



Katrina Emmel, Ph.D.
GRAS Associates, LLC
27499 Riverview Center Blvd.
Bonita Springs, FL 34134

Re: GRAS Notice No. GRN 000735

Dear Dr. Emmel:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000735. We received the GRAS notice that you submitted on behalf of Glycosyn, LLC (Glycosyn) and FrieslandCampina Domo B.V. (FrieslandCampina) on October 2, 2017, and filed it on October 19, 2017. Glycosyn and FrieslandCampina submitted amendments to the notice on December 12, 2017, January 5, 2018,¹ February 12, 2018, and April 5, 2018,² that included clarification of the confidential designation in Appendix 8 and the intended uses and use levels of the notified substance.

The subject of the notice is 2'-fucosyllactose (2'-FL) for use as an ingredient in milk- and soy-based, non-exempt infant formulas for term infants and in toddler formulas at a maximum level of 2.4 g/L of formula as consumed; infant and toddler foods at levels of 0.24-1.2 g/serving; and in the following food categories at levels of 0.28-1.2 g/serving: beverages and beverage bases; breakfast cereals; dairy product analogs; frozen dairy desserts and mixes; gelatins, puddings, and fillings; grain products and pastas; jams and jellies; milk and milk products; processed fruits and fruit juices; and sweet sauces, toppings, and syrups.³ The notice informs us of Glycosyn and FrieslandCampina's view that these uses of 2'-FL are GRAS through scientific procedures.

Glycosyn and FrieslandCampina describe 2'-FL as a white powder that consists of a minimum of 90% 2'-O-fucosyllactose, with minor amounts of lactose derived from milk, allo-lactose, glucose, galactose, and fucose. 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). They also state that their 2'-FL is chemically identical to the 2'-FL present in human milk.

Glycosyn and FrieslandCampina describe the method of manufacture for 2'-FL. 2'-FL is produced from lactose and glucose using a modified strain of *Escherichia coli* K-12

¹ GRN 000735 included an appendix that Glycosyn and Friesland Campina initially designated confidential in the notice. In the January 5, 2018 amendment, Glycosyn and Friesland Campina provided a corrected version of Appendix 8 that removes unintended confidential markings.

² Glycosyn and FrieslandCampina requested that the intended use in medical foods be withdrawn.

³ Glycosyn and FrieslandCampina state that 2'-FL is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.

GI724 referred to as E997.⁴ 2'-FL is secreted into the fermentation medium and the microbial biomass is removed by microfiltration. The filtered supernatant is subjected to additional filtration, cationic, anionic, and absorbent resin chromatography, and then concentrated by reverse osmosis. The pH of the concentrated solution is adjusted with citric acid, and then the solution is pasteurized and spray dried to obtain 2'-FL powder. Glycosyn and FrieslandCampina state that all reagents and processing aids used in the manufacture of 2'-FL are food-grade and are used in accordance with U.S. regulations or are GRAS for their intended uses.

Glycosyn and FrieslandCampina provide specifications for 2'-FL. Specifications include the minimum content of 2'-FL ($\geq 90\%$) and limits on lactose ($\leq 3\%$), allo-lactose ($\leq 2\%$), glucose ($\leq 2\%$), galactose ($\leq 2\%$), fucose ($\leq 2\%$), moisture ($\leq 5\%$), lead (≤ 0.05 mg/kg), protein ($\leq 0.01\%$), and microbes, including no detectable *Cronobacter sakazakii* or *Salmonella* serovars in a 25 g sample. Glycosyn and FrieslandCampina provide the results of five non-consecutive batch analyses of 2'-FL to demonstrate that it can be made to meet these specifications.

Glycosyn and FrieslandCampina estimate the dietary exposure to 2'-FL using consumption data from the 2013-2014 National Health and Nutrition Examination Survey. Glycosyn and FrieslandCampina report the mean and 90th percentile dietary exposures to 2'-FL to be 354 and 498 mg/kg body weight (bw)/day (d), respectively, for infants up to 6 months of age, 192 and 311 mg/kg bw/d, respectively, for infants 7 to 11 months of age, 40 and 101 mg/kg bw/d, respectively, for toddlers 1 to 3 years of age, and 36 and 80 mg/kg bw/d, respectively, for the total population.

Glycosyn and FrieslandCampina discuss published and unpublished safety data and information on human milk oligosaccharides to support the safe use of 2'-FL. They report that a literature search was conducted through July 2017. Glycosyn and FrieslandCampina summarize published human studies in infants on absorption, distribution, metabolism, and excretion. Glycosyn and FrieslandCampina state that 2'-FL does not undergo significant digestion in the upper gastrointestinal tract and only a minor fraction is absorbed intact and enters the circulation.

Glycosyn and FrieslandCampina discuss the results of published and unpublished studies in animals. They discuss a published subchronic oral toxicity study where juvenile Wistar rats were administered 2'-FL by gavage with doses up to 6000 mg/kg bw/d for 90 days with a 4-week recovery period. Glycosyn and FrieslandCampina state that 2'-FL was well tolerated up to 5000 mg/kg bw/d, and did not elicit any adverse treatment-related, toxicologically relevant effects in other groups. Glycosyn and FrieslandCampina discuss a published 20-day oral toxicity study in neonatal pigs fed a liquid diet containing up to 2000 mg 2'-FL/L (equivalent to 292 mg 2'-FL/kg bw/d in males and 299 mg 2'-FL/kg bw/d in females) that did not impact piglet growth and did

⁴ *E. coli* strain E997 was developed using both traditional genetics and recombinant DNA techniques, including modifications to genes encoding proteins involved in sugar metabolism. Glycosyn and FrieslandCampina state that *E. coli* K-12 and its derivatives are non-toxigenic and non-pathogenic. We note our conclusion that *E. coli* K-12 is non-toxigenic and non-pathogenic (55 FR 10932 at 10934, March 23, 1990).

not result in any adverse health effects. Glycosyn and FrieslandCampina describe an unpublished 90-day oral toxicity study in rats conducted with the 2'-FL that is the subject of the notice at doses up to 10% in the diet (equivalent to doses up to 7990 mg 2'-FL/kg bw/d), stating that no adverse effects were noted in the study. Glycosyn and FrieslandCampina also incorporate into the notice an unpublished 90-day dietary study in rats from GRN 000571⁵ to corroborate their GRAS conclusion. Glycosyn and FrieslandCampina summarize multiple genotoxicity studies and note that 2'-FL is neither mutagenic nor genotoxic.

Glycosyn and FrieslandCampina summarize several published human studies on 2'-FL conducted in infants and adults. The studies in infants fed infant and toddler formulas containing up to 1.0 g 2'-FL/L alone or in combination with 1.4 g galacto-oligosaccharides (GOS)/L or 0.6 g lacto-N-neotetraose/L showed normal growth and no serious adverse events. Glycosyn and FrieslandCampina also cite published references stating that most infants are exposed to 2'-FL due to its presence in human milk. Glycosyn and FrieslandCampina state that toxicological studies on structurally similar substances to 2'-FL (i.e., GOS, fructo-oligosaccharides, and isomalto-oligosaccharides) further support their GRAS conclusion.

We note that GRN 000735 referred to a panel of individuals (Glycosyn and FrieslandCampina's GRAS panel). However, because the notice provided publicly available information supporting Glycosyn and FrieslandCampina's conclusion, we completed our evaluation without considering the deliberations of Glycosyn and FrieslandCampina's GRAS panel.

Based on the totality of the data and information described above, Glycosyn and FrieslandCampina conclude that 2'-FL is GRAS for its intended use in food.

Standards of Identity

In the notice, Glycosyn and FrieslandCampina state their intention to use 2'-FL in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations (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

⁵ 2'-FL for use as an ingredient in non-exempt, milk-based term infant formulas and in toddler formulas at a maximum level of 2 g/L of reconstituted formula was the subject of GRN 000571. We evaluated this notice and responded in a letter dated November 6, 2015, stating that we had no questions at that time regarding Jennewein Biotechnologie, GmbH's GRAS conclusion.

issue under these labeling provisions. Glycosyn and FrieslandCampina cite 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 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 Glycosyn and FrieslandCampina’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 Glycosyn and FrieslandCampina’s notice concluding that 2'-FL 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 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(II).

Conclusions

Based on the information that Glycosyn and FrieslandCampina provided, as well as other information available to FDA, we have no questions at this time regarding Glycosyn and FrieslandCampina'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 000735 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**

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