



William J. Rowe  
 GRAS Associates, LLC  
 11810 Grand Park Ave.  
 Suite 500  
 North Bethesda, MD 20852

Re: GRAS Notice No. GRN 001024

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001024. We received the notice that you submitted on behalf of Blue California on July 28, 2021, and filed it on November 17, 2021. Blue California submitted amendments to the notice on March 18, 2022, April 29, 2022, October 6, 2022, December 14, 2022, January 19, 2023, January 23, 2023, February 9, 2023, and March 2, 2023, providing additional clarifying information about the production organism, the 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% to 100% in a variety of food categories as described in Table 1.<sup>1</sup> The notice informs us of Blue California’s view that these uses of D-psicose are GRAS through scientific procedures.

Table 1. Food categories and intended use levels

<b>Food Category</b>	<b>Use Level (%)</b>
Bakery products (rolls, cakes, pies, pastries, and cookies; low calorie or dietetic, rolls, cakes, and pastries)	10
Non-alcoholic beverages (low- and reduced-calorie, sugar-free)	3.5
Hard candy	50
Soft candy (low- and reduced-calorie, sugar-free)	25
Chewing gum	50
Cereals, regular	2
Cereals (low- and reduced-calorie, sugar-free)	5
Coffee mix	30
Confections and frostings	5
Dressings for salads	5

<sup>1</sup> Blue California states that D-psicose is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture.

<b>Food Category</b>	<b>Use Level (%)</b>
Frozen dairy desserts (ice cream, soft serve, sorbet; low- and reduced-calorie, sugar-free)	5
Gelatins, puddings, and fillings (low- and reduced-calorie, sugar-free)	10
Fat-based creams	10
Jams and jellies	10
Sugar	10
Sugar substitutes	100
Sweet sauces and syrups (low- and reduced-calorie, sugar-free)	10
Yogurt and frozen yogurt (low- and reduced-calorie, sugar-free)	5
Alcoholic beverages (pre-mixed cocktails, wine coolers, and malt beverages; low- and reduced-calorie)	3.5

Blue California describes D-psicose (also known as D-allulose) as an off-white to white powder containing a minimum of 97% D-psicose. D-psicose is a monosaccharide (C-3 epimer of D-fructose) with a molecular weight of 180.16 g/mole and the CAS Registry No. 551-68-8.

Blue California describes the method of manufacture of D-psicose. D-psicose is manufactured from neutralized fructose syrup by enzymatic epimerization in the presence of a D-psicose 3-epimerase enzyme preparation produced by *Escherichia coli* K-12 strain 49761 expressing a gene encoding the enzyme from *Thermoclostridium caenicola*. Blue California states that *E. coli* K-12 strain 49761 is non-pathogenic and non-toxicogenic, and is deposited in the Addgene culture collection in Watertown, Massachusetts.

The D-fructose substrate is mixed with the enzyme preparation to convert D-fructose to D-psicose. The reaction is allowed to proceed for 12 hours, followed by heating the reaction mixture to 85 °C for 20 minutes to denature the enzymes. The crude D-psicose solution is centrifuged and filtered to remove denatured protein and then clarified with activated carbon, followed by ion exchange chromatography to remove impurities. The resulting D-psicose solution is subjected to a separation chromatography system to separate D-psicose from fructose and is then concentrated. Subsequently, the purified D-psicose concentrate is crystallized using an ethanol-water mixture and dried yielding the D-psicose powder. Blue California states that D-psicose is produced in accordance with current good manufacturing practices. Blue California states that all raw materials, and processing aids are food grade, and are used in accordance with applicable U.S. regulations or were concluded to be GRAS for their respective uses. Blue California states that no components of the fermentation media are allergens or are derived from allergenic sources.

Blue California provides specifications for D-psicose that include D-psicose content (≥97% dry weight), ash (<0.5%), ethanol (<1,000 mg/kg), methanol (<200 mg/kg), lead (<0.5 mg/kg), arsenic (<0.5 mg/kg), cadmium (<0.5 mg/kg), mercury (<0.5 mg/kg), and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). Blue

California presents the results of the analyses of five non-consecutive batches to demonstrate that D-psicose can be manufactured to meet the specifications. Based on the results from their accelerated stability study, Blue California states that D-psicose is stable for up to 6 months at 40 °C, 75% relative humidity.

Blue California provides an eaters-only dietary exposure estimate for D-psicose from the intended uses to be 9.4 g/person (p)/d (0.13 g/kg body weight (bw)/d) at the mean and 22.7 g/d (0.32 g/kg bw/d) at the 90<sup>th</sup> 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). In addition, Blue California estimates an eaters-only cumulative dietary exposure from the intended uses of D-psicose and background sources (GRN 000828<sup>2</sup>) to be 9.8 g/p/d (0.14 g/kg bw/d) at the mean and 22.9 g/p/d (0.33 g/kg bw/d) at the 90<sup>th</sup> percentile for the U.S. population aged 2 years and older.

Blue California summarizes publicly available safety data for D-psicose from prior GRAS notice submissions on D-psicose and from updated literature searches through March 2022. Blue California states that no new *in vitro*, carcinogenicity, genotoxicity, or mutagenicity studies pertaining to the safety of D-psicose were identified in the updated literature search.

Blue California discusses *in vitro* genotoxicity and mutagenicity studies, and *in vivo* absorption, distribution, metabolism, and excretion studies in rats and humans, acute oral administration studies in male rats and dogs, a 34-day subchronic feeding study in rats, 2 90-day feeding studies in rats, a 12-week feeding study in dogs, and an 18-month chronic feeding study in rats in support of the safe use of D-psicose in food. Based off these data, Blue California concludes that D-psicose is non-genotoxic and not carcinogenic. Blue California states that, based on animal studies, D-psicose is generally considered well tolerated at doses up to 5,000 mg/kg bw/d. Additionally, Blue California discusses a recent, published reproductive toxicity study in rats, where no adverse effects were noted up to the highest dose tested (2,000 mg/kg bw/d).

Blue California discusses multiple human tolerability studies on the safety of orally consumed D-psicose. Blue California notes that the maximum tolerable single dose level for D-psicose in humans was reported to be 0.50 and 0.60 g/kg bw/d for males and females, respectively. Blue California notes that the highest cumulative dietary exposure of their D-psicose for any subpopulation is 0.48 g/kg bw/d (children aged 2-12 years).

Blue California states that *E. coli* K-12 is a common industrial strain and has safely been used in the production of other ingredients that have been concluded to be GRAS for their intended uses (e.g., GRNs 000155, and 000308).<sup>3</sup> Blue California states that *E. coli* K-12 strain 49761 contains no antibiotic resistance genes and is not known to

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<sup>2</sup> The subject of GRN 000828 is D-psicose. We evaluated GRN 000828 and responded in a letter dated March 2, 2020, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

<sup>3</sup> The subjects of GRNs 000155 and 000308 are alpha-cyclodextrin and L-leucine, respectively. We evaluated these notices and responded in letters dated December 22, 2004, and April 30, 2010, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

produce any toxic amines.

Based on the totality of data and information described above, Blue California concludes that D-psicose is generally recognized as safe for its intended uses.

### **Standards of Identity**

In the notice, Blue California 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 section 301(ll)(1)-(4) applies. In our evaluation of Blue California'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 Blue California provided, as well as other information available to FDA, we have no questions at this time regarding Blue California'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 001024 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.  
Carlson -S

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