



Claire Kruger, Ph.D.
Spherix Consulting Group, Inc.
11821 Parklawn Drive
Rockville, MD 20852

Re: GRAS Notice No. GRN 000896

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000896. We received the notice that you submitted on behalf of Olygose on November 18, 2019 and filed it on February 20, 2020. Olygose submitted amendments to the notice on April 29, 2020, June 10, 2020, and September 18, 2020, that clarified the identity of the substance and provided additional information on the specifications, literature search, manufacturing process, dietary exposure and use level.

The subject of the notice is alpha-galacto-oligosaccharides (α -GOS) for use as an ingredient in non-exempt infant formulas for term infants at up to 8 g/L and in beverages (carbonated/non-carbonated, juice, flavored water), coffee and tea, including ready to drink iced coffee and teas, sports drinks, energy drinks, meal replacement beverages, soups, dairy and dairy product analogs, processed fruit and vegetable juices, sugars and sweets, baby cereals, baby foods, and toddler foods at levels ranging from 0.5 to 6 g/serving.¹ The notice informs us of Olygose's view that these uses of α -GOS are GRAS through scientific procedures.

Olygose provides information on the identity and composition of α -GOS. Olygose describes α -GOS as a non-digestible, alpha-linked galacto-oligosaccharide derived from pea (*Pisum sativum*) solubles; it is a mixture of bi-, tri-, and tetra-saccharides composed of one to three galactose units linked via α (1-6) glycosidic bonds to glucose at the reducing end. Olygose produces α -GOS as a white powder and as a clear liquid. Olygose states that α -GOS syrup and powder both contain approximately 4% melibiose, 43% manninotriose, and 49% verbascotetraose.

Olygose describes the manufacturing process for α -GOS from the pea solubles starting material. The pea solubles are centrifuged to remove any solids and then the supernatant fraction undergoes a series of filtration steps to remove protein. The resulting filtrate is demineralized using ion-exchange resins and subjected to sulfuric acid hydrolysis to remove the terminal fructose from the oligosaccharides. The mixture is neutralized with sodium hydroxide and cooled, and then the remaining monosaccharides are removed using nanofiltration. The resulting oligosaccharide

¹ Olygose states that α -GOS is not intended for use in products subject to regulation by the U.S. Department of Agriculture.

solution is further purified using activated carbon and is then heated, filtered, and then evaporated to yield a syrup, which can be spray-dried to form a powder. Olygose indicates that all processing aids, raw materials, and food contact materials are authorized for their use. Olygose states that α -GOS is manufactured using good manufacturing practices.

Olygose provides specifications for α -GOS syrup and powder that include dry matter (DM; > 72% for the syrup and > 95% for the powder), limits for α -GOS ($96 \pm 3\%$ of the DM), protein (< 0.5 % DM), ash (< 0.5% DM), digestible sugars² (< 5 % DM), lead (< 1 mg/kg), arsenic (≤ 1 mg/kg), cadmium (<1 mg/kg), and mercury (< 1 mg/kg), as well as limits for microorganisms, including *Salmonella* (absent in a 125 g sample) and *Cronobacter sakazakii* (absent in a 25 g sample). Olygose provides the results of the analysis of three non-consecutive batches to demonstrate conformance with these specifications. Olygose notes that potential sugar degradation products (e.g., 5-(hydroxymethyl) furfural) resulting from the acid-hydrolysis of sugars are not detected in the finished products using a high-performance liquid chromatography (HPLC) method with pulsed amperometric detection (PAD) with a limit of detection of 2 mg/kg. Olygose states that all analytical methods are either compendial methods or validated internal methods. Olygose states that α -GOS powder and syrup are stable under ambient (50-85° F, <75% relative humidity) storage conditions for at least 12 months.

Olygose provides estimates of the dietary exposure to α -GOS based on its intended uses in infant formulas and conventional foods. Olygose provides user-only exposure estimates for α -GOS of 4.3 g/p/d at the mean and 8.5 g/p/d at the 90th percentile for the U.S. population aged 2 years or older using food consumption data from the 2013-2014 National Health and Nutrition Examination Survey (NHANES). The estimated exposures to α -GOS for infants 0 to 1 year of age is estimated to be 0.7 g/p/day at the mean and 1.7 g/p/d at the 90th percentile. Olygose also estimates exposures to α -GOS for other sub-populations. Olygose states that α -GOS will be used as an alternative for other GOS products; therefore, there will be no impact on the cumulative exposure to GOS.

Olygose discusses the results of published genotoxicity, subchronic rat, and neonatal piglet studies on α -GOS to support its GRAS conclusion. Olygose states that the genotoxicity studies (Ames test and *in vitro* chromosome aberration study) showed that α -GOS is not genotoxic. Olygose also reports that the results of their 90-day GLP study in rats conducted following Organization for Economic Cooperation and Development-compliant guidelines, except for the use of a single dose, showed that the no-observed-adverse-effect-level (NOAEL) for α -GOS was 2000 mg/kg/day. Olygose also conducted a three-week feeding study in neonatal piglets to assess the effect of 8.0 g/L of α -GOS as an infant formula ingredient on infant development. Olygose stated that α -GOS was determined to be safe and well-tolerated at this level of ingestion in their piglet study and supported their intended use in non-exempt infant formulas at 8 g/L. Olygose included the results of two published clinical studies (separate dose effect and

² Olygose defines digestible sugars as the monosaccharides (glucose, galactose and fructose), as well as the disaccharides (sucrose and maltose).

formulation effect studies) on α -GOS in overweight adults to support the safety of their product. Olygose states that the results of these clinical studies showed that α -GOS was well-tolerated and produced no adverse effects. Since α -GOS is manufactured from pea solubles, Olygose states that the results of unpublished immunoblotting and ELISA inhibition assays demonstrated the absence of proteins and dun pea allergens in α -GOS.

Olygose includes the opinion of a panel of individuals (Olygose's GRAS panel). Based on its review, Olygose's GRAS panel concluded that α -GOS is safe based on scientific procedures under the conditions of its intended use.

Based on the totality of evidence, Olygose concludes that α -GOS is GRAS for its intended use.

Standards of Identity

In the notice, Olygose states its intention to use α -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 α -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 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.

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 Olygose's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing α -GOS 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(ll)(1)-(4) applies. In our evaluation of Olygose's notice concluding that α -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 α -GOS. Accordingly, our response should not be construed to be a statement that foods containing α -GOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Olygose provided, as well as other information available to FDA, we have no questions at this time regarding Olygose's conclusion that α -GOS is GRAS under its intended conditions of use. This letter is not an affirmation that α -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 000896 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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