



Donald F. Schmitt, MPH
ToxStrategies, Inc.
931 W. 75th St., Suite 137, PMB 255
Naperville, IL 60565

Re: GRAS Notice No. GRN 000928

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000928. We received the notice that you submitted on behalf of Cargill, Inc. (Cargill) on February 26, 2020 and filed it on August 5, 2020. Cargill submitted amendments to the notice on October 30, 2020, November 12, 2020, and January 25, 2021 containing additional information regarding the production organism, analytical methods, specifications, manufacturing process, intended use, dietary exposure, and safety.

The subject of the notice is dried *Saccharomyces cerevisiae* yeast fermentate (dried yeast fermentate) for use as an ingredient in milk, flavored milks and milk drinks, milk products, frozen yogurt, 100% fruit juices, processed juice drinks, ready-to-drink tea, sport/fitness water beverages, fruit flavored drinks, breads, ready-to-eat (RTE) bars, RTE dry cereals, hard candy, mints, tofu, and soups/broth at a level of 500 mg/serving¹. The notice informs us of Cargill's view that this use of dried yeast fermentate is GRAS through scientific procedures.

Our use of the term, "dried yeast fermentate," in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "dried yeast fermentate."

Cargill describes dried yeast fermentate as brownish, crystalline-appearing particles and a free-flowing powder that has a characteristic toasted, savory odor. Dried yeast fermentate is composed of proteins, lipids, carbohydrates, cellulose and minerals.

¹ Cargill states that dried yeast fermentate is not intended for use in infant formula, in products under the jurisdiction of the United States Department of Agriculture, or in products where a standard of identity would preclude its use.

Cargill states that dried yeast fermentate is hygroscopic and only partially soluble in water.

Cargill states that dried yeast fermentate is produced from a non-genetically engineered *S. cerevisiae* strain derived from a *S. cerevisiae* strain deposited in the American Type Culture Collection (ATCC), identified as ATCC 7752. Cargill states that *S. cerevisiae* strain ATCC 7752 is a non-pathogenic, non-toxicogenic, food-grade yeast. Cargill explains that dried yeast fermentate is manufactured following three general steps: aerobic propagation, anaerobic fermentation, and dehydration. The initial yeast culture is placed in a bioreactor containing the fermentation medium which is composed of food-grade materials, including an appropriate fermentable sugar source, vitamins, minerals, a nitrogen source, and potable water. Cargill states that none of the raw materials used in the fermentation are major allergens or are derived from major allergens. *S. cerevisiae* is produced by continuous fermentation. When the cell mass reaches the desired growth, the contents are transferred into the next bioreactor for the subsequent anaerobic fermentation step. A solution containing food-grade fermentable sugars, corn steep water, and potable water is added to the yeast biomass. Following the anaerobic fermentation, the resulting liquid is dehydrated² and then further milled or flaked to the desired particle size range before packaging. Cargill states that the resulting dried product contains dead yeast cells, fermentation medium, and fermentation by-products. Cargill states that dried yeast fermentate is manufactured in accordance with current good manufacturing practices (cGMP).

Cargill provides specifications for dried yeast fermentate that include protein ($\geq 25\%$ (w/w)); total dietary fiber ($\geq 10\%$ (w/w)); total polyphenols ($\geq 3\%$ (w/w)); moisture ($\leq 8\%$ (w/w)); water activity (< 0.5 (w/w)); heavy metals, including lead (< 0.5 mg/kg); and limits for microorganisms, including *Salmonella* serovars (absent in 25 g). Cargill provides the analyses from three non-consecutive lots to demonstrate that dried yeast fermentate can be manufactured to meet the specifications. Cargill provides results of stability studies after 67 weeks at room-temperature followed by accelerated testing for 6 months. Cargill states that testing was performed after ambient storage and at interim intervals under accelerated conditions and that no significant changes were observed.

Cargill provides a dietary exposure estimate for the proposed uses of dried yeast fermentate consumption based on food consumption data from the 2013-2016 National Health and Nutrition Examination Survey. Cargill estimates the mean and 90th percentile dietary exposure for dried yeast fermentate to be 2.2 g/person (p)/d and 3.8 g/p/d, respectively for the U.S. population. Cargill states that presuming the dried yeast fermentate contains a maximum yeast-equivalent of 33% by weight, the mean and 90th percentile dietary exposures for yeast from the proposed uses of dried yeast fermentate are estimated to be 0.72 g/p/d and 1.26 g/p/d, respectively.

Cargill states that *S. cerevisiae* has a history of safe use in human food or human food production. Cargill describes the published safety data and information identified

² Cargill explains that the dehydration step includes a continuous drying process performed at 200 °F for 5 minutes. During this process, Cargill collects and analyzes samples of the product to confirm that the *S. cerevisiae* cells are killed, and unable to grow.

in a comprehensive literature search to support the safety of dried yeast fermentate. Cargill describes a published acute oral toxicity study with dried yeast fermentate that showed no toxicity at 2,000 mg/kg body weight (bw) in rats. Cargill also summarizes a published 90-day gavage study in rats where daily administration of dried yeast fermentate at doses up to 1,500 mg/kg bw/d did not result in observable toxicity. Additionally, Cargill discusses a published chronic (one-year) toxicity study in rats where daily administration of dried yeast fermentate at doses up to 800 mg/kg bw/d was well tolerated without mortality, toxic clinical symptoms, or any treatment-related changes in clinical chemistry, urinalysis, or histopathology.

Referencing published literature, Cargill states that dried yeast fermentate is neither mutagenic nor genotoxic. Additionally, Cargill summarizes three published human studies to corroborate the safety of dried yeast fermentate. In healthy subjects who consumed dried yeast fermentate daily at doses of 500 mg/d for up to 12 weeks, no serious adverse effects or abnormalities in any of the laboratory serologic parameters were observed.

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

Based on the totality of data and information discussed above, Cargill concludes that dried yeast fermentate produced in accordance with cGMP and meeting appropriate food grade specifications, is GRAS under the conditions of its intended use.

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 dried yeast fermentate 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 ONFL in CFSAN. OFAS 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.

Potential Requirement for a Color Additive Petition

In the notice, Cargill notes that dried yeast fermentate is a brownish powder. As such, the use of dried yeast fermentate in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color

additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000928 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OFAS.

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 Cargill's notice concluding that dried yeast fermentate 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 dried yeast fermentate. Accordingly, our response should not be construed to be a statement that foods containing dried yeast fermentate, 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 dried yeast fermentate is GRAS under its intended conditions of use. This letter is not an affirmation that dried yeast fermentate 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 000928 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

Digitally signed by Susan
J. Carlson -S
Date: 2021.05.14
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Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition