



Timothy S. Murbach, ND, DABT
Senior Scientific & Regulatory Consultant
AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle, Washington 98112

Re: GRAS Notice No. GRN 000816

Dear Mr. Murbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000816. We received the notice you submitted on behalf of Prenexus Health, Inc. (Prenexus) on October 1, 2018, and filed it on November 30, 2018. We received an amendment to the notice clarifying the intended uses and dietary exposure estimates for the subject of the notice on March 6, 2019.

The subject of the notice is xylooligosaccharides (XOS) from sugarcane for use as a texturizer and food ingredient in a variety of food categories (excluding infant formula and foods under the jurisdiction of the United States Department of Agriculture) at levels up to 2.4 grams (g)/serving. The notice informs us of Prenexus' view that this use of XOS is GRAS through scientific procedures.

Prenexus provides information about the identity of XOS. Prenexus describes XOS (1,4- β -xylooligosaccharides) as an off white to tan powder with a slightly sweet taste. Prenexus describes XOS as a non-digestible polymer of D-xylopyranosyl (xylose) residues linked by β -(1 \rightarrow 4) glycosidic bonds. The degree of polymerization varies between 2 to 20 xylose residues.

Prenexus describes the method of manufacture for XOS. Prenexus states that XOS is derived from eight varieties of food-grade high-fiber hybrid sugarcane (*Saccharum* species). Prenexus states that the harvested raw sugarcane is shredded then washed with water and pressed to recover fiber solids. Hot water is then circulated through the solids under pressure to extract the XOS. The crude extract is subjected to multiple filtration steps followed by an ion exchange and decolorization step. The resulting extract is concentrated and dried to obtain the final XOS product that is packaged. Prenexus states that XOS product is produced using food-grade materials and in accordance with current good manufacturing practices.

U.S. Food and Drug Administration
Center for Food Safety Applied Nutrition
5001 Campus Drive
College Park, MD 20740
www.fda.gov

Prenexus provides specifications for the XOS product. These include color (off white to light tan), total solids (>93%), XOS (>75%), sugars (glucose, fructose, xylose and sucrose (<12%)), moisture (<7%), other (polyphenols and organic acids (<3%)), arsenic (<0.2 mg/kg), cadmium (<0.2 mg/kg), lead (<0.2 mg/kg), and mercury (<0.2 mg/kg). Specifications also include limits for microorganisms. Prenexus provides the results of analyses of three non-consecutive batches to demonstrate that the XOS can be produced to meet the specifications.

Prenexus provides estimates of dietary exposure to XOS based on background uses, its intended uses, and food consumption data reported in the National Health and Nutrition Examination Survey (NHANES; 2013-14). Prenexus states that the intended uses of XOS are substitutional in terms of the XOS content for the uses in the food categories specified in previous XOS notices (GRNs 000458¹ and 000343²). Prenexus estimates that the mean and 90th percentile dietary exposures to XOS for consumers (ages ≥2 years) would be 12.6 and 20.7 g/person/day (d), respectively, or 0.214 and 0.415 g/kilogram body weight (g/kg bw)/d respectively.

Prenexus discusses published information to support the safety of XOS. Prenexus incorporates, into GRN 000816, published toxicity studies cited in GRNs 000458 and 000343 and discusses the fate of XOS in the gastrointestinal tract. Prenexus states that XOS is a non-digestible carbohydrate that is fermented in the colon to produce short chain fatty acids. Prenexus discusses toxicity studies cited in GRNs 000458 and 000343 including acute, short term (14 days), and subchronic studies, as well as *in vitro* and *in vivo* genotoxicity assays. Prenexus states that these studies did not reveal any toxicologically relevant treatment-related adverse effects, and no evidence of mutagenicity. Prenexus also incorporates human clinical studies cited in GRNs 000458 and 000343 and states that the results of these studies demonstrate that XOS is well-tolerated. Prenexus conducted an updated literature search through September 2018 and identified a recently published dog study. In the dog study, XOS was administered by gavage daily for 26 weeks, and Prenexus states that no treatment-related adverse effects were reported up to a dose level of 2.5 g/kg bw/d.

Based on the data and information presented in the notice, Prenexus concludes that XOS derived from sugarcane is GRAS for its intended use.

Standards of Identity

In the notice, Prenexus states its intention to use XOS in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of

¹ GRN 000458 describes the use of xylooligosaccharides in a number of food categories. FDA evaluated this notice and responded in a letter dated August 23, 2013, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

² GRN 000343 describes the use of wheat bran extract composed primarily of xylo- and arabinooligosaccharides in a number of food categories. FDA evaluated this notice and responded in a letter dated November 22, 2010, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

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 & Cosmetic (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. Prenexus describes XOS as having certain health benefits. If products containing XOS 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(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 Prenexus' notice concluding that XOS 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 XOS. Accordingly, our response should not be construed to be a statement that foods containing XOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Prenexus provided, as well as other information available to FDA, we have no questions at this time regarding Prenexus' conclusion that XOS is GRAS under its intended conditions of use. This letter is not an affirmation that XOS 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 000816 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

Digitally signed by
Michael A. Adams -S

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