Juan Cristián Santa María
Tate & Lyle
5450 Prairie Stone Parkway
Hoffman Estates, IL 60192

Re: GRAS Notice No. GRN 001057

Dear Mr. Santa María:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001057. We received Tate & Lyle (T&L)'s notice on October 5, 2021, and filed it on July 7, 2022. T&L submitted amendments to the notice on July 15, 2022, September 1, 2023, September 5, 2023, September 15, 2023, September 28, 2023, October 3, 2023, October 13, 2023, and December 7, 2023, providing additional clarifying information about the intended use, manufacturing process, specifications, dietary exposure assessment, and an updated literature search.

The subject of the notice is D-psicose for use as a sweetener at levels ranging from 2.5% to 25% in a variety of food categories as described in Table 1.[1] The notice informs us of T&L'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 (%)**
Nutritional beverages	2.5
Nutritional beverages intended for children	3.5
Cereals, ready-to-eat (RTE) and cooked, regular	12
Cereals, RTE and cooked, low-calorie, reduced-calorie, sugar-free	12
Cereals, RTE, grain-free, no sugar, high-protein	20
Frozen dairy products (ice cream, soft serve, sorbet), low-calorie, reduced-calorie, sugar-free	8
Nutrition bars	15
Ketchup and barbecue sauces	10
Cranberries, dried	25
Jerky (meat- or poultry-based)	15

T&L describes D-psicose (also known as D-allulose) as an off-white crystalline powder containing >99.1% D-psicose or a colorless to slightly yellow syrup containing >95% D-

[1] T&L states that D-psicose is not intended for use in infant formula.

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.

T&L states that D-psicose is manufactured from starch derived from corn (*Zea mays* L.) a multi-step process. Corn starch is converted to corn syrup and ultimately to D-glucose by enzymatic hydrolysis using alpha-amylase and glucoamylase. D-Glucose is then D- glucoisomerase. The resulting is separated by chromatography to yield a product containing >85% D-fructose. D-fructose then undergoes epimerization into D-psicose in the presence of D-psicose 3-epimerase.[2] The resulting mixture is separated by chromatography to yield an enriched D-psicose solution that is concentrated, decolorized with activated carbon, and subjected to ion exchange chromatography. Subsequently, the purified solution is further concentrated via evaporation to yield a D-psicose syrup that can be concentrated, crystallized, centrifuged, washed, and dried yielding the crystalline D-psicose. T&L states that D-psicose is manufactured in accordance with good manufacturing practices using enzymes and processing aids that are food grade and conform with applicable U.S. regulations.

T&L provides specifications for D-psicose that include D-psicose content (>95% in syrup or >99.1% in crystalline powder, dry weight), total non-psicose saccharides (<5% in syrup or <0.9% in crystalline powder), dry solids (70-78% in syrup), moisture (< 0.5% in crystalline powder), ash (<0.5% in crystalline powder), pH (3-4.5 for syrup), sulfur dioxide (<10 mg/kg), lead (<0.1 mg/kg), arsenic (<0.1 mg/kg), cadmium (<0.1 mg/kg), mercury (<0.01 mg/kg) and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). T&L presents the results from the analyses of three non-consecutive batches to demonstrate that D-psicose can be manufactured to meet the specifications. T&L states that D-psicose in the crystalline powder form is stable for 30 months and in the syrup form it is stable for 9 months at 25° C and <50% relative humidity.

T&L estimates an eaters-only dietary exposure to D-psicose from the intended uses to be 5.4 g/person (p)/d at the mean and 11.9 g/p/d at the 90th percentile for the U.S. population aged 2 years and older based on food consumption data from the 2017-2018 National Health and Examination Survey (NHANES). T&L estimates an eaters-only cumulative dietary exposure to D-psicose to be 12.3 g/p/d at the mean and 24.5 g/p/d at the pseudo-90th percentile[3] for the US population aged 2 years and older.

T&L summarizes publicly available safety data for D-psicose from prior GRAS notices on D-psicose and from updated literature searches through August 2023. T&L states that

[2] T&L states that glucoisomerase and D-psicose 3-epimerase are purchased and are derived from genetically engineered strains of *Streptomyces rubiginosus* strain "DP-Pzn37" and *Escherichia coli* K12, respectively. The strains used to produce these enzymes are non-pathogenic and non-toxigenic. T&L states that both glucoisomerase and D-psicose 3-epimerase are not expected to be present in the final product.

[3] 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).

no pivotal studies were identified that would contradict their conclusion that the intended uses of D-psicose are safe.

T&L discusses studies on D-psicose absorption, distribution, metabolism and excretion (ADME), acute (rats and dogs) and subchronic (rats) toxicity, reproductive and developmental toxicity, mutagenicity, genotoxicity, chronic toxicity in animals, and clinical studies involving human tolerance. Based on these data, T&L concludes that D-psicose is non-genotoxic and non-carcinogenic. T&L states that no adverse effects attributable to D-psicose were observed in multiple animal studies including in 90-day studies (1670-2000 mg/kg body weight (bw)/d) and in a chronic study (approximately 1300 mg/kg bw/day). Additionally, T&L discusses a reproductive toxicity study in rats published in 2019, where no adverse effects were noted up to the highest dose tested (2000 mg/kg bw/d).

T&L discusses multiple human tolerance studies on the safety of orally consumed D-psicose. T&L states that the established no observed adverse effect level (NOAEL) for the onset of diarrhea in humans from consuming D-psicose is 0.5 g/kg bw for men and 0.6 g/kg bw for women. T&L estimates that the highest cumulative dietary exposure for D-psicose is 26.6 g/p/d for the 19 years and older subpopulation.

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

Standards of Identity

In the notice, T&L 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.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 001057, we

coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers.

FSIS has reviewed the use of D-psicose for use as a sweetener in meat and poultry jerkies. This review was performed in accordance with the procedures outlined in the Memorandum of Understanding between FDA and FSIS to provide T&L with restrictions, conditions of use, or prohibitions that FSIS may have regarding the use of the substance.

Specifically, T&L is requesting the use of D-psicose for use as a sweetener in meat and poultry jerkies at levels up to 15%. FSIS has completed its review and has no objection to the use of D-psicose for use as a sweetener as described above.

Regarding labeling, the ingredient is required to be labeled as "D-psicose," "D-allulose," or "allulose," in the ingredients statement of the products in which it is used.

FSIS requested that we advise you to seek regulatory guidance from its Risk Management and Innovations Staff (RMIS) about the use of D-psicose in meat, poultry, and egg products. You should direct such an inquiry to Stephanie Hretz, Director, RMIS, Office of Policy and Program Development, FSIS by email at Stephanie.Hretz@usda.gov.

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 T&L'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 T&L provided, as well as other information available to FDA, we have no questions at this time regarding T&L'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 001057 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.01.25 20:38:02 -05'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
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cc: Stephanie Hretz, M.P.H.
Director
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