Richard W. Lane, Ph.D.
Lane Toxicology Consulting, LLC
4423 Snowcap Lane
Broomfield, CO 80023

Re: GRAS Notice No. GRN 000972

Dear Dr. Lane:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000972. We received the notice that you submitted on behalf of NutriLeads B.V (NutriLeads) on September 16, 2020 and filed it on March 11, 2021. NutriLeads submitted amendments on August 16, 2021, September 14, 2021, and October 1, 2021, providing additional information regarding their modified manufacturing process, raw material supplier, specifications for lead and total ash, intended uses, use level, revised dietary exposure estimates, and the exclusion of uses in products under the jurisdiction of the United States Department of Agriculture (USDA).

The subject of the notice is rhamnogalacturonan-I (RG-I) enriched fraction from carrot pomace (cRG-I) for use as ingredient in food categories as described in Table 1.[1] The notice informs us of NutriLeads' view that this use of cRG-I is GRAS through scientific procedures.

Table 1. Intended food categories and use levels of cRG-I.

Food category	Food uses	Maximum use level (g/100g)
Nonalcoholic Beverages and Beverage Bases	"Energy" Drinks	0.52
	Enhanced, Flavored, Carbonated, or Fortified Water Beverages	0.52
	Non-Milk Based Meal Replacements, Protein, and Nutritional Beverages	0.78
	Soft Drinks (including Regular and Diet)	0.52
	Sport or Electrolyte Drinks, Fluid Replacement Drinks	0.52
Breakfast Cereals	Hot Breakfast Cereals	0.78
	Ready-To-Eat Breakfast Cereal	

[1] NutriLeads indicates that cRG-I is neither intended for use in foods for where standards of identity preclude its use nor is cRG-I intended for use in foods under the jurisdiction of the USDA.

Food category	Food uses	Maximum use level (g/100g)
	Puffed Cereals	12.52
	High-Fiber Cereals	4.7
	Biscuit-Type Cereals	3.13
Dairy Product analogs	Non-Dairy Milk	0.78
	Non-Dairy Cream	12.52
	Non-Dairy Yogurts	1.10
	Non-Dairy Ice Creams	1.18
Grain Products	Cereal and Granola Bars	4.7
	Energy Bars, Protein Bars, and Meal Replacement Bars	4.7
Milk Products	Dry Milks	0.78
	Evaporated or Condensed Milk	6.26
	Fermented Milks, Plain or Flavored	0.78
	Flavored Milk, Milk Drinks, and Mixes, Milk Shakes	0.78
	Milk-Based Meal Replacement and Nutritional Beverages	0.78
	Plain or Flavored Yogurt	1.1
	Yogurt Drinks	2
Processed Fruits and Fruit Juices	Fruit Drinks and Ades including Smoothies	0.78
	Fruit Juices and Nectars	0.78
Processed Vegetables and Vegetable Juices	Vegetable Juices, Nectars and Blends	0.78
Snack Foods	Snack Foods (Potato Chips, Popcorn, Pretzels and Corn-based Savory Snacks)	6.26
Soups and Soup Mixes	Soups (Prepared and Canned)	0.76

Our use of the term “cRG-I” 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 "cRG-I."

NutriLeads provides information on the chemical identity and composition of cRG-I. NutriLeads states that cRG-I is obtained from the edible parts of the carrot (*Daucus carota* L.) and describes it as an off-white to beige powder containing ≥ 75% total carbohydrate, ≤ 6% protein, and ≤ 2% fat. NutriLeads states that the main polysaccharide component of cRG-I is RG-I, the highly branched pectin fragment with a molecular weight between 10 and 1000 kDa.

NutriLeads describes the manufacturing process for cRG-I and states that all materials used in the process are food grade and follow current good manufacturing practice. cRG-I is produced from carrot pomace via enzymatic hydrolysis using a pectinase enzyme preparation containing pectin lyase (EC 4.2.2.10) [2] and polygalacturonase (EC 3.2.1.15). [3,4] The enzyme preparation is added to the carrot pomace dispersed in water. The enzymes are inactivated by heat treatment and the fraction containing cRG-I is subject to sterilization and centrifugation. Low molecular weight sugars are removed, and the resulting product is concentrated, pasteurized, and dried to yield cRG-I.

NutriLeads provides specifications for total carbohydrate (≥ 75%) major monosaccharides (uronic acids (< 35%), rhamnose (6-19%), arabinose (14-30%), and galactose (9-26%)), and total dietary fiber (≥ 70%).[5] Other specifications include limits for moisture (≤ 10%), protein (≤ 6%), total ash (≤ 5%), arsenic (≤ 0.1 mg/kg), cadmium (≤ 1.0 mg/kg), mercury (≤ 0.1 mg/kg), lead (≤ 1.0 mg/kg), and microorganisms, including total plate count (≤ 10000 CFU/g), yeast and mold (each ≤ 100 CFU/g), *Salmonella* serovars (absent in 25 g), *Escherichia coli* (< 10 CFU/g). NutriLeads provides the results of five non-consecutive batch analyses to demonstrate that cRG-I can be manufactured to meet the specifications.

NutriLeads provides characterization information for cRG-I, including the monosaccharide profile, mineral content, degree of methylation (9-17% methylated), and acetylation (38-50% acetylated) of cRG-I. Nutrileads demonstrates that cRG-I is stable for at least one year at 25 °C.

Based on the 2015-2016 NHANES food consumption data, NutriLeads estimates the mean and the 90th percentile eaters-only dietary exposures to cRG-I to be 5.9 g and 11.2 g/person (p)/day (d) (99 mg and 198 mg/kg body weight (bw)/d), respectively, for the total U.S. population.

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[2] Pectinase from *A. aculeatus* was the subject of GRAS petition 5G0297, which was filed by FDA on April 8, 1985.

[3] Pectinase from *A. niger* was the subject of GRN 000089. We evaluated this notice and responded in a letter dated April 3, 2002, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[4] NutriLeads states that the enzymes meet the recommended purity specifications for food-grade enzymes established by the Food Chemicals Codex (FCC, 9th ed.) and the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA, 2006).

[5] AOAC Official Method 2011.25 Insoluble, Soluble, and Total Dietary Fiber in Foods. FDA understands that NutriLeads' use of the term "dietary fiber" is for the purpose of the specifications for cRG-I.

NutriLeads notes that carrots have a long history of consumption. Additionally, NutriLeads states that pectins, the family of fibers to which RG-I belongs, are a common component of the diet, considered GRAS for use in food in the U.S. and consumed globally with no reports indicating adverse health effects in humans. NutriLeads discusses toxicological data in support of the safety of cRG-I and provides a list of peer-reviewed publications. These data were used in support of safety pertaining to digestion, fermentation, bacterial mutagenicity, allergenicity and toxicity of cRG-I. NutriLeads states that cRG-I is undigested, unabsorbed, and fermented by gut microflora, similar to pectin and other oligosaccharides. NutriLeads discusses in detail one relevant published toxicological study series completed under current OECD guidelines that includes *in vitro* mutagenicity and genotoxity assays, and a dose-range finding study and 90-day oral toxicity study in rats. Based on these data, NutriLeads concludes that cRG-I is non-mutagenic, non-genotoxic, non-cytotoxic, and well tolerated at high doses (up to 10% of the diet). NutriLeads additionally indicates that their literature search did not reveal data suggesting genotoxicity, mutagenicity, or toxicity of pectins, pectin fractions, or other materials derived from carrot.

NutriLeads includes the report of a panel of individuals (NutriLeads' GRAS panel). Based on its review, NutriLeads' GRAS panel concluded that cRG-I is safe under the conditions of its intended use.

Based on the totality of evidence, NutriLeads concludes that cRG-I is GRAS for its intended use.

Standards of Identity

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

Conclusions

Based on the information that NutriLeads provided, as well as other information available to FDA, we have no questions at this time regarding NutriLeads' conclusion that cRG-I is GRAS under its intended conditions of use. This letter is not an affirmation that cRG-I 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 000972 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.03.25 19:32:39 -04'00'

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