



Bradley J. Lampe, M.P.H.  
NSF International  
789 N. Dixboro Road  
Ann Arbor, MI 48105

Re: GRAS Notice No. GRN 000854

Dear Mr. Lampe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000854. We received the notice that you submitted on behalf of Industrializadora Intergral del Agave SA de CV (IIDEA) on April 4, 2019 and filed it on May 16, 2019. IIDEA submitted amendments to the notice on September 4, 2019, October 25, 2019, and November 12, 2019, that provided clarifications regarding the subject of the notice, specifications, analytical methods, and IIDEA's GRAS panel report.

The subject of the notice is agave mixed fructans from *Agave tequilana* Weber var. *azul* (agave mixed fructans) for use as a bulking agent, texturizing agent, or source of reduced energy carbohydrate for use as a sugar replacer, fat replacer, and/or texture modifier in 42 food categories (excluding infant formula and meat and poultry products) at the following use levels: 1 g/serving in infant and toddler foods, 5 g/serving in ready-to-eat breakfast cereals, and 0.5–15 g/100 g in other foods.<sup>1</sup> The notice informs us of IIDEA's view that these uses of agave mixed fructans are GRAS through scientific procedures.

Our use of the term, "agave mixed fructans from *Agave tequilana* Weber var. *azul*" or "agave mixed fructans" 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 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 Labeling (ONFL) in the Center for Food Safety and Applied Nutrition (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "agave mixed fructans from *Agave tequilana* Weber var. *azul*" or "agave mixed fructans."

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<sup>1</sup>IIDEA states that serving sizes correspond to reference amounts commonly consumed per eating occasion as set forth in 21 CFR 101.12.

IIDEA provides information on the source, identity, and composition of agave mixed fructans. IIDEA states that agave mixed fructans are extracted from the pine of *Agave tequilana* Weber var. *azul*. Agave mixed fructans are a mixture of oligo- and polysaccharides consisting of fructose units joined by  $\beta(2-1)$  and  $\beta(2-6)$  linkages, with typically one terminal glucose unit or an internally linked glucose unit per molecule. The degree of polymerization (DP) ranges from 3 to 29, which corresponds to a molecular weight range of 527–4739 Da. Agave mixed fructans have the chemical formula  $C_{6n}H_{10n+2}O_{5n+1}$ . IIDEA describes agave mixed fructans as a white powder containing  $\geq 98\%$  total carbohydrates.

IIDEA describes the method of manufacture of agave mixed fructans. The agave pines are milled and subjected to a series of mechanical extractions. The agave bagasse (biomass) is separated and removed. The extracted juice undergoes three filtration steps. After the final filtration, the resulting juice is concentrated by evaporation and spray dried to a powder. IIDEA states that the only processing aid employed in the manufacturing process of agave mixed fructans is perlite as a filter aid and that no solvents or other chemicals are used. IIDEA states that agave mixed fructans are manufactured in accordance with current good manufacturing practices.

IIDEA provides specifications for agave mixed fructans that include a minimum content of total carbohydrates ( $\geq 98\%$ ) and agave mixed fructans ( $\geq 88\%$ ), limits for fructose ( $\leq 10\%$ ), glucose ( $\leq 3.5\%$ ), disaccharides ( $\leq 2\%$ ), ash ( $\leq 5\%$ ), lead ( $< 0.02$  mg/kg), mercury (0.01 mg/kg), arsenic ( $< 0.05$  mg/kg), chromium ( $< 2$  mg/kg), cadmium ( $< 0.01$  mg/kg), antimony ( $< 0.5$  mg/kg), and microorganisms. IIDEA provides the results of non-consecutive batch analyses to demonstrate that agave mixed fructans can be manufactured to meet the specifications. Based on the stability of similar products, IIDEA states that agave mixed fructans are stable for a period of three years.

Agave mixed fructans, like inulin-type fructans, are not digested but fermented by colonic microflora. IIDEA states that the use of agave mixed fructans will be substitutional for the use of inulin from the chicory root ( $\geq 90\%$  inulin) that was the subject of GRN 000118 and its supplement.<sup>2</sup> IIDEA states that the following estimates of dietary exposure at the 90<sup>th</sup> percentile were reported for inulin in GRN 000118: 5.7 g/day(d) for non-breastfeeding infants  $< 1$  year of age, 13.7 g/d for non-breastfeeding children aged 1 to  $< 2$  years, and 19.2 g/d for the general population ( $\geq 2$  years of age). IIDEA also states that inulin-type fructans occur naturally in a variety of edible fruits and vegetables and reports a background average dietary exposure to inulin-type fructans from the diet to be 1–4 g/d at the 97<sup>th</sup> percentile in the U.S. The use of agave mixed fructans will not result in an increase in the overall consumption of nondigestible fructans, such as inulin, but will provide an alternative source of nondigestible fructans in food categories in which inulin from chicory root is currently used.

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<sup>2</sup>Inulin from the chicory root ( $\geq 90\%$  inulin) was the subject of GRN 000118. FDA evaluated this notice and its supplement, and responded in letters dated May 5, 2003 and January 16, 2008, respectively, stating that the agency had no questions at that time regarding the notifier's conclusions.

IIDEA discusses publicly available data and information supporting the safety of agave mixed fructans. IIDEA states that fructans are a form of nondigestible soluble fiber. Like other fructans, agave mixed fructans pass intact into the colon where they are subject to fermentation by colonic microflora. IIDEA briefly discusses published short-term and long-term animal studies, as well as genetic toxicity studies on agave mixed fructans and similar fructans. These studies did not show any toxicologically relevant effects or genotoxic effects. IIDEA discusses human studies with agave mixed fructans and other fructans demonstrating that agave mixed fructans are well tolerated following oral consumption. IIDEA also notes that Carabin and Flamm (1999) concluded that inulin-type fructans are safe for human consumption, and that up to 20 g/d of inulin and/or oligofructose is well tolerated. IIDEA reports the opinion of several international regulatory authorities on the safety of consumption of inulin and other fructans, and notes that inulin is legally classified as a food or food ingredient in most countries, including all EU countries, Australia, Canada, and Japan. IIDEA states that the scientific literature search covered the period through November 2018.

We note that IIDEA included the report of a panel of individuals (IIDEA's GRAS panel) dated December 9, 2016. IIDEA did not provide an updated report and requested that FDA consider the notice without the GRAS panel report. Because the notice provided publicly available information supporting IIDEA's conclusion, we completed our evaluation without considering IIDEA's GRAS panel report.

Based on the totality of data and information available, IIDEA concludes that the intended uses of agave mixed fructans are GRAS.

### **Standards of Identity**

In the notice, IIDEA states its intention to use agave mixed fructans 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 to as nutrient content claims and health claims). If products containing agave mixed fructans 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 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.<sup>3</sup>

### **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 IIDEA's notice concluding that agave mixed fructans 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 agave mixed fructans. Accordingly, our response should not be construed to be a statement that foods containing agave mixed fructans, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

### **Conclusions**

Based on the information that IIDEA provided, as well as other information available to FDA, we have no questions at this time regarding IIDEA's conclusion that agave mixed fructans are GRAS under its intended conditions of use. This letter is not an affirmation that agave mixed fructans 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)(1), the information in this notice described in 21 CFR 170.225(c)(2) through (c)(5) will be accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J.  
Carlson -S  
Date: 2020.01.21 14:49:32 -05'00'

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

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<sup>3</sup>The definition of "dietary fiber" in 21 CFR 101.9(c)(6)(i) was added by FDA's final rule revising the nutrition and supplement facts labels (81 FR 33742, May 27, 2016). This final rule, among other things, defines dietary fiber as non-digestible soluble and insoluble carbohydrates (with three or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with three or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health.