DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

FEB 10 2009

Dr. Jianhua Zhu
President
BioNeutra Inc.
9419-20th Avenue, N.W.
Edmonton Research Park
Edmonton, Alberta
CANADA T6N 1E5

Re: GRAS Notice No. GRN 000246

Dear Dr. Zhu:

The Food and Drug Administration (FDA) is responding to the notice, dated March 17, 2008, 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). FDA received the notice on April 1, 2008, filed it on April 4, 2008, and designated it as GRAS Notice No. GRN 000246.

The subject of the notice is isomalto-oligosaccharide mixture (IMOM). The notice informs FDA of the view of BioNeutra Inc. (BioNeutra) that IMOM is GRAS, through scientific procedures, for use as an ingredient in a variety of foods, including meat products, at maximum levels ranging from 1.5 to 15 grams per serving (g/serving) as detailed in Table 1 below.

Table 1: Intended food uses, maximum use levels, and amount of IMOM per serving

Food Use	Maximum Use Level (percent)	IMOM Per Serving (g)*
Baked goods and baking mixes	25	15
Beverages and beverage bases	5	12
Breakfast cereals	20	10
Condiments and relishes	20	5
Dairy product analogs	5	12
Mayonnaise and mayonnaise-type dressings	30	7
Salad dressings	30	9
Frozen dairy desserts and mixes	10	10
Gelatins, puddings, and fillings	15	15
Gravies and sauces	20	14
Hard candies	100	10
Jams and jellies	75	11
Meal replacement bars and mixes	25	10
Meat products	5	2.5
Milk and milk products	5	5.5
Nut products	10	3
Processed fruits and fruit juices	5	7
Snack foods	5	1.5
Soft candy	40	14
Sugar substitutes	100	4
Sweet sauces, toppings, and syrups	50	15
Processed vegetables and vegetable juices	15	15
*Reference amounts customarily consumed per eating occasion, 21 CFR 101.12		

As part of its notice, BioNeutra includes the report of a panel of individuals (BioNeutra's GRAS panel) who evaluated the data and information that are the basis for BioNeutra's GRAS determination. BioNeutra considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food.

BioNeutra describes both syrup and powder formulations of IMOM. BioNeutra defines isomalto-oligosaccharides as relatively short glucose oligomers containing characteristic α-D-1,6 linkages[1] and indicates that the product manufactured by the firm is mainly comprised of such oligomers. BioNeutra states that approximately 77 and 73 percent of the syrup and powder formulations, respectively, are composed of oligosaccharides between three and six degrees of polymerization. Mono- and disaccharides constitute (15 to 20 percent) and larger oligomers (≥ seven glucose units) account for the remainder.

BioNeutra describes the method of manufacture and product specifications for IMOM. BioNeutra states that all substances used in the manufacturing process are appropriate for food use. Starch from a variety of sources (e.g., corn, wheat, rice, cassava, barley, oats,

[1] Among the isomalto-oligosaccharides identified by BioNeutra in the product it manufactures are isomaltose, panose, isomaltotetraose, isomaltopentaose, and isomaltohexaose.

potato, peas, beans, and lentils) is mixed with water to create a slurry. Enzymes are added to hydrolyze the starch amylose and amylopectin polysaccharides and then to form isomalto-oligosaccharides. Yeast is added to consume excess glucose. The mixture is then heated to inactivate the yeast and promote evaporation of yeast-generated ethanol. The mixture is purified and the product is either spray-dried (powder formulation) or evaporated (syrup formulation). Specifications provided for IMOM include the content of isomaltose and higher oligosaccharides (three to ten glucose units) and limits on the content of glucose, sulfated ash, lead, arsenic and microbial contaminants. Specifications for the syrup formulation also include dried solids and pH; specifications for the powder formulation include solubility in water and moisture.

BioNeutra estimates that the intake of IMOM would be approximately 30 grams per person per day. This estimate is based on the assumed consumption of two servings of foods containing the highest use level identified (15 g/serving).

BioNutra discusses the safety evaluation for IMOM based on a variety of published studies and other data and information, including;

- well-established metabolic profiles of the simple saccharide components of IMOM (maltose, isomaltose).
- published studies and other information related to the absorption, digestion, metabolism, and excretion of isomalto-oligosaccharides (IMO) similar to those in the IMOM described in this notice. IMO preparations are partially hydrolyzed to glucose and absorbed; as is common with other non-digestible carbohydrates, the remainder is metabolized by gut microflora.
- published acute, subchronic, and chronic safety studies of various IMO preparations in rats. In some of these studies, IMO consumption was associated with decreased food efficiency or increased intestinal weight, which is consistent with the limited digestibility of IMO and proliferation of colon microflora. BioNeutra concluded that these observations did not raise concerns about adverse effects on human health.
- published studies and other information concerning various effects in the gut expected from or attributed to bacterial fermentation of IMO specifically, and non-digestible carbohydrates generally. BioNeutra concluded that the intended use of IMOM would not have adverse effects on human health.
- published tolerance studies of various IMO preparations in humans, in light of the potential for microbial fermentation of IMO in the lower intestine.

On the basis of all the data and information listed above, BioNeutra concludes that consumption of IMOM under the conditions of its intended use would not produce adverse effects on human health and would be well-tolerated with respect to gastrointestinal effects.

Standards of Identity

In the notice, BioNeutra states its intention to use its IMOM 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 product 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 (FFDCA), a food is misbranded if its labeling is false or misleading in any particular. Section 403(r) of the FFDCA lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. In describing the intended use of IMOM and in describing the information that BioNeutra relies on to conclude that IMOM is GRAS under the conditions of its intended use, BioNeutra raises a potential issue under these labeling provisions of the FFDCA. If products that contain IMOM bear any claims on the label or in labeling, such claims are the purview of the Office of Nutrition, Labeling and Dietary Supplements (ONLDS) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety neither consulted with ONLDS on this labeling issue nor evaluated the information in your notice to determine whether it would support any claims made about IMOM on the label or in labeling.

Use in Meat and Poultry Products

During our evaluation of GRN 000246, we consulted with the Labeling and Program Delivery Division of the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA). Under the Federal Meat Inspection Act and the Poultry Products Inspection Act, FSIS is responsible for determining the efficacy and suitability of food ingredients in meat and poultry products as well as prescribing safe conditions of use. Suitability relates to the effectiveness of the ingredient in performing the intended purpose of use and the assurance that the conditions of use will not result in an adulterated product, or one that misleads consumers.

FSIS advised that BioNeutra's notice does not include any efficacy or suitability data for meat products on which FSIS could base a decision. FSIS requested that FDA advise BioNeutra to seek regulatory guidance from FSIS about the use of IMOM in meat and poultry products. Inquiries should be directed to Dr. John Hicks, Risk Management Division, Office of Policy and Program Development,[2] Food Safety and Inspection Service, 1400 Independence Ave., S.W., Room 3549, South Agriculture Building, Washington, DC 20250-3700. The telephone number for that office is (202) 205-0210 and the telefax number is (202) 720-0582.

Section 301(ll) of the FFDCA

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FFDCA to, among other things, add section 301(ll). Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the

[2] Effective June 1, 2008, the Office of Policy and Program Development of FSIS has transferred the review process of ingredient submissions from the Labeling and Program Delivery Division to the Risk Management Division.

FFDCA, 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 its review of BioNeutra's notice that IMOM is GRAS for its intended uses, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing IMOM. Accordingly, this response should not be construed to be a statement that foods that contain IMOM, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by BioNeutra, as well as other information available to FDA, the agency has no questions at this time regarding BioNeutra's conclusion that IMOM is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of IMOM. As always, it is the continuing responsibility of BioNeutra to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000246, as well as a copy of the information in this notice that conforms to the information in the proposed GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov. To view or obtain an electronic copy of the text of the letter, follow the hyperlinks from the "Food" topic to the "Food Ingredients and Packaging" section to the "Generally Recognized as Safe (GRAS)" page where the GRAS Inventory is listed.

Sincerely,

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

cc: John Hicks, DVM, MPH
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