



Steven Overgaard
GRAS Associates, LLC
27499 Riverview Center Blvd.
Suite 212
Bonita Springs, FL 34134

Re: GRAS Notice No. GRN 000729

Dear Mr. Overgaard:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000729. We received the notice that you submitted on behalf of Neo Cremar Co., Ltd. (Neo Cremar) on September 6, 2017,¹ and filed it on October 3, 2017. We received an amendment to the notice clarifying the intended uses, dietary exposure estimates, and specifications for the subject of the notice on December 18, 2017.

The subject of the notice is galacto-oligosaccharides (GOS) for use as an ingredient in milk-based, non-exempt infant formulas for term infants at a level up to 7.8 g GOS/L of reconstituted or ready-to-feed formula; and in milk and milk products, soups, bakery products, cereals, fruit and vegetable juices, jellies and jams, and nonalcoholic beverages at maximum levels up to 11 g/serving. The notice informs us of Neo Cremar's view that these uses of GOS are GRAS through scientific procedures.²

Neo Cremar describes the identity and composition of GOS. The product is a mixture of β -linked di- to octasaccharides composed of one to seven galactose units linked to glucose at the reducing end. Neo Cremar states that the O- β -D-galactopyranosyl-(1 \rightarrow 4)-O- β -galactopyranosyl-(1 \rightarrow 4)- β -D-glucose is the predominant saccharide in GOS.

Neo Cremar describes the method of manufacture for eight GOS formulations. GOS is produced from lactose, derived from either cow's or goat's milk,³ and treatment with a β -galactosidase enzyme preparation from a non-toxicogenic and non-pathogenic strain of *Bacillus circulans*. The enzymatic reaction is terminated with heat treatment and then processed into liquid or powder formulations. The processes for liquid formulations include pH adjustment, filtration, decolorization, ion-exchange chromatography, and

¹ Neo Cremar has confidential markings in the notice. In an email correspondence dated September 15, 2017, Neo Cremar informed FDA that the confidential markings were made in error.

² Neo Cremar states that GOS is not intended for use in foods under the jurisdiction of the United States Department of Agriculture.

³ Neo Cremar states that although cow's and goat's milk are the sources of lactose used in the production of GOS, it is unlikely that an allergic-type response would be observed with a finished GOS formulation since allergens found in milk are not likely to be present in lactose after its extraction and due to the additional purification steps involved in the production of GOS.

evaporation to obtain syrups containing $\geq 55\%$ or 57% GOS. A powder formulation containing $\geq 33\%$ GOS is obtained by blending with maltodextrin, followed by filtration, evaporation, and spray drying. Neo Cremar describes processes for GOS formulations with higher GOS concentrations that include a fermentation step with a non-toxicogenic and non-pathogenic strain of *Saccharomyces cerevisiae* following the termination of the β -galactosidase reaction. After fermentation, the product is decolorized, filtered, and subjected to ion exchange chromatography, and then either evaporated to form syrups containing $\geq 70\%$ or $\geq 75\%$ GOS or spray-dried to form powders containing $\geq 70\%$ or $\geq 75\%$ GOS. Neo Cremar notes that all materials used in the manufacture of GOS are food grade and meet applicable regulations.

Neo Cremar provides specifications for eight formulations of GOS that include minimum levels of galacto-oligosaccharides ($\geq 33, 55, 57, 70,$ or 75% on a dry matter basis (DM)) and galactose ($\geq 0.8\%$ DM), and dry matter content for liquid formulations (74 to 76%). Specifications include limits on lactose ($\leq 23\%$ DM), glucose ($\leq 22\%$ DM), ash ($< 0.3\%$), nitrogen ($\leq 0.1\%$), nitrite (≤ 2 mg/kg), lead (≤ 1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.06 mg/kg), and mercury (≤ 0.1 mg/kg), as well as limits on microbial contaminants, including *Cronobacter sakazakii* (not detected in a 300 g sample) and *Salmonella* serovars (not detected in a 75 g sample). Neo Cremar provides the results of three non-consecutive batch analyses conducted with each formulation to demonstrate compliance with these specifications.

Neo Cremar provides estimates of dietary exposure to GOS based on its intended uses and food consumption data from the 2003-2004 National Health and Nutrition Examination Survey. Neo Cremar states that the intended uses of GOS are substitutional for previously notified uses and the dietary exposure to GOS is not expected to change significantly. Neo Cremar describes the estimates of the dietary exposure provided in GRN 000620⁴ for the use of GOS in infant formulas. The mean and 90th percentile dietary exposures are reported to be 6.4 and 9.2 g/person/day, respectively, for infants up to 6 months in age, 5.6 and 8.6 g/person/day, respectively, for infants 7 to 12 months of age, and 3.0 and 7.1 g/person/day, respectively, for toddlers 1 to 2 years of age. Neo Cremar describes the estimates of the dietary exposure provided in GRN 0000334,⁵ where the mean and 90th percentile exposures to GOS for the total population were reported to be 12.2 g/person/day (0.28 g/kg body weight (bw)/day) and 25.3 g/person/day (0.70 g/kg bw/day), respectively.

Neo Cremar summarizes published and unpublished safety data for GOS, including information on metabolism, short- and long-term toxicity in experimental animals, and

⁴ GOS was the subject of GRN 000620, which informed FDA of the view of Nestlé Nutrition (Nestlé) that GOS is GRAS, through scientific procedures, for use as an ingredient in non-exempt infant formulas for term infants and in follow-on formulas at a level providing up to 7.8 g/L of reconstituted or ready-to-drink formula. FDA evaluated this notice and responded in a letter dated July 21, 2016, stating that the agency had no questions at that time regarding Nestlé's GRAS conclusion.

⁵ GOS was the subject of GRN 000334, which informed FDA of the view of Yakult Pharmaceutical Industry Co., Ltd. (Yakult) that GOS is GRAS, through scientific procedures, for use as an ingredient in term infant formula at a concentration of 7.2 g/L and in other food categories. FDA evaluated this notice and responded in a letter dated October 27, 2010, stating that the agency had no questions at that time regarding Yakult's GRAS conclusion.

tolerance studies in human adults and infants.⁶ Neo Cremer discusses published 90-day oral toxicity studies in rats and states that there was no evidence of toxicity at the highest dose levels of GOS tested, up to 5 g/kg bw/day. Neo Cremer states that an even higher dose administered in an unpublished corroborative study did not produce any adverse effects. Neo Cremer states that published studies also showed that GOS has no reproductive or developmental toxicity. Neo Cremer states that GOS is neither mutagenic nor genotoxic. Neo Cremer states that GOS has been extensively reviewed by national and international agencies including FDA, the Scientific Committee on Food, and the Food Standards Australia New Zealand, and has been demonstrated to be safe for use as an ingredient in a variety of foods, including infant formulas.

Published studies in humans show that GOS is well-tolerated. In published clinical studies, nutritional and physiological effects of GOS-containing infant formulas in premature infants, term infants, and infants with atopic disorders has been investigated. Findings from these studies demonstrate that the addition of GOS to infant formulas at use levels up to 7.8 g/L is well tolerated.

Neo Cremer reports that it conducted a literature search on the safety of GOS through July 17, 2017, and identified new data and information relevant to the safety of GOS. Neo Cremer states that the new studies did not report any adverse effects of GOS and, therefore, do not contradict the current safety conclusions.

Neo Cremer includes the statement of a panel of individuals (Neo Cremer's GRAS panel). Based on its review, Neo Cremer's GRAS panel concluded that GOS is safe under the conditions of its intended use.

Based on the data and information summarized above, Neo Cremer concludes that GOS is GRAS for its intended use.

Standards of Identity

In the notice, Neo Cremer states its intention to use GOS 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.

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). The notice raises a potential

⁶ Neo Cremer did not specify whether the GOS it used to conduct safety studies was derived from cow's milk or goat's milk. However, the GOS used in safety studies conducted by other investigators and discussed by Neo Cremer was derived from cow's milk.

issue under these labeling provisions. In the notice, Neo Cremar cites studies that describe GOS as having certain health benefits. 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 eight foods or food groups (i.e., milk⁷, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. GOS produced from lactose derived from cow’s milk may require labeling under the FD&C Act because it may contain protein derived from cow’s milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review 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 Neo Cremar’s 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 the 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 Neo Cremar’s notice concluding that GOS 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 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(II).

⁷ Section 312(c) of the FD&C defines the term “milk” as sweet milk of cows.

Conclusions

Based on the information that Neo Cremar provided, as well as other information available to FDA, we have no questions at this time regarding Neo Cremar's 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 000729 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition