



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

Re: GRAS Notice No. GRN 000693

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000693. We received the notice you submitted on behalf of Samyang Corporation (SAMYANG) on February 2, 2017, and filed it on March 20, 2017. We received amendments to the notice on May 12, 2017, and June 9, 2017. The May 12, 2017, amendment corrects literature citations and removes an intended use of flavor modifier thus resulting in the intended use as stated in the next paragraph. The June 9, 2017, amendment provides details about the cloned gene and additional information on the transformation genetics of the enzyme gene, allergen potential of the cloned enzyme, and an analysis of the non-toxicity/non-pathogenicity of the production microorganism.

The subject of the notice is D-psicose. The notice informs FDA of the view of Samyang that D-psicose is GRAS, through scientific procedures, for use as a sugar substitute in bakery products, beverages, cereals, chewing gums, confections and frostings, frozen dairy desserts, yogurt and frozen yogurt, dressings for salads, gelatins, pudding and fillings, hard and soft candies, jams and jellies, sugar, sugar substitutes, sweet sauces and syrups, and fat-based creams at levels ranging from 2 to 100%.

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 describes the manufacturing process for four D-psicose products, three of which are syrups and one of which is a powder. D-psicose is manufactured from fructose in aqueous solution by enzymatic epimerization in the presence of magnesium chloride. Fructose syrup (>50% solids concentration) is passed through a matrix consisting of

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non-viable *Corynebacterium glutamicum* expressing the enzyme D-psicose-3-epimerase<sup>1</sup> from *Clostridium scindens* that is immobilized to calcium alginate gel beads. 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). Subsequently, the D-psicose solution is concentrated with an evaporator to produce syrups with various D-psicose concentrations (product 1, ≥20% D-psicose; product 2, ≥50% D-psicose; product 3, ≥90% D-psicose). Crystallization of the D-psicose solution followed by drying yields the powdered product 4 (≥98% D-psicose).

Samyang provides specifications for all four D-psicose products. These include specifications for D-psicose content (ranging from ≥20% to ≥90% D-psicose, depending on the product), water; and, limits for lead (≤0.5 mg/kg), arsenic (≤0.5 mg/kg), and microbiological contaminants. Samyang presents the results of analyses of three batches of each product that show that they comply with the specifications.

Samyang estimates the dietary exposure levels 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 (above the age of 2) is 11.0 g/d at the mean and 30.0 g/d at the 90<sup>th</sup> 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 90<sup>th</sup> percentile. Samyang notes that because the intended uses and use levels of D-psicose in this notice are a combination of those described in GRN 000400 and GRN 000498<sup>2</sup> for D-psicose, the estimated dietary exposures in GRN 000693 are slightly higher than those described in GRN 000400 and GRN 000498. Samyang notes that the use of D-psicose is substitutional for the food uses described in GRN 000400 and GRN 000498. Additionally, Samyang states that these estimates are conservative since it is not likely that D-psicose will be used at the maximum levels in all of the intended food categories.

Samyang discusses the safety of D-psicose, noting an updated search of the literature through December 2016. Samyang summarizes published safety information described in GRN 000400 and GRN 000498 and states that the information on metabolism and the safety data in these notices are incorporated into GRN 000693. Samyang also discusses additional published studies of D-psicose not mentioned in the previous notices, including one single-dose study in dogs and five additional repeat-dose studies in rats and mice that ranged from 8 to 60 weeks. In evaluating the results from these additional published studies, Samyang concludes that none of these studies contradict the safety of D-psicose from its intended use. Samyang states that there are no new studies, relating to tolerability or adverse effects, of D-psicose in humans since the

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<sup>1</sup>Samyang states that the D-psicose-3-epimerase enzyme is produced from *C. scindens* and states that the production microorganism used is non-toxic and non-pathogenic.

<sup>2</sup>GRN 000400 and GRN 000498 described the intended use of D-psicose in various food categories. We evaluated GRN 000400 and responded with a letter on June 18, 2012, stating that we had no questions at that time regarding CJ Cheiljedang, Inc.'s GRAS conclusion. We evaluated GRN 000498 and responded with a letter on June 12, 2014, stating that we had no questions at that time regarding Matsutani Chemical Industry Company's GRAS conclusion.

previous notices, and concludes that the maximum tolerable level in humans remains 0.5 g/kg bw/d for males and 0.6 g/kg bw/d for females. These values correspond to 45-46 g/person/d for an average American consumer aged 20 years or older. Samyang states that the only known side effect of ingesting large amounts of poorly digestible carbohydrates such as D-psicose is gastrointestinal discomfort, which is usually transient and not considered to be of toxicological significance. Thus, Samyang concludes that the intended use of D-psicose does not raise any safety concerns.

Samyang includes the report of a panel of individuals (Samyang's GRAS panel). Based on its review, Samyang's GRAS panel concluded that D-psicose is safe under the conditions of its intended use.

Based on the data and information described above, Samyang concludes that D-psicose is GRAS for its intended use in food.

### **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**

In describing dietary D-psicose as a macronutrient, Samyang raises a potential issue under the labeling provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular. Section 403(r) of the FD&C Act lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. If products that contain D-psicose bear any claims on the label or in labeling, such claims are 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 neither consulted with ONFL on this labeling issue nor evaluated the information in your notice to determine whether it would support any claims made about D-psicose on the label or in labeling.

### **Section 301(II) of the FD&C Act**

Section 301(II) 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(II)(1)-(4) applies. In its review of Samyang's notice that D-psicose is GRAS for the intended use, FDA did not consider whether section 301(II) or any of its

exemptions apply to foods containing D-psicose. Accordingly, this response should not be construed to be a statement that foods that contain D-psicose, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

## **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 000693 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

**Michael A. Adams -**

**S**

**Dennis M. Keefe, Ph.D.**

**Director**

**Office of Food Additive Safety**

**Center for Food Safety**

**and Applied Nutrition**

Digitally signed by Michael A. Adams -S  
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