U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Dietrich Conze, Ph.D.
Spherix Consulting Group, Inc.
751 Rockville Pike
Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 001171

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001171. We received the notice that you submitted on behalf of Geltor, Inc. (Geltor) on November 8, 2023, and filed it on February 12, 2024. Geltor submitted amendments to the notice on June 3, 2024, August 15, 2024, September 6, 2024, September 27, 2024, and October 15, 2024. These amendments provided additional information on the identity of the ingredient, intended uses, manufacturing method, specifications, estimates of dietary exposure, and the safety narrative.

The subject of the notice is collagen polypeptide produced by *Escherichia coli* K-12 S9188 (collagen polypeptide) for use as a source of collagen polypeptides at levels ranging from 2 to 95% in various foods as described in Table 1.[1] The notice informs us of Geltor's view that collagen polypeptide is GRAS through scientific procedures.

Table 1. Intended food categories and maximum use levels for collagen polypeptide.

Food Category	Maximum Use Levels (%, w/w)
Sports drinks, flavored bottled water, and powdered fruit and sports drinks, reconstituted	2
Powdered fruit and sports drinks, not reconstituted	20
Packaged coffee and tea beverages	5.5
Instant coffee and tea	5.5
Coffee and tea, powdered, not reconstituted	55
Coffee and tea pods	2
Yogurt beverages	2.5
Milk substitutes	2.5

[1] Geltor states that collagen polypeptide is not intended for use in infant formula, products under the jurisdiction of the U.S. Department of Agriculture, or in foods for which standards of identity preclude its use.

Food Category	Maximum Use Levels (%, w/w)
Coffee creamer (liquid and powder forms)	20
Nutritional beverages and beverage bases	4.5
Nutritional bars	25
Protein powders	95
Gummies	10
Chocolate confections (excluding chocolate bars)	10
Meat, poultry, and fish analogs	12

Our use of the term, "collagen polypeptide produced by *Escherichia coli* K-12 S9188" or "collagen polypeptide" in this letter is not our recommendation of those terms as appropriate common or usual names 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 Nutrition Center for Excellence. The Office of Pre-Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for "collagen polypeptide."

Geltor describes collagen polypeptide as a white to pale yellow powder comprised of ≥80% protein on a dry weight basis. Geltor states collagen polypeptide also contains 2% carbohydrates, ≤9% moisture, and ≤6% ash. Geltor states that collagen polypeptide contains 188 amino acids from the collagen domain found in chicken (*Gallus gallus domesticus*, UniProt ID: A0A8V0XCL7_CHICK, residues 554 to 742) collagen type XXIa and has a molecular weight of 17.915 kDa.

Geltor states that the *E. coli* production organism is non-toxigenic and non-pathogenic and is a well characterized production organism with a history of safe use in the food industry. Geltor states that the recipient strain used on the construction of the production strain, K-12 S9188, is *E. coli* K-12 NCM3722. The production strain was constructed through transformation with a multi-copy plasmid carrying a signal peptide sequence from *Rosenbergiella nectarea* fused to the collagen polypeptide gene.[2] The production organism contains a kanamycin resistance gene, but Geltor notes that this is not expected to impact safety as production strain-derived DNA residues are not expected to be present in the final product. Further, Geltor states that the production strain is not capable of genetic transfer. Geltor states that they confirmed sequence integrity by polymerase chain reaction and DNA sequencing. Geltor states that the production strain is not expected to be present in the final product.

Geltor provides a description of the manufacturing process for collagen polypeptide.

[2] Geltor also performed deletions of several genes to improve stability of the strain and the protein, as well as insertion of an expression cassette carrying the viral T7 RNA polymerase and duplication of the native *lacI* transcriptional repressor gene.

Geltor states that none of the raw materials used during the manufacturing process are derived from major allergens. Geltor states that a working stock of *E. coli* K-12 S9188 is sequentially expanded in culture medium to produce the biomass under controlled conditions. The collagen polypeptide is secreted into the fermentation media and then recovered by an initial centrifugation step. The supernatant undergoes microfiltration, ultrafiltration, diafiltration, and is then spray dried. Geltor states that collagen polypeptide is manufactured in accordance with good manufacturing practices and that all raw materials and processing aids are food grade and are used in accordance with an appropriate U.S. regulation, are GRAS for their intended use, or are the subject of an effective food contact notification.

Geltor provides specifications for collagen polypeptide that include protein content (≥80% on a dry weight basis), moisture (≤9%), ash (≤6%), and limits for arsenic (≤0.2 mg/kg), cadmium (≤0.1 mg/kg), lead (≤0.1 mg/kg), mercury (≤0.05 mg/kg), and microorganisms. Geltor provides results from the analyses of three non-consecutive batches to demonstrate that collagen polypeptide can meet the provided specifications. Geltor states that collagen polypeptide has a shelf-life of 24 months from the date of manufacture when stored at room temperature and ambient humidity.

Geltor estimates the eaters-only dietary exposures to collagen polypeptide from the intended uses to be 17 g/person (p)/d (0.23 g/kg body weight (bw)/d) at the mean and 35 g/p/d (0.47 g/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older based on food consumption data from the 2017-March 2020 Pre-pandemic National Health and Nutrition Examination Survey (NHANES). Geltor states that collagen polypeptide is intended to substitute for other sources of added collagen polypeptides in conventional food products. Thus, Geltor states that the intended uses of collagen polypeptide will not increase the overall dietary exposure to collagen polypeptides.

Geltor discusses the safety of consuming collagen polypeptide by discussing that humans are commonly exposed to collagen in food, the safety of the production strain *E. coli* S9188 and the metabolic fate and allergenic potential of collagen polypeptide. The metabolic fate of collagen polypeptide following oral consumption is expected to be like that of other proteins, i.e., the protein is expected to be digested in the gastrointestinal tract. Geltor evaluates the *in vitro* protein digestibility of two batches of collagen polypeptide. Samples were digested with trypsin and chymotrypsin in a neutral buffer to simulate the physiological conditions of intestinal digestion. Undigested proteins were then removed by trichloroacetic acid precipitation, and the concentration of the remaining free amines were compared to the concentration of the remaining free amines from casein. Geltor discusses an unpublished Ames assay that demonstrated that collagen polypeptide is not mutagenic. Geltor states that the likelihood of collagen polypeptide triggering sensitization and/or allergic response is no greater than that posed by the ingestion of chicken meat or bovine or fish collagen.

Based on the totality of data and information included in their notice, Geltor concludes that collagen polypeptide is GRAS for its intended uses.

Standards of Identity

In the notice, Geltor states its intention to use collagen polypeptide 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 (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 collagen polypeptide 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 ONFL. OPMAS 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 Geltor's notice concluding that collagen polypeptide 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 collagen polypeptide. Accordingly, our response should not be construed to be a statement that foods containing collagen polypeptide, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Geltor provided, as well as other information available to FDA, we have no questions at this time regarding Geltor's conclusion that collagen polypeptide is GRAS under its intended conditions of use. This letter is not an affirmation that collagen polypeptide 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 001171 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Mical E. Honigfort -S

Digitally signed by Mical E. Honigfort -S
Date: 2024.10.22 07:47:03 -04'00'

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