U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Riëtte L. van Laack, Ph.D.
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005

Re: GRAS Notice No. GRN 001242

Dear Dr. van Laack:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001242. We received the GRAS notice you submitted on behalf of BENEO GmbH (BENEO) on December 23, 2024, and filed it on February 19, 2025. BENEO submitted amendments to the notice on May 19, 2025, and June 25, 2025, that clarified the intended use, manufacturing, specifications, dietary exposure, and aspects of the safety narrative.

The subject of the notice is short-chain fructooligosaccharides (scFOS) for use as a bulking agent and ingredient in 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); cultured dairy beverages; dairy product analogs; muffins and quick breads; sauces, gravies, and condiments; snacks; sorbet and sherbet; soups; foods for young children (12-24 months old); yogurt; drinkable yogurt; and meal replacement shakes at levels ranging from 0.4% to 15%.[1] BENEO states that scFOS is not intended for use in products under the U.S. Department of Agriculture's jurisdiction. The notice informs us of BENEO's view that this use of scFOS is GRAS through scientific procedures.

BENEO provides information on the identity and composition of scFOS (CAS Registry No. 308066-66-2). scFOS is described as a colorless to slightly yellow, viscous syrup with a minimum content of 83% scFOS on a dry-matter (DM) basis with the remaining DM consisting of sucrose, glucose, and fructose. BENEO describes scFOS as fructan oligosaccharides that are linear chains of fructose with β-(2-1) linkages with and without a terminal glucose residue. scFOS primarily consists of fructans with 2, 3, or 4 fructose residues that are referred to as 1-kestose, nystose, or fructofuranosylnystose, respectively.

BENEO describes the manufacturing process for scFOS. BENEO states that scFOS is synthesized using an enzyme produced by a strain of *Trichoderma reesei* expressing a gene for invertase from *Aspergillus niger*.[2] The

manufacturing process starts with an aqueous sucrose solution that is adjusted to the desired pH, and the enzyme is added at a controlled temperature. Following reaction completion, the mixture is subjected to an activated carbon treatment and ion-exchange resin to remove the enzyme and portions of the unconverted sucrose, glucose, and fructose. The resulting solution is evaporated to obtain a syrup with the specified DM content. BENEO states that scFOS is manufactured according to current good manufacturing practices, and all raw materials and processing aids are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for their respective uses, or are the subject of an effective food contact notification.

BENEO provides specifications for scFOS that include a minimum content of total scFOS (≥ 83% on a DM basis), and limits for sugars (≤ 17% DM of glucose, fructose, and sucrose combined), DM (75 ± 1 %), conductivity (≤ 250 µS/cm), pH (4 - 7), arsenic (≤ 0.05 mg/kg), cadmium (≤ 0.05 mg/kg), lead (≤ 0.05 mg/kg), mercury (≤ 0.01 mg/kg), and microorganisms, including *Salmonella* serovars (absent in 375 g), *Cronobacter* spp. (absent in 333 g), and *Listeria monocytogenes* (absent in 125 g). BENEO provides the results of five non-consecutive batch analyses to demonstrate that scFOS can be manufactured to meet these specifications.

BENEO discusses the results of a stability study conducted with scFOS stored at ambient temperature (≤ 25 °C) for up to ~40 weeks. BENEO concludes that scFOS is stable under the conditions tested; however, BENEO noted small decreases in pH and scFOS content over the test period. BENEO states that temperature-dependent hydrolysis of scFOS over time also results in a gradual decrease in pH.

BENEO estimates the dietary exposure to scFOS, stating that because the intended uses are the same as in GRN 001006, they would be substitutional for other sources of scFOS. Therefore, BENEO does not expect the cumulative dietary exposure to scFOS to change. BENEO incorporates the dietary exposure estimates from GRN 001006 that are based on the same intended uses and food consumption data from the 2015-2016 National Health and Nutrition Examination Survey. BENEO reports the mean and 90th percentile eaters-only dietary exposure to scFOS for the U.S. population aged 2 years and older to be 10 g/person (p)/d (0.16 g/kg body weight (bw)/d) and 18 g/p/d (0.33 g/kg bw/d), respectively, and the mean and 90th percentile eaters-only dietary exposure to scFOS for young children aged 1 to 2 years to be 10 g/person (p)/d (0.8 g/kg bw/d) and 17 g/p/d (1.32 g/kg bw/d), respectively.

While the intended uses of scFOS do not include infant formula, BENEO discusses the dietary exposure to scFOS for the infant population and incorporates information from GRN 000797,[1] which provided dietary exposure estimates from uses in infant formula. BENEO states that the highest estimated dietary exposure to scFOS from the intended use in infant formula is up to 1,090 mg/kg bw/d. BENEO notes that this assumes that infant formula consumption is the sole source of nutrition and dietary exposure to scFOS from the consumption of other foods containing scFOS

would offset the consumption of infant formula and not increase the overall dietary exposure to scFOS.

BENEO reviewed published safety data and information for similar scFOS ingredients from previous GRNs and performed a comprehensive search of the scientific literature, updated through May 2025. BENEO states that scFOS is resistant to digestion in the upper GI tract, noting that it is instead partially fermented by gut microbiota in the large intestine, and, if absorbed, is excreted primarily in urine as intact scFOS. BENEO notes that these data do not indicate any adverse effects on intestinal enzymes or gut microbiota. BENEO summarizes numerous published pivotal toxicology studies with scFOS or inulin-type fructans previously evaluated in GRNs 000044, 000118, 000392, 000477, 000537, 000576, 000605, 000623, 000717, 000797, 000849, 000854, 000990, 001006, and 001019;[1] including a series of *in vivo* and *in vitro* genotoxicity and mutagenicity studies, and *in vivo* acute, subacute, chronic, carcinogenicity, and developmental and reproductive toxicity studies. From these data, BENEO concludes that scFOS is neither mutagenic nor genotoxic and is free from adverse effects from acute exposure (single dose) up to 9,000 mg/kg bw/d and from chronic daily exposure up to 2,664 mg/kg bw/d for 2 years, which are the highest doses tested. BENEO also discusses published tolerability data for oral exposure to scFOS in humans, including infants and young children. From these data, BENEO concludes that doses up to 20 g/d are generally well tolerated in adults. Regarding allergenicity, BENEO states that scFOS does not contain detectable amounts of protein and is therefore considered non-allergenic.

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

Standards of Identity

In the notice, BENEO states its intention to use scFOS 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 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 Nutrition Center of Excellence. The Office of Pre-Market 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(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 BENEO's 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 BENEO provided, as well as other information available to FDA, we have no questions at this time regarding BENEO'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 001242 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2025.07.14 09:19:07 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program

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1. BENEO notes that the intended uses for scFOS are the same as described in GRN 001006. Various fructans were the subjects of GRNs 000044, 000118, 000392, 000477, 000537, 000576, 000605, 000623, 000717, 000797, 000849, 000854, 000990, 001006, and 001019. We evaluated these notices and responded in letters dated November 22, 2000, May 5, 2003, May 7, 2012, March 4, 2014, February 6,

2015, December 9, 2015, March 17, 2016, August 1, 2016, February 13, 2018, November 15, 2018, October 30, 2019, January 21, 2020, October 8, 2021, January 19, 2022, and February 27, 2023, respectively, stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

2. ^ BENEO notes that the enzyme preparation is the subject of GRN 001173. We evaluated this notice and responded in a letter dated August 15, 2024, stating that we had no questions at that time regarding the notifier’s GRAS conclusion.