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

Re: GRAS Notice No. GRN 001029

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001029. We received the notice that you submitted on behalf of L&P Food Ingredient Co., Ltd (L&P) on September 15, 2021, and filed it on March 8, 2022. L&P submitted amendments to the notice on June 7, 2022, October 17, 2022, June 7, 2023, and July 24, 2023, providing additional information on the manufacturing process, specifications, intended uses, dietary exposure, and safety information.[1]

The subject of the notice is D-psicose for use a sweetener at levels from 2.1% to 100% in the food categories listed in Table 1.[2] The notice informs us of L&P's view that these uses of D-psicose are GRAS through scientific procedures.

Table 1. Food categories and intended use levels

Food Category	**Use Level (%)**
Bakery products (rolls, cakes, pies, pastries, and cookies; low-calorie or dietetic)	10
Non-alcoholic beverages (low- and reduced-calorie, sugar-free)	2.1
Hard candy (low-calorie)	70
Soft candy (low- and reduced-calorie, sugar-free)	25
Chewing gum	50
Ready-to-eat cereals (<5% sugar)	10
Coffee mix	30
Frozen dairy desserts (ice cream, soft serve, sorbet; low- and reduced-calorie, sugar-free)	5
Fat-based creams	10

[1] The October 17, 2022 amendment included data that L&P designated confidential. In the July 24, 2023 amendment, L&P provided a brief narrative to explain how experts could get to a GRAS conclusion of safety without the confidential information.
[2] L&P states that D-psicose is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

Sugar substitutes	100
Yogurt and frozen yogurt (low- and reduced-calorie, sugar-free)	5

L&P describes D-psicose (also known as D-allulose) as a white crystalline powder containing ≥98.5% D-psicose or a pale-yellow syrup containing ≥95% D-psicose. D-psicose is a monosaccharide (C-3 epimer of D-fructose) with a molecular weight of 180.16 g/mol and the CAS Registry No. 551-68-8.

L&P describes the method of manufacture of D-psicose. A neutralized D-fructose syrup (≥55% solids) is passed through an immobilized matrix of non-viable *Bacillus subtilis* strain 168[3] bacteria expressing D-psicose 3-epimerase. Enzymatic epimerization of the fructose occurs resulting in conversion D-psicose. The crude D-psicose solution is decolorized using activated carbon and then further purified using ion exchange chromatography to remove ionic impurities. The resulting solution is subjected to a separation chromatography system to separate D-psicose from fructose and other sugars. The purified solution is then concentrated yielding D-psicose syrup, and can then be crystallized, washed, and dried to yield the D-psicose powder. L&P states that all raw materials are food grade and are used in accordance with applicable U.S. regulations or were concluded to be GRAS for their respective uses, and that D-psicose is produced in accordance with current good manufacturing practices. L&P states that no components of the fermentation media are allergens or are derived from allergenic sources.

L&P provides specifications for D-psicose that include D-psicose content (≥95% in syrup or ≥98.5% in powder, dry weight), Brix (≥71 °Bx; syrup), and limits for D-fructose (≤2% in syrup, or ≤1.5% in powder), ash (≤0.5%), lead (≤0.1 mg/kg), arsenic (≤0.1 mg/kg), cadmium (≤0.1 mg/kg), and microorganisms, including *Salmonella* serovars (absent in 25 g). L&P presents the results of the analyses of four non-consecutive batches to demonstrate that D-psicose can be manufactured to meet the specifications. Based on the results of their accelerated stability studies, L&P concludes the shelf life of D-psicose is 2 years at ~25 °C under airtight and light-protected conditions.

L&P estimates the eaters-only dietary exposure for D-psicose from the intended uses to be 8.0 g/person (p)/d (0.11 g/kg body weight (bw)/d) at the mean and 17.6 g/p/d (0.24 g/kg bw/d) at the 90th percentile for the U.S. population aged 1 year and older, based on food consumption data from the 2017-2018 National Health and Examination Survey (NHANES). L&P states that the intended uses of D-psicose would be substitutional for uses of D-psicose previously described in GRNs 000400, 000498, 000693, and 000828[4] and therefore, there will be no increase in the cumulative dietary exposure to D-psicose.[5]

[3] L&P states that the *B. subtilis* strain 168 is non-pathogenic and non-toxigenic.
[4] GRNs 000400, 000498, 000693, and 000828 describe intended uses of D-psicose. We evaluated those GRNs and responded in letters dated June 18, 2012, June 12, 2014, August 28, 2017, and March 2, 2020, respectively, stating that we had no questions at that time regarding each notifier's GRAS conclusion.
[5] We note that the most recent eaters-only dietary exposure estimated in GRN 000693 and cited in GRN 000828 was 11 g/person (p)/d (0.16 g/kg body weight (bw)/d) at the mean and 30 g/p/d (0.42 g/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older using food consumption data from the 2007-2010 NHANES.

L&P states that a literature search was conducted through May 2021 and provides a discussion of the data and information supporting the safety of D-psicose including newly published safety studies. L&P notes that the subjects of this notice, in powder and syrup forms, are equivalent to the ingredients which were the subjects of GRNs 000693 and 000828, respectively. L&P states that the majority of D-psicose is absorbed in the small intestine and the D-psicose that reaches the large intestine (approximately 20%) is not readily fermented by the bacteria typically present in the human gut. L&P summarizes the results of published studies previously discussed in GRN 000693 including subchronic toxicity tests in rats and dogs and a chronic toxicity test in rats. L&P also discusses a published 90-day repeated dose toxicity study in rats which showed no toxicologically relevant effects at doses up to 5 g/kg bw/d, the highest dose tested, and a reproductive toxicity study in rats which showed no toxicologically relevant effects at doses up to 2 g/kg bw/d, the highest dose tested. L&P further states that D-psicose is not carcinogenic. L&P summarizes the results of human studies for D-psicose in healthy adults to support safety. L&P states that its proposed intended conditions of use are identical to those previously evaluated by FDA, and further, L&P intends to add its D-psicose as ingredients in low-calorie or dietetic foods, which are foods typically consumed by adults.

Based on the totality of the data and information, L&P concludes that D-psicose is GRAS for its intended use.

Standards of Identity

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

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing D-psicose bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction

into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of L&P's notice concluding that D-psicose is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing D-psicose. Accordingly, our response should not be construed to be a statement that foods containing D-psicose, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that L&P provided, as well as other information available to FDA, we have no questions at this time regarding L&P's conclusion that D-psicose is GRAS under its intended conditions of use. This letter is not an affirmation that D-psicose is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001029 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.08.04 17:52:34 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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