Susan S. Cho, Ph.D.
NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029

Re: GRAS Notice No. GRN 000828

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000828. We received the notice you submitted on behalf of Samyang Corporation (Samyang) on November 28, 2019, and filed it on March 25, 2019. Samyang submitted an amendment to the notice on November 11, 2019, that provided additional information about the organism used in the manufacture of the notified substance.

The subject of the notice is D-psicose for use as a sugar substitute in bakery products (rolls, cakes, pastries, cakes, low calorie, or dietetics); non-alcoholic beverages (low- or reduced-calorie, sugar-free); cereals (regular, low- and reduced-calorie, sugar-free); chewing gums; confections and frostings; frozen dairy desserts (ice cream, soft serve, sorbet; low- and reduced-calorie, sugar-free); yogurt and frozen yogurt (low- and reduced-calorie, sugar-free); dressings for salads; gelatins, pudding, and fillings (low- and reduced-calorie, sugar-free); hard and soft candies (low- and reduced-calorie, sugar-free); jams and jellies; sugar; sugar substitutes; sweet sauces and syrups (low- and reduced-calorie, sugar-free); and fat-based creams at levels ranging from 2 to 100%.[1] The notice informs us of Samyang's view that this use of D-psicose is GRAS through scientific procedures.

Samyang provides information about the identity of D-psicose (also known as D-allulose). D-psicose is a monosaccharide with a molecular weight of 180.16 and the CAS Registry No. 551-68-8. Samyang states that D-psicose will be used as a syrup containing either a minimum of 10 or 90% D-psicose, or as a crystalline product containing 98% D-psicose.

Samyang describes the method of manufacture of D-psicose. D-psicose is manufactured from fructose in aqueous solution by enzymatic epimerization in the presence of manganese sulfate or magnesium sulfate. Fructose syrup (>50% solids concentration) is passed through a matrix consisting of non-viable *Microbacterium foliorum*[2] possessing D-psicose-3-epimerase activity that is immobilized to calcium alginate gel beads.

[1] D-psicose is not intended to be added to infant formula or to foods under the USDA's jurisdiction.
[2] Samyang states that the production microorganism used is non-toxic and non-pathogenic.

The fructose is enzymatically converted to D-psicose at 50°C. The D-psicose solution is clarified by pressure filtration with active carbon, followed by ion exchange chromatography to remove any impurities (salts, amino acids, peptides, and proteins). The resulting syrup is the minimum 10% D-psicose product. This product is further purified through separation chromatography and concentrated to produce the minimum 90% D-psicose product. Subsequently, the minimum 90% D-psicose solution is further concentrated by evaporation, then crystallized and dried yielding the powdered product (98% D-psicose).

Samyang provides specifications for D-psicose. These include specifications for D-psicose content for each product (≥98% crystalline; or ≥90%, or ≥10% syrup), moisture (≤2% crystalline; or ≤ 65%, or ≤ 35%, respectively, syrup), and limits for lead (≤0.5 mg/kg), arsenic (≤0.5 mg/kg), cadmium (≤0.5 mg/kg), and microorganisms. Samyang presents the results of analyses of five batches that show the product can be manufactured to meet these specifications.

Samyang estimates the dietary exposure to D-psicose from its intended use in foods using the data from the National Health and Nutrition Examination Survey (NHANES 2007-2010). The dietary exposure to D-psicose for the U.S. population aged 2 years and older is 11.0 g/d at the mean and 30.0 g/d at the 90th percentile. On a body weight basis, these estimates are 0.16 g/kg body weight (bw)/d at the mean and 0.42 g/kg bw/d at the 90th percentile. Samyang notes that because the intended uses and use levels of D-psicose in this notice are identical to those in GRN 000693,[3] there would be no change in dietary exposure, as this product would be used interchangeably with the D-psicose in that notice. Samyang also notes that these estimates are highly amplified since it is not likely that D-psicose will be used at the maximum levels in all the intended food categories.

Samyang states that a literature search was done through October 2018 and discusses published information since FDA's review of GRN 000693. Based on published studies, Samyang states that part of the orally administered D-psicose is absorbed in the digestive tract and excreted without being significantly metabolized. Unabsorbed D-psicose is fermented to short chain fatty acids by intestinal microflora in the colon or is excreted in the feces. Samyang discusses several published animal studies, including subchronic toxicity studies in rats and dogs and a chronic toxicity study in rats. From the chronic toxicity study in rats, Samyang concludes that up to 1,280 mg D-psicose/kg bw/day, the highest level tested, is well-tolerated. Samyang discusses several published human studies and concludes that the maximum tolerable level of orally administered D-psicose is 33.0-36.0 g/day for an adult weighing 60 kg. Samyang further states that the production microorganism *M. foliorum* SYG27B-MF is a non-toxigenic, non-pathogenic strain that is suitable for use in the production of D-psicose.

Based on the totality of evidence, Samyang concludes that D-psicose is GRAS for its intended use.

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[3] D-psicose was the subject of GRN 000693. We evaluated that notice and responded in a letter dated August 28, 2017, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Standards of Identity

In the notice, Samyang 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 Code of Federal Regulations. 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 Samyang'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 Samyang provided, as well as other information available to FDA, we have no questions at this time regarding Samyang'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 000828 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.03.02 11:57:32 -05'00'

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