U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Evangelia C. Pelonis
Keller and Heckman LLP
1001 G Street, NW
Washington, DC 20001

Re: GRAS Notice No. GRN 000537

Dear Ms. Pelonis:

The Food and Drug Administration (FDA, we) completed our evaluation of the supplement that you submitted on behalf of Ingredion, Inc. (Ingredion) to GRN 000537. We received the supplement on September 9, 2024. The supplement addresses a change in the enzyme used during the manufacturing process and minor changes in the specifications and manufacturing process for the subject of GRN 000537. Ingredion submitted clarifying information on November 8, 2024, regarding the specifications.

We previously responded to GRN 000537 on February 6, 2015. We stated that we had no questions at that time regarding Ingredion's conclusion that short-chain fructooligosaccharides (scFOS) is GRAS for the intended use as an ingredient in non-exempt infant formula for term infants at levels up to 500 mg/100 ml, as consumed.

In the supplement dated August 29, 2024, Ingredion informs us of a change in the β-fructofuranosidase enzyme used to manufacture scFOS. GRN 000537 described the use of an enzyme derived from *Aspergillus fijiensis*. According to the supplement, the new β-fructofuranosidase enzyme that Ingredion intends to use is produced by a strain of *Trichoderma reesei* expressing a gene for invertase from *Aspergillus niger* and is the subject of GRN 001173.[1] In the supplement, Ingredion states that the new enzyme acts in the same manner as the original enzyme described in GRN 000537. Ingredion states that several additional minor changes in the manufacturing process of scFOS were evaluated in GRN 001006.[2] In the supplement, Ingredion notes minor changes to the specifications for scFOS (e.g., reduced limits for heavy metals) and provides results from the analyses of three non-consecutive batches to demonstrate that scFOS can be manufactured to conform with the specifications. Ingredion states there is no change to the intended use of scFOS described in GRN 000537, and therefore, no change in the dietary exposure to scFOS is expected. Additionally, Ingredion conducted an updated review of the scientific literature through August 2024 and concludes that the safety of scFOS continues to be confirmed.

[1] We evaluated GRN 001173 and responded in a letter dated August 15, 2024, stating that we had no questions at that time regarding the notifier's GRAS conclusion.
[2] We evaluated GRN 001006 and responded in a letter dated January 19, 2022, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Based on the available data and information, Ingredion concludes that scFOS is GRAS under the intended conditions of use.

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 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.

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 Ingredion's GRAS supplement 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 the Office of Critical Foods in the Nutrition Center of Excellence.

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 supplement 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 the supplement to GRN 000537 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Mical E. Honigfort -S

Digitally signed by Mical E. Honigfort -S
Date: 2024.11.26 09:23:38 -05'00'

for 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