



Ricardo Carvajal
Hyman, Phelps & McNamara, P.C.
700 13th Street NW, Suite 1200
Washington, DC 20005-5929

Re: GRAS Notice No. GRN 000681

Dear Mr. Carvajal:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000681. We received the notice that you submitted on behalf of Evonik Creavis GmbH (Evonik) on November 15, 2016, and filed it on November 29, 2016. We received amendments to the notice containing additional information on Evonik's safety studies and specifications for the subject of the notice on February 22, 2017, and March 29, 2017.

The subject of the notice is dried isomaltulose syrup for use as a sweetener in foods and beverages, at the same use levels as sucrose. The notice informs us of Evonik's view that this use of dried isomaltulose syrup is GRAS through scientific procedures.

Evonik describes the identity and composition of dried isomaltulose syrup. Evonik describes dried isomaltulose syrup as a water soluble, white or colorless, crystalline powder. Evonik states that dried isomaltulose syrup is $\geq 80\%$ isomaltulose, which is a disaccharide consisting of one glucose and one fructose unit linked by an α -1,6-glycosidic bond. Evonik notes that the sweetness of isomaltulose is about half that of sucrose.

Evonik describes the manufacturing process for dried isomaltulose syrup. Evonik states that immobilized cells of *Protaminobacter rubrum*¹ strain CBS 574.77 convert food-grade sucrose to isomaltulose. Evonik states that the cells of *P. rubrum* are immobilized in a matrix of calcium alginate and the cells become non-viable during immobilization. Evonik explains that calcium alginate is insoluble under both acidic and alkaline conditions and it is not present in dried isomaltulose syrup. Evonik states that *P. rubrum* produce sucrose isomerase, which catalyzes the isomerization of sucrose to isomaltulose. The eluent isomaltulose syrup is then sterilized with heat, demineralized by passing it through food-grade ion-exchange columns, concentrated by evaporation, and dried under reduced pressure and elevated temperature to produce dried isomaltulose syrup.

¹ The agency notes that *Protaminobacter rubrum* is considered a name without standing and is properly classified as *Serratia plymuthica*.

Evonik provides specifications for dried isomaltulose syrup. Specifications include a minimum content of isomaltulose ($\geq 80\%$), trehalulose ($\leq 12\%$), glucose ($\leq 3\%$), fructose ($\leq 4\%$), saccharose ($\leq 4\%$), protein (≤ 1 mg/kg), and water ($\leq 7\%$). Specifications also include limits on isomelezitose (a trisaccharide) and other oligosaccharides ($\leq 2\%$). Evonik provides the results of five batch analyses of dried isomaltulose syrup to demonstrate compliance with these specifications. Evonik also provides a specification for lead (≤ 0.1 mg/kg) and submitted the lead analysis from one lot that shows compliance with the specification.

Evonik provides estimates of the dietary exposure to dried isomaltulose syrup. Evonik assumes dried isomaltulose syrup will replace all sucrose added to foods. Evonik estimates the dietary exposure to sucrose by two methods: 1) by using the market disappearance data for sucrose from the USDA Sugar and Sweeteners Yearbook, Evonik estimates a per capita sucrose intake of about 50 g/d or about 0.84 g/kg body weight (bw)/d for a 60 kg consumer; and, 2) by using data from the USDA's National Health and Nutrition Examination Survey, Evonik estimates a dietary exposure to sucrose of 0.66 g/kg bw/d at the mean and 1.3 g/kg bw at the 90th percentile for a 60 kg consumer. Based on these data from the two methods, Evonik estimates the dietary exposure to added isomaltulose as a sucrose substitute is unlikely to exceed 1.0-1.3 g/kg bw/d, even among children and the 90th percentile consumers.

Evonik discusses published studies in animals, healthy children (ages ranging from 5 to 11 years), and adults, as well as adults with impaired glucose metabolism (type-1 diabetes and type-2 diabetes) to support the safety of consumption of dried isomaltulose syrup. Evonik incorporates published safety data and information by reference from GRN 000184² and briefly discusses the main findings. Citing published information, Evonik states that the metabolic fates of isomaltulose and sucrose are identical; the only difference is that isomaltulose is hydrolyzed at a slower rate, thereby releasing glucose and fructose at a slower rate. In an oral toxicity study in rats, administration of isomaltulose through diet for 13 weeks produced no adverse effects at the highest dose tested (7.0 and 8.1 g/kg bw/d in males and females, respectively). In two other studies in rats, administration of isomaltulose or isomaltulose syrup orally for 26 weeks produced no adverse effects at the highest dose tested, which was 4.5 g/kg bw/d of isomaltulose or isomaltulose syrup. Evonik states that in humans, a single exposure of 75 g isomaltulose in adults and 41 g isomaltulose in children 5 to 11 years of age was well tolerated and did not produce any adverse effects. Evonik notes that neither isomaltulose nor isomaltulose syrup are genotoxic.

Evonik states that the current intake of sucrose, added to food, by adults and children is unlikely to exceed 1 - 1.3 g/kg bw/d. Evonik notes that assuming a complete substitution of sucrose by isomaltulose syrup (dried), the total daily intake of isomaltulose will not

² Isomaltulose was the subject of GRN 000184, which informed FDA of the view of SÜDZUCKER AG Mannheim/Ochsenfurt (SÜDZUCKER) that isomaltulose is GRAS, through scientific procedures, for use as nutritive sweetener in a variety of food categories and beverages. FDA responded in a letter dated March 20, 2006, stating that the agency had no questions at that time regarding SÜDZUCKER's GRAS conclusion.

exceed 1 - 1.3 g/kg bw/d. Evonik further states that such level of exposure is well tolerated by both adults and children.

Evonik notes that individuals with hereditary fructose intolerance should totally avoid the intake of any fructose-containing foods or foods that yield fructose upon digestion, such as sucrose and isomaltulose.

Evonik reports that a literature search was conducted through the beginning of April 2016 on the safety of isomaltulose to identify new data and information relevant to the safety of dried isomaltulose syrup. Evonik states that although publications on the digestion and absorption were found, no additional safety studies of isomaltulose appeared in the scientific literature since FDA's response letter to GRN 000184 and the authorizations of isomaltulose as a novel food by the European Commission and the FSANZ.

Evonik further discusses the safety of consumption of trehalulose, since dried isomaltulose syrup contains 8-9% trehalulose. In a published study in rats, administration of isomaltulose syrup containing 45.7% trehalulose for 26 weeks was well tolerated and produced no adverse effects at the highest dose tested (4.5 g isomaltulose syrup/kg bw/d, corresponding to 3.2 g/kg bw/d dried isomaltulose syrup). Evonik also cites a published *in vitro* study that demonstrated that trehalulose could be readily hydrolyzed and absorbed in the form of glucose and fructose, though not as rapidly as sucrose. Evonik states that this high absorption rate explains the high intestinal tolerance of trehalulose.

Evonik includes the report of a panel of individuals (Evonik's GRAS panel). Based on its review, Evonik's GRAS panel concluded that dried isomaltulose syrup is safe under the conditions of its intended use.

Based on the data and information summarized above, Evonik concludes that dried isomaltulose syrup is GRAS for its intended use.

Section 301(II) of the Federal Food, Drug, and Cosmetic Act (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 Evonik's notice concluding that dried isomaltulose syrup 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 dried isomaltulose syrup. Accordingly, our response should not be construed to be a statement that foods containing dried isomaltulose syrup, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Evonik provided, as well as other information available to FDA, we have no questions at this time regarding Evonik's conclusion that dried isomaltulose syrup is GRAS under its intended conditions of use. This letter is not an affirmation that dried isomaltulose syrup 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 000681 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**
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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