



Fred Beekmans
Director, R&D and Quality
Darling Ingredients
Kanaaldijk Noord 20-21
5691 NM Son
THE NETHERLANDS

Re: GRAS Notice No. GRN 000713

Dear Mr. Beekmans:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000713. We received Rousselot BVBA's (Rousselot's)¹ notice on June 1, 2017, and filed it on August 8, 2017. Rousselot submitted amendments to the notice on October 5, 2017, and January 26, 2018,² concerning the method of manufacture, specifications, and intended technical effect.

The subject of the notice is hydrolyzed porcine trachea cartilage (HPTC) for use as an ingredient in certain baked goods, beverages, milk products, fruit juices, and candies at levels of 1.2 to 2 g per serving. The notice informs us of Rousselot's view that this use of HPTC is GRAS through scientific procedures.

HPTC is produced by enzymatic hydrolysis of porcine trachea cartilage, sourced in a food-grade manner from healthy animals. Residual meat is removed from the cartilage prior to cutting and washing with water. The pH of the solution is adjusted if necessary. Using only water as a solvent, enzymatic hydrolysis is carried out using a food-grade protease preparation from *Bacillus licheniformis*. Afterwards, the non-hydrolyzed cartilage and other residues are discarded. The remaining solution is heated to inactivate any residual hydrolytic enzymes. The cooled solution is filtered, concentrated, sterilized and spray-dried. Rousselot states that processing aids used in the manufacture of HPTC are suitable for use in the production of food and conform to appropriate federal regulations.

The notice gives specifications for HPTC including Type II collagen ($\geq 60\%$), chondroitin sulfate (10-25%), hyaluronic acid (0.1-1.0%), water ($\leq 12\%$), and residue on ignition ($\leq 10\%$); residues on ignition indicate the presence of unspecified salts in HPTC. Specifications are also provided for heavy metals, including arsenic (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and lead (≤ 0.1 mg/kg), limits for various microbiological contaminants, and for copper (≤ 30 mg/kg) and zinc (≤ 50 mg/kg). Rousselot states that three non-consecutive batches of HPTC met these specifications and provides these batch analyses.

¹ Rousselot is a subsidiary of Darling Ingredients

² Rousselot's original method of manufacture included the optional use of hydrogen peroxide. The amendment of January 26, 2018 explicitly removed hydrogen peroxide from the manufacturing process.

Rousselot intends to use HPTC in baked goods and baking mixes, beverages and beverage bases, milk products, processed fruits and fruit juices and soft candy at levels from 0.56% to 5% of serving size (1.2 to 2 g per serving). The notice provides estimates of the dietary exposure to the main components of HPTC, collagen and chondroitin sulfate, based on upper-bound assumptions³ about these intended uses combined with NHANES intake data. The all-user dietary exposure to collagen was 1.3 g/person/day at the mean and 3.0 g/p/d at the 90th percentile, or 26 mg/kg bodyweight/day and 58.5 mg/kg bw/d respectively on a bodyweight basis. The all-user dietary exposure to chondroitin sulfate (based on its maximum level of 25% in HPTC) was 0.5 g/p/d at the mean and 1.0 g/p/d at the 90th percentile, or 9.1 mg/kg bw/d and 20.1 mg/kg bw/d respectively on a bodyweight basis.

Rousselot notes that at high concentrations hydrolyzed pork cartilage may impart off-flavors to the foods to which it is added.

Rousselot discusses published data and information from studies in animals and humans to support the safety of its intended use of HPTC and its components, collagen and chondroitin sulfate. Rousselot states that no animal studies have been conducted in which the HPTC that is the subject of this notice was evaluated. However, Rousselot discusses data in two animal studies of a product containing 10% hyaluronic acid, 60% type II collagen, and 20% chondroitin sulfate to support the safety of this HPTC. These studies include metabolic studies, an acute toxicity study, and a 90-day subchronic toxicity study conducted in Sprague-Dawley rats. Rousselot reports that no adverse effects were observed by the study authors at the highest doses tested in the acute and subchronic studies; the maximum dose in the subchronic study was approximately equivalent to 600 mg type II collagen and 200 mg chondroitin sulfate/kg bw/d. Rousselot states that no clinical studies have been conducted in which this HPTC was evaluated. Rousselot instead discusses the results of clinical trials in which cartilage-derived products were consumed. The products were derived from bone, skin, or connective tissue obtained from sharks, fish, chicken, pigs, or cows. They were consumed for 28 to 180 days, at levels up to 10,000 mg collagen peptides and 600 mg chondroitin sulfate. Rousselot reports that these consumed products were well tolerated and no adverse effects were attributable to these products. Rousselot notes that there is no data to indicate any unusual allergenic potential particular to the HPTC that is the subject of this notice.

Rousselot includes the statement of a panel of individuals (Rousselot's GRAS panel). Based on its review, Rousselot's GRAS panel concluded that HPTC is safe under the conditions of its intended use.

Based on the data and information contained in the notice regarding safety, as well as the findings of the GRAS panel, Rousselot concludes that the firm's intended use of HPTC is GRAS.

³ That HPTC would be added to all products within a food category at the maximum intended use level.

Standards of Identity

In the notice, Rousselot states its intention to use HPTC in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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). The notice raises a potential issue under these labeling provisions. This issue consists of a potential relationship between intake of collagen and chondroitin sulfate and effects on joint health. If products containing HPTC 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 Rousselot's notice concluding that HPTC 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 HPTC. Accordingly, our response should not be construed to be a statement that foods containing HPTC, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).


Conclusions

Based on the information that Rousselot provided, as well as other information available to FDA, we have no questions at this time regarding Rousselot's conclusion that HPTC is GRAS under its intended conditions of use. This letter is not an affirmation that HPTC 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 000713 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**

 Digitally signed by Michael
A. Adams -S
Date: 2018.04.05 17:00:10
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Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
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