Madhu Soni, Ph.D.
Soni & Associates Inc.
749 46th Square
Vero Beach, FL 32968

Re: GRAS Notice No. GRN 000990

Dear Dr. Soni:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000990. We received the notice that you submitted on behalf of Tata Chemicals Limited (Tata Chemicals) on January 25, 2021, and filed it on April 22, 2021.[1] Tata Chemicals submitted amendments to the notice on July 19, 2021, and September 2, 2021, that clarified the intended use, manufacturing process, specifications, dietary exposure, and safety studies in Part 6 of the notice.

The subject of the notice is short-chain fructooligosaccharides (scFOS) for use as an ingredient in cow milk-based, non-exempt infant formulas for term infants at a level, as consumed, up to 400 mg scFOS/100 mL formula for infants 0-6 months of age and up to 500 mg scFOS/100 mL formula for infants >6 months of age. The notice informs us of Tata Chemicals' view that these uses of scFOS are GRAS through scientific procedures.

Tata Chemicals provides information about the identity and composition of scFOS (CAS Registry No. 308066-66-2). Tata Chemicals describes two forms of scFOS, which include a white to light-yellow syrup and off-white to light-yellow powder. Tata Chemicals describes scFOS as fructan oligosaccharides that consist of linear chains of fructose with β(2-1) linkages and a terminal glucose residue. scFOS primarily consists of fructans with 2, 3, or 4 fructose residues that are referred to as 1-kestose, nystose, and fructofuranosylnystose, respectively.

Tata Chemicals describes the manufacturing process for scFOS, which is synthesized using a β-fructofuranosidase from a wild-type strain of *Aureobasidium pullulans*. Tata Chemicals states that *A. pullulans* is non-pathogenic and non-toxicogenic and that it is registered under the Microbial Type Culture Collection (MTCC5490). The production strain is inoculated into a fermentation medium and grown to the desired concentration, and then sucrose is added to the medium to stimulate the production of the intracellular

[1] Tata Chemicals clarified information on the intended infant formula protein base in an update on April 21, 2021.

enzyme. The biomass is separated by filtration under sterile conditions, then combined with a sucrose solution under controlled conditions to produce scFOS. The reaction is terminated by heating, which inactivates the enzyme and cellular biomass. The mixture is filtered to remove the biomass, and the filtrate is then subjected to a series of purification steps, including treatment with activated carbon, ion exchange resins, filtration, and chromatography. The resulting solution is concentrated by evaporation under vacuum and pasteurized to obtain a liquid (i.e., syrup) formulation of scFOS. Tata Chemicals states that the liquid formulation may optionally be spray dried to obtain a powdered form of scFOS. Tata Chemicals states that all raw materials and processing aids used in the manufacture of scFOS are food-grade and that scFOS is manufactured according to current good manufacturing practices.

Tata Chemicals provides specifications for the syrup and powder forms of scFOS. These specifications include minimum content of total scFOS (≥ 95% on a dry basis (DB)), 1-kestose (≥ 30% DB), nystose (≥ 45% DB), and fructofuranosylnystose (≥ 5% DB). Specifications also include limits on total fructose (≥ 67% DB), glucose (≤ 33% DB), residual sugars (≤ 5% DB of glucose, fructose, and sucrose combined), ash (≤ 0.1%), moisture (≤ 25% for the syrup form and ≤ 5% for the powder form), and lead (≤ 0.02 mg/kg), as well as limits on microorganisms, including *Cronobacter sakazakii* (absent in 10 g) and *Salmonella* serovars (absent in 25 g). Tata Chemicals provides the results of three non-consecutive batch analyses each for the powder and liquid forms to demonstrate that scFOS can be manufactured to meet these specifications.

Tata Chemicals discusses the dietary exposure to scFOS. They state that the intended use is identical to that described in GRNs 000537 and 000797[2] and summarize the dietary exposure estimates provided in those notices. Tata Chemicals reports that infants with the highest infant formula intake are 14–27 days of age based on published estimates of daily energy intakes by formula-fed infants. The 90th percentile caloric intakes for this age group are 141.3 kcal/kg body weight (bw)/d for boys and 138.9 kcal/kg bw/d for girls. Based on a caloric density for infant formula of 67 kcal/100 mL and the maximum intended use level, Tata Chemicals estimates the 90th percentile dietary exposure to scFOS to be up to 1035 mg/kg bw/d.

Tata Chemicals provides data and information to support the safety of the use of scFOS and states that an updated literature search was conducted through December 2020. Tata Chemicals notes that scFOS is not hydrolyzed by intestinal enzymes, but rather reaches the colon where it is fermented by colonic bacteria. Tata Chemicals discusses a publication that includes an acute toxicity, dose-range finding (14 days), and repeated dose 90-day oral gavage toxicity study in rats using their scFOS ingredient as the test article. Based on these published findings, Tata Chemicals states that administering scFOS at levels up to 9000 mg/kg bw/d, the highest dose tested, is safe and without any adverse toxicological findings. Additional toxicity studies using other scFOS ingredients were also discussed by Tata Chemicals and include acute, subacute, subchronic, chronic, developmental and reproductive, and mutagenicity and genotoxicity studies. Based on

[2] scFOS and FOS were the subjects of GRNs 000537 and 000797, respectively. We evaluated these notices and responded in letters dated February 6, 2015, and November 15, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

this information, Tata Chemicals concludes that scFOS is safe. Tata also summarizes and discusses published and unpublished clinical studies in infants and incorporates data and information into the notice from GRN 000537[2] to support the safe use of scFOS in infant formula.

Based on the totality of the data and information, Tata Chemicals concludes that scFOS is GRAS for its intended use.

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 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.

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 Tata Chemicals' GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing scFOS 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 Tata Chemicals' notice concluding that scFOS 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 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(ll).

Conclusions

Based on the information that Tata Chemicals provided, as well as other information available to FDA, we have no questions at this time regarding Tata Chemicals' 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 000990 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.10.08 17:46:03 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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