Justyna Pałasińska
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SPAIN

Re: GRAS Notice No. GRN 001103

Dear Ms. Pałasińska:

This letter revises our response letter to GRN 001103 signed on November 22, 2023. The purpose of this revised letter is to describe that, optionally, the protein concentrate may be precipitated with ethanol and subjected to further washes prior to drying. While this optional drying step may include "spray drying", it is not limited to "spray drying" and may employ other methods of drying. This revision is included on page 3, line 8 of this revised response letter.

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 01103. We received the notice that you submitted on behalf of NapiFeryn BioTech Sp. z o. o. (NapiFeryn) on September 7, 2022, and filed it on February 9, 2023. NapiFeryn submitted amendments to the notice on July 11, 2023, August 28, 2023, September 21, 2023, October 3, 2023, October 19, 2023, and October 31, 2023, providing clarifying information regarding use levels, specifications, safety information, and an updated literature search.

The subject of the notice is canola protein isolate for use as a source of protein, formulation aid, nutrient supplement, stabilizer, thickener, and texturizer at the maximum use levels specified in Table 1.[1] The notice informs us of NapiFeryn's view that these uses of canola protein isolate are GRAS through scientific procedures.

Table 1. Intended uses of canola protein isolate and corresponding maximum use levels

Intended uses	Maximum use level (%)
Bakery products and baking mixes	30
Non-alcoholic beverages and beverage bases (fruit and/or vegetable drinks, smoothies, energy drinks)	15
Coffee and tea (including instant)	10

[1] NapiFeryn states that canola protein isolate is not intended for use in infant formula and in products under the jurisdiction of the United States Department of Agriculture.

Breakfast cereals	60
Grain products, pastas	20
Milk products and dairy alternatives	35
Egg substitutes and egg product alternatives	20
Fats, oils, and salad dressings	15
Meat product alternatives	35
Fruit and water ices	20
Batters and breadings	10
Spices and seasoning mixes	5
Protein and nutritional powders	100
Nutritional and protein bars	40
Nut products	40
Processed fruits, vegetables, legumes	30
Sauces, dips, gravies, and condiments	15
Snack foods	60
Soup and soup mixes	20
Confections, candies, and frostings	40
Jams, jellies, gelatins, puddings, fillings	25
Sweet sauces, toppings, and syrups	15

Our use of the term, "canola protein isolate," in this letter is not our recommendation of that term 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 non-standardized 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 "canola protein isolate."

NapiFeryn describes canola protein isolate as a white to off-white powder obtained from rapeseed press cake that is a byproduct of rapeseed (canola) oil production. The press cake used in the manufacture of canola protein isolate is the crushed seed of *Brassica napus* and/or *B. juncea* and/or *B. rapa*.[2] NapiFeryn states that canola protein isolate contains ≥90% protein (dry matter basis) with the protein fraction consisting of 70-95% cruciferins and 5-30% napins.

NapiFeryn describes the manufacturing process for canola protein isolate that begins with an aqueous extraction of cold-pressed rapeseed cake to yield an aqueous extract and a solid residue slurry. The aqueous crude extract containing the protein fraction is filtered and centrifuged. Processing aids may be added to aid in the clarification process. The clarified extract is subjected to ultrafiltration and diafiltration to concentrate the

[2] NapiFeryn states that rapeseed press cake is sourced solely from low-erucic acid rapeseed varieties.

protein and remove carbohydrates and anti-nutritional factors. Processing aids may be added to the extract prior to or during diafiltration to improve the effectiveness of the process and to protect the protein from oxidation and browning. The concentrate is spray dried to obtain the final canola protein isolate. NapiFeryn states that optionally the concentrate may be treated with ethanol to precipitate the protein fraction and remove residual anti-nutritional factors. The precipitated solid protein fraction is separated and may be subjected to further washes with ethanol or ethyl acetate prior to drying. NapiFeryn states that canola protein isolate is manufactured according to current good manufacturing practices using food grade raw materials and processing aids that are appropriate for use in the manufacture of food in the U.S.

NapiFeryn provides specifications for canola protein isolate that include total protein (≥90%), carbohydrates (≤7%), fat (≤2%), ash (≤4%), moisture (≤7%), fiber (≤0.5%), glucosinolates (≤1 mmol/kg), phytates (≤1.5%), lead (≤0.35 mg/kg), mercury (≤0.1 mg/kg), arsenic (≤0.15 mg/kg), cadmium (≤0.2 mg/kg), ethanol (<600 mg/kg), ethyl acetate (<600 mg/kg), sulfur dioxide (<10 mg/kg), and limits for microorganisms. NapiFeryn provides the results from the analyses of five non-consecutive batches to demonstrate that canola protein isolate can be manufactured to meet these specifications. NapiFeryn states that canola protein isolate is stable for at least 24 weeks at 25 °C and 60% relative humidity.

NapiFeryn estimates the dietary exposure to canola protein isolate from the intended uses using food consumption data from the 2017-2018 National Health and Nutrition Examination Survey. NapiFeryn estimates the eaters-only dietary exposure to canola protein isolate to be 34.94 g/person (p)/d (0.5 g/kg body weight (bw)/d) at the mean and 74.5 g/p/d (1.06 g/kg bw/d) at the 90th percentile for the U.S. population aged 2 years and older. NapiFeryn states that the intended uses of canola protein isolate will be substitutional for other sources of canola protein and therefore, dietary exposure to protein is not expected to increase.

NapiFeryn discusses the publicly available safety data for canola (rapeseed) protein and incorporates by reference the safety data and information discussed in prior GRAS conclusions from GRNs 000327, 000386, and 000683.[3] NapiFeryn reports that a comprehensive literature search for canola protein was conducted up to July 2023 and did not identify any studies which would contradict its GRAS conclusion.

NapiFeryn discusses anti-nutritional factors naturally present in canola, including glucosinolates, erucic acid, phenolic compounds, phytic acid, and protease inhibitors. NapiFeryn notes that the levels of these compounds are reduced as a result of the canola protein isolate manufacturing process, and ultimately are present at levels comparable to or lower than other canola ingredients with GRAS status.[4] NapiFeryn also

[3] The subjects of GRNs 000327, 000386, and 000683 are cruciferin-rich and napin-rich canola/rapeseed protein isolates, hydrolyzed canola protein isolate, and canola protein isolate, respectively. FDA evaluated these notices and responded in letters dated August 23, 2010, December 28, 2011, and May 10, 2017, stating that we had no questions at that time regarding the respective notifiers' GRAS conclusions.
[4] NapiFeryn provides the analytical data for erucic acid, total phenolics, phytic acid, glucosinolates, and trypsin inhibitor activity for five lots of canola protein isolate.

summarizes two 13-week dietary feeding studies in rats using rapeseed preparations which were previously described in GRN 000327. NapiFeryn states that canola protein isolate, subject of this notice, is compositionally similar to the test articles used in these feeding studies.[5] In these studies, rats were fed either cruciferin-rich or napin-rich canola protein at levels up to 20% of their diet. The authors noted an increase in thyroid weight at the highest dose tested, but concluded this was not a test-article related effect as it was not correlated with any histopathological changes.

NapiFeryn summarizes the results of their bioinformatics analysis of the canola protein isolate sequence to assess the potential for allergenicity. NapiFeryn states that canola protein isolate is unlikely to cause an allergic reaction in consumers who are not allergic to mustard or other *Brassicaceae* family members.

Based on the totality of the data and information, NapiFeryn concludes that canola protein isolate is GRAS for its intended use.

Standards of Identity

In the notice, NapiFeryn states its intention to use canola protein isolate 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 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 canola protein isolate 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 Federal Food, Drug, and Cosmetic Act (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

[5] NapiFeryn provides data, including amino acid profiles and anti-nutritional factor levels, for canola protein isolate and the test articles used in the 13-week studies to establish equivalency.

section 301(ll)(1)-(4) applies. In our evaluation of NapiFeryn's notice concluding that canola protein isolate 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 canola protein isolate. Accordingly, our response should not be construed to be a statement that foods containing canola protein isolate, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that NapiFeryn provided, as well as other information available to FDA, we have no questions at this time regarding NapiFeryn's conclusion that canola protein isolate is GRAS under its intended conditions of use. This letter is not an affirmation that canola protein isolate 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 001103 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

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Susan J. Carlson, Ph.D.
Director
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