



Elizabeth McCartney
Regulatory Affairs Specialist
DuPont Nutrition & Health
3329 Agriculture Drive
Madison, WI 53716

Re: GRAS Notice No. GRN 000736

Dear Ms. McCartney:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000736. We received DuPont Nutrition & Health's (DuPont N&H) notice on October 2, 2017, and filed it on October 26, 2017. DuPont N&H submitted an amendment to the notice on February 6, 2018, to correct the NCBI accession number for *Lactobacillus paracasei* Lpc-37.

The subject of the notice is *Lactobacillus casei* subspecies *paracasei* Lpc-37 (*L. paracasei* Lpc-37) for use as an ingredient in yogurt and other dairy products, soy products, beverages, chewing gum, and confectionary snacks, at a level that ensures at least 10^{10} CFU/serving throughout the shelf life of the product. The notice informs us of DuPont N&H's view that this use of *L. paracasei* Lpc-37 is GRAS through scientific procedures.

DuPont N&H states that *L. paracasei* is a lactic acid bacteria (LAB); a grouping of bacteria characterized by the production of lactic acid as the major metabolic end product of carbohydrate metabolism and other physiological traits. *L. paracasei* occurs naturally in food and in the digestive tract of humans and other animals. DuPont N&H notes that *L. paracasei* Lpc-37 is non-pathogenic and non-toxicogenic.

DuPont N&H states that *L. paracasei* Lpc-37 is produced in a batch type fermentation process where proteins, carbohydrates, vitamins, and minerals are blended with water, sterilized, and then inoculated with the production strain. Each fermentation product uses a defined growth medium and controlled fermentation growth conditions (pH and temperature). After growth, the bacteria are pelleted, freeze-dried, milled, and then blended and packaged. DuPont N&H states that *L. paracasei* Lpc-37 is manufactured in compliance with FDA's current good manufacturing practice guidelines in an FDA regulated and inspected facility. DuPont N&H also states that no allergens are present in the final product.

DuPont N&H states that they have obtained a draft genome sequence of *L. paracasei* Lpc-37 using published methods and deposited it at the NCBI database under accession

U.S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
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number NOKL00000000. The genome sequence contains no evidence of genes conferring pathogenicity or production of toxins.

DuPont N&H provides specifications for *L. paracasei* Lpc-37, including color (beige), odor, taste, viable cell count ($\geq 4 \times 10^{11}$ CFU/g), non-lactic acid bacterium cell count ($< 5 \times 10^3$ /g), enterococci (< 100 /g), coliforms (negative by test in 10 g), *Escherichia coli* (negative by test in 0.3 g), Staphylococcus (coagulase (+); negative by test in 40 g), Salmonella (negative in 40 g), Listeria (negative in 25 g), molds and yeasts (< 200 CFU/g). DuPont N&H provides data from four non-consecutive lots to demonstrate that the *L. paracasei* Lpc-37 product meets the specifications. Additionally, DuPont N&H provides two-year stability data of *L. paracasei* Lpc-37.

DuPont N&H estimates that the average individual consumes about 20 servings/day of all foods combined and a conservative estimate of the total dietary exposure at 5×10^{11} CFU/serving multiplied by 10 servings/day would yield a maximum intake of 5×10^{12} CFU/person/day of conventional food. It is unlikely that a consumer would consume 10 servings /day of foods containing *L. paracasei* Lpc-37 and the concentration of *L. paracasei* Lpc-37 will decline over the shelf-life of the food. Thus, the maximum ingestion is likely less than 5×10^{12} CFU/day and well within levels known to be safe.

DuPont N&H states that *L. paracasei* is classified as a LAB; a functional grouping of bacteria that are anaerobic, yet aerotolerant; Gram-positive; strictly fermentative for lactic acid as the major metabolic end-product of fermentation; generally non-spore forming; and, non-pathogenic and non-toxigenic. DuPont N&H discusses the long safe historical use of LAB in foods and the negligible occurrences of opportunistic infections (usually in hosts with underlying health issues), despite the high level of consumption, and how *Lactobacillus*, generally, and *L. paracasei*, specifically, have been safely used in fermented foods. DuPont N&H cites publications that support the safe consumption of LAB, including *L. paracasei*. Additionally, DuPont N&H provides corroborative safety data from several placebo-controlled studies in which humans were fed a variety of bacteria, including different strains of *L. paracasei*; none of the studies reported any adverse effects. DuPont N&H also presented the results of studies in which humans were fed foods with added *L. paracasei*; including artichokes, milk, and yogurt. None of the studies showed any adverse effects.

Based on the data and information provided, DuPont N&H concludes that the intended use of *L. paracasei* Lpc-37 is GRAS.

Standards of Identity

In the notice, DuPont N&H states its intention to use *L. paracasei* Lpc-37 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). The notice raises a potential issue under these labeling provisions. In the notice, DuPont N&H cites studies that describe *L. paracasei* as having certain health benefits. If products containing *L. paracasei* Lpc-37 bear any nutrient content or health claims on the label or in labeling, such claims are the 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(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 our evaluation of DuPont N&H's notice concluding that *L. paracasei* Lpc-37 is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing *L. paracasei* Lpc-37. Accordingly, our response should not be construed to be a statement that foods containing *L. paracasei* Lpc-37 if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that DuPont N&H provided, as well as other information available to FDA, we have no questions at this time regarding DuPont N&H's conclusion that *L. paracasei* Lpc-37 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. paracasei* Lpc-37 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 000736 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

Digitally signed by
Michael A. Adams -S
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