

Yue Yang, Ph.D.
Cataya Bio (Shanghai) Co., Ltd.
88 Daerwen Road, 4F/Building 2
Pudong New District, Shanghai, 201203
CHINA

Re: GRAS Notice No. GRN 001238

Dear Dr. Yang:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001238. We received Cataya Bio (Shanghai) Co., Ltd. (Cataya Bio)'s notice on December 10, 2024, and filed it on February 28, 2025. Cataya Bio submitted an amendment to the notice on June 4, 2025, that clarified the intended use, manufacturing, and aspects of the safety narrative.

The subject of the notice is 2'-fucosyllactose (2'-FL) for use as an ingredient in non-exempt infant formula^[1] for term infants at a maximum use level of 2.4 g/L as consumed, and in other food categories at the maximum levels shown in Table 1.^[2] The notice informs us of Cataya Bio's view that these uses of 2'-FL are GRAS through scientific procedures .

Table 1: Intended food categories and use levels for 2'-FL

Food Categories	Maximum use levels (g/kg or g/L)
Breads and baked goods, gluten-free	48
Carbonated beverages	1.2
Enhanced or fortified waters	1.2
Sports, isotonic, and "energy" drinks	6
Hot breakfast cereals, prepared	31
Ready-to-eat (RTE) cereals, puffed	80
RTE cereals, high fiber	40
RTE cereals, biscuit-type	40
Coffee and tea ^[3]	10
Milk substitutes	1.2
Beverage whiteners (powdered)	600
Beverage whiteners (liquid)	80
Non-dairy yogurt	12
Frozen dairy-based desserts	17
Puddings, custards, and mousses	17
Fruit pie filling	14.1
Fruit filling in bars, cookies, yogurt, cakes	30

Food Categories	Maximum use levels (g/kg or g/L)
Non-exempt infant formula for term infants	2.4
Formula intended for young children (>12 months)	2.4
Hot cereals for infants and young children, prepared (from dry instant) and ready-to-serve	12
Other foods for infants and young children: yogurt, fruits, vegetables, “toddler” meals, desserts	12
Other drinks for infants and young children: juice and yogurt drinks	10
Infant snacks: crackers, pretzels, cookies, and other dry snack items	57
Jams, jellies, preserves, and fruit butters	60
Meal replacement bars, general use	30
Cereal bars, including snack, granola, and breakfast bars	30
Meal replacement bars for weight management	40
Meal replacement drinks for general use (including nutritional drinks, smoothies), milk and non-milk based	5
Meal replacement drinks for weight management, milk and non-milk based	12
Milk-based meal replacement beverages for children (e.g., pediatric nutritional drinks)	12
Unflavored pasteurized and sterilized milk	1.2
Buttermilk	1.2
Flavored and fermented milks	1.2
Yogurt	12
Fruit juices and nectars	1.2
Fruit-flavored drinks and ades	1.2
Vegetable juices and nectars	1.2
Sugar substitutes: table-top sweeteners	300
Syrups used to flavor milk beverages	7
Nutritional drinks for pregnant women	12
Oral and enteral tube feeding formulas for ages ≥ 11 years	20

Cataya Bio describes the identity and composition of 2'-FL, stating that 2'-FL is a white to off-white or ivory powder containing a minimum of 94% (dry weight basis (DW)) 2'-FL. Cataya Bio notes that 2'-FL is a trisaccharide consisting of L-fucose, D-galactose, and D-glucose. The chemical name for 2'-FL is α -L-fucopyranosyl-(1 \rightarrow 2)- β -D-galactopyranosyl-(1 \rightarrow 4)-D-glucopyranose and the CAS registry number is 41263-94-9.

Cataya Bio states that 2'-FL is produced by fermentation using a genetically engineered production strain derived from the host strain *Corynebacterium glutamicum* ATCC 13032. Cataya Bio constructed the production strain through gene deletions and insertion of five genes encoding enzymes involved in carbohydrate biosynthesis and transport, including an α -1,2-fucosyltransferase for fucosylation of lactose to produce 2'-FL. Cataya Bio states that all genetic modifications are verified by whole genome sequencing and the strain is non-pathogenic and non-toxigenic.

Cataya Bio describes the two-stage manufacturing process, which includes fermentation and purification stages. In the first stage, 2'-FL is produced from lactose and glucose or sucrose during fermentation of *C. glutamicum* under controlled conditions and is secreted into the fermentation medium. After fermentation is complete, 2'-FL production is stopped by heat treatment and the microbial biomass is removed from the fermentation medium by microfiltration. The second stage consists of a series of purification steps. The filtrate is subjected to ultrafiltration to remove large molecules, such as proteins, and then concentrated by nanofiltration and evaporation. The concentrate is treated with activated charcoal, electro dialysis, and ion-exchange resins to remove inorganic salts and organic matter. Chromatography is used to remove saccharide impurities, and the final 2'-FL product is obtained by spray-drying. Cataya Bio states that 2'-FL is manufactured according to current good manufacturing practices, and all raw materials and processing aids are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for their respective uses, or are the subject of an effective food contact notification.

Cataya Bio provides specifications for 2'-FL, which include the minimum content of 2'-FL ($\geq 94\%$ DW), and limits on 3,2'-difucosyl-D-lactose ($\leq 2.0\%$ DW), D-lactose ($\leq 3.0\%$ DW), L-fucose ($\leq 2.0\%$ DW), 2'-fucosyl-D-lactulose ($\leq 1.0\%$ DM), moisture ($\leq 9.0\%$), residual proteins (≤ 100 mg/kg), ash ($\leq 0.5\%$), pH (3.0-7.5), heavy metals, including lead (≤ 0.02 mg/kg), and microorganisms, including *Cronobacter* spp. (absent in 10 g), *Listeria monocytogenes* (absent in 25 g), and *Salmonella* serovars (absent in 25 g). Purity specifications are consistent with the 2'-FL monograph in the 14th edition of the Food Chemicals Codex. Cataya Bio provides the results from five non-consecutive batch analyses to demonstrate that 2'-FL can be manufactured to meet the specifications.

Cataya Bio provides the results of a stability study conducted with five batches of 2'-FL held for 26 weeks under accelerated storage conditions (40°C, 75% relative humidity). Based on the results of this study, Cataya Bio concludes that the shelf-life of 2'-FL is two years when stored under ambient temperatures (8° to 25°C) in the sealed original packaging.

Cataya Bio discusses the dietary exposure to 2'-FL and states that the intended uses are substitutional for those described in previous GRAS notices;⁴⁴ therefore, they do not expect the dietary exposure to 2'-FL to change. Cataya Bio summarizes the dietary exposure estimates presented in GRN 001051, which includes previously notified uses, including in non-exempt infant formula for term infants and additional food categories. Based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey, Cataya Bio reports the eaters-only dietary exposure to 2'-FL at the mean and 90th percentile for infants 0-6 months of age to be 2.4 and 4.4 g/person (p)/d (360 and 578 mg/kg body weight (bw)/d), respectively. The mean and 90th percentile dietary exposures to 2'-FL for infants 7-12 months of age are estimated to be 4.3 and 7.7 g/p/d (474 and 812 mg/kg bw/d), respectively. The mean and 90th percentile dietary exposures to 2'-FL for the total population aged 2 years and older are estimated to be 4.2 and 9.1 g/p/d (65 and 146 mg/kg bw/d), respectively, and for children 1-2 years of age to be 2.9 and 5.7 g/p/d (237 and 477 mg/kg bw/

d), respectively. The highest dietary exposures were observed for adults 65 years of age and older where the mean and 90th percentile eaters-only dietary exposures are 5.2 and 11.0 g/p/d (67 and 148 mg/kg bw/d), respectively.

Cataya Bio incorporates into the notice the publicly available scientific data and information supporting the safety of 2'-FL that was previously discussed in prior notices, including GRNs 000546, 000932, 001014, 001051, and 001060. Cataya Bio states that 2'-FL is chemically and structurally equivalent to that in human milk, and compositionally similar to other 2'-FL ingredients. Cataya Bio summarizes information on the absorption, distribution, metabolism, and excretion of 2'-FL, background consumption of 2'-FL in human milk, and toxicity studies that were discussed in prior GRAS notices for 2'-FL. This includes repeated dose subchronic studies in rats, tolerability studies in neonatal piglets, and clinical studies in both infants and adults. Cataya Bio concludes that there was no evidence of toxicity from these studies. Further, Cataya Bio discusses new scientific literature on 2'-FL, including piglet studies and clinical studies in healthy infants, that were identified in an updated literature search conducted through May 2025. Cataya Bio states that the results of these studies provide further corroborative evidence in support of this GRAS conclusion.

Based on the totality of the data and information, Cataya Bio concludes that 2'-FL is GRAS for its intended use.

Standards of Identity

In the notice, Cataya Bio states its intention to use 2'-FL 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, & 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). 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 Nutrition Center of Excellence. The Office of Pre-Market Additive Safety (OPMAS) 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) or a food ingredient that contains protein derived from one of those foods. 2'-FL may require labeling under the FD&C Act because it may contain protein derived from soybean. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OPMAS. Questions related to food labeling in general should be directed to the ONFL.

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 Cataya Bio'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 the Office of Critical Foods in the Nutrition Center of Excellence.

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 Cataya Bio'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 Cataya Bio provided, as well as other information available to FDA, we have no questions at this time regarding Cataya Bio'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 001238 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Susan J.
Carlson -S**

Digitally signed by Susan J.
Carlson -S
Date: 2025.06.17 16:26:03
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Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary
Supplements, and Innovation
Human Foods Program

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1. ^Cataya Bio states that the use of 2'-FL in non-exempt infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based).
 2. ^Cataya Bio states that 2'-FL is not intended for use in products under the U.S. Department of Agriculture's jurisdiction and in foods for which standards of identity do not permit its addition.
 3. ^The category of coffee and tea includes ready-to-drink (e.g., bottled, flavored, pre-sweetened) coffee and tea and powder mixes used to prepare coffee and tea. For dietary exposure estimates, it is assumed that the intended uses of 2'-FL do not include plain brewed coffee or tea.
 4. ^2'-FL (referred to as 2'-O-fucosyllactose in earlier GRNs) for use in non-exempt infant formula for term infants, and in multiple additional food categories is the subject of GRNs 000546, 000571, 000650, 000735, 000749, 000852, 000897, 000932, 001014, 001051, and 001060. We responded in letters dated September 16, 2015, November 6, 2015, November 23, 2016, April 6, 2018, April 23, 2018, November 15, 2019, June 12, 2020, February 18, 2021, July 15, 2022, November 21, 2023, and April 4, 2023, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.