Donald F. Schmitt, M.P.H.
Senior Managing Scientist
ToxStrategies, Inc.
931 W. 75th St., Suite 137, PMB 263
Naperville, IL 60565

Re: GRAS Notice No. GRN 000789

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000789. We received the notice that you submitted on behalf of Cargill, Inc. (Cargill) on June 22, 2018, and filed it on July 20, 2018. Cargill submitted an amendment to the notice on September 5, 2018, clarifying the intended uses of erythritol.

The subject of the notice is erythritol produced through fermentation by *Moniliella pollinis* for use as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer in a variety of foods as described in Table 1 (below).[1] The notice informs us of Cargill's view that these uses of erythritol are GRAS through scientific procedures.

Table 1. Food Uses by Use Level

Food Uses	**Use Level (%)**
Hot cereal (oatmeal – instant or cooked)	3
Alcoholic lite beer and coolers; Flavored quenchers; Reduced- and low-calorie carbonated and non-carbonated beverages (excluding soy-based drinks); Fruit-based slushies; Dairy drinks (chocolate and flavored milks); Fruit-based smoothies	3.5
Yogurt	5
Soy, almond, cashew, coconut and other plant-based drinks	6

[1] In its September 5th amendment, Cargill clarifies that erythritol is intended for use in sauces and toppings used in "pour over" applications on meat products. According to Cargill, the sauces and toppings will not be used within, or as part of, the actual meat product. Cargill concludes that the intended uses of erythritol described in GRN 000789 do not fall under the jurisdiction of the United States Department of Agriculture.

Food Uses	**Use Level (%)**
Non-dairy toppings; Frozen desserts (regular ice cream, soft serve, sorbet, frozen yogurt); Puddings (instant, phosphate set); Salty snacks	10
Baked goods and baking mixes (excluding regular bread); Bars (granola, high protein); Cookies; Barbecue sauce; Tomato sauce; Low calorie salad dressings; Fillings (fruit, custard, cream, pudding); Jams and jellies; Canned fruit (syrup); Regular or low-calorie syrups or toppings	15
Cakes	25
Ready-to-eat cereals	30
Fruit novelty snacks (e.g., fruit peel, fruit candy bar, fruit leathers, fruit creams, fruit snack candy, gummy fruits); Non-chocolate candies; Soft chocolate candies	45
Fat-based cream used in modified-fat or low-calorie cookies, cakes and pastries;	60
Chewing gum	75
Hard candy (mints, pressed, candies, cough drops)	99
Sugar substitutes	100

Cargill provides information about the chemical identity and specifications for erythritol. Erythritol is identified by CAS Registry No. 149-32-6 and the empirical formula is $C_4H_{10}O_4$. Cargill describes erythritol as odorless white crystals and provides specifications, including purity (> 95.5%), reducing sugars (<0.3%), ribitol and glycerol (<0.1%), microbial limits, and limits on lead (<0.5 mg/kg). Cargill states that erythritol is manufactured to meet the specifications in the Food Chemicals Codex, 10th Edition (2017) monograph. The analytical results from three non-consecutive batches demonstrate that erythritol can be manufactured to meet the specifications.

Cargill states that erythritol is manufactured through fermentation of a simple sugar solution, such as glucose or sucrose, using a pure culture of *M. pollinis*; this microorganism was also utilized in the production of erythritol described in GRNs 000076 and 000401. Following fermentation, the culture is heated to kill the microorganism and filtered to remove the cellular material. The solution is then subjected to a softening resin to remove inorganic salts. The softened solution is passed through chromatography and ion exchange resins to remove organic impurities. The resulting filtrate may be decolorized using activated charcoal. The solution is then ultrafiltered and cooled, followed by removal of erythritol crystals by centrifugation. The crystals are washed with cold water, dried, sifted, and packaged. In an alternative manufacturing process without the chromatography/ion exchange resin steps, the softened solution is pumped through a crystallizer and cooled to promote crystal formation. The resulting erythritol crystals are washed and dissolved in water, ultrafiltered, decolorized with charcoal (as needed), and then subjected to a second crystallization. The crystals are separated by centrifugation, dried, sifted, and then packaged, as above. Regardless of the manufacturing method, the finished food grade product is not less than 99.5% erythritol.

Cargill includes information about the estimated dietary exposure to erythritol. It states that the estimates in the current submission for the exposure to erythritol were determined based on all existing and intended food uses and use levels for erythritol in conjunction with food consumption data included in the U.S. National Health and Nutrition Examination Surveys 2013-2014. For the total population, Cargill estimates that the mean and 90th percentile of dietary exposure to erythritol are 32.1 and 63.0 g/person/day, respectively. For the subpopulations, the highest estimated dietary exposures are in male adults at 35.6 and 69.6 g/person/day (0.6 and 1 g/kg body weight/day) for the mean and 90th percentiles, respectively. Cargill notes that the inclusion of assumptions (that erythritol will be used in all intended foods at the maximum use levels) in its view leads to highly conservative estimates. Cargill further notes that the probable exposure would be half of these estimates, in line with estimates from the previously reviewed notices, 13 and 30 g/person/day (0.2 and 0.5 g/kg body weight/day) for the mean and 90th percentiles, respectively.

Cargill explains that the use of erythritol is self-limiting as a result of product texture or flavor profile and that these technological effects can affect consumer acceptability.

Cargill discusses the safety of erythritol. The safety discussion refers to safety reviews by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) and incorporates in the notice published toxicity studies addressed in GRNs 000076, 000208, 000382, and 000401.[2] These published toxicity studies on erythritol include acute; short-term (4 weeks); subchronic; chronic and carcinogenicity, reproductive and developmental; and *in vitro* and *in vivo* mutagenicity and genotoxicity assay, as well as several absorption, distribution, metabolism, and excretion studies. Cargill states that the studies did not reveal any toxicologically relevant treatment-related adverse effects. Cargill also discusses a recently published subchronic study in which Beagle dogs were administered erythritol by oral intubation for 13 weeks,[3] noting that no toxicological adverse effects were observed at the highest dose tested (5 g/kg body weight/day). Cargill states that an updated literature search was conducted through October 2017 and did not reveal any new data or information on the effects of erythritol that would contradict its safe use.

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

Based on the totality of the evidence, Cargill concludes that the intended uses of erythritol are GRAS.

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[2] Erythritol was the subject of GRNs 000076, 000208, 000382, and 000401. We evaluated these notices and responded in letters dated September 11, 2001; January 25, 2007; November 21, 2011; and March 22, 2012, respectively, stating that we had no questions at those times regarding the notifiers' conclusions.
[3] Unpublished data from this study were considered by the FAO/WHO Joint Expert Committee on Food Additives, which established an Acceptable Daily Intake for erythritol of "not specified" during the Committee's 53rd meeting (1999); this study was subsequently published in 2017.

Standards of Identity

In the notice, Cargill states its intention to use erythritol 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.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Cargill's notice concluding that erythritol 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 erythritol. Accordingly, our response should not be construed to be a statement that foods containing erythritol, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Cargill provided, as well as other information available to FDA, we have no questions at this time regarding Cargill's conclusion that erythritol is GRAS under its intended conditions of use. This letter is not an affirmation that erythritol 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 000789 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M. Keefe -S

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Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
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