



Haresh P. Madeka, Ph.D.  
BASF Corporation  
Nutrition & Health NA  
100 Park Ave.  
Florham Park, NJ 07932

Re: GRAS Notice No. GRN 000852

Dear Dr. Madeka:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000852. We received BASF Corporation's (BASF) notice on March 29, 2019. In an email sent to you on May 16, 2019, we requested clarification regarding the intended use of the subject of the notice in infant formulas. You responded in an email dated May 20, 2019, that the use is intended for non-exempt formulas for term infants. We filed the notice on May 21, 2019. BASF submitted an amendment to the notice on August 12, 2019, that contained additional information about the literature searches conducted, the intended use in infant formulas, the source of lactose used in the production growth media, and the residual protein specification.

The subject of the notice is 2'-fucosyllactose (2'-FL) for use as an ingredient in beverages and beverage bases; breakfast cereals; dairy product analogues; frozen dairy desserts and mixes; gelatins, puddings, and fillings; grain products and pastas; jams and jellies; whole and skim milk; milk products; processed fruits and fruit juices; and sweet sauces, toppings, and syrups at levels ranging from 0.28 to 1.2 g/serving; in non-exempt formulas for term infants at 0.24 g/serving (2.4 g/L); in toddler formulas at 0.24 g/serving (2.4 g/L); and in baby foods at levels ranging from 0.24 to 1.2 g/serving. The notice informs us of BASF's view that these uses of 2'-FL are GRAS through scientific procedures.

BASF provides information about the identity and composition of 2'-FL. BASF states that 2'-FL is a trisaccharide based on the monosaccharide L-fucose and the disaccharide D-lactose and is naturally abundant in human breast milk. BASF describes the subject of the notice as a white to off-white powder consisting mainly of 2'-FL and minor quantities of other chemically-related sugars, including D-lactose, L-fucose, 2'-difucosyl-D-lactose, and 2'-fucosyl-D-lactulose.

BASF describes the production microorganism as the genetically engineered strain *Escherichia coli* LU20297,<sup>1</sup> which is capable of producing 2'-FL and is derived from *E.*

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<sup>1</sup>LU20297 has been deposited at the DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen) with the deposit number DSM 32665.

*coli* K 12 JM 109. BASF describes the manufacturing process for 2'-FL as four major activities: fermentation, isolation, purification and packaging/product release. BASF states that all raw materials are of food or pharmaceutical grade quality and all processing aids are suitable for use in food. The manufacturing process is summarized as follows: 2'-FL is biosynthesized with a well-controlled fermentation process using the production organism *E. coli* K 12 LU20297. At the end of the fermentation, the main components of the fermentation broth are biomass, 2'-FL, D-lactose<sup>2</sup>, 2'-difucosyl-D-lactose, residual inorganic salts, and minor amounts of organic acids. The resulting product is isolated and purified using several processing steps. The first step separates the living and intact cells from the fermentation broth by either cross-flow microfiltration or centrifugation. The liquid phase containing 2'-FL is further filtered by a cross-flow filtration process with an ultrafiltration membrane to remove large molecules. Before or after ultrafiltration, the product can be concentrated using vacuum evaporation or filtration. An adsorbent is used to remove color impurities and other hydrophobic impurities from the solution. The decolorized, crude 2'-FL solution is then further demineralized by ion exchange adsorbent and/or electro dialysis. Prior to final purification, the crude 2'-FL solution is concentrated by filtration and/or vacuum evaporation to the desired concentration. The concentrated solution is further purified by crystallization. The crystallized product is removed from the mother liquor by filtration or centrifugation. The crystals are washed using suitable solvents to remove impurities and the crystals are dried. The crystalline 2'-FL can be used as the final product. Alternatively, the crystals can be re-dissolved, filtered, and dried.

BASF provides specifications for 2'-FL as follows: 2'-FL ( $\geq 90\%$  on water-free basis); D-lactose ( $\leq 3.0\%$ ); L-fucose ( $\leq 2.0\%$ ); 2'-difucosyl-D-lactose ( $\leq 2.0\%$ ); 2'-fucosyl-D-lactulose ( $\leq 2.0\%$ ); pH (3.2 to 7.5); sulfated ash ( $\leq 1.5\%$ ); acetic acid ( $\leq 1.0\%$ ); water ( $\leq 9.0\%$  by weight); lead ( $\leq 0.05$  mg/kg); cadmium ( $\leq 0.05$  mg/kg); mercury ( $\leq 0.05$  mg/kg); arsenic ( $\leq 0.1$  mg/kg); endotoxin ( $\leq 10$  endotoxin units/mg); residual protein ( $\leq 0.01\%$ ); total microbial aerobic count ( $< 500$  colony forming units (CFU)/g); yeasts and molds ( $< 100$  CFU/g); Enterobacteria and other Gram-negative bacteria (absent in 10 g); *Cronobacter sakazakii* (absent in 10 g); *Salmonella* serovars (absent in 25 g); and *Listeria monocytogenes* (absent in 25 g). BASF analyzed six batches of 2'-FL and the results demonstrate conformance with the stated specifications. BASF states that its 2'-FL is of equivalent quality as that produced by chemical synthesis or from other microbial sources. BASF states that 2'-FL is stable for at least 6 months at 40°C (75% relative humidity) when it is stored in the original unopened bag.

BASF provides estimates of consumer-only dietary exposure to 2'-FL based on the intended uses and food consumption data from the 2013-2014 National Health and Nutrition Examination Survey. The dietary exposures to 2'-FL for the total population are 1.70 g/person (p)/day (d) (36 mg/kg body weight (bw)/d) at the mean and 3.54 g/p/d (80 mg/kg bw/d) at the 90<sup>th</sup> percentile. BASF reports that the mean and 90<sup>th</sup> percentile dietary exposures to 2'-FL for infants from 0-5 months are 1.91 g/p/d and 3.00 g/p/d (315 and 532 mg/kg bw/d), respectively. The mean and 90<sup>th</sup> percentile

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<sup>2</sup> Lactose is a disaccharide sourced from cow's milk. BASF provided specification parameters for the lactose used in the fermentation media during production of 2'-FL that indicate the lactose may contain traces of cow milk protein.

dietary exposures to 2'-FL for infants from 6-11 months are 2.28 g/p/d and 3.86 g/p/d (259 and 447 mg/kg bw/d), respectively. The mean and 90<sup>th</sup> percentile dietary exposures to 2'-FL for toddlers from 12-35 months are 1.83 g/p/d and 2.97 g/p/d (148 and 243 mg/kg bw/d), respectively.

BASF also provides estimates of consumer-only dietary exposure to 2'-FL for non-breastfed infants and toddlers from the use in non-exempt formulas. The mean and 90<sup>th</sup> percentile dietary exposures to 2'-FL for non-breastfed infants from 0-5 months are 2.14 g/p/d and 2.88 g/p/d (354 and 498 mg/kg bw/d), respectively. The mean and 90<sup>th</sup> percentile dietary exposures to 2'-FL for non-breastfed infants from 6-11 months are 1.67 g/p/d and 2.56 g/p/d (192 and 311 mg/kg bw/d), respectively. The mean and 90<sup>th</sup> percentile dietary exposures to 2'-FL for non-breastfed toddlers from 12-35 months are 0.39 g/p/d and 1.14 g/p/d (40 and 101 mg/kg bw/d), respectively.

BASF discusses the data and information discussed in previous GRAS notices on 2'-FL.<sup>3</sup> BASF states that 2'-FL undergoes partial fermentation in the colon and is mostly excreted in the feces. BASF discusses two published oral toxicity studies in rats. In one study, up to 5000 mg 2'-FL/kg bw/d, administered by gavage for 90 days, did not produce toxicologically relevant effects. In a 14-day feeding study, up to 10% 2'-FL administered through diet, equivalent to  $\geq 7250$  mg 2'-FL/kg bw/d, did not produce toxicologically relevant effects. BASF discusses a published 20-day oral toxicity study in neonatal pigs in which the administration of 2'-FL in a milk replacement formula from birth to age 3 weeks at concentrations up to 2000 mg 2'-FL/L/d was well tolerated. BASF states that the production strain is non-toxicogenic and non-pathogenic. Summarizing several published and unpublished studies, BASF concludes that 2'-FL is neither mutagenic nor genotoxic. BASF summarizes several studies in infants and adults fed 2'-FL and states that 2'-FL is well-tolerated and infants consuming 2'-FL show normal growth. BASF conducted a literature search through October 2018 and did not retrieve any information that would contradict its conclusion that 2'-FL is GRAS for the intended use.

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

### **Standards of Identity**

In the notice, BASF 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 Code of Federal Regulations. 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.

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<sup>3</sup> GRNs 000546, 000571, 000650, 000735, and 000749 describe the use of 2'-fucosyllactose or 2'-O-fucosyllactose in various infant formulas and conventional food categories. FDA evaluated these notices and responded in letters dated September 16, 2015, November 6, 2015, November 23, 2016, April 6, 2018, and April 23, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

## **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 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 ONFL. 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 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 Food Ingredients in OFAS. Questions related to food labeling in general should be directed to 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 BASF’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 BASF’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 BASF provided, as well as other information available to FDA, we have no questions at this time regarding BASF'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 000852 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.  
Carlson -S

 Digitally signed by Susan J.  
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