



Dietrich B. Conze, Ph.D.  
Spherix Consulting Group, Inc.  
751 Rockville Pike Unit 30-B  
Rockville, MD 20852

Re: GRAS Notice No. GRN 001076

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001076. We received the notice that you submitted on behalf of Vitalus Nutrition, Inc. (Vitalus) on January 26, 2022, and filed it on September 13, 2022. Vitalus submitted amendments to the notice on December 22, 2022, and January 5, 2023, that clarified the use level, manufacturing, specifications, and provided an up-to-date literature search.

The subject of the notice is galacto-oligosaccharides (GOS) for use as an ingredient in powdered, ready-to-feed, and concentrated liquid forms of cow milk-based, non-exempt infant formula for term infants at a maximum level of 7.8 g/L of infant formula, as consumed. GOS is also for use as an ingredient in milk and milk products; soups; coconut beverages; bakery products; ready-to-eat cereals; jams, jellies, and preserves; and non-alcoholic beverages at maximum levels ranging from 0.55 to 33.4%.<sup>1</sup> The notice informs us of Vitalus' view that these uses of GOS are GRAS through scientific procedures.

Vitalus describes GOS as a clear to slight-yellow syrup that contains  $\geq 57\%$  GOS on a dry matter (DM) basis, with the remainder being primarily lactose, glucose, and galactose. Vitalus states that GOS is a mixture of  $\beta$ -linked di- to octa-saccharides with one to seven galactose units linked to glucose at the reducing end, and the trisaccharide as the predominant constituent.

Vitalus describes the method of manufacture for GOS from lactose derived from cow milk whey. Lactose is dissolved in water and the solution is heated under agitation, followed by temperature and pH adjustment. A  $\beta$ -galactosidase preparation purified from a non-toxigenic and non-pathogenic strain of *Bacillus circulans* is added to the solution to catalyze the hydrolysis of lactose and the transgalactosylation reaction that

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<sup>1</sup> Vitalus states that GOS is not intended for use in products under the U.S. Department of Agriculture's jurisdiction or in foods for which standards of identity do not permit its addition.

forms GOS. The enzyme is subsequently inactivated by pH adjustment, and the resulting mixture is filtered and subjected to adsorption and ion exchange resins. The resulting product is concentrated by evaporation and homogenized by passing it through a screen to obtain the final GOS syrup. Vitalus states that GOS is manufactured using food-grade materials.

Vitalus provides specifications for GOS, which include minimum levels of GOS ( $\geq 57\%$  DM), DM (74-78%), and limits on lactose ( $\leq 28\%$  DM), glucose ( $\leq 22\%$  DM), galactose ( $\leq 5\%$  DM), nitrogen ( $\leq 0.032\%$ ), sulfated ash ( $\leq 0.3\%$ ), lead ( $\leq 0.2\text{mg/kg}$ ), and microorganisms, including *Salmonella* serovars (not detected in 25 g) and *Cronobacter sakazakii* (not detected in 25 g).<sup>2</sup> Vitalus provides the results from five non-consecutive batch analyses to demonstrate that GOS can be manufactured to meet the specifications. Vitalus states GOS is stable for at least 8 months at 18-25 °C.

Vitalus provides estimates of dietary exposure to GOS based on the intended uses and food consumption data from the 2003-2004 National Health and Nutrition Examination Survey. Vitalus states that the intended uses of GOS are substitutional for previously notified uses and that the dietary exposure to GOS is not expected to change. Vitalus describes the dietary exposure estimates provided in GRN 000620<sup>3</sup> for the use of GOS in infant formula. The mean and 90<sup>th</sup> percentile dietary exposures are reported to be 6.4 and 9.2 g/person (p)/d, respectively, for infants up to 6 months of age, 5.6 and 8.6 g/p/d, respectively, for infants 7 to 12 months of age, and 3.0 and 7.1 g/p/d, respectively, for children 1 to 2 years of age. Vitalus describes the dietary exposure estimates provided in GRN 000721<sup>3</sup> for the use of GOS in selected conventional foods and reports the mean and 90<sup>th</sup> percentile dietary exposures to GOS for the total population (all ages) to be 12.2 g/p/d (0.28 g/kg body weight (bw)/d) and 25.3 g/p/d (0.70 g/kg bw/d), respectively.

Vitalus discusses the metabolism and safety of GOS. Vitalus states that GOS passes through the upper gastrointestinal tract until it reaches the large intestine, where it is hydrolyzed to glucose and galactose and is subsequently metabolized to short chain fatty acids, CO<sub>2</sub>, and H<sub>2</sub> gas by the intestinal microbiota. Vitalus incorporates into the notice safety sections from GRNs 000236, 000721, and 000729.<sup>4</sup> Vitalus states that the subject of this notice is compositionally similar, including in the degree of polymerization, to the subject of GRN 000236 based on manufacturing processes and product specifications. Thus, Vitalus concludes that the safety information used for GRN 000236 can be used to assess the safety of the intended use of GOS in this notice. Vitalus discusses a published 90-day rat oral toxicity study of this GOS, which did not show any article-related adverse effects up to highest dose tested. Furthermore, Vitalus discusses published and unpublished toxicity studies with other preparations of GOS,

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<sup>2</sup> The method used for the *C. sakazakii* test is validated for this sample size.

<sup>3</sup> GOS is the subject of GRNs 000620 and 000721. We evaluated these notices and responded in letters dated July 21, 2016, and December 19, 2017, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

<sup>4</sup> GOS is the subject of GRNs 000236 and 000729. We evaluated these notices and responded in letters dated July 28, 2008, and March 27, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

including genotoxicity studies, oral toxicity studies in neonatal rats and piglets, and developmental and reproductive studies in rats, all of which support the safety of the intended use. Vitalus conducted an updated literature search through December 2022 and discusses newly identified published studies with another GOS preparation, including *in vitro* genotoxicity studies, a subchronic, repeat-dose oral toxicity study, and a juvenile toxicity study in Sprague-Dawley rats. Vitalus states that while no human studies have been done with the GOS that is the subject of this notice, Vitalus discusses 10 newly published studies in infants, children, and adults with various preparations of GOS since GRN 000729. Vitalus states that all human studies support the safety and tolerability of GOS from their intended uses.

Based on the totality of the data and information, Vitalus concludes that GOS is GRAS for its intended use.

### **Standards of Identity**

In the notice, Vitalus states its intention to use GOS 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 GOS 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 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. GOS 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 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 Vitalus' GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing GOS 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 Vitalus' notice concluding that GOS 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 GOS. Accordingly, our response should not be construed to be a statement that foods containing GOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

## **Conclusions**

Based on the information that Vitalus provided, as well as other information available to FDA, we have no questions at this time regarding Vitalus' conclusion that GOS is GRAS under its intended conditions of use. This letter is not an affirmation that GOS 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 001076 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.  
Carlson -S  
Date: 2023.03.02 14:07:41 -05'00'

Susan J. Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition