



Fernando Schved, Ph.D.
Galam Ltd.
Kibbutz Maanit
M.P. Menashe
3785500, ISRAEL

Re: GRAS Notice No. GRN 000717

Dear Dr. Schved:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000717. We received Galam Ltd. (Galam)'s notice on July 3, 2017, and filed it on August 15, 2017. We received amendments to the notice clarifying the intended uses and use levels of the subject of the notice on October 20, 2017, and October 25, 2017.

The subject of the notice is short-chain fructo-oligosaccharides (scFOS) for use as a bulking agent and as a general-purpose food ingredient in various food categories, including substitutes for meat, poultry, and fish; nutritional bars; breakfast cereals; beverages and juices; cakes; cheese; cream; confectionery; cookies; crackers; dessert toppings and fillings; hard candy; ice cream; infant foods; jams and jellies; milks (acidophilus; flavored and unflavored; evaporated and condensed); muffins and quick bread; sauces, gravies, and condiments; snacks; sorbet and sherbet; soups; toddler (12-24 months old) foods; and yogurt at levels ranging from 0.4 to 6.7%. The notice informs us of Galam's view that this use of scFOS is GRAS through scientific procedures.^{1,2}

Galam describes the identity and composition of scFOS. The product is a mixture of oligomers consisting of sucrose with one, two, or three additional fructose units attached to the fructose unit of sucrose by β -2-1 glycosidic linkages.

Galam describes the manufacturing process for scFOS, which is synthesized using an enzyme preparation with fructosyltransferase activity. The fructosyltransferase enzyme preparation is derived from a non-genetically modified strain of *Aspergillus aculeatus* that Galam describes as non-pathogenic and non-toxicogenic. Galam states that the enzyme preparation is immobilized on a cross-linked polystyrene divinylbenzene ion exchange resin. A sucrose syrup solution is passed through the ion exchange resin containing the immobilized enzyme preparation. The eluate from the reaction column that contains >55% scFOS is purified by column chromatography to reduce the monosaccharide content. The scFOS solution is purified further using activated carbon to remove organic impurities. The resulting solution is either evaporated to produce a concentrated syrup or spray-dried to produce a powder. Galam states that the raw

¹ Galam states that scFOS is not intended for use in foods under the jurisdiction of the United States Department of Agriculture, nor is it intended for use in infant formulas.

² Galam states that the food categories and use levels are the same as those in GRN 000044 and GRN 000605.

materials and processing aids used in the manufacture of scFOS are food-grade materials used in accordance with current good manufacturing practices and are permitted for use in food by U.S. regulations or are GRAS for their respective uses.

Galam provides specifications for scFOS that include fructo-oligosaccharides ($95\pm 2\%$ dry weight basis), water ($\leq 25\%$ for syrup and $\leq 5\%$ for powder), sugars (sucrose, glucose, fructose ($5\pm 2\%$ dry weight basis)), arsenic (≤ 1 mg/kg), lead (≤ 1 mg/kg), residual proteins (0.01%), and limits on microbial contaminants. Galam provides analytical data from two nonconsecutive batches of the syrup and powdered scFOS products to demonstrate compliance with these specifications.

Galam provides an estimate of the dietary exposure to scFOS based on that in GRN 000044.³ Galam states that the intended use levels and food categories described in GRN 000717 are the same as those described in GRN 000044 and that the uses of scFOS that are the subject of GRN 000717 are substitutional for the FOS described in GRN 000044. The reported estimates for scFOS as described in GRN 000044 were generated using the 1994 -1996 USDA Continuing Survey of Food Intakes by Individuals (CSFII) data for food consumption. Two-day average dietary intake data were used. Based on these data, for the population group aged 20 years and older, Galam estimates that the mean dietary exposure to scFOS is 4.37 g per person per day (g/p/d) (60 mg/kg bodyweight (bw)/d for a 70 kg individual), and the 90th percentile dietary exposure is 9.09 g/p/d (127 mg/kg bw/d for a 70 kg individual).

Galam discusses published studies in animals and humans to support the intended use of the scFOS that is the subject of GRN 000717. Galam states that scFOS and related fructans are resistant to digestion in the upper gastrointestinal tract and reach the large intestine primarily intact where microbial fermentation occurs. Galam states that unfermented scFOS is excreted in the feces. Galam lists several acute and repeat-dose toxicological studies in mice and rats that are discussed in a publication and also cited in GRNs 000044, 000537,⁴ 000605,⁵ and 000623.⁶ In a 90-day study discussed in GRN

³ FOS was the subject of GRN 000044, which informed FDA of the view of GTC Nutrition Company (GTC) that FOS is GRAS, through scientific procedures, for use as a bulking agent in acidophilus milk, nutritional bars, baby food, nutritional beverages, biscuits, cakes, confectionery, cookies, crackers, flavored and unflavored milks, hard candy, ice cream and frozen yogurt, jams and jellies, muffins, ready-to-eat cereals, sorbet, soup, and yogurt at varying levels. FDA evaluated this notice and responded in a letter dated November 22, 2000, stating that the agency had no questions at that time regarding GTC's GRAS conclusion. Subsequently to a supplement from GTC dated January 26, 2007, that expanded GTC's intended uses of FOS, FDA responded in a letter June 1, 2007, stating that the agency had no questions at that time regarding GTC's GRAS conclusion.

⁴ scFOS was the subject of GRN 000537, which informed FDA of the view of Ingredion Incorporated (Ingredion) that scFOS is GRAS, through scientific procedures, for use as an ingredient in term infant formulas. Ingredion intended to use scFOS at levels up to 400 milligrams per 100 milliliters (mg/100 ml) in starter formula (as consumed) and 500 mg/100 ml in follow-on formula (as consumed). FDA evaluated this notice and responded in a letter dated February 6, 2015, stating that the agency had no questions at that time regarding Ingredion's GRAS conclusion.

⁵ FOS was the subject of GRN 000605, which informed FDA of the view of Tata Chemicals Limited (Tata) that FOS is GRAS, through scientific procedures, for use as an ingredient in acidophilus milk; analogs and substitutes for meat, poultry or fish; bars; breakfast cereals; beverages and juices; cakes; cheese; cream; confectionery; cookies; crackers; dessert toppings and fillings; hard candy; ice cream; infant foods (0-12

000044 and cited by Galam, there were no toxicologically relevant effects in rats fed scFOS at levels up to 20,400 mg/kg bw/d. In a published 104-week chronic study in male and female rats, dietary administration of 2,170 and 2,664 mg/kg bw/d of scFOS, respectively, was well tolerated. Galam also cites published tolerance studies conducted in humans. Galam states that no toxicologically relevant effects of scFOS have been reported in human studies. Galam reports that it conducted a comprehensive literature search to October 2016 to identify new data and information relevant to the tolerance of scFOS in children and adults. Galam states that their search identified one study conducted in children and five studies conducted in adults. Galam states that the results of these studies do not contradict the current safety conclusions.

Galam includes the report of a panel of individuals (Galam's GRAS panel). Based on its review, Galam's GRAS panel concluded that scFOS is safe under the conditions of its intended use.

Based on the data and information summarized above, Galam concludes that scFOS is GRAS for its intended use.

Standards of Identity

In the notice, Galam states its intention to use scFOS 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 issue under these labeling provisions. In the notice, Galam cites studies that describe

months); jams and jellies; milk, flavored and unflavored; milk, evaporated and condensed; muffins and quick bread, sauces, gravies and condiments; snacks, sorbet and sherbert; soup; toddler foods (12-24 months); and yogurt at levels ranging from 0.4 to 6.7%. FDA evaluated this notice and responded in a letter dated March 17, 2016, stating that the agency had no questions at that time regarding Tata's GRAS conclusion.

⁶ FOS was the subject of GRN 000623, which informed FDA of the view of New Francisco Biotechnology Corporation (NFBC) that FOS is GRAS, through scientific procedures, for use as an ingredient in conventional foods, including substitutes for meat, poultry, and fish; nutritional bars; breakfast cereals; beverages and juices; cakes; cheese; cream; confectionery; cookies; crackers; dessert toppings and fillings; hard candy; ice cream; infant foods; jams and jellies; milks (acidophilus; flavored and unflavored; evaporated and condensed); muffins and quick bread; sauces, gravies, and condiments; snacks; sorbet and sherbert; soups; toddler (12-24 months old) foods; and yogurt at levels in the range 0.4 to 6.7%. FDA evaluated this notice and responded in a letter dated August 1, 2016, stating that the agency had no questions at that time regarding NFBC's GRAS conclusion.

scFOS as having certain health benefits. If products containing scFOS 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.

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 Galam's notice concluding that scFOS 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 scFOS. Accordingly, our response should not be construed to be a statement that foods containing scFOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Galam provided, as well as other information available to FDA, we have no questions at this time regarding Galam's conclusion that scFOS is GRAS under its intended conditions of use. This letter is not an affirmation that scFOS 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 000717 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A.
Adams -S

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