



Amy B. Smith, Ph.D.  
DuPont Nutrition and Health  
3329 Agriculture Drive  
Madison, WI 53716

Re: GRAS Notice No. GRN 000722

Dear Dr. Smith:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000722. We received the notice from DuPont Nutrition and Health (DuPont) on August 7, 2017 and filed it on August 23, 2017. We received amendments to the notice on October 20, 2017, and November 20, 2017. The amendments contained additional information about product specifications, dietary exposure estimates, and safety.

The subject of the notice is *Lactobacillus plantarum* strain Lp-115 (*L. plantarum* Lp-115) for use as an ingredient in conventional foods, including yogurt and other dairy products, soy products, beverages, chewing gum, and confectionary snacks at  $1 \times 10^{10}$  colony forming units (CFU)/serving. The notice informs us of DuPont's view that this use of *L. plantarum* Lp-115 is GRAS through scientific procedures.

DuPont provides the identity and composition of *L. plantarum* Lp-115. DuPont describes *L. plantarum* Lp-115 as a white to cream-colored powder. DuPont states that *L. plantarum* Lp-115 is a Gram-positive, lactic acid bacterium, which was isolated from plant silage. The strain was deposited in ATTC as SD5209.

DuPont describes the manufacture of *L. plantarum* Lp-115. The strain is fermented under pH- and temperature-controlled aseptic conditions and monitored for contamination.<sup>1</sup> After fermentation, the culture is concentrated by centrifugation and cryoprotectants are added. The concentrate is pelletized and freeze-dried, then milled and blended with excipients. DuPont states that all ingredients used are food-grade or safe and legal for their intended uses and the manufacturing process is consistent with current good manufacturing practice.

DuPont provides specifications for *L. plantarum* Lp-115. These include a minimum of  $7 \times 10^{11}$  CFU/g and microbial limits for non-lactic acid bacteria cell count (<5000 CFU/g), yeasts and molds (<100 CFU/g), *Salmonella* (absent in 40 g), *Listeria* (absent in 25 g). DuPont provides batch analyses for four non-consecutive lots to confirm that the product meets the stated specifications.

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<sup>1</sup> DuPont states that each fermentation product has a defined growth medium.

DuPont states that *L. plantarum* Lp-115 is intended for use at up to  $1 \times 10^{10}$  CFU/serving as an ingredient in conventional foods, including yogurt and other dairy products, soy products, beverages, chewing gum, and confectionary snacks. DuPont intends that *L. plantarum* Lp-115 to be added at levels up to  $5 \times 10^{11}$  CFU/serving to ensure that the intended use level is maintained throughout the shelf life.

DuPont estimates the dietary exposure to *L. plantarum* Lp-115. DuPont intends for *L. plantarum* Lp-115 to be used in conventional foods at  $10^{10}$  CFU/serving. Based on an estimate of consumption of 10 servings per day, DuPont estimates the dietary exposure of *L. plantarum* Lp-115 at  $10^{11}$  CFU/day. DuPont states that because it is unlikely that 10 servings per day will be consumed and that the CFU will decline over the shelf-life, DuPont states that a likely exposure is  $6 \times 10^{10}$  CFU/day.

DuPont discusses published and unpublished studies to support the safety of consumption of *L. plantarum* Lp-115. DuPont discusses the results of animal studies, which demonstrate that consumption of *L. plantarum* Lp-115 did not induce acute or subchronic toxicity. DuPont discusses results of different published studies where *L. plantarum* Lp-115 was administered to rats and mice in daily doses ranging from  $1 \times 10^8$  to  $1 \times 10^9$  CFU/animal for up to 8 weeks. Although these studies were not designed to evaluate the toxicity of *L. plantarum* Lp-115, the treatments were well tolerated and no adverse events were reported. In an unpublished acute toxicity study in rats, no adverse effects were observed at doses of  $4.2 \times 10^{12}$  CFU/kg body weight. DuPont describes the results of published human studies conducted to investigate the effects of consumption of *L. plantarum* strains in healthy adults, including the elderly, as well as adults and children with underlying conditions, including irritable bowel syndrome, ulcerative colitis, and atopic dermatitis. In a study with the longest duration and the highest level consumed, *L. plantarum* 299v was consumed by adults with ulcerative colitis at levels up to  $4.5 \times 10^{10}$  CFU/day for 24 weeks with no adverse events reported. DuPont also discusses the results of human clinical trials where *L. plantarum* Lp-115 was consumed by adults at levels up to  $2 \times 10^{11}$  CFU/day for up to 90 days; while safety data were not specifically reported in those studies, *L. plantarum* Lp-115 was well-tolerated. DuPont concludes that the studies presented support safety of ingestion of *L. plantarum* Lp-115 at up to  $1 \times 10^{10}$  CFU/day.

DuPont discusses published literature demonstrating that *L. plantarum* has been isolated from the human gastrointestinal tract of healthy individuals and that *L. plantarum* is present at up to  $10^{12}$  CFU/g in many fermented foods with a long history of safe consumption. Additionally, DuPont states that *L. plantarum* strains have been used in food products in Europe and dietary supplements in the United States. DuPont states that the European Food Safety Authority conferred the Qualified Presumption of Safety status to *L. plantarum* in 2007 and has maintained its status through the current 2016 publication. DuPont also states that *L. plantarum* is included in the International Dairy Federation inventory of microbial food cultures with a documented use in human foods and was maintained in the 2012 update.

DuPont discusses the results of unpublished studies demonstrating that *L. plantarum* Lp-115 is susceptible to antibiotics and lacks acquired, functional, or transferable

antibiotic resistance genes. DuPont states that *L. plantarum* Lp-115 is inherently resistant to clindamycin. Additionally, they note that *L. plantarum* Lp-115 does not possess genes encoding hemolysin.

DuPont includes the report of a panel of individuals (DuPont's GRAS panel). Based on its review, DuPont's GRAS panel concluded that *L. plantarum* Lp-115 is safe under the conditions of its intended use.

Based on the totality of information discussed above, DuPont concludes that *L. plantarum* Lp-115 is GRAS for its intended use.

### **Standards of Identity**

In the notice, DuPont states its intention to use *L. plantarum* Lp-115 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 (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 cites studies that describe *L. plantarum* Lp-115 as conferring certain health benefits. If products containing *L. plantarum* Lp-115 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(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's notice concluding that *L. plantarum* Lp-115 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. plantarum* Lp-115. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* Lp-115 if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

## Conclusions

Based on the information that DuPont provided, as well as other information available to FDA, we have no questions at this time regarding DuPont's conclusion that *L. plantarum* Lp-115 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* Lp-115 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 000722 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.

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