



Emily Madden, Ph.D.
Intertek Health Sciences Inc.
2233 Argentia Road, Suite 201
Mississauga, Ontario L5N 2X7
CANADA

Re: GRAS Notice No. GRN 001193

Dear Dr. Madden:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001193. We received Sichuan Ingia Biosynthetic Co., Ltd. (Sichuan Ingia)'s notice on February 21, 2024 and filed it on July 30, 2024. Sichuan Ingia submitted amendments to the notice on October 8, 2024 and October 9, 2024, that clarified the production strain identity, manufacturing process, specifications, dietary exposure, and safety information.

The subject of the notice is D-psicose for use as a sweetener at levels ranging from 2% to 100% in a variety of food categories as described in Table 1.¹ The notice informs us of Sichuan Ingia'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)	3-5
Cereals, regular	2
Cereals (low- and reduced-calorie, sugar-free)	5
Chewing gum	50
Coffee mix	30
Confections and frostings	5
Dressings for salads	5
Fat-based creams	10
Frozen dairy desserts (ice cream, soft serve, sorbet: low- and	5

¹ Sichuan Ingia states that D-psicose is not intended for use in infant formula, infant foods, or in products under the jurisdiction of the United States Department of Agriculture.

Food Category	Use level (%)
reduced-calorie, sugar free)	
Gelatins, pudding, fillings (low- and reduced-calorie, sugar-free)	10
Hard candies, low-calorie (including pressed candy, mints)	50
Jams and jellies	10
Soft candies (non-chocolate, plain chocolate, chocolate coated) (low- and reduced-calorie, sugar-free)	25
Sugar	10
Sugar substitutes	100
Sweet sauces and syrups, low- and reduced-calorie, sugar-free	10
Yogurt (regular and frozen), low- and reduced-calorie, sugar-free	5
Grain-based cereal bars and protein bars	15

Sichuan Ingia describes D-psicose (also known as D-allulose) as a white or yellowish powder containing $\geq 98\%$ 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.

Sichuan Ingia describes the method of manufacture of D-psicose. D-psicose is manufactured from fructose by enzymatic epimerization in the presence of D-psicose 3-epimerase produced by fermentation of *Escherichia coli* K-12 MG1655-DPE-01. Sichuan Ingia describes that the production strain *E. coli* MG1655-DPE-01 is a strain of *E. coli* K-12 MG1655 carrying a plasmid for expression of a gene encoding the enzyme from *Ruminococcus* sp. Sichuan Ingia states that *E. coli* MG1655-DPE-01 is deposited with the China General Microbiological Culture Collection Center (CGMCC) and was assigned the deposition number CGMCC 7.563.

Sichuan Ingia states that *E. coli* K-12 is non-pathogenic and non-toxigenic. Sichuan Ingia states that *E. coli* K-12 MG1655 has safely been used in the production of other ingredients that have been concluded to be GRAS for their intended uses (e.g., GRNs 000749, 000897 and 000951).² Sichuan Ingia confirms that whole genome sequencing of the production strain *E. coli* MG1655-DPE-01 revealed no genetic modifications that would lead to harmful antimicrobial or secondary metabolites when compared to the reference genome sequence, and it does not generate undesirable secondary metabolites during fermentation.

E. coli K12 MG1655-DPE-01 is added to a D-fructose solution containing phosphate and manganese salts and heated to 60 °C for 16 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 decolorized and desalinated using activated carbon, and subjected to pressure filtration and ion exchange chromatography to remove impurities. The resulting solution is further purified through separation

² The subject of GRNs 000749 and 000897 is 2'-O-fucosyllactose and the subject of GRN 000951 is 3-fucosyllactose. We evaluated these notices and responded in letters dated April 23, 2018, June 12, 2020 and August 12, 2021, respectively, stating that we had no questions at that time regarding each notifier's GRAS conclusion.

chromatography, concentrated, and crystallized using ethanol. The crystals are separated by centrifugation, washed, and dried to yield D-psicose ($\geq 98\%$). Sichuan Ingia states that D-psicose is manufactured in accordance with good manufacturing practices and that all raw materials and processing aids are food-grade and are used in accordance with U.S. regulations or are GRAS for their intended use.

Sichuan Ingia provides specifications for D-psicose that include D-psicose content ($\geq 98\%$), fructose ($\leq 1.5\%$), glucose ($\leq 0.5\%$), loss on drying ($\leq 1\%$), ash ($\leq 0.1\%$), ethanol (≤ 1000 mg/kg), methanol (≤ 200 mg/kg), lead (≤ 0.1 mg/kg), arsenic (≤ 0.13 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). Sichuan Ingia provides the results from the analyses of three non-consecutive batches to demonstrate that D-psicose can be manufactured to meet the specifications. Based on results of their stability studies, Sichuan Ingia states that D-psicose is stable for at least 24 months at 25 °C and 60% relative humidity, and up to 6 months at 40 °C and 75% relative humidity.

Sichuan Ingia estimates the eaters-only dietary exposure for D-psicose from the intended uses to be 4.2 g/person (p)/d at the mean and 7.2 g/p/d at the 90th percentile for the U.S. population aged 2 year and older based on food consumption data from the 2017-2018 National Health and Examination Survey (NHANES). Sichuan Ingia notes that the intended uses of D-psicose are substitutional for the uses notified in previous GRAS notices for D-psicose (GRNs 000400, 000498, 000693, 000828, 001024, 001029, 001057)³ and therefore, there will be no increase in the cumulative dietary exposure to D-psicose from the intended uses. In addition, Sichuan Ingia incorporates the eaters-only cumulative dietary exposure estimate for D-psicose from GRN 001057, 12.3 g/p/d at the mean and 24.5 g/p/d at the pseudo-90th percentile⁴ for the U.S. population aged 2 years and older based on food consumption data from the 2017-2018 NHANES.

Sichuan Ingia discusses the publicly available safety data for D-psicose from prior GRAS submissions on D-psicose and from an updated comprehensive literature search through January 2024. Sichuan Ingia summarizes the published absorption, distribution, metabolism, and excretion studies in rats and humans, and concludes that D-psicose through oral exposure is mostly absorbed in the small intestine and excreted in urine. Sichuan Ingia states that unabsorbed D-psicose is fermented by the intestinal microbiota into short-chain fatty acids or is excreted in the feces. Sichuan Ingia discusses genotoxicity and mutagenicity studies with D-psicose in addition to several published

³ The subject of GRNs 000400, 000498, 000693, 000828, 001024, 001029, 001057 was D-psicose. We evaluated those GRNs and responded in letters dated June 18, 2012, June 12, 2014, August 28, 2017, March 2, 2020, March 2, 2023, August 4, 2023, and January 25, 2024, respectively, stating that we had no questions at that time regarding each notifier's GRAS conclusion.

⁴ The pseudo-90th percentile dietary exposure approximates the dietary exposure at the 90th percentile by doubling the mean dietary exposure as described in FDA's "Guidance for Industry: Estimating Dietary Intake of Substances in Food" (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-estimating-dietary-intake-substances-food>).

acute and subchronic oral toxicity studies in rats and dogs, reproductive and developmental toxicity studies in rats, and a chronic toxicity study in rats. Sichuan Ingia states that D-psicose is not genotoxic or carcinogenic. Sichuan Ingia concludes that no toxicologically relevant adverse effects were observed in the animal studies, including in a 90-day repeated-dose toxicity study at doses up to 5,000 mg/kg body weight (bw)/d, the highest dose tested.

Sichuan Ingia also summarizes published human clinical studies with D-psicose, including tolerability studies in adults and children. Sichuan Ingia states that the maximum tolerable level in a single-dose study was 0.5 and 0.6 g/kg bw/d for adult males and females, respectively. Sichuan Ingia notes that in a separate study in adults, when D-psicose was consumed throughout the course of a day, the maximum tolerable levels were higher at 0.9 g/kg bw/d. Additionally, Sichuan Ingia discusses a published acute tolerability study with D-psicose conducted in healthy children (6 to 8 years old). Sichuan Ingia notes that D-psicose was well-tolerated in children up to the highest dose tested (4.2 g).

Based on the totality of data and information described above, Sichuan Ingia concludes that D-psicose is GRAS for its intended uses.

Standards of Identity

In the notice, Sichuan Ingia 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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a “major food allergen” declare the allergen’s presence (section 403(w)). The FD&C Act defines a “major food allergen” as one of nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a

food ingredient that contains protein derived from one of those foods. D-psicose may require labeling under the FD&C Act because it may contain protein derived from soybean. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in the Office of Pre-Market Additive Safety. Questions related to food labeling in general 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 Sichuan Ingia’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 Sichuan Ingia provided, as well as other information available to FDA, we have no questions at this time regarding Sichuan Ingia’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 001193 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Mical E.

Honigfort -S

Digitally signed by Mical
E. Honigfort -S
Date: 2024.12.12
09:51:27 -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