



Jianhua Zhu, Ph.D.
BioNeutra North America Inc.
9068-25 AVE
Edmonton, Alberta, T6N 1J4
CANADA

Re: GRAS Notice No. GRN 000674

Dear Dr. Zhu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000674. We received the notice, dated October 5, 2016, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal) on October 5, 2016, and filed it on October 27, 2016. We received amendments to the notice on November 2, 2016, March 1, 2017, March 17, 2017, and June 27, 2017, providing additional information regarding exposure estimates and safety, as well as confirming the intended conditions of use.

FDA published the GRAS final rule on August 17, 2016 (81 FR 54960), with an effective date of October 17, 2016. As GRN 000674 was pending on the effective date of the GRAS final rule, we requested additional information consistent with the format and requirements of the final rule. We received an amendment responding to this request on November 2, 2016.

The subject of the notice is isomalto-oligosaccharide mixture with reduced mono- and disaccharides (RIMOM). The notice informs FDA of the view of BioNeutra North America Inc. (BioNeutra) that RIMOM is GRAS, through scientific procedures, for use as an ingredient in baked goods and baking mixes; beverages and beverage bases; breakfast cereals; condiments and relishes; dairy product analogs; mayonnaise and mayonnaise-type dressings; salad dressings; frozen dairy desserts and mixes; gelatins, puddings, and fillings; gravies and sauces; hard candies; jams and jellies; meal replacement bars and mixes; milk and milk products; nut products; processed fruits and fruit juices; snack foods; soft candy; sugar substitutes; sweet sauces, toppings and syrups; processed vegetables and vegetable juices; soups and soup mixes at levels ranging from 4.38 percent to 87.66 percent of the final product.¹

Our use of the term, "isomalto-oligosaccharide mixture with reduced mono- and disaccharides" or "RIMOM" 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

¹ BioNeutra states that these food categories and use levels are similar to those described in GRN 000246, excluding uses in "meat and poultry." FDA responded to the notice in a letter dated February 10, 2009, stating that the agency had no questions at that time regarding BioNeutra's GRAS determination. Subsequently to a supplement for use in soups and soup mixes (excluding meat and poultry products under USDA jurisdiction), FDA responded in a letter dated June 1, 2016, stating that the agency had no questions at that time regarding BioNeutra's GRAS determination.

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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 Labelling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for “isomalto-oligosaccharide mixture.”

BioNeutra discusses the identity of RIMOM, describing it as an isomalto-oligosaccharide mixture comprised primarily of oligosaccharides containing 3 to 9 glucose units. RIMOM is a clear to light yellow syrup or a white spray-dried powder. BioNeutra notes that RIMOM differs from the IMOM that was the subject of GRN 000246 only by reduced mono- and disaccharides in the mixture, effectively concentrating larger molecular weight (>degree of polymerization of 3 or DP3) components in RIMOM that is the subject of GRN 000674.

BioNeutra describes the manufacture of RIMOM, noting that the starting material for RIMOM is starch, which is hydrolyzed enzymatically and then fermented by *Saccharomyces cerevisiae*, which removes glucose. Subsequently, the material is filtered to further reduce the concentrations of mono- and disaccharides (glucose, maltose, and isomaltose). The notifier states that the manufacturing process is consistent with cGMP. The final product is a syrup or a spray-dried powder.²

BioNeutra provide specifications for the product. These include specifications for total carbohydrates (>99.5%, dry basis), total oligomer content (≥91%, dry basis), and limits for arsenic (≤0.1 mg/kg), mercury (≤0.1 mg/kg) and lead (≤0.1 mg/kg), and microbial contaminants. The notifier provided analytical data from five nonconsecutive lots of the product, confirming compliance with these specifications.

BioNeutra cites the exposure estimate they conducted for GRN 000246. The dietary exposure estimate for isomalto-oligosaccharide mixture (IMOM) in GRN 000246 assumed that two servings per day of sucrose would be replaced with the notified substance. The estimated maximum dietary exposure to the entire carbohydrate content of IMOM was 30 g/d that resulted in an exposure of 25 g/d to the 3- to 9-glucose oligosaccharide fraction. BioNeutra states that the intended use levels of RIMOM in the present notice are proportionately lower than those for IMOM in GRN 000246 in order to provide the same concentration of oligosaccharides with a degree of polymerization of 3 or greater in the finished food. BioNeutra estimates that the maximum exposure to RIMOM will be approximately 26.3 g/d to provide an exposure of approximately 25 g/d to the 3- to 9-glucose oligosaccharide fraction.

Therefore, the notifier concluded that the estimated dietary exposure to the 3- to 9-glucose oligosaccharide fraction that will result from the intended uses of its present product will be the same as that for GRN 000246, but the exposure to mono- and disaccharides in the present product will be lower. Furthermore, in its amendment of November 2, 2016, the notifier explained that the RIMOM product that is the subject of this notice will replace the uses of the IMOM product that was the subject of GRN 000246, thus the overall exposure estimate will not increase.

² The notifier states that this manufacturing method differs from the one in GRN 000246 in the extra filtration step that reduces mono- and disaccharides.

BioNeutra discusses publicly available data and information on the metabolic fate of IMOM, as well as toxicological and safety studies in both animals and humans. BioNeutra summarizes the data and information relevant to safety of IMOM in GRN 000246, as well as information made available since the submission of GRN 000246. BioNeutra reports that an updated literature search was conducted through January 2016 and notes that no new data and information were found that are, or may appear to be, inconsistent with its conclusion that RIMOM is GRAS under the conditions of its intended use. BioNeutra also states that components of RIMOM are normal constituents in the human diet, present in fermented foods such as miso, soy sauce, and sake.

BioNeutra states that published *in vitro* and *in vivo* animal and human studies demonstrate that the oral consumption of IMOM, the subject of GRN 000246, results in nearly complete digestion to glucose in the gastrointestinal tract, while any remaining undigested components are fermented in the colon.

BioNeutra discusses one six-week toxicity study in rats that showed no toxicologically relevant adverse effects at levels up to 20 g IMOM/kg body weight (bw)/d. In addition, BioNeutra notes that a one-year toxicity study also reported no relevant adverse effects in rats fed 3% IMOM in drinking water (approximately 3-5 g/kg bw/d). BioNeutra also states that IMOM, with or without metabolic activation, was neither mutagenic nor genotoxic based on *in vitro* assays. BioNeutra also discusses, as additional evidence for safety, several efficacy studies, both published and unpublished, that did not report any toxicologically relevant adverse effects.

BioNeutra discusses potential gastrointestinal effects associated with RIMOM. BioNeutra notes that some published reports suggested a threshold of equal to or greater than 1.5 g/kg bw/d for induction of transient diarrhea from single bolus of IMOM. As supportive evidence, BioNeutra describes its own unpublished human studies that supported up to 36 g/d of IMOM is tolerable.

Based on the data and information described above, BioNeutra concludes that RIMOM is GRAS for its intended use in food.

Standards of Identity

In the notice, BioNeutra states its intention to use RIMOM 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 as nutrient content claims and health claims). The notice raises a potential issue under these labeling provisions. In describing the information that BioNeutra relies on to conclude that RIMOM is GRAS, BioNeutra discussed studies that show potential physiological effects of RIMOM that BioNeutra views as beneficial. If products containing RIMOM bear any nutrient content or health claims on the label or in labeling, such claims are the subject to the applicable requirements and are under the purview of ONFL. OFAS 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(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of BioNeutra's notice concluding that RIMOM is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing RIMOM. Accordingly, our response should not be construed to be a statement that foods containing RIMOM, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that BioNeutra provided, as well as other information available to FDA, we have no questions at this time regarding BioNeutra's conclusion that RIMOM is GRAS under its intended conditions of use. This letter is not an affirmation that RIMOM 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 000674 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams

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Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A. Adams -S
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