



Angela Lim
DuPont Nutrition and Health
DuPont Experimental Station - E320
200 Powder Mill Road
Wilmington, DE 19803

Re: GRAS Notice No. GRN 000749

Dear Ms. Lim:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000749. We received DuPont Nutrition and Health (DuPont)'s notice on December 12, 2017 and filed it on December 19, 2017. DuPont submitted amendments to the notice on February 26, 2018, and March 12, 2018, that contained additional information clarifying the safety data used to support general recognition and corrected typographical errors, respectively.

The subject of the notice is 2'-O-fucosyllactose (2'-FL) for use as an ingredient in non-exempt infant formulas for term infants and in toddler formulas up to 2.4 g/L, in infant and toddler foods up to 12 g/kg, and in toddler drinks up to 1.2 g/L. The notice informs us of DuPont's view that these uses of 2'-FL are GRAS through scientific procedures.

DuPont describes 2'-FL as a white to off-white powder containing a minimum of 82% 2'-O-fucosyllactose. The chemical name for 2'-FL is α -D-fucopyranosyl-(1 \rightarrow 2)- β -D-galactopyranosyl-(1 \rightarrow 4)-D-glucopyranose (CAS No. 41263-94-9).

DuPont describes the method of manufacture for 2'-FL. It is produced from lactose derived from cow's milk and sucrose using a modified strain of *Escherichia coli* K-12, referred to as MG1655 INB3051.¹ The fermentation is conducted under defined conditions to optimize 2'-FL production and secretion into the medium. After fermentation, cell biomass, endotoxins, and large molecules are removed using microfiltration or ultrafiltration. The filtrate is concentrated, treated with ion exchange resins and activated carbon, and then filtered. The resulting product is concentrated to crystallize 2'-FL. The 2'-FL crystals may be used as is or dissolved in water and spray dried. DuPont states that all ingredients are food-grade or conform to specifications in the Food Chemicals Codex (10th edition).

¹ The production strain contains multiple gene deletions. Genes from four species encoding functions for sugar metabolism and transport were inserted into the chromosome to permit the production of 2'-FL. DuPont states that *E. coli* K-12 and its derivatives are non-toxicogenic and non-pathogenic. We note our conclusion that *E. coli* K-12 is non-toxicogenic and non-pathogenic (55 FR 10932 at 10934, March 23, 1990).

DuPont provides specifications for 2'-FL that include the minimum content of 2'-FL ($\geq 82\%$) and limits on lactose ($< 8\%$), difucosyllactose ($< 7\%$), total other carbohydrates² ($< 6\%$), moisture ($\leq 9\%$), lead (≤ 0.05 mg/kg), arsenic (≤ 0.2 mg/kg), cadmium (≤ 0.05 mg/kg), mercury (≤ 0.1 mg/kg), protein (≤ 100 mg/kg), and microbes (no detectable *Cronobacter sakazakii* or *Salmonella* serovars in a 100 g sample). DuPont provides the results of five non-consecutive batch analyses of 2'-FL to demonstrate that it can be made to meet these specifications.

DuPont estimates the dietary exposure to 2'-FL using consumption data from the National Health and Nutrition Examination Survey (2009-2012). DuPont reports the mean and 90th percentile dietary exposures to 2'-FL to be 2.93 g/day (d) (449.7 mg/kg body weight (bw)/d) and 5.29 g/d (712.4 mg/kg bw/d), respectively, for infants up to 6 months of age, 4.63 g/d (520.2 mg/kg bw/d) and 8.36 g/d (987.1 mg/kg bw/d), respectively, for infants 7 to 12 months of age, and 1.12 g/d (84.9 mg/kg bw/d) and 1.97 g/d (146 mg/kg bw/d), respectively, for toddlers 13 to 36 months of age. DuPont notes that the uses are substitutional for those described in GRNs 000546, 000571, and 000650;³ therefore, they do not expect dietary exposure to 2'-FL to change.

DuPont discusses published and unpublished safety data and information on the use of 2'-FL. They incorporate data and information into the notice from GRNs 000546, 000571, and 000650 and report that a literature search was conducted through June 2017. DuPont states the 2'-FL that is the subject of GRN 000749 is chemically identical to that found in human milk and to the subjects of GRNs 000546, 000571, 000650. DuPont states that most of the 2'-FL reaches the large intestine undigested, and subsequently either serves as a substrate for fermentation by gut microflora or is excreted unchanged in the feces. DuPont states that 2'-FL is not mutagenic based on a published bacterial reverse mutation assay. DuPont also discusses a published 3-week subacute oral toxicity study in neonatal pigs that did not exhibit any treatment-related adverse effects up to the highest dose tested of 291.7 mg/kg bw/d in males and 298.9 mg/kg bw/d in females. DuPont also discusses a published 90-day subchronic oral toxicity study in neonatal rats that showed the No Observed Adverse Effect Level to be 5000 mg/kg bw/d. DuPont discusses endpoints related to safety and physiology in published and unpublished human studies that corroborate the safety of 2'-FL. DuPont cites and discusses other published and unpublished information, including an evaluation by the European Food Safety Authority Panel on Dietetic Products, Nutrition, and Allergies.

DuPont includes the statement of a panel of individuals (DuPont's GRAS panel). Based on its review, DuPont's GRAS panel concluded that 2'-FL is safe under the conditions of its intended use.

Based on the totality of the data and information described above, DuPont concludes

² DuPont specifies a limit of 6% for other carbohydrates that includes 3-fucosyllactose, 2-fucosyl-D-lactulose, fucosylgalactose, glucose, galactose, fucose, sorbitol, galactitol, mannitol, and trihexose.

³ 2'-FL was the subject of GRNs 000546, 000571, 000650. We evaluated these notices and responded in letters dated September 16, 2015; November 6, 2015; and November 23, 2016, respectively, stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

that 2'-FL is GRAS for its intended use in food.

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. DuPont cites studies that describe 2'-FL as having certain health benefits. If products containing 2'-FL 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 (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.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a “major food allergen” declare the allergen’s presence (section 403(w)). The FD&C Act defines a “major food allergen” as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. 2'-FL derived from lactose may require labeling under the FD&C Act because it may contain protein derived from cow’s milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in OFAS. Questions related to food labeling in general should be directed to ONFL.

Intended Use in Infant Formula

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to DuPont’s GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing 2'-FL to make the submission required by section 412. Infant formulas are the purview of 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 2'-FL

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 2'-FL. Accordingly, our response should not be construed to be a statement that foods containing 2'-FL, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

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 2'-FL is GRAS under its intended conditions of use. This letter is not an affirmation that 2'-FL 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 000749 is accessible to the public at 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.
Adams -S
Date: 2018.04.23 16:00:50 -04'00'