Evangelia Pelonis
Keller and Heckman LLP
1001 G St., NW
Suite 500W
Washington, DC 20001

Re: GRAS Notice No. GRN 001006

Dear Ms. Pelonis:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001006. We received the notice that you submitted on behalf of Ingredion Incorporated (Ingredion) on April 2, 2021 and filed it on July 29, 2021. Ingredion submitted amendments to the notice on October 8, 2021 and December 16, 2021 that provided additional information on the manufacturing process, enzyme production organism, specifications, stability, and estimated dietary exposure.

The subject of the notice is short-chain fructooligosaccharides (scFOS) for use as a bulking agent and an 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); cultured dairy beverages; dairy product analogs; muffins and quick bread; sauces, gravies, and condiments; snacks; sorbet and sherbet; soups; toddler (12-24 months old) foods; yogurt; drinkable yogurt; and meal replacement shakes at levels ranging from 0.4% to 15%. The notice informs us of Ingredion's view that these uses of scFOS are GRAS through scientific procedures.[1,2]

Ingredion provides information about the identity and composition of scFOS (CAS Registry No. 308066-66-2). Ingredion describes two forms of scFOS that include a colorless syrup and a colorless powder. Ingredion describes scFOS as fructan oligosaccharides that are 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, or fructofuranosylnystose, respectively.

Ingredion describes the manufacturing process for scFOS, and states that all raw

[1] Ingredion 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] Ingredion states that the food categories and use levels are the same as those in GRN 000044 with the following modifications: an increased use level in bars (up to 15%), an increased use level and expanded category for dairy beverages to include cultured dairy beverages (up to 1.3%) and drinkable yogurts (up to 3.2%), and additional uses in meal replacement shakes at up to 2.5% and dairy analog beverages at up to 1.3%.

materials and processing aids used in the manufacture of scFOS are food grade and used in accordance with applicable U.S. regulations. Ingredion states that scFOS is synthesized using a β-fructofuranosidase from *Aspergillus fijiensis*. Ingredion states that *A. fijiensis* is the same production strain that was described in GRN 000044 and GRN 000537, is non-pathogenic and non-toxic, and is classified under the American Type Culture Collection (ATCC) number 20611. The manufacturing process starts with an aqueous sucrose solution that is adjusted to the desired pH, and β-fructofuranosidase is added at a controlled temperature. Following completion of the reaction, the enzyme is inactivated. The product is then treated with diatomaceous earth and subjected to ion exchange purification. The pH of the resulting solution is adjusted with potassium hydroxide, and liquid chromatography is used to remove sugar byproducts. Following an evaporation step, the solution is subjected to an additional ion exchange step and carbon filtration. The resulting solution is evaporated to obtain the liquid form of scFOS that may be then spray-dried to obtain the powder form of scFOS.

Ingredion provides specifications for the liquid and powder forms of scFOS. Specifications include minimum content of total scFOS (≥ 95% on a dry basis (DB)), 1-kestose (≥ 30% DB for powder form and 30-42% DB for liquid form), nystose (≥ 45% DB for powder form and 45-57% DB for liquid form), and fructofuranosylnystose (≥ 5% DB for powder form and 5-15% DB for liquid form), limits for sugars (≤ 5% DB of glucose, fructose, and sucrose combined), moisture for powder form (≤ 5%) or dry matter for liquid form (70-73%), ash (≤ 0.05%), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), as well as limits on microorganisms. Ingredion provides the results of three non-consecutive batch analyses of the powder form of scFOS to demonstrate that scFOS can be manufactured to meet these specifications.

Ingredion provides estimates of dietary exposure to scFOS that include updated estimates that are based on the intended uses described in GRN 000044 and estimates that include the expanded intended uses described in GRN 001006. All estimates are based on food consumption data from the 2015-1016 National Health and Nutrition Examination Survey. Ingredion estimates the mean and 90th percentile eaters-only dietary exposures to scFOS for the U.S. population aged 2 years and older from the intended uses in GRN 000044 to be 8 g/person (p)/day (d) (0.12 g/kg body weight (bw)/d) and 13 g/p/d (0.24 g/kg bw/d), respectively. For the expanded intended uses of scFOS in GRN 001006, Ingredion estimates the mean and 90th percentile eaters-only dietary exposures for the U.S. population aged 2 years and older to be 10 g/p/d (0.16 g/kg bw/d) and 18 g/p/d (0.33 g/kg bw/d), respectively.

Ingredion states that several GRNs with fructooligosaccharides (FOS) or scFOS as the notified substance were previously reviewed by FDA.[3] Ingredion states that their scFOS is chemically identical to other fructan products on the market. Ingredion summarizes

[3] FOS was the subject of GRNs 000044, 000605, 000623, and 000797. We evaluated these notices and responded in letters dated November 22, 2000, March 17, 2016, August 1, 2016, and November 15, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions. scFOS was the subject of GRNs 000537 and 000717. We evaluated these notices and responded in letters dated February 6, 2015 and February 13, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

toxicological studies discussed in previous GRNs. These included *in vitro* genotoxicity studies, acute and subchronic studies, combined chronic and carcinogenicity studies, and a developmental and reproductive toxicity study. These studies support the lack of toxicologically relevant effects at the highest dose tested. Ingredion also discusses studies in infants and adults that showed no serious treatment-related adverse events. Ingredion notes that scFOS products are oligosaccharides with essentially no protein component and thus unlikely to pose any risk for allergic effects. Ingredion states that they conducted an updated literature search through March 2021 and found no publication that would raise questions regarding the safety of scFOS for its intended use.

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

Standards of Identity

In the notice, Ingredion 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, 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). 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(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 Ingredion'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 Ingredion provided, as well as other information available to FDA, we have no questions at this time regarding Ingredion'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 001006 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.01.19 13:46:22 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition