U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Stella Si
Anchor Center for Certification
No. 1295 Chuan Qiao Road, Building #2, Suite 302
Pudong, Shanghai 201206
CHINA

Re: GRAS Notice No. GRN 001188

Dear Ms. Si:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001188. We received the notice that you submitted on behalf of Shandong Starlight So True Biological Technology Co., Ltd (Starlight) on January 6, 2024, and filed it on May 24, 2024. Starlight submitted amendments to the notice on August 14, 2024, August 28, 2024, and October 20, 2024, providing information clarifying the intended uses, batch analyses, specifications, and safety data.

The subject of the notice is D-psicose for use as a sweetener at levels ranging from 2.1% to 100% in a variety of food categories as described in Table 1.[1] The notice informs us of Starlight's view that these uses of D-psicose are generally recognized as safe (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
Ready-to-eat cereals (<5% sugar)	10
Chewing gum	50
Coffee mix	30
Fat-based cream used in modified fat/calorie cookies, cakes, and pastries	10
Frozen dairy desserts (ice cream, soft serve, sorbet: low-and reduced-calorie, sugar-free)	5
Hard candies, low-calorie (including pressed candy, mints)	70
Soft candies, low-calorie (non-chocolate, plain chocolate, chocolate coated)	25
Sugar substitutes	100

[1] Starlight states that D-psicose is not intended for use in infant formula or in products under the jurisdiction of the U.S. Department of Agriculture.

Food Category	Use level (%)
Yogurt and frozen yogurt (low- and reduced-calorie, sugar-free)	5

Starlight describes D-psicose (also known as D-allulose) as a white crystal or powder containing ≥98% 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.

Starlight describes the method of manufacture of D-psicose. D-psicose is manufactured from D-fructose in an aqueous solution by enzymatic epimerization in the presence of D-psicose 3-epimerase preparation produced by *Bacillus subtilis* SK38.001 expressing a gene encoding the enzyme from *Clostridium scindens* ATCC 35704.[2] The wet *B. subtilis* SK38.001 preparation is added to a D-fructose solution (55-60%) and heated to 55 °C for 12 hours to convert D-fructose to D-psicose. The reaction mixture is then heated to 85 °C for 20 minutes to stop the bioconversion process. The crude D-psicose solution is filtered and then decolorized using activated carbon, subjected to pressure filtration and ion exchange chromatography to remove impurities, and concentrated. The resulting concentrate is further purified through separation chromatography, concentrated, crystallized, washed, and dried to produce D-psicose. Starlight states that D-psicose is manufactured in accordance with good manufacturing practices and that all raw materials and processing aids are food grade and conform with U.S. regulations. Starlight states that none of the raw materials used in the manufacture of D-psicose are or are derived from major food allergens.

Starlight provides specifications for D-psicose that include D-psicose content (≥98%, dry weight basis), D-fructose (≤2%, dry weight basis), moisture (≤1%), ash (≤0.1%), lead (≤0.1 mg/kg), arsenic (≤0.1 mg/kg), cadmium (≤0.1 mg/kg), mercury (≤0.1 mg/kg), and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). Starlight provides the results from the analyses of five (three for *Salmonella* serovars) non-consecutive batches to demonstrate that D-psicose can be manufactured to meet the specifications. Based on results of their accelerated stability study at 40 °C and 75% relative humidity, Starlight estimates that the shelf life of D-psicose is two years when preserved hermetically in packaging at room temperature.

Starlight notes that the intended food categories and use levels of D-psicose are identical to those notified in GRN 001029[3] and provides the eaters-only dietary exposure from the intended uses reported in GRN 001029: 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). Starlight notes that there will be no increase in the current cumulative dietary exposure to D-psicose from the intended uses.

[2] Starlight states that *B. subtilis* SK38.001 is non-toxigenic and non-pathogenic, is not known to produce biogenic amines, and is not present in the final D-psicose.

[3] The subject of GRN 001029 is D-psicose. We evaluated GRN 001029 and responded in a letter dated August 4, 2023, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Starlight summarizes publicly available safety data for D-psicose from prior GRNs for D-psicose (see GRNs 000400, 000498, 000693, 000828, 001024, and 001029)[4] and from updated literature searches through August 2023. Starlight discusses studies on D-psicose absorption, distribution, metabolism, and excretion (ADME), acute (rats and dogs) and subchronic (rats and dogs) toxicity, reproductive and developmental toxicity, mutagenicity, genotoxicity, chronic toxicity in animals, and clinical studies involving human tolerance. Based on these data, Starlight concludes that D-psicose is non-genotoxic and non-carcinogenic. Starlight states that no adverse effects attributable to D-psicose were observed in multiple animal studies including in 90-day studies (1670-2000 mg/kg bw/d) and in a chronic study (approximately 1300 mg/kg bw/d). Additionally, Starlight discusses a reproductive toxicity study in rats in which no adverse effects were observed up to the highest dose tested (2000 mg/kg bw/d). Starlight discusses multiple human tolerance studies on the safety of orally consumed D-psicose. Starlight states that up to 0.5 g/kg bw for men and 0.6 g/kg bw for women of D-psicose were well tolerated. Starlight states that its intended conditions of use of D-psicose are identical to those previously evaluated by FDA and does not identify additional issues of toxicological concern.

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

Standards of Identity

In the notice, Starlight 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 Nutrition Center of Excellence. The Office of Pre-Market 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.

[4] The subject of GRNs 000400, 000498, 000693, 000828, and 001024 is D-psicose. We evaluated these notices and responded in letters dated June 18, 2012, June 12, 2014, August 28, 2017, March 2, 2020, and March 2, 2023, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

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 Starlight'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 Starlight provided, as well as other information available to FDA, we have no questions at this time regarding Starlight'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 001188 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Mical E. Honigfort -S

Digitally signed by Mical E. Honigfort -S
Date: 2024.11.19 14:52:31 -05'00'

for Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program