



James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 000951

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000951. We received the notice that you submitted on behalf of Danisco USA, Inc.¹ (Danisco) on June 2, 2020 and filed it on October 2, 2020. We received amendments to the notice on February 25, 2021, April 27, 2021, June 2, 2021, July 7, 2021, and July 23, 2021 that reduced the intended use level, updated the dietary exposure assessment, provided additional information regarding the manufacturing process and analytical methods, and clarified safety data.

The subject of the notice is 3-fucosyllactose (3-FL) for use as an ingredient in cow milk-based and soy-based non-exempt infant formula for term infants and formula intended for young children aged 1-3 years at a level of 0.04 g/serving (0.44 g/L)² as consumed; juices, drinks, and foods for infants and young children under 3 years of age at levels ranging from 0.03 to 0.09 g/serving (0.44 to 4.4 g/kg); cereal and nutrition bars; enhanced and “fortified” waters; “energy” and “sport” drinks and mixes; breakfast cereals; milk substitutes; yogurts; fermented milk, flavored milk, and mixes; smoothies; milk-based meal replacement beverages; fruit juices and nectars (including fruit-based beverages); vegetable juices; and in oral and enteral tube feeding formulas at levels ranging from 0.07 to 0.88 g/serving (0.26 to 8.8 g/kg). The notice informs us of Danisco’s view that this use of 3-FL is GRAS through scientific procedures.

Danisco describes 3-FL as a white to ivory-colored powder containing $\geq 90\%$ 3-FL and small amounts of lactose, fucose, galactose, and glucose. The chemical name for 3-FL is 6-deoxy- α -L-galactopyranosyl-(1 \rightarrow 3)-[β -D-galactopyranosyl-(1 \rightarrow 4)]-D-glucopyranose (CAS Registry Number 41312-47-4). 3-FL is a trisaccharide composed of L-fucose, D-

¹ When the notice was submitted, the notifier was doing business as DuPont Nutrition and Biosciences (DuPont). In an amendment received on February 25, 2021, we were informed that DuPont was acquired by Danisco USA, Inc.

² In an amendment received on April 27, 2021, Danisco reduced the intended use level of 3-FL to 0.44 g/L in infant formula consistent with the 3-FL use level indicated in GRN 000925. We evaluated GRN 000925 and responded in a letter dated February 8, 2021, stating that we had no questions at the time regarding the notifier’s GRAS conclusion. Danisco also lowered the intended use level of 3-FL in all other stated food categories.

galactose, and D-glucose units. Danisco states that their 3-FL product is chemically and structurally identical to the 3-FL present in human milk.

Danisco describes the production organism used in the manufacturing process for 3-FL. The production organism is *Escherichia coli* K12 MG1655 strain INB008971, which Danisco states is non-pathogenic and non-toxicogenic. Danisco indicates that the production strain has been genetically modified for growth on sucrose through insertion of well characterized heterologous genes, endogenous genes for overexpression, and deletion of genes encoding unwanted proteins to facilitate production of 3-FL. Danisco states that the production strain genome has been subjected to whole genome sequencing and is genetically stable for 70 generations.

Danisco states that 3-FL is manufactured in two main stages. In the fermentation stage, the production organism is grown in a lactose-sucrose based medium supplemented with trace minerals, vitamins, and amino acids. In the post-fermentation stage, 3-FL is purified and selectively concentrated via a series of steps involving microfiltration and/or ultrafiltration, nanofiltration, ion exchange, activated carbon, sterile filtration, and evaporation. A β -galactosidase enzyme may be used prior to the nanofiltration step to hydrolyze residual lactose. The resulting crystals are centrifuged and optionally dissolved in water and spray dried. Danisco states that all materials used in the manufacturing processes are food-grade and authorized for their respective uses in the U.S., and that 3-FL is manufactured following current good manufacturing practices.

Danisco provides specifications for 3-FL that include the minimum content of 3-FL ($\geq 90\%$), and limits for lactose ($\leq 5\%$), fucose ($\leq 3\%$), galactose/glucose ($\leq 3\%$), other carbohydrates ($\leq 3\%$), protein (≤ 100 mg/kg), ash ($\leq 0.5\%$), moisture ($\leq 5\%$), lead (≤ 0.05 mg/kg), and microorganisms, including *Salmonella* serovars (absent in 100 g), and *Cronobacter sakazakii* (absent in 100 g). Danisco provides the results of the analysis of four nonconsecutive batches to demonstrate that 3-FL can be manufactured to meet the specifications.

Danisco estimates the mean and 90th percentile eaters-only dietary exposures to 3-FL for infants aged 0–6 months to be 0.33 and 0.55 g/person (p)/day (d) (0.053 and 0.088 g/kg body weight (bw)/d), respectively, and for infants aged 7–12 months to be 0.374 and 0.682 g/p/d (0.042 and 0.077 g/kg bw/d), respectively. The mean and 90th percentile eaters-only exposures for toddlers aged 13–35 months are reported to be 0.396 and 0.968 g/p/d (0.033 and 0.084 g/kg bw/d), respectively. Danisco reports the mean and 90th percentile eaters-only dietary exposures to 3-FL for the total U.S. population to be 0.484 and 1.1 g/p/d (0.009 and 0.022 mg/kg bw/d), respectively. Danisco states that oral and enteral tube feeding formulas are intended to be consumed in amounts of up to 3 servings per day and that the maximum anticipated dietary exposure to 3-FL from its use in these formulas is 2.64 g/p/d (0.047 g/kg bw/d for a 56-kg adolescent and 0.035 g/kg bw/d for a 75-kg adult).

Danisco provides data and information supporting the safety of 3-FL and states that a literature search was conducted through March 2019. Danisco notes that most of the 3-FL consumed passes through the gastrointestinal tract undigested. Although a low level

of absorption does occur, systemic exposure resulting from 3-FL supplementation of infant formula or food is consistent with levels resulting from breast milk consumption. Danisco discusses a published study containing an acute oral toxicity study and a 90-day repeated dose feeding study (both in rats) as well as *in vivo* and *in vitro* genotoxicity studies demonstrating no toxicologically relevant effects.

Danisco includes the statement of a panel of individuals (Danisco's GRAS panel). Based on its review, Danisco's GRAS panel concluded that 3-FL is safe under the conditions of its intended use.

Based on the totality of the data and information, Danisco concludes that 3-FL is GRAS for its intended use.

Standards of Identity

In the notice, Danisco states its intention to use 3-FL in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations (21 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 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 3-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 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 nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame (effective January 1, 2023)) or a food ingredient that contains protein derived from one of those foods. 3-FL derived from lactose requires labeling under the FD&C Act because it contains protein derived from milk.

Intended Use in Infant Formulas

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 Danisco's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing 3-FL to make the submission required by section 412. Infant formulas are the purview of ONFL.

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 Danisco's notice concluding that 3-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 3-FL. Accordingly, our response should not be construed to be a statement that foods containing 3-FL, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Danisco provided, as well as other information available to FDA, we have no questions at this time regarding Danisco's conclusion that 3-FL is GRAS under its intended conditions of use. This letter is not an affirmation that 3-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

000951 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

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Susan Carlson, Ph.D.
Director
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