

June 17, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-0725; Comments of the Center for Science in the Public Interest (CSPI) on The Declaration of Allulose and Calories from Allulose on Nutrition and Supplement Facts Labels, Draft Guidance for Industry

The Center for Science in the Public Interest (CSPI) appreciates the opportunity to comment on the Food and Drug Administration's draft guidance for industry regarding the declaration of allulose and calories from allulose on Nutrition and Supplement Facts Labels.

Summary: FDA Should Consider Warning Consumers about the Adverse Effects of Allulose

Allulose is a sugar substitute that appears to result in only negligible increases in blood glucose or insulin levels and has fewer calories than sugar because it is poorly absorbed. CSPI therefore supports FDA's intention to exclude allulose from the amount declared in the total and added sugar declarations, and to use 0.4 calories per gram of allulose when calculating the calories from allulose in a serving of product.

However, it is precisely because allulose is poorly absorbed that we are concerned about its potential adverse effects, such as nausea, bloating, headache, diarrhea, and abdominal pain. To our knowledge, those adverse effects have been explored in only two¹ studies—both unblinded and non-randomized, and one unavailable on PubMed. These small studies, conducted on only healthy adults and with limited statistical power, are thoroughly inadequate to determine the potential impact of allulose on gastrointestinal symptoms in the population as a whole. We are particularly concerned that these adverse effects may harm children and people with irritable bowel syndrome, a condition that is estimated to affect 10 to 12 percent of the population.² Those concerns will grow as the popularity and consumption of allulose increases, in part spurred by this draft guidance.

¹ There are three other human studies mentioned in the GRNs, but only one of those looked for any GI effects; it was a study in 17 subjects, using fairly low dose (5 g/meal, 3x/day) and found one male had symptoms “that could not be unrelated to treatment” including diarrhea, borborygmus, and increased defecation frequency. This ingested several test meals at one sitting, He discontinued the treatment for 12 days but did not recover immediately.

² Ford AC, Moayyedi P, Chey WD, Harris LA, Lacy BE, Saito YA, Quigley EMM; ACG Task Force on Management of Irritable Bowel Syndrome. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. [Am J Gastroenterol](#). 2018 Jun;113(Suppl 2):1-18. doi: 10.1038/s41395-018-0084-x.

Allulose is a novel substance that will be unfamiliar to many consumers. While its use in limited quantities may be appropriate, consumers deserve to be informed of its potential adverse effects. Such symptoms may lead consumers to seek and undergo unnecessary medical testing, seeking a cause in the absence of information that these adverse effects stem from allulose.

A warning would provide critical transparency, allowing consumers, including children, who are sensitive to the effects to respond accordingly. A warning would also facilitate its appropriate use. In the absence of this type of warning, market incentives may lead to its over-use, and rather than being a tool for lowering sugar consumption, it could become a focus of public suspicion and avoidance.

Below we outline the basis for our views and propose that the Agency consider a warning label and additional studies to ensure the safe use of allulose.

FDA Reviews of Allulose GRAS Notifications

In the draft guidance and the Federal Register notice of its availability issued on April 18, 2019, FDA announced its intention is to allow manufacturers to exclude allulose from the amount declared in the total and added sugar declarations, and to use 0.4 calories per gram of allulose when calculating the calories from allulose in a serving of product. This announcement was based on the Agency's review of the scientific evidence related to allulose and metabolism, caloric value, and dental caries, as well as information provided in citizen petitions and in relevant comments.

FDA previously sent three [“no questions” letters](#) (in 2012, 2014, and 2017) in response to three Generally Recognized as Safe (GRAS) notifications regarding proposed uses of allulose (also called D-psicose or psicose) (GRN 400, GRN 498, GRN 693).³

Allulose Is a Poorly Digested Carbohydrate and Studies in Healthy Adults Raise Concerns about Gastrointestinal Effects

GRN 400 describes an investigation in 10 healthy volunteers. Subjects received 0.4 g/kg-bw/day for the first dose, and the dose was increased by 0.1 g/kg-bw/day to 0.9 g/kg-bw/day. There is no indication whether the study was blinded, and CSPI was not able, despite efforts, to obtain a copy of the study, which does not appear in PubMed.⁴ According to FDA's “no questions” letter sent in response to GRN 400,

“Cheiljedang [the manufacturer of allulose] states that gastrointestinal disturbances ranging from diarrhea, borborygmi, lower abdominal pain, nausea, and distention were reported at doses above 0.5 g/kg bw/d. These effects are also seen with other poorly

³ FDA ceased to evaluate two other GRAS notifications at the notifier's request (GRN 755, GRN 647). In the case of GRN 755, FDA informed the notifier that its request to replace five study reports on the safety of the production organism with data from unpublished and nonpublic sources raised concerns, since data and information establishing the safety of allulose (D-psicose) must be publicly available. In the case of GRN 647, the request came after FDA raised issues during its review; the notifier resubmitted its request as GRN 693.

⁴ Iida T, Kishimoto Y, Yoshikawa Y et al. Estimation of maximum non-effective level of D-psicose in causing diarrhea in human subjects. *J Advd Food Ingrid* 10:15-19, 2007.

digested carbohydrates. The authors of the clinical study concluded that the maximum tolerable levels in humans were 0.5 g/kg bw/d in men and 0.6 g/kg bw/d in women, which corresponds to 33.3 g/d in men and 31.0 g/d in women, calculated based on the mean body weights.”

Since FDA sent its “no questions” letters, a new study was published on gastrointestinal tolerance of allulose, in December 2018.⁵ This clinical trial of 30 healthy adults with normal BMI (15 male, 15 female) that were recruited through an advertisement was funded by the Korean government. Two separate open-label experiments were performed. The aim of the first was to identify the maximum single dose of allulose for occasional ingestion. The second was aimed at identifying the maximum daily intake of allulose for regular ingestion. The two experiments were conducted a week apart, and a meal was provided before allulose consumption. The maximum doses for occasional and for regular ingestion were defined as the dose administered just before a dose that caused a severe level of symptoms.

In the first experiment, which was completed by 29 subjects, the dose of allulose in a beverage was gradually increased in steps of 0.1 g/kg-bw to identify the maximum single dose for occasional ingestion. The doses were given daily for a week before being increased, and a wash-out period of one week was given every other week to avoid adaptation. In the second experiment, conducted on nineteen subjects, the initial dose was 0.2 g/kg-bw and again increased at 0.1 g/kg-bw/day increments (spread out at scheduled times during the day), without wash-out periods. Subjects were asked to record the incidences and magnitudes of the GI responses for the 24-hour period following the consumption of the test products.

Based on the results from both experiments, the authors suggested a maximum single dose of 0.4 g/kg-bw (24g for a 60 kg person) and a maximum total daily intake of 0.9 mg/kg-bw (54 g for a 60 kg person). These were based (as defined above) on the development of severe GI symptoms in the two studies at the next highest dose.

All 29 subjects in the first experiment were given varying doses of allulose and also given the same varying doses of sucrose.

In the first experiment, when 0.5 g/kg-bw allulose was administered, 13 subjects out of 29 (44.83%) reported diarrhea and four (13.79%) had severe symptoms; at the same dose of sugar, four subjects reported diarrhea, and none were severe. Compared to the same dose of sugar, significantly higher symptoms of diarrhea ($p=0.004$), abdominal distention ($p=0.039$), and abdominal pain ($p=0.031$) were reported on allulose.

Some participants reported a slightly higher number of symptoms than usual even at the lowest dose tested (0.1 g/kg-bw). For example, five subjects reported nausea at 0.1 g/kg-bw allulose, whereas only one subject reported nausea at the same dose of sugar. Similarly, four subjects each reported bloating, diarrhea, and headache at 0.1 g/kg-bw allulose, whereas two each reported those symptoms at the same dose of sucrose.

⁵ Han Y, Choi BR, So YK et al. [Gastrointestinal tolerance of d-allulose in healthy and young adults. A non-randomized controlled trial.](#) *Nutrients* 10(12): 2010, December 2018.

In the second experiment, when 1.0 g/kg-bw was given, severe levels of nausea (one subject), abdominal pain (one subject), headache (one subject), anorexia (one subject), and diarrhea (two subjects) were reported.

These studies have several shortcomings. First, they have limited statistical power since they only included 10-30 participants. Second, the studies are not representative of the general population, as they only tested healthy adults. Children, who are predicted to have the highest g/kg-bw intake of allulose (see below), were not included. Nor were people with irritable bowel syndrome, who may be particularly sensitive to poorly absorbed carbohydrates, including fructans and polyols.⁶ Finally, it appears that the studies were not blinded or randomized, and one was designed to identify a maximum tolerable dose based only on severe gastrointestinal symptoms.

Exposure to Allulose in Children Raises Concerns

According to the most recent GRAS Notice (693), children aged 2-12 years (users only) are estimated to consume the highest amounts of allulose, on a body weight basis, with a mean estimated daily intake (EDI) of 0.19g/kg-bw/day and a 90th percentile EDI of 0.50 g/kg bw/day (14.2 g/day). Males 19 years and older (uses of allulose) are estimated to consume the largest amount per day (mean 13.0 g/day; 90th percentile 36.3 g/day (0.39 g/kg-bw/day)).

Significantly, the 90th percentile dose for children is at or above some of the maximum tolerable doses derived from the 2007 and 2018 studies in adults (see above).

Furthermore, FDA's stated intention to exclude allulose from the amount declared in the total and added sugar declarations and to use 0.4 calories per gram of allulose when calculating calories/serving has generated a great deal of excitement in the industry and predictions about a surge in use of allulose.⁷ If individuals consume more allulose as a result of an expansion in marketing, more consumers, including children, are likely to exceed levels known to have adverse effects.

Safety Assessments of Allulose Failed to Address its Likely Adverse Effects in Children or Adults

Although the EDIs fall below reference levels derived from single dose, 34-day, 90-day, and 12-18 month studies in animals, these reference levels fail to adequately capture symptoms such as

⁶ Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. [A Randomized Controlled Trial Comparing the Low FODMAP Diet vs. Modified NICE Guidelines in US Adults with IBS-D](#). Am J Gastroenterol. 2016 Dec;111(12):1824-1832. doi: 10.1038/ajg.2016.434; Eswaran S, Chey WD, Jackson K, Pillai S, Chey SW, Han-Markey T. [A Diet Low in Fermentable Oligo-, Di-, and Monosaccharides and Polyols Improves Quality of Life and Reduces Activity Impairment in Patients With Irritable Bowel Syndrome and Diarrhea](#). Clin Gastroenterol Hepatol. 2017 Dec;15(12):1890-1899.e3. doi: 10.1016/j.cgh.2017.06.044.

⁷ For example, see Watson E, [FDA guidance could prompt surge of interest in low-cal, tooth-friendly, rare sugar allulose](#). Food Navigator, April 17, 2019; Watson E, [Sweeteners in focus: Where next for allulose, stevia, isomaltulose?](#) Food Navigator, April 23, 2019; Siegner C, [FDA will exempt allulose from 'added sugar' labeling rules](#). Food Dive, April 25, 2019; Watson E, [Tate & Lyle: The first two things consumers look for on the Nutrition Facts panel now are calories and sugar](#)," Food Navigator, May 13, 2019;

nausea, bloating, headache, diarrhea, abdominal pain, and other symptoms that are reported in the human studies.

CSPI is concerned that consumers, especially children, will experience diarrhea and other symptoms from this poorly digested carbohydrate. Such symptoms may lead consumers to seek and undergo unnecessary medical testing, seeking a cause for such symptoms, in the absence of information that these adverse effects stem from allulose.

Furthermore, CSPI is concerned that there has been no assessment of the cumulative effect of poorly digested carbohydrates. As noted in FDA's response letter to GRN 400 (quoted above) describing the gastrointestinal disturbances caused by allulose, "these effects are also seen with other poorly digested carbohydrates." As stated in 21 CFR 170.3(i) as well as 21 CFR 570.3(i), in determining safety, the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet, shall be considered.

CSPI's comments to the Nutrition Innovation Strategy docket noted that poorly digested fibers approved for use by the agency are proliferating in foods. We noted:

As part of its Nutrition Facts panel update, the FDA reviewed the science underlying a range of processed (isolated or synthetic) fibers that are added to foods and has approved a number of them as dietary fiber for labeling purposes. While many consumers may expect dietary fiber to improve satiety or regularity and help them meet dietary recommendations for diets that are higher in fiber, most of the processed fibers approved thus far by the FDA have been approved on the basis of other benefits.

...

Moreover, many processed fibers are simply poorly absorbed carbohydrates that have significant adverse gastrointestinal effects, including abdominal discomfort, flatus, and diarrhea. Some fibers, such as fructooligosaccharides and isomaltooligosaccharides, can provide sweetness and yet are declared on Nutrition Facts panels as fibers instead of added sugars. That creates large incentives to add these ingredients to foods as sugar replacements, since doing so will allow manufacturers to reduce the apparent added sugar and boost the apparent dietary fiber in their products. The FDA should consider whether warnings are needed to inform consumers, where relevant, that these fibers may cause gastrointestinal symptoms and discomfort when present above a certain level, in a manner similar to the warnings that the agency requires for some sugar alcohols that trigger similar effects.

Allulose presents similar concerns. As with the novel fibers that FDA has approved, and for which the added sugars line creates an incentive for use, FDA should require a warning as to adverse effects.

Moreover, the safety of using allulose and these novel fibers, under current law, must be assessed with regard to the cumulative effects, including the cumulative physiological effects related to GI symptoms. In the absence of such consideration by FDA, over time the agency may face

warranted public concerns that the added sugars line, and the agency decision-making related to it, have given rise to a host of new health problems for consumers.

Recommendations: FDA Must Warn Consumers of the Adverse Effects of Allulose

Given the lack of familiarity with allulose amongst consumers and the likelihood of symptoms as the use of allulose and other poorly digested carbohydrates increases, CSPI requests that the agency impose additional labeling requirements, similar to those required for sorbitol and mannitol, warning consumers that consumption of allulose may result in symptoms such as nausea, bloating, headache, diarrhea, or abdominal pain. FDA should take into account that children, because of their small size and propensity for eating sweets, are at greater risk of adverse effects.

We recommend that labels state, “Excess consumption of allulose may cause diarrhea or other adverse gastrointestinal effects.”

FDA should also simultaneously require additional studies to better determine levels of allulose that trigger unwanted adverse effects, especially in children and vulnerable sub-populations. These studies should be randomized and blinded.

In addition, FDA should ensure that all safety evaluations, including GRAS determinations generally, and specifically for poorly digested carbohydrates, consider the cumulative effect of the substance, taking into account any chemically or pharmacologically related substance or substances in the diet.