Susan Cho, Ph.D.
AceOne RS, Inc.
5903 Hampton Forest Way
Fairfax, VA 22030

Re: GRAS Notice No. GRN 001148

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001148. We received the notice that you submitted on behalf of Daesang Corporation (Daesang) on May 5, 2023, and filed it on October 31, 2023. Daesang submitted amendments to the notice on March 18, 2024, June 7, 2024, and June 13, 2024, providing additional clarifying information about the production organism, the manufacturing process, revised heavy metal 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 2.1% to 100% in a variety of food categories as described in Table 1.[1] The notice informs us of Daesang'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
Beverages, carbonated, non-alcoholic, low-calorie	3.5
Beverages, non-carbonated, non-alcoholic, low- or reduced-calorie, sugar-free	2.1
Cereals, ready-to-eat (RTE) and cooked, regular	12
Cereals, RTE and cooked, low- or reduced-calorie, sugar-free	12
Cereals, RTE (<5% sugar)	10
Cereals, RTE, grain-free, no sugar, high-protein	20
Chewing gum	50
Coffee mix	30
Confections and frostings	5
Dressings for salads	5

[1] Daesang states that D-psicose is not intended for use in infant formula or in products that are under the jurisdiction of the United States Department of Agriculture.

Food Category	**Use level (%)**
Fat-based cream used in modified fat/calorie cookies, cakes, pastries, and pies	10
Frozen dairy desserts (ice cream, soft serve, sorbet: low- or reduced-calorie, sugar-free)	8
Gelatins, pudding, fillings (low- or reduced-calorie, sugar-free)	10
Hard candies (low-calorie)	70
Soft candies (non-chocolate, plain chocolate, chocolate coated) (low- or reduced-calorie, sugar-free)	25
Jams and jellies	10
Sugar	10
Sugar substitutes	100
Sweet sauces and syrups, low- or reduced-calorie, sugar-free	10
Yogurt (regular and frozen), low- or reduced-calorie, sugar-free	5
Nutrition bars, grain-based cereal bars, protein bars	15
Alcoholic beverages (premixed cocktails, wine coolers, hard seltzers, and malt beverages), low- or reduced-calorie; low- or reduced-sugar	3.5
Nutritional beverages	2.5
Nutritional beverages for children	3.5
Ketchup and barbeque sauces	10
Cranberries, dried	25

Daesang describes D-psicose (also known as D-allulose) as a white crystalline powder containing ≥98 % D-psicose or a light-yellow syrup containing ≥65% 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.

Daesang describes the method of manufacture of D-psicose. D-psicose is manufactured from D-fructose syrup by enzymatic epimerization in the presence of D-psicose-3-epimerase enzyme preparation produced by *Corynebacterium glutamicum* strain KCCM 80101 expressing a gene encoding the enzyme from *Flavonifractor plautii*. Daesang states that *C. glutamicum* strain KCCM 80101 is non-pathogenic and non-toxigenic, and is deposited in the Korean Culture Center of Microorganisms (KCCM) in Seoul, South Korea.

C. glutamicum strain KCCM 80101 is immobilized on sodium alginate beads in the presence of manganese sulfate or magnesium sulfate. Enzymatic epimerization of the D-fructose occurs resulting in conversion to D-psicose. The crude D-psicose solution is decolorized using activated carbon, subjected to ion exchange chromatography to remove impurities, and then concentrated. The resulting concentrate is further purified through separation chromatography, decolorized, subjected to ion exchange chromatography and concentrated to yield a D-psicose syrup (≥65%), which is subsequently dried to produce crystalline D-psicose (≥98%). Daesang states that D-psicose is manufactured in accordance with good manufacturing practices and that all raw materials, processing aids and ion exchange resins are food grade and are used in

accordance with applicable U.S. regulations. Daesang states that no raw materials used in the manufacture of D-psicose are allergens or are derived from allergenic sources.

Daesang provides specifications for D-psicose that include D-psicose content (≥65% in syrup or ≥98 % in powder), total non-D-psicose saccharides (<3% in syrup or <2% in powder), moisture (<33% in syrup or <5% in powder), Brix (≥63 in syrup), ash (≤0.5%), lead (≤0.1 mg/kg), arsenic (≤0.1 mg/kg), cadmium (≤0.1 mg/kg), and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). Daesang 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 the stability studies, Daesang states that D-psicose in the powder form is stable for at least 4 months at 25 °C, 65% relative humidity, and at 40 °C, 75% relative humidity.

Daesang notes that the intended uses of D-psicose are substitutional for uses notified in previous GRAS notices for D-psicose (GRNs 000400,000498, 000693, 000828, 001024, 001029, 001057)[2] and therefore, there will be no increase in the cumulative dietary exposure to D-psicose. In addition, Daesang incorporates the eaters-only cumulative dietary exposure estimate for D-psicose from GRN 001057 of 12.3 g/person (p)/d at the mean and 24.5 g/p/d at the pseudo-90th percentile[3] 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).

Daesang summarizes publicly available safety data for D-psicose from prior GRAS notices on D-psicose and from updated literature searches through February 2024. Daesang discusses studies on D-psicose absorption, distribution, metabolism and excretion (ADME), acute (rats) 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, Daesang concludes that D-psicose is non-genotoxic and non-carcinogenic. Daesang 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/d). Additionally, Daesang 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). Daesang discusses multiple human tolerance studies on the safety of orally consumed D-psicose. Daesang 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.

As the intended uses of D-psicose are substitutional for uses described in previous GRAS

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[2] The subject of GRNs 000400,000498, 000693, 000828, 001024, 001029, and 001057 is D-psicose. We evaluated these 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 regrading each notifier's GRAS conclusion.

[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).

notices for D-psicose that were submitted to FDA and received response letters stating that we had no questions at that time regarding each notifier's GRAS conclusion and there will be no increase in the cumulative dietary exposure to D-psicose, there were no additional issues of toxicological concern identified by Daesang.

Daesang states that *C. glutamicum* is widely used in the production of other ingredients that have been concluded to be GRAS for their intended uses (e.g., GRN 000932).[4] While *C. glutamicum* strain KCCM 80101 contains a gene encoding for kanamycin resistance (*nptII)*, this was used as a selection marker during the construction of the production strain, and Daesang states that *C. glutamicum* strain KCCM 80101 is not capable of transferring *nptII* to co-cultured microorganisms.

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

Standards of Identity

In the notice, Daesang 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

[4] The subject of GRN 000932 is 2′-fucosyllactose. We evaluated GRN 000932 and responded in a letter dated February 18, 2021, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

section 301(ll)(1)-(4) applies. In our evaluation of Daesang'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 Daesang provided, as well as other information available to FDA, we have no questions at this time regarding Daesang'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 001148 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

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Director
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