Debra Levine
Ingredion Incorporated
10 Finderne Avenue, Suite C
Bridgewater, NJ 08807

Re: GRAS Notice No. GRN 000818

Dear Ms. Levine:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000818. We received Ingredion's notice on October 4, 2018, and filed it on February 19, 2019. Ingredion submitted an amendment to the notice dated July 25, 2019, that provided additional information confirming that the product is produced in conformance with the food grade specifications described in the notice.

The subject of the notice is isomalto-oligosaccharides mixture (IMO) for use as a general purpose sweetener, such as a table-top sweetener, and to partially or completely replace added sweeteners in processed food products, and as a bulking agent at levels determined by current good manufacturing practice.[1] The notice informs us of Ingredion's view that these uses of IMO are GRAS through scientific procedures.

Our use of the term, "isomalto-oligosaccharides mixture" or "IMO," 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. The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "isomalto-oligosaccharides mixture."

Ingredion provides information regarding the identity and composition of IMO and describes it as a colorless or light yellow, transparent syrup. Ingredion states that although the term "isomalto-oligosaccharides" refers strictly to the glucosyl oligosaccharides containing α-(1-6)-linkages, commercially available IMO preparations are generally accepted as a mixture of glucosyl oligosaccharides with both α-(1-6) and α-(1-4)-linkages. The term has also been extended to include preparations containing glucosyl oligosaccharides with α-(1-6)-linkages together with small proportions of α-(1-

[1] Ingredion states that the intended uses exclude infant formula and foods under the jurisdiction of the United States Department of Agriculture.

3)- or α-(1-2)-linkages.[2]

Ingredion states that IMO is produced primarily by enzyme-catalyzed hydrolysis and transglycosylation of corn starch. Ingredion describes that the IMO preparation begins with a corn starch slurry. Calcium ions and α-amylase are added under a pH-controlled environment to create ideal conditions for liquefaction. The starch is gelatinized and partially hydrolyzed by heating. IMO is produced by adjusting the pH and temperature of the liquefied starch, and adding saccharification enzymes (α-amylase, pullulanase, and transglucosidase). The pH is then lowered to inactivate the enzymes and stop the reaction. The suspended solids and insoluble impurities are then removed by a vacuum drum filter with diatomite (i.e., "clarification" step). Next, activated carbon is added to remove any residual enzymes and corn proteins, as well as colors, odors, and other impurities (i.e., "decolorization step"). An ion-exchange resin is then used to remove any ionic impurities (e.g., salts, amino acids). Finally, an evaporator is used to reduce the water content and concentrate the mixture into a syrup. Ingredion states that a chromatography step may be used to remove the mono- and di-saccharides from the IMO preparation depending on the end use.

Ingredion states that it also produces a formulation of IMO where the liquefied starch is sequentially converted into dextrose by glucoamylase, then into high-fructose corn syrup (HFCS) by glucose isomerase. The HFCS is added back to the liquefied starch prior to being subjected to the saccharification reaction and subsequent processing steps. The resulting preparation contains approximately 30% fructose and 30% dextrose on a dried weight basis and has 80 to 85% of the sweetness of sucrose, which may be desired for certain food applications. Ingredion states that the corn starch and all processing aids are food-grade and meet the specifications established in the Food Chemicals Codex (11th edition).

Ingredion provides specifications for IMO. These include specifications for IMO content (minimum of 14% on a dry basis); Brix (minimum 75); pH (4.5 to 7); ash (sulfated) (maximum 0.3%); lead (≤ 0.1 mg/kg); and limits for microorganisms. Ingredion provides analytical data from 5 batches of nonconsecutive lots of the product, confirming the product can be produced in compliance with these specifications.

Ingredion states that IMO, which is the subject of GRN 000818, is intended for use as a general purpose sweetener and bulking agent in foods generally and serves as a replacement for other IMO ingredients that have been the subject of previous GRAS notices (GRN 000246 and GRN 000674)[3] and cites the exposure estimates included in those notices. Ingredion notes that in GRN 000246, it was estimated that the dietary exposure to a similar IMO would not exceed 30 g/person (p)/d based on the assumption

[2] Ingredion stated that IMO content is defined as IMO components with a degree of polymerization from 2 to 7 (i.e., isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltohexaose, and isomaltoheptaose). The remaining components are represented by monosaccharides (glucose) and the "malto-" forms of the glucosyl oligosaccharides that are present.

[3] Isomalto-oligosaccharide mixture was the subject of GRN 000246 and GRN 000674. We evaluated these notices and responded in letters dated February 10, 2009, and July 5, 2017, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

that individuals would consume only two servings daily of foods to which the ingredient has been added as a replacement for sucrose. Ingredion anticipates that the exposure to the IMO, which is the subject of GRN 000818, in the U.S. will be comparable to that for the subject of GRN 000246 (i.e., 30 g/p/d), given that the intended uses are similar.

Ingredion discusses published and unpublished studies on the metabolic fate of IMO, as well as toxicological and safety studies in animals and humans to support the safety of IMO. Ingredion reports that they conducted a comprehensive literature search on the safety of IMO through August 2018. Ingredion states that the components of IMO are normal constituents in the human diet and are present in honey and certain fermented foods such as miso, sake, and soy sauce. Ingredion discusses the metabolic fate of IMO and summarizes the published *in vitro* studies using rat jejunum and intestinal mucosa and *in vivo* studies in animals and humans. Ingredion states that ingestion of IMO in humans results in complete digestion with a high gastrointestinal tolerance.

Ingredion discusses a published acute oral toxicity study in which male Wistar rats were administered IMO by gavage with doses up to 44 g/kg bw. The oral LD50 value of IMO was estimated to be more than 44.0 g/kg bw. Ingredion discusses a published one-year oral toxicity study in rats fed 3% IMO in drinking water (approximately 3-5 g/kg bw/d). The results indicate that IMO was well tolerated and did not elicit any adverse treatment-related, toxicologically relevant effects. Ingredion states that published *in vitro* genotoxicity assays demonstrate that IMO is neither mutagenic nor genotoxic.

Ingredion describes published human studies using IMO, which is the subject of GRN 000818, that provides evidence of tolerability of 68.5 g of IMO syrup matched with control (dextrose solution) for 50 g of total carbohydrate content (~25 g IMO on a dry weight basis). Ingredion also summarizes several published and unpublished efficacy studies that did not report any toxicologically relevant adverse effects, providing further support for the safe use of IMO.

Based on the data and information described above, Ingredion concludes that IMO is GRAS for its intended use in food.

Standards of Identity

In the notice, Ingredion states its intention to use IMO 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.

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

Conclusions

Based on the information that Ingredion provided, as well as other information available to FDA, we have no questions at this time regarding Ingredion's conclusion that IMO is GRAS under its intended conditions of use. This letter is not an affirmation that IMO 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 000818 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.12.18 16:04:17 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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