Laith M. Abu-Taleb, Esq.
Cambridge Crops, Inc. d/b/a Mori
440 Rutherford Avenue
Boston, MA 02129

Re: GRAS Notice No. GRN 001026

Dear Mr. Abu-Taleb:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001026. We received Cambridge Crops, Inc. d/b/a Mori (Cambridge Crops)'s notice on July 9, 2021,[1] and filed it on November 18, 2021. Cambridge Crops submitted amendments to the notice on March 30 and May 5, 2022, that included clarification of the intended use and identity of the notified substance, method of manufacture, and specifications.

The subject of the notice is a solution of partially hydrolyzed silk fibroin derived from *Bombyx mori* cocoons (silk fibroin) for use as a surface-finishing agent to extend the shelf life of the foods listed in Table 1.[2] The notice informs us of Cambridge Crops' view that these uses of silk fibroin are GRAS through scientific procedures.

Table 1. Foods and the corresponding maximum use levels of silk fibroin

Food	Maximum use level[#] (mg/kg)
Fish fillet (excluding Silurifomes fish), peeled shellfish, seafood eaten raw	415
Fruits with edible peels, fruit salads with unpeeled fruits	385
Vegetables with edible peels, vegetables in snackable form	315
Sliced cheese, pizza cheese topping	750
Hard candies, candy bars, nuts, cookies, cereal and meal bars, chewing gum	980
[#]The use levels of silk fibroin are based on the dehydrated form of silk fibroin (silk fibroin powder).	

[1] Cambridge Crops provided an update on October 6, 2021, that included confirmation that any information marked as "trade secret/confidential" is not confidential and that the intended use in fish excludes catfish.
[2] In the amendment dated March 30, 2022, Cambridge Crops stated that the intended use of silk fibroin excludes food products regulated by the U.S. Department of Agriculture and foods where standards of identity preclude its use.

Our use of the terms, "a solution of partially hydrolyzed silk fibroin derived from *Bombyx mori* cocoons" or "silk fibroin," in this letter is not our recommendation of those terms as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient 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 regarding the appropriate common or usual name for "silk fibroin."

Cambridge Crops provides information on the source, identity, and composition of silk fibroin. Cambridge Crops states that silk fibroin is produced from cocoon fibers of domesticated silkworm (*Bombyx mori*) and describes it as a colorless to yellow aqueous solution (5% weight/volume, w/v). Fibroin is designated by the CAS Registry Number 9007-76-5. Cambridge Crops states that intact native silk fibroin is a protein consisting of a heavy chain (325–390 kDa), a light chain (25–26 kDa), and a P25 glycoprotein (25–30 kDa) in a 6:6:1 ratio. The partially hydrolyzed silk fibroin, which is the subject of the notice, is a mixture of polypeptides with an average molecular weight range between approximately 50 kDa to 350 kDa composed primarily of glycine (42–46%), alanine (29–31%), serine (9–12%), and tyrosine (4–5%).[3]

Cambridge Crops describes the manufacturing process for silk fibroin. Following the removal of silkworms, the cocoons are boiled in an alkaline solution to isolate fibroin and remove sericin through a degumming process that leads to a partial hydrolysis of the fibroin. The fibroin is washed with water and subsequently solubilized in an aqueous solution of calcium chloride or another chaotropic salt. The chaotropic salt is then removed from the solution by dialysis. The resulting silk fibroin may be applied to foods or dehydrated by spray drying to a silk fibroin powder that is reconstituted with water prior to application on foods. Cambridge Crops states that all materials and processing aids used in the manufacture of silk fibroin are food grade and are used in accordance with applicable U.S. regulations, and that silk fibroin is manufactured using current good manufacturing practices.

Cambridge Crops provides specifications for silk fibroin that include protein content (3.5–6%), limits for ash, fat, and carbohydrates (<0.1% each), arsenic (<0.5 mg/kg), lead (<0.5 mg/kg), and microorganisms. Cambridge Crops provides the results of the analyses of three nonconsecutive batches to demonstrate that silk fibroin can be manufactured to meet the specifications. Based on the results of an accelerated stability study, Cambridge Crops determined that silk fibroin powder is stable for 317 days under standard storage conditions.

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[3] In the amendment dated March 30, 2022, Cambridge Crops states that the manufacturing process does not result in formation of silk fibroin nanoparticles and provides the particle-size distribution data to support its statement. In the amendment dated May 5, 2022, Cambridge Crops clarifies the particle size distribution data.

Cambridge Crops estimates dietary exposure to silk fibroin based on the intended uses in Table 1 and food consumption data from the 2013-2016 National Health and Nutrition Examination Survey (NHANES). Cambridge Corps estimates the mean and 90th percentile eaters-only dietary exposures to silk fibroin[4] to be 82 and 174 mg/person (p)/day (d) (1.34 and 2.92 mg/kg bw/d), respectively, for the U.S. population aged 2 years and older.

Cambridge Crops discusses the safety of consumption of silk fibroin by discussing the following information: absorption, distribution, metabolism and excretion (ADME) of silk fibroin; a 14-day oral range finding study, and a 28-day oral toxicity study of silk fibroin in rats; mutagenicity and genotoxicity studies; *in vitro* digestibility of silk fibroin in simulated gastric fluid, and bioinformatic analysis of the silk fibroin sequence. The ADME of silk fibroin as a protein is published and widely disseminated textbook information on protein turnover in the gut and amino acid metabolism. All other studies discussed in the notice are also published. Cambridge Crops states that there were no test article-related adverse effects in the toxicity studies even at the highest dose tested (500 mg/kg bw/d) and that silk fibroin raises no mutagenicity and genotoxicity concern as revealed by an Ames test and an *in vivo* mouse erythrocyte micronucleus test. Based on the results of the digestibility study, Cambridge Crops concludes that orally consumed silk fibroin will be digested in the stomach like dietary proteins. From its bioinformatic analysis of the silk fibroin sequence, Cambridge Crops concludes that silk fibroin does not contain allergenic or potentially IgE cross-reactive sequences. Additionally, using liquid chromatography-mass spectroscopy, Cambridge Crops further evaluated several purified silk fibroin samples for the possible presence of any manufacturing contaminants with allergenic potential, such as the allergenic proteins found in silkworms, pupa, or cocoon. Cambridge Crops states that no such allergenic proteins were detected in silk fibroin samples. Therefore, Cambridge Crops concludes that oral consumption of silk fibroin is not likely to cause any allergenicity or toxicity concern. Further, Cambridge Crops discusses published supportive studies conducted in animals with various forms of silkworm powder or silkworm extract for various durations and doses and concludes that these studies did not produce any data or information that would contradict Cambridge Crops' conclusion that silk fibroin is safe for consumption at the intended level of use.

Based on the totality of the data and information, Cambridge Crops concludes silk fibroin is GRAS for its intended use.

Potential Labeling Issues

Under section 403(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if it contains any chemical preservative, unless the label states that fact. Under section 403(i)(2) of the FD&C Act, a food is misbranded unless its label bears the common or usual name of each ingredient. Further, under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any way. Cambridge Crops' intended use of silk fibroin constitutes use as a preservative. Therefore, the

[4] The estimates represent dietary exposure to silk fibroin protein as consumed, not dietary exposure to 5% silk fibroin.

ingredient statement on labels of food products containing silk fibroin must comply with the labeling regulations implemented in sections 403(k) and 403(i)(2) of the FD&C Act. For example, 21 CFR 101.22(j) requires that the label of a food with an added chemical preservative must declare both the common or usual name of the ingredient and a separate description of its function. Further, food that is subjected to any form of preservation, except as provided in 21 CFR 101.95(c), may not be labeled as "fresh." Questions related to food labeling should be directed to ONFL.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Cambridge Crops describes silk fibroin as colorless to yellow. As such, the use of silk fibroin in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 001026 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in the Office of Food Additive Safety.

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 Cambridge Crops' notice concluding that silk fibroin 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 silk fibroin. Accordingly, our response should not be construed to be a statement that foods containing silk fibroin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Cambridge Crops provided, as well as other information available to FDA, we have no questions at this time regarding Cambridge Crops' conclusion that silk fibroin is GRAS under its intended conditions of use. This letter is not an affirmation that silk fibroin 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 001026 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.08.11 17:37:42 -04'00'

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