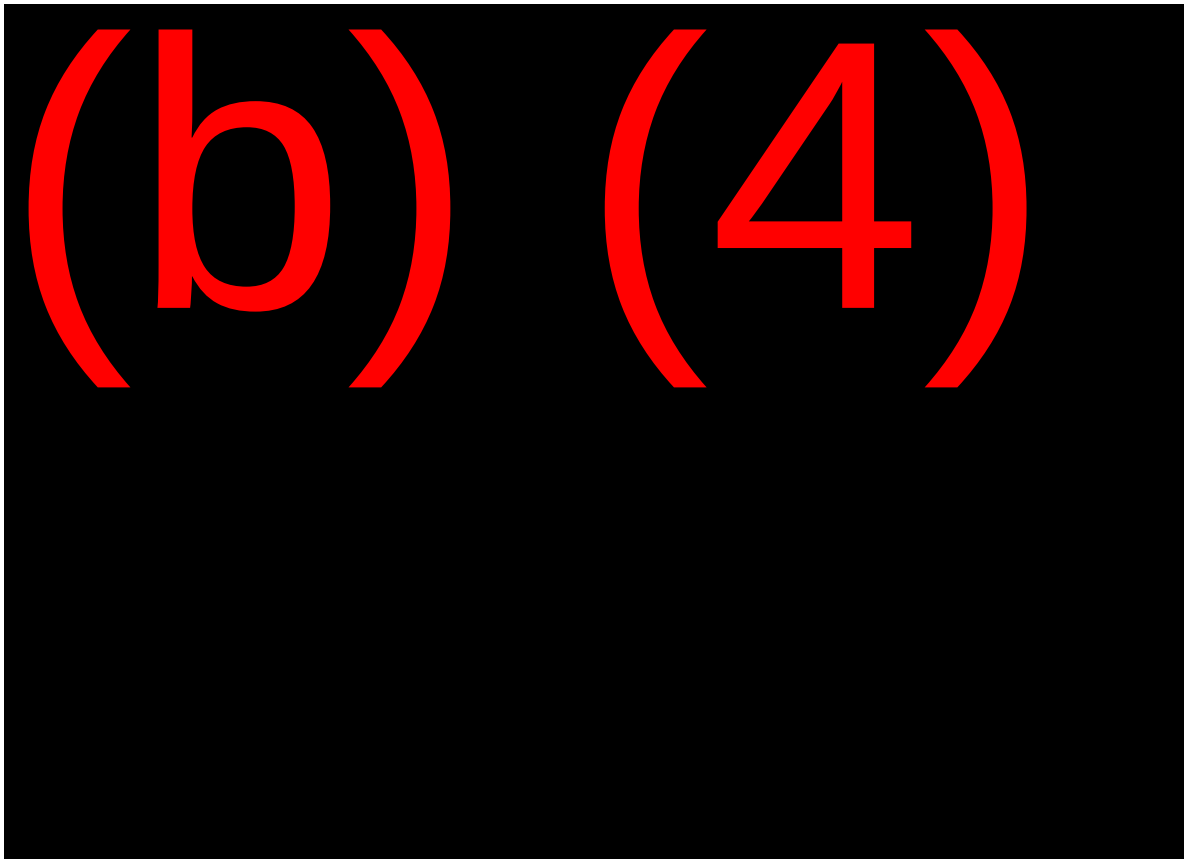
样品性状：粉末　　样品数量：约30g（1包）

其他信息：——

分析检测结果

分析项目	检测结果	计量单位	检测方法
二氧化硫	未检出（定量限0.0100）	g/kg	参照 GB 5009.34-2016
备 注	——。		

以下空白


(b) (4)

L&P Food Ingredient Co.,Ltd

PRODUCTION SPECIFICATION DATA SHEET

Product:	D-Allulose
Storage:	Cool, dry, damp-proof, avoid light.
Shelf life:	24 months.

SPECIFICATIONS

Items	Standard Limits	Analytical Method
Appearance	White powder, no obvious impurities	Visual
Odor	No odor	/
D-Allulose (dry wt.)	≥98.5%	HPLC
Fructose	≤1.5%	HPLC
Moisture	≤1.0%	AOAC 941.14
pH (of 40% aq.)	3.0 - 7.0	pH meter
Ash, wt/wt	≤0.5%	AOAC 900.02
Pb	≤0.1 mg/kg	AOAC 2015.01
As	≤0.1 mg/kg	AOAC 2015.01
Cd*	≤0.1 mg/kg	AOAC 2015.01
Total Plate Count	≤1000 CFU/g	AOAC 2002.07
Mold and Yeast	≤50 CFU/g	AOAC 997.02
Coliforms	≤0.43 MPN/g	AOAC 989.11
Staphylococcus aureus*	Negative/25g	AOAC 987.09
Salmonella*	Negative/25g	AOAC 987.09

The items with * are tested periodically.

Quality Dept. Of L&P Food Ingredient Co., Ltd.
Oct. 11,2022

FOOD INGREDIENT CO., LTD. L&P QUALITY DEPT.

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L&P Food Ingredient Co.,Ltd

PRODUCTION SPECIFICATION DATA SHEET

Product:	D-Allulose
Storage:	Cool, dry, damp-proof, avoid light.
Shelf life:	24 months.

SPECIFICATIONS

Items	Standard Limits	Analytical Method
Appearance	Pale yellow liquid, no obvious impurities	Visual
Odor	No odor	/
Brix	≥71.0%	Brix Meter
D-Allulose (dry wt.)	≥95.0%	HPLC
Fructose	≤2.0%	HPLC
pH	3.0 - 7.0	pH meter
Ash, wt/wt	≤0.5%	AOAC 900.02
Pb	≤0.1 mg/kg	AOAC 2015.01
As	≤0.1 mg/kg	AOAC 2015.01
Cd*	≤0.1 mg/kg	AOAC 2015.01
Total Plate Count	≤1000 CFU/g	AOAC 2002.07
Mold and Yeast	≤50 CFU/g	AOAC 997.02
Coliforms	≤0.43 MPN/g	AOAC 989.11
Staphylococcus aureus*	Negative/25g	AOAC 987.09
Salmonella*	Negative/25g	AOAC 987.09

The items with * are tested periodically.

Quality Dept. Of L&P Food Ingredient Co., Ltd.
Oct. 11,2022

FOOD INGREDIENT CO., LTD. L&P QUALITY DEPT.

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Web: www.lpfoods-wy.com

Statement of analytical methods used for D-allulose

We, L&P Food Ingredient Co.,Ltd., hereby to certify that all analytical methods used for D-allulose batch analysis of the specifications parameters are validated for their respective purpose.

L&P Food Ingredient Co., Ltd

Oct.9th.2022

FOOD INGREDIENT CO., LTD. L&P QUALITY DEPT.

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Viebrock, Lauren

From: Amy Mozingo <amozingo@gras-associates.com>
Sent: Wednesday, June 7, 2023 4:31 PM
To: Viebrock, Lauren
Cc: William J. Rowe
Subject: [EXTERNAL] RE: GRN 1029 Questions
Attachments: GRN 1029_Response to FDA questions 2023.05.25.pdf

Hi Lauren,
Please find attached the response to the questions posed on May 25, 2023 for GRN 1029.
Regards
Amy
Amy Mozingo, MS
VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
O: 301-461-8929| C: 772-532-3454
LinkedIn | Twitter | Blog

From: Amy Mozingo <amozingo@gras-associates.com>
Sent: Monday, June 5, 2023 5:38 PM
To: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Cc: William J. Rowe <wrowe@nutrasource.ca>
Subject: RE: GRN 1029 Questions

Hi Lauren,
We are in receipt of the questions and should have a response back to you before end of the week.
Regards,
Amy

Amy Mozingo, MS
VP US Nutra Regulatory Sciences
GRAS Associates a Nutrasource Pharmaceutical and Nutraceutical Services company
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From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Sent: Thursday, May 25, 2023 9:30 AM
To: Amy Mozingo <amozingo@gras-associates.com>
Cc: William J. Rowe <wrowe@nutrasource.ca>
Subject: GRN 1029 Questions

Dear Ms. Mozingo,

Please find attached the follow-up questions for GRN 1029. Thank you.

Best,
Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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June 7, 2023

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Petition Review
5001 Campus Drive
College Park, MD 20740-3835

Attention: Dr. Lauren Viebrock
Re: GRN 001029—Response to Questions Posed in an Email Dated May 25, 2023

Dear Dr. Viebrock:

Per your request, GRAS Associates, LLC, acting as the agent for L&P Food Ingredient Co., Ltd., is providing responses to FDA's requests for additional clarification as denoted in your email dated May 25, 2023.

***FDA Question 1**:*
On page 18 of GRN 001029, L&P states that allulose is intended to be used in the same food categories and at the same maximum use levels as those described in GRNs 000400, 000693, and 000828. For the administrative record, please confirm that your proposed uses of allulose will be substitutional with the uses of allulose that were previously concluded to be GRAS and therefore, there will be no increase in the cumulative dietary exposure to allulose.

Response:
We confirm that the uses will be substitutional for uses of allulose that were previously concluded to be GRAS and therefore, there will be no increase in the cumulative dietary exposure to allulose.

FDA Question 2:
In the amendment dated October 17, 2022, the notifier provided a summary of the dietary exposure to allulose using food consumption data from the 2017-2018 National Health and Nutrition Examination Survey (NHANES). For the administrative record, please provide the NHANES food codes and corresponding use levels for allulose that were used to estimate the dietary exposure to allulose from the intended uses.

Response:
The food categories and use levels used for the analysis are provided in Table 1. The food codes used in the analysis are provided in Appendix 1.

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Table 1. Food Categories and Use Levels for Calculation

FOOD CATEGORY	MAXIMUM LEVEL (%)
Rolls, cake, pie, pastries, and cookies -low-calorie and diet	10
Chewing gum	50
Fat-based cream used in modified fat/calorie cookies, cakes, and pastries	10
Hard candies, low calorie (including pressed candy, mints)	70
Frozen dairy desserts (regular ice cream, soft serve, sorbet)	5
Carbonated beverages	2.1
Non-carbonated beverages - reduced and low calorie	2.1
Soft candies – low calorie (non-chocolate, plain chocolate, chocolate coated)	25
Sugar substitutes	100
Yogurt (regular and frozen)	5
Ready-to-eat cereals (<5% sugar)	10
Coffee mix	30

FDA Question 3:

In response to toxicology question 3 in the October 17, 2022 amendment, L&P stratified the dietary exposure for children ages 5 and under by age (Tables 1 and 2 of the amendment) and estimated the 90th percentile eaters-only dietary exposure for infants less than 1 year of age to be 0.49 g/kg bw/d. Although not intended for use (or marketed in products consumed by infants), there appears to be some consumption of products containing allulose by this subpopulation. Can you please explain how the dietary exposure estimate for infants less than one year of age is not a concern?

Response:

The intended use of the ingredient does not include foods that are targeted to infants and young children. The intended use is in low calorie and dietetic foods, which are not typically fed to infants. The dietary exposure estimate for infants less than one year of age is not a concern for the following reasons.

- Consumer only/Eaters only data was presented in the October 17, 2022 amendment. Individuals are considered “consumers” if they reported consumption of one or more food products from the selected food codes on either Day 1 or Day 2 of the survey. The consumer only data is not indicative of regular daily consumption but a snapshot that in one of the two days of the survey reporting the food was consumed. It is not expected that infants would be regular or high consumers of low-calorie or dietic foods.
- Food codes selected from the 2017-2018 NHANES dataset included food categories as surrogates to estimate intake. For example, the 2017-2018 dataset does not contain any “lite” or “reduced calorie” food codes for yogurt (regular and frozen); therefore, low fat and nonfat yogurts were selected, and all frozen yogurt food codes were selected. Similarly, only one “less sugar” food code was identified for ready to eat cereals, so lower sugar cereals were selected as surrogates to generate a “high use” scenario of intake. Selecting these surrogates to estimate intake of lower-calorie or dietetic options likely resulted in an overestimation of intake for infants and young children as it is not expected that caregivers would select, and feed products marketed as low-calorie or dietetic to infants.

- The number of infants reporting use of the selected food codes are low (n=25), only 8.3% of the total population of infants less than 1 year of age. Small sample sizes of n<30 for estimates of the mean and n<80 for estimates of the 90th percentile, respectively, may not be considered statistically reliable due to the limited sampling size. The Per Capita intake analysis may be more statistically reliable in this case as it accounts for the total population of infants under 1 year of age (n=301). Per Capita mean and 90th percentile of D-allulose intake (g/kg bw/day) for this population group are 0.02 and 0.00, respectively which is in line with the expectation that infants would not be regular consumers of foods containing allulose.

In summary, the intended use is not in infant food or food formulated specifically for young children. The intended use is in low-calorie/reduced calorie and dietetic foods. Surrogate food codes were selected in cases where dietetic or low-calorie food codes for a food category were not available. The food categories for which surrogate food codes were used included yogurt (regular and frozen) and ready to eat low sugar cereals. Consumer Only/Eaters Only data was used which includes the intake if the food was reported to be consumed in either Day 1 or Day 2 of the survey, which is a snapshot in time and not indicative of chronic daily consumption. The numbers reported for infants consuming these foods were low, which brings into question the statistical reliability of the consumer-only intake reported. Per Capita intake analysis may be more statistically reliable as it accounts for the entire population group. Considering this information and that low-calorie/reduced-calorie foods are not typically selected for infant feeding; the dietary exposure estimate for consumer-only infants is not a safety concern.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact me via email.

Sincerely,

Amy Mozingo, MS
Vice President US Nutra Regulatory Sciences
GRAS Associates, LLC
11810 Grand Park Ave
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North Bethesda, MD 20852

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Appendix 1. Food Codes Utilized in the Intake Analysis/Exposure Assessment

Food Code	Food Name
53104300	Cake, carrot, diet
53105500	Cake, chocolate, with icing, diet
53108220	Snack cake, chocolate, with icing or filling, reduced fat and calories
53109220	Snack cake, not chocolate, with icing or filling, reduced fat and calories
53123500	Cake, shortcake, with whipped topping and fruit, diet
51161030	Roll, sweet, with fruit, frosted, diet
53260030	Cookie, chocolate chip, sugar free
53260200	Cookie, oatmeal, sugar free
53260300	Cookie, sandwich, sugar free
53260400	Cookie, sugar or plain, sugar free
53260500	Cookie, sugar wafer, sugar free
53260600	Cookie, peanut butter, sugar free
12220280	Whipped topping, sugar free
51154510	Roll, diet
92192030	Coffee, mocha, instant, pre-lightened and pre-sweetened with low calorie sweetener, not reconstituted
92192040	Coffee, mocha, instant, decaffeinated, pre-lightened and pre-sweetend with low calorie sweetener, not reconstituted
92193020	Coffee, instant, pre-lightened and pre-sweetened with low calorie sweetener, not reconstituted
92193025	Coffee, instant, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener, not reconstituted
92121030	Coffee, mocha, instant, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92121040	Coffee, instant, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92121041	Coffee, instant, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92121050	Coffee, mocha, instant, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener, reconstituted
92130005	Coffee, pre-lightened and pre-sweetened with low calorie sweetener
92130006	Coffee, decaffeinated, pre-lightened and pre-sweetened with low calorie sweetener
92130030	Coffee, pre-sweetened with low calorie sweetener
92130031	Coffee, decaffeinated, pre-sweetened with low calorie sweetener
12210280	Coffee creamer, liquid, fat free, sugar free, flavored
12210505	Coffee creamer,powder, sugar free, flavored
12210310	Coffee creamer, liquid, sugar free, flavored
13130100	Light ice cream, NFS
13130300	Light ice cream, vanilla

13130310	Light ice cream, chocolate
13135000	Light ice cream sandwich, vanilla
13135010	Light ice cream sandwich, chocolate
13140000	Light ice cream bar, vanilla
13140100	Light ice cream bar, vanilla, chocolate coated
13140115	Light ice cream bar, chocolate
13140710	Creamsicle, light
13142100	Light ice cream cone, vanilla, prepackaged
13142110	Light ice cream cone, chocolate, prepackaged
13161600	Fudgesicle, light
11411410	Yogurt, Greek, low fat milk, plain
11411420	Yogurt, Greek, nonfat milk, plain
11434010	Yogurt, Greek, low fat milk, fruit
11434020	Yogurt, Greek, nonfat milk, fruit
11435020	Yogurt, Greek, low fat milk, flavors other than fruit
11435030	Yogurt, Greek, nonfat milk, flavors other than fruit
11411200	Yogurt, low fat milk, plain
11411300	Yogurt, nonfat milk, plain
11432000	Yogurt, low fat milk, fruit
11433000	Yogurt, nonfat milk, fruit
11434200	Yogurt, low fat milk, flavors other than fruit
11434300	Yogurt, nonfat milk, flavors other than fruit
91106010	Sugar substitute and sugar blend
91107000	Sugar substitute, sucralose, powder
91108000	Sugar substitute, stevia, powder
91108010	Sugar substitute, stevia, liquid
91108020	Sugar substitute, monk fruit, powder
91200000	Sugar substitute, powder, NFS
91200005	Sugar substitute, liquid, NFS
91200040	Sugar substitute, saccharin, powder
91200110	Sugar substitute, saccharin, liquid
91201010	Sugar substitute, aspartame, powder
95322200	Sports drink, low calorie (Gatorade G2)
95322500	Sports drink, low calorie (Powerade Zero)
95323000	Sports drink, low calorie
92900200	Fruit flavored drink, powdered, not reconstituted, diet
92513010	Slush frozen drink, no sugar added
92550400	Vegetable and fruit juice drink, with high vitamin C, diet
92550610	Fruit flavored drink, with high vitamin C, diet
92550620	Fruit flavored drink, diet
92552000	Fruit flavored drink, with high vitamin C, powdered, reconstituted, diet

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92552010	Fruit flavored drink, powdered, reconstituted, diet
92305090	Tea, iced, instant, black, pre-sweetened with low calorie sweetener
92305110	Tea, iced, instant, black, decaffeinated, pre-sweetened with low calorie sweetener
92305920	Tea, iced, instant, green, pre-sweetened with low calorie sweetener
92307510	Iced Tea / Lemonade juice drink, light
92307520	Iced Tea / Lemonade juice drink, diet
92308010	Tea, iced, brewed, black, pre-sweetened with low calorie sweetener
92308040	Tea, iced, brewed, black, decaffeinated, pre-sweetened with low calorie sweetener
92308510	Tea, iced, brewed, green, pre-sweetened with low calorie sweetener
92308540	Tea, iced, brewed, green, decaffeinated, pre-sweetened with low calorie sweetener
92309020	Tea, iced, bottled, black, diet
92309030	Tea, iced, bottled, black, decaffeinated, diet
92309510	Tea, iced, bottled, green, diet
94100200	Water, bottled, sweetened, with low calorie sweetener
92550030	Fruit juice drink, with high vitamin C, light
92550035	Fruit juice drink, light
92550040	Fruit juice drink, diet
92550110	Cranberry juice drink, with high vitamin C, light
92550200	Grape juice drink, light
92550350	Orange juice beverage, 40-50% juice, light
92550360	Apple juice beverage, 40-50% juice, light
92550370	Lemonade, fruit juice drink, light
92550380	Pomegranate juice beverage, 40-50% juice, light
92550405	Vegetable and fruit juice drink, with high vitamin C, light
92552020	Fruit juice drink, reduced sugar (Sunny D)
92400100	Soft drink, NFS, diet
92410320	Soft drink, cola, diet
92410350	Soft drink, cola, decaffeinated, diet
92410370	Soft drink, pepper type, diet
92410400	Soft drink, pepper type, decaffeinated, diet
92410420	Soft drink, cream soda, diet
92410520	Soft drink, fruit flavored, diet, caffeine free
92410560	Soft drink, fruit flavored, caffeine containing, diet
92410620	Soft drink, ginger ale, diet
92410720	Soft drink, root beer, diet
92410820	Soft drink, chocolate flavored, diet
92411610	Soft drink, cola, fruit or vanilla flavored, diet
92411620	Soft drink, cola, chocolate flavored, diet
95312400	Energy drink, low calorie (Monster)
95312410	Energy drink, sugar free (Monster)
95312500	Energy drink, sugar free (Mountain Dew AMP)

95312550	Energy drink, sugar free (No Fear)
95312555	Energy drink, sugar-free (NOS)
95312600	Energy drink, sugar-free (Red Bull)
95312700	Energy drink, sugar free (Rockstar)
95312800	Energy drink, sugar free (Vault)
95313200	Energy drink, sugar free
92410250	Carbonated water, sweetened, with low-calorie or no-calorie sweetener
93301183	Whiskey and diet cola
93301191	Rum and diet cola
93301215	Vodka and diet cola
92410315	Soft drink, cola, reduced sugar
91770030	Dietetic or low calorie candy, chocolate covered
91770000	Dietetic or low calorie candy, NFS
91770010	Dietetic or low calorie gumdrops
91770020	Dietetic or low calorie hard candy
91770050	Dietetic or low calorie mints
91802000	Chewing gum, sugar free
91703080	Caramel, all flavors, sugar free
57000100	Cereal, oat, NFS
57101000	Cereal (Kellogg's All-Bran)
57103000	Cereal (Post Alpha-Bits)
57106050	Cereal (Post Great Grains Banana Nut Crunch)
57123000	Cereal (General Mills Cheerios)
57132000	Cereal (General Mills Chex Corn)
57134000	Cereal, corn flakes
57135000	Cereal (Kellogg's Corn Flakes)
57137000	Cereal, corn puffs
57148000	Cereal (Kellogg's Crispix)
57151000	Cereal, crispy rice
57206700	Cereal (General Mills Fiber One)
57206710	Cereal (General Mills Fiber One Honey Clusters)
57207000	Cereal, bran flakes
57208000	Cereal (Kellogg's All-Bran Complete Wheat Flakes)
57209000	Cereal (Post Bran Flakes)
57214000	Cereal (Kellogg's Frosted Mini-Wheats)
57228000	Granola, homemade
57230000	Cereal (Post Grape-Nuts)
57237100	Cereal (Post Honey Bunches of Oats Honey Roasted)
57237200	Cereal (Post Honey Bunches of Oats with Vanilla Bunches)
57237300	Cereal (Post Honey Bunches of Oats with Almonds)
57241200	Cereal (Post Shredded Wheat Honey Nut)

57301500	Cereal (Kashi 7 Whole Grain Puffs)
57301505	Cereal (Kashi Autumn Wheat)
57301510	Cereal (Kashi GOLEAN)
57301530	Cereal (Kashi Heart to Heart Honey Toasted Oat)
57303100	Cereal (General Mills Kix)
57303105	Cereal (General Mills Honey Kix)
57304100	Cereal (Quaker Life)
57305160	Cereal (Malt-O-Meal Blueberry Muffin Tops)
57306700	Cereal (Malt-O-Meal Toasted Oat Cereal)
57308400	Cereal (General Mills Cheerios Multigrain)
57321900	Cereal (Nature's Path Organic Flax Plus)
57326000	Cereal (Barbara's Puffins)
57327450	Cereal (Quaker Toasted Oat Bran)
57327500	Cereal (Quaker Oatmeal Squares)
57336000	Cereal (General Mills Chex Rice)
57337000	Cereal, rice flakes
57339000	Cereal (Kellogg's Rice Krispies)
57340000	Cereal, puffed rice
57344000	Cereal (Kellogg's Special K)
57401100	Cereal, toasted oat
57408100	Cereal (Uncle Sam)
57411000	Cereal (General Mills Chex Wheat)
57416000	Cereal, puffed wheat, plain
57417000	Cereal (Post Shredded Wheat)
57418000	Cereal (General Mills Wheaties)
57125010	Cereal (General Mills 25% Less Sugar Cinnamon Toast Crunch)
11459990	Frozen yogurt, NFS
11460000	Frozen yogurt, vanilla
11460100	Frozen yogurt, chocolate
11460500	Frozen yogurt, soft serve, vanilla
11460510	Frozen yogurt, soft serve, chocolate
11461200	Frozen yogurt sandwich
11461210	Frozen yogurt bar, vanilla
11461220	Frozen yogurt bar, chocolate
11461250	Frozen yogurt cone, chocolate
11461260	Frozen yogurt cone, vanilla
11461300	Frozen yogurt cone, vanilla, waffle cone
11461320	Frozen yogurt cone, chocolate, waffle cone

Viebrock, Lauren

From: Amy Mozingo <amozingo@gras-associates.com>
Sent: Monday, July 24, 2023 3:47 PM
To: Viebrock, Lauren
Cc: William J. Rowe
Subject: [EXTERNAL] RE: GRN 1029 Confidential
Attachments: Response to FDA Question_ GRN 1029 _24July2023.pdf

Dear Dr. Viebrock,
Please find attached our response to the inquiry. Also note that we also include a correction to a value presented in Table 10 of the GRAS submission.
Regards
Amy

Amy Mozingo, MS
VP US Nutra Regulatory Sciences
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From: Viebrock, Lauren <Lauren.Viebrock@fda.hhs.gov>
Sent: Thursday, July 20, 2023 12:10 PM
To: Amy Mozingo <amozingo@gras-associates.com>
Cc: William J. Rowe <wrowe@nutrasource.ca>
Subject: GRN 1029 Confidential

Dear Mr. Rowe and Ms. Mozingo,

During our review of GRAS Notice No. 001029, we noted that a document submitted as part of the October 17, 2022 amendment in response to our question #3 is labeled confidential. Data and information used to support a GRAS conclusion must be generally available and generally recognized and therefore cannot be confidential. Please clarify whether that information is considered confidential or if it was incorrectly designated confidential. If it is considered confidential, please provide a brief narrative to explain how experts could get to a GRAS conclusion of safety without the confidential information. Please let me know if you have any questions.

If you have questions or need further clarification, please feel free to contact me. Thank you in advance for your attention to our comments.

Regards,

Lauren

Lauren VieBrock, Ph.D.
Regulatory Review Scientist/Microbiology Reviewer

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July 24, 2023

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Attention: Dr. Lauren Viebrock
Re: GRN 001029—Response to Questions Posed in an Email Dated July 20, 2023

Dear Dr. Viebrock:

Per your request, GRAS Associates, LLC, acting as the agent for L&P Food Ingredient Co., Ltd., is providing a response to FDA's request.

FDA Request:
During our review of GRAS Notice No. 001029, we noted that a document submitted as part of the October 17, 2022 amendment in response to our question #3 is labeled confidential. Data and information used to support a GRAS conclusion must be generally available and generally recognized and therefore cannot be confidential. Please clarify whether that information is considered confidential or if it was incorrectly designated confidential. If it is considered confidential, please provide a brief narrative to explain how experts could get to a GRAS conclusion of safety without the confidential information. Please let me know if you have any questions.

Response:
Thank you for the opportunity to clarify. Appendix 3 (HPLC analysis) of the October 17, 2022 amendment was correctly marked as Business Confidential. An Expert Panel could arrive at a GRAS conclusion without this confidential HPLC attachment regarding other sugars for the following reasons:

1. The fructose used in the manufacturing process was high purity (96-98%) and food grade, as noted in item 1 on p. 9 of the GRAS dossier.
2. Data regarding the content of "fructose and other sugars" in the finished products is provided in the stability section of the GRAS dossier (see Tables 8, 9, 10, & 11). The Day 0 content of fructose and other sugars (%) is ~1.45% for the D-allulose syrup and ~0.55% for the crystalline D-allulose.

As noted in the October 17, 2022 response to FDA, "other sugars" refers to some mono and disaccharides from the raw material fructose. Therefore, the total content of residual fructose and other sugars derived from the fructose raw material is ~1.45% for the D-allulose syrup and ~0.55% for the crystalline D-allulose. Given that the residual fructose and other sugars are derived from a high purity

food grade raw material and the low concentration of the components in the finished product, the information does not alter the GRAS conclusion of safety for the finished allulose product. The HPLC analysis is not pivotal information required to reach a GRAS conclusion.

Additionally, we would like to correct an error in Table 10 of the dossier. The acceptance criteria for fructose and other sugars is entered as <1.5%. The acceptance criteria should be <2%.

Sincerely,

Amy Mozingo, MS
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