818

Ingredion Incorporated
10 Finderne Avenue Suite C
Bridgewater, NJ 08807

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October 2, 2018

Dr. Paulette Gaynor
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Dr.
College Park, MD 20740

Dear Dr. Gaynor,

Re: Notification of GRAS Status for Bioligo™ Isomalto-oligosaccharides

In accordance with 21 CFR §170 Subpart E, Ingredion Incorporated ("Ingredion") is respectfully notifying the United States (U.S.) Food and Drug Administration (FDA) of their conclusion that Bioligo™ isomalto-oligosaccharides (IMOs) is Generally Recognized as Safe (GRAS) under its intended conditions of use.

The U.S. FDA has already issued "no questions" responses regarding the conclusion that other commercially available preparations of IMOs are GRAS for their intended uses in foods (GRN 246; GRN 674)[1]. Similar to these other preparations, Bioligo™ IMOs is produced by Ingredion through the enzyme-catalyzed transglycosylation of hydrolyzed corn starch. However, whereas other IMO preparations with GRAS status in the U.S. are intended for addition to a list of specified food categories at maximum use levels ranging from 5 to 100%, Ingredion's Bioligo™ IMOs are intended for use as a general-purpose sweetener and bulking agent in foods at levels determined by current Good Manufacturing Practices. As detailed in the GRAS notice, the available data and information support the conclusion that the intended uses of Bioligo™ IMOs are GRAS, based on scientific procedures.

One paper copy of the GRAS notice for Bioligo™ IMOs is included in this submission, and an electronic copy is available on the accompanying compact disc (CD). The electronic and paper copies of the GRAS notice are identical. The enclosed electronic files were scanned for viruses prior to submission and are certified as being virus-free.

Please do not hesitate to contact me if you have any questions or concerns regarding this GRAS notice.

Yours sincerely,

[redacted]

Debra Levine
Director, Product Assurance & Regulatory Affairs
debra.levine@ingredion.com
Ingredion Incorporated

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[1] A GRAS notice has also been recently submitted for another isomalto-oligosaccharide preparation, to which the FDA's response is still currently pending (GRN 779).

Notification of GRAS Status for Isomalto-oligosaccharides (Bioligo™)

Submitted by:
Ingredion Incorporated
10 Finderne Avenue, Suite C
Bridgewater, New Jersey
08807

Submitted to:
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD
20740

September 28, 2018

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List of Figures and Tables

Part 1. §170.225 Signed Statements and Certification

Ingredion Incorporated ("Ingredion") hereby submits this Generally Recognized as Safe (GRAS) notice in accordance with 21 CFR §170 Subpart E, §170.203 through §170.285, to the United States (U.S.) Food and Drug Administration (FDA). Ingredion has concluded that their Bioligo™ isomalto-oligosaccharides mixture is GRAS under its intended conditions of use and therefore it is not subject to the premarket approval requirements in Section 409 of the Federal Food, Drug, and Cosmetic Act.

Ingredion certifies that, to the best of their knowledge, this GRAS notice constitutes a complete, representative, and balanced submission that includes all relevant information, both favorable and unfavorable, known to Ingredion and pertinent to the evaluation of safety and GRAS status of the use of Bioligo™ isomalto-oligosaccharides.

Signed,

Oct 2, 2018

Debra Levine
Director, Product Assurance & Regulatory Affairs
debra.levine@ingredion.com
Ingredion Incorporated

Date

1.1 Name and Address of Notifier

Ingredion Incorporated
10 Finderne Avenue, Suite C
Bridgewater, New Jersey
08807

1.2 Name of Notified Substance

The substance that is the subject of this GRAS notice is isomalto-oligosaccharides (abbreviated as IMOs).

1.3 Intended Conditions of Use

Ingredion intends to market their isomalto-oligosaccharides mixture (Bioligo™ IMOs) as a food ingredient in the U.S., specifically, as a general-purpose sweetener and bulking agent. Bioligo™ IMOs are intended for use as a table-top sweetener, and to partially or completely replace added sweeteners in processed food products, at levels determined by current Good Manufacturing Practices.

Bioligo™ IMOs is not intended for addition to infant formula, or to meat and poultry products that are subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA).

1.4 Statutory Basis for GRAS

The conclusion of GRAS status for the intended uses of Ingredion's Bioligo™ IMOs is made through scientific procedures, in accordance with 21 CFR §170.30 (a) and (b) (U.S. FDA, 2018).

1.5 Availability of Information

The data and information that serve as the basis for the conclusion of the GRAS status for Ingredion's Bioligo™ IMOs will be made available to the FDA, if requested either during or after the evaluation of this GRAS notice. This data and information will be maintained at the address specified below:

Ingredion Incorporated
10 Finderne Avenue, Suite C
Bridgewater, New Jersey
08807

Upon request, Ingredion will allow the FDA to review and copy the data and information at the aforementioned address during customary business hours. Alternatively, Ingredion will provide the FDA with a complete copy of the data and information that are the basis for the conclusion of the GRAS status for Bioligo™ IMOs, either in an electronic format that is accessible for the FDA's evaluation, or on paper.

The data and information presented in Parts 2 through 7 of this notice do not contain any trade secret, commercial, or financial information that are privileged or confidential. Therefore, none of the data and information presented herein are exempt from the Freedom of Information Act, 5 U.S.C. Section 552.

Part 2. §170.230 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1 Identity

2.1.1 Common Name and Trade Names

Common Name: Isomalto-oligosaccharides (abbreviated as IMOs)

Trade Name: Bioligo™ IMOs

2.1.2 Chemical Name, Chemical Abstract Service (CAS) Number, and Structural Formula

Technically, even though the term "isomalto-oligosaccharides" refers strictly to 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 (Goffin *et al*., 2011). The term has also been extended to include preparations containing glucosyl oligosaccharides with α-(1,6)-linkages together with small proportions of α-(1,3)- or α-(1,2)-linkages (Goffin *et al*., 2011). IMOs occur naturally in honey and a variety of fermented foods, such as miso, sake, and soy sauce (White and Hoban, 1959; Hondo and Mochizuki, 1979; Nishino *et al.*, 1981; Nunokawa, 1981; Tungland and Meyer, 2002).

Ingredion manufactures their Bioligo™ IMOs syrup products through the enzyme-catalyzed transglycosylation of hydrolyzed starch. This method is also commonly used by other manufacturers for the commercial production of IMOs (Goffin *et al.*, 2011; Madsen *et al.,* 2017). Alternatively, IMOs can also be produced *via* bacterial fermentation of sucrose in the presence of a maltose acceptor mediated by a glucosyltransferase enzyme (*i.e.*, dextransucrase) (Goffin *et al.*, 2011; Madsen *et al.,* 2017). The identity of the major saccharide forms that are present in Ingredion's IMO preparations, including their chemical names, molecular formula, and Chemical Abstract Service registry number, are summarized in Table 2.1.2-1 below. The structural formulas of these constituents are presented in Figure 2.1.2-1.

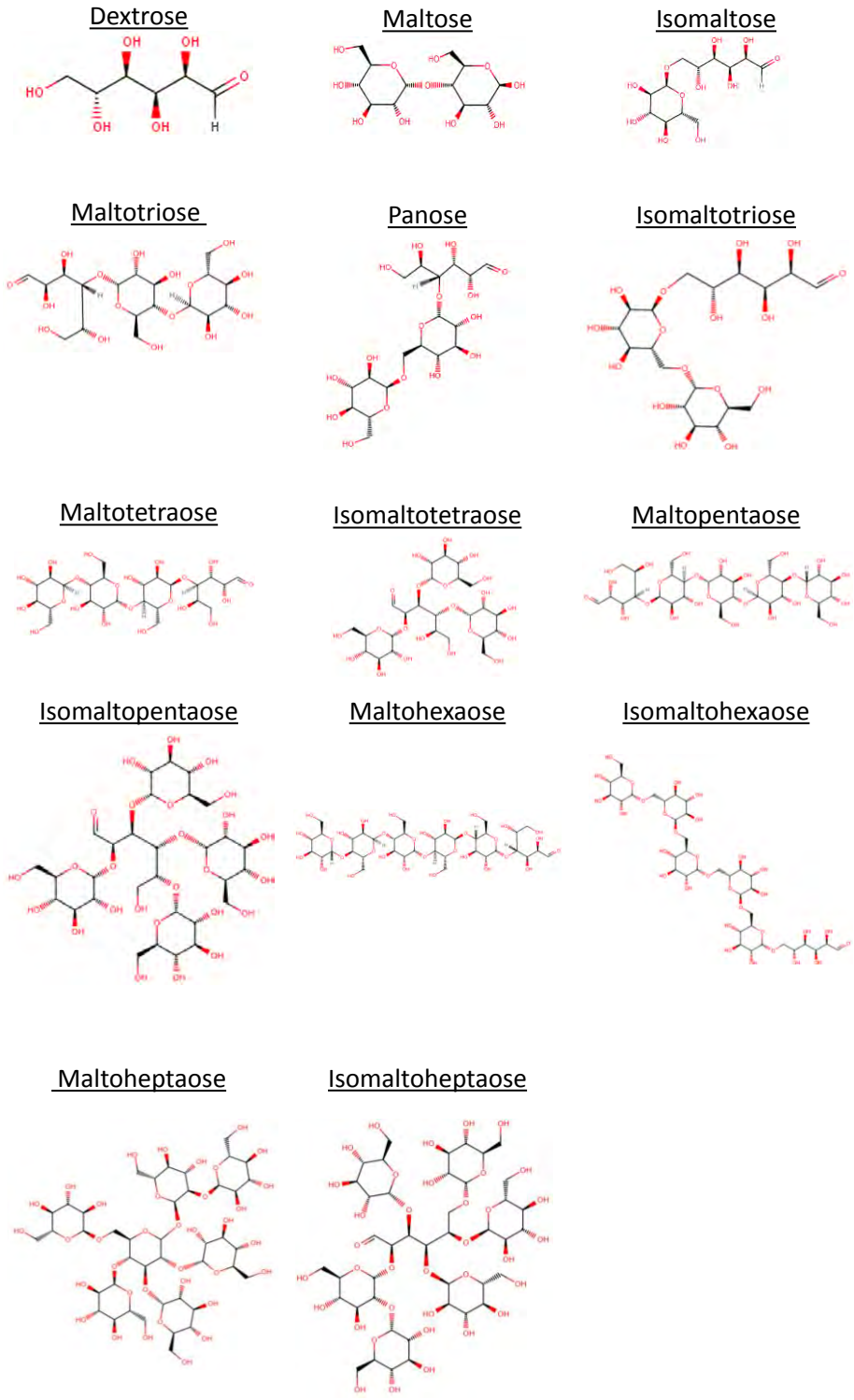
Table 2.1.2-1 Identity of the Major Saccharides in Bioligo™ IMOs

Degree of Polymerization (DP)[a]	Common Name	Chemical Name	Molecular Formula	CAS No.
DP1	D-Glucose	D-Glucose	$C_6H_{12}O_6$	50-99-7
DP2	Maltose	4-O-α-D-glucopyranosyl-D-glucose	$C_{12}H_{22}O_{11}$	69-79-4
	Isomaltose	6-O-α-D-glucopyranosyl-D-glucose	$C_{12}H_{22}O_{11}$	499-40-1
DP3	Maltotriose	O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-D-glucose	$C_{18}H_{32}O_{16}$	1109-28-0
	Isomaltotriose	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose	$C_{18}H_{32}O_{16}$	3371-50-4
	Panose	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,4)-D-glucose	$C_{18}H_{32}O_{16}$	33401-87-5
DP4	Maltotetraose	O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-D-glucose	$C_{24}H_{42}O_{21}$	34612-38-9
	Isomaltotetraose	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose	$C_{24}H_{42}O_{21}$	35997-20-7
DP5	Maltopentaose	O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-D-glucose	$C_{30}H_{52}O_{26}$	34620-76-3
	Isomaltopentaose	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose	$C_{30}H_{52}O_{26}$	6082-32-2
DP6	Maltohexaose	O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-D-glucose	$C_{36}H_{62}O_{31}$	34620-77-4
	Isomaltohexaose	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)- O-α-D-glucopyranosyl-(1,6)-D-glucose	$C_{36}H_{62}O_{31}$	6175-02-6
DP7	Maltoheptaose	O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-O-α-D-glucopyranosyl-(1,4)-D-glucose	$C_{42}H_{72}O_{36}$	1980-14-9
	Isomaltoheptaose	O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-O-α-D-glucopyranosyl-(1,6)-D-glucose	$C_{42}H_{72}O_{36}$	6513-12-8

CAS, Chemical Abstract Service; IMOs, isomalto-oligosaccharides

[a] Saccharides that have DP greater than 7 are present in Ingredion's IMO preparations but these have not been individually identified.

Figure 2.1.2-1 Structural Formula of the Major Saccharides in Bioligo™ IMOs



2.2 Method of Manufacture

2.2.1 Raw Materials and Processing Aids

Corn starch is the raw material used in the production of Ingredion's IMO preparations. The enzymes that catalyze the hydrolysis and trans-glycosylation of corn starch to produce the Bioligo™ IMOs are safe and accepted for such purposes (see Table 2.2.1-1). Other processing aids include the use of calcium chloride (liquefaction step), diatomite as a filter aid (clarification step), activated carbon (decolorization step), and ion-exchange resins. The corn starch and all of the processing aids employed are food-grade and meet the specifications established in the Food Chemicals Codex.

Table 2.2.1-1 Regulatory Status of the Enzymes Employed in the Production of Bioligo™ IMOs

Enzyme	Source	Regulatory Status in the U.S.
α-Amylase	Non-GM *Aspergillus oryzae*	α-Amylase is generally permitted for use in the modification of starch under 21 CFR §172.892 (U.S. FDA, 2018).
α-Amylase	Derived from *Bacillus licheniformis* carrying a gene encoding alpha-amylase from *Bacillus stearothermophilus*	α-Amylase is generally permitted for use in the modification of starch under 21 CFR §172.892 (U.S. FDA, 2018). α-Amylase from this source is concluded GRAS for use as a processing aid in the liquefaction of starch during the production of syrups[a] (GRN 24) (Novo Nordisk, 1999; U.S. FDA, 2000). The GRAS notice was issued a "no questions" response by the FDA.
Pullanase	Derived from *Bacillus licheniformis* carrying a gene encoding pullulanase from *Bacillus deramificans*	Pullanase is generally permitted for use in the modification of starch under 21 CFR §172.892. Pullanase from this source is concluded GRAS for use as a processing aid in the manufacture of starch hydrolysates and high fructose corn syrup[a] (GRN 72) (Genencor International Inc., 2001; U.S. FDA, 2001). The GRAS notice was issued a "no questions" response by the FDA.
Transglucosidase	Non-GM *Aspergillus niger*	Concluded GRAS for use in starch processing[a] by the supplier (Amano Enzyme Inc.).
Glucoamylase	Non-GM *Aspergillus niger*	Glucoamylase is generally permitted for use in the modification of starch under 21 CFR §172.892 (U.S. FDA, 2018).
Glucose isomerase	*Streptomyces rubiginosus* (self-cloned)	Affirmed GRAS for use in food with no limitation other than cGMP under 21 CFR §184.1372 (U.S. FDA, 2018).

CFR, Code of Federal Regulations; cGMP, current Good Manufacturing Practice; FDA, U.S. Food and Drug Administration; GM, genetically modified; GRAS, Generally Recognized as Safe; GRN, Generally Recognized as Safe (GRAS) notice; IMOs, isomalto-oligosaccharides; U.S., United States

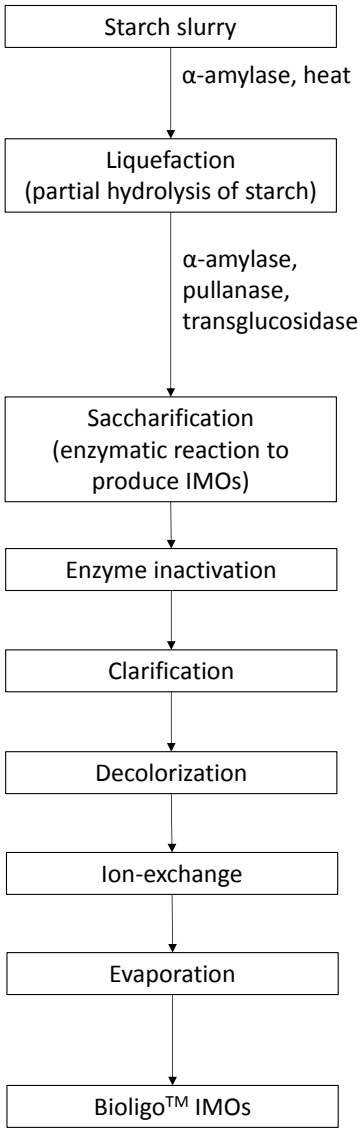
[a] At minimum levels necessary to accomplish the intended technical effect, in accordance with cGMP.

2.2.2 Manufacturing Process

The manufacturing process for Ingredion's Bioligo™ IMOs is outlined in the flowchart presented in Figure 2.2.2-1. The production of the IMO preparations begins with a corn starch slurry. Ideal conditions for liquefaction are created by adding calcium ions and a thinning enzyme (α-amylase) under a pH-controlled environment. The starch is gelatinized and partially hydrolyzed by heating. IMOs are produced by adjusting the pH and temperature of the liquefied starch, and adding saccharification enzymes (α-amylase, pullulanase, and transglucosidase). The pH is lowered to inactivate the enzymes and stop the reaction. The suspended solids and insoluble impurities are removed by vacuum drum filter with diatomite (*i.e.*, "clarification" step). Next, activated carbon is used to remove residual enzymes and corn proteins, as well as colors, odors and other insoluble/soluble impurities (*i.e.*, "decolorization step"). Ion-exchange resin is then used to remove ionic impurities (*e.g.*, salts, amino acids). An evaporator is used to reduce the water content and concentrate the mixture into a syrup.

Depending on the end use, Ingredion may apply a chromatography step to remove the mono- and di-saccharides from the Bioligo™ IMOs preparation. Ingredion also produces a formulation of Bioligo™ IMOs where following the liquefaction step, 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 before 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 it has 80 to 85% of the sweetness of sucrose, which may be desired for certain food applications.

Figure 2.2.2-1 Main Production Steps for Bioligo™ IMOs



2.3 Product Specifications

Considering that the Bioligo™ IMOs are produced by the enzyme-catalyzed transglycosylation of hydrolyzed corn starch, the resulting syrup is also largely composed of carbohydrates, with only trace amounts of proteins and fats present (<0.5% each), as indicated below in Table 2.3-1.

Table 2.3-1 Composition of Bioligo™ IMOs

Parameter	Typical Values
Total carbohydrates (g/100 g)[a]	74 to 75
Protein (g/100 g)	0.4
Total fat (g/100 g)	0.1

IMOs, isomalto-oligosaccharides
[a] Calculated as total solids in the Bioligo™ IMOs syrup. The remainder of the preparation is accounted for by water.

The specifications established by Ingredion for their Bioligo™ IMOs are presented in Table 2.3-2 below. The Bioligo™ IMOs are specified to contain a minimum Brix value of 75. Additionally, the Bioligo™ IMOs are specified to contain minimum 14% IMOs on a dry weight basis, with IMOs defined by Ingredion to include the "isomalto-" components with a degree of polymerization (DP) ranging from 2 to 7 (*i.e.*, isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose and isomaltoheptaose). The remaining components are represented by monosaccharides (glucose) and the "malto-" forms of the glucosyl oligosaccharides that are present. Maximum acceptable limits for lead and microbial contaminants are also included in the specifications. Of note, Ingredion manufactures their Bioligo™ IMOs in South Korea, and the preparations that are intended for use in the U.S. meets the regulatory specifications for IMOs as defined in South Korean *Standards and Specification for Foods*.

Table 2.3-2 Specifications for Bioligo™ IMOs

Parameter	Specification	Method of Analysis
Appearance	Colorless or light yellow, transparent syrup	Visual
Brix	Min. 75	Refractometer, at 20°C
IMO content[a] (% dry basis)	Min. 14	By HPLC
pH	4.5 to 7	10% solution
Ash (sulfated %)	Max. 0.3	Korea Food Codex
Lead (ppm)	Max. 0.1	Korea Food Codex
Standard Plate Count (cfu/g)	Max. 1,000	Korea Food Codex
Yeast and Mold (cfu/g)	Max. 100	Korea Food Codex
Escherichia coli (per 25 g)	Negative	Korea Food Codex
Salmonella (per 25 g)	Negative	Korea Food Codex

cfu, colony-forming units; HPLC, high-performance liquid chromatography; IMOs, isomalto-oligosaccharides; Max., maximum; Min., minimum; ppm, parts per million
[a] IMO content defined as IMO components from DP2 to DP7 (isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose, and isomaltoheptaose).

Part 3. 170.235 Dietary Exposure

3.1 Estimated Intake

Ingredion's Bioligo™ IMOs are intended to be used as a table-top sweetener, and as a partial or complete replacement for general-purpose sweeteners and bulking agent that are added to various processed foods. As mentioned, Bioligo™ IMOs will not be added to infant formula or to meat and poultry products that are regulated by the FSIS of the USDA.

Other commercially available preparations of IMOs have been concluded GRAS for their intended uses, which have been notified and issued a "no questions" response from the U.S. FDA [GRAS notice (GRN) 246; GRN 674)][1] (BioNeutra Inc., 2008, 2016; U.S. FDA, 2009, 2017). Ingredion's Bioligo™ IMOs are intended to serve as a replacement for these other IMO preparations, given that they may also be used in foods as alternative sweeteners and bulking agents. For instance, BioNeutra Inc. ("BioNeutra") has concluded that their Vitasugar™ IMO is GRAS for use as an alternative sweetener in range of specified foods at maximum levels ranging from 1.5 to 15 g/serving (GRN 246) (BioNeutra Inc., 2008; U.S. FDA, 2009). Similar to Ingredion's Bioligo™ IMOs, BioNeutra manufactures Vitasugar™ through the enzyme-catalyzed transglycosylation of hydrolyzed starch, but with an additional yeast fermentation step included during the final processing steps to reduce the content of monosaccharides (glucose). In a subsequent notice, BioNeutra Inc. also concluded that another IMO preparation (termed "VF-DP3-IMO"), which is obtained using the same production process as Vitasugar™ but with an additional filtration step to remove the mono- and disaccharides, is GRAS (GRN 674) (BioNeutra Inc., 2016; U.S. FDA, 2017).

To estimate the exposure to Bioligo™ that would occur from its intended uses as a general-purpose sweetener in foods in the U.S., comparisons can be drawn to the intake estimates of added sugars from the diet. The Dietary Guidelines for Americans 2015-2020 (DGA) recommends that the daily dietary intake of added sugars[2] should be limited to less than 10% of total calories (U.S. DHHS & USDA, 2015; USDA/DHHS, 2015). Based on a 2,000 kcal diet, and a caloric value of 4 kcal/g for digestible carbohydrates, this corresponds to a daily reference value of 50 g of added sugars per day for adults and children ≥4 years and older (21 CFR §101.9;

[1] A GRAS notice has also been submitted by Baolingbao Biology Co., Ltd. for the use of IMOs in a variety of specified foods at inclusion levels ranging from 5 to 100% (GRN 779). As of September 2018, the FDA's response to this notice is still indicated as "pending", and no further details are available for review by Ingredion.

[2] In the DGA, added sugars are defined as "*Syrups and other caloric sweeteners used as a sweetener in other food products. Naturally occurring sugars such as those in fruit or milk are not added sugars. Specific examples of added sugars that can be listed as an ingredient include brown sugar, corn sweetener, corn syrup, dextrose, fructose, glucose, high-fructose corn syrup, honey, invert sugar, lactose, malt syrup, maltose, molasses, raw sugar, sucrose, trehalose, and turbinado sugar*".

U.S. FDA, 2016). The National Cancer Institute has estimated the usual intake of added sugars using data collected from the 2007-2010 National Health and Nutrition Examination Survey (NHANES) (NCI, 2018). A subset of the data is reproduced in Table 3.1-1 below. Amongst the total population (age 1 year and older), the mean and 90th percentile intake of added sugars was estimated at 67 g/day and 122 g/day, respectively. Additionally, the USDA recently conducted analysis on the intake of added sugars using the day 1 dietary data collected from the What We Eat in America component of the 2013-2014 cycle of the NHANES (Bowman *et al.*, 2017). From the 1-day data, it was estimated that for all individuals age 2 years and older, the mean intake of added sugars was estimated at 17.4 teaspoon equivalents (tsp. eq.) or 73 g (Bowman *et al.*, 2017).

Although the Bioligo™ IMOs are intended for use as a general-purpose sweetener, they will not completely replace all of the added sugars that are currently in the food supply. In the GRAS notice for Vitasugar™, it was estimated that intake of Vitasugar™ would not exceed 30 g/person/day on the assumption that individuals would consume only 2 servings daily of foods to which Vitasugar™ has been added as a replacement for sucrose (GRN 246) (BioNeutra Inc., 2008; U.S. FDA, 2009). It is anticipated that the exposure to Bioligo™ IMOs in the U.S. will be in comparable ranges as those that have been estimated for Vitasugar™ (*i.e.*, 30 g/person/day), given that they are intended for similar uses in foods.

Table 3.1-1 Daily Intake of Added Sugar Estimated by the NCI Using NHANES 2007-2010

Population Group	Age Group (years)	Number of Persons in Sample	Intake of Added Sugars (g/day)[a,b]	
			Mean	90th percentile
Male	1 to 3	774	38	63
	4 to 8	1001	63	98
	9 to 13	850	86	152
	14 to 18	808	98	171
	19+	5,623	78	142
Females	1 to 3	715	34	57
	4 to 8	894	57	90
	9 to 13	867	71	119
	14 to 18	727	70	118
	19+	5,858	57	100
Total	**1+**	**18,117**	**67**	**122**

NCI, National Cancer Institute; NHANES, National Health and Nutrition Examination Survey

[a] The NCI presented the intake of added sugar as teaspoons per day. The values were converted to grams per day by Ingredion using the assumption noted by NCI that 1 teaspoon of added sugar is equivalent to the same amount of total sugars as 1 teaspoon (4 g) of table sugar (sucrose).

[b] Added sugars are defined in the Food Patterns Equivalents Database (2007-2008; 2009-2010) as "*sugars that are added to foods as an ingredient during preparation, processing, or at the table. Added sugars do not include naturally occurring sugars such as lactose present in milk and fructose present in fruits. Examples of added sugars include brown sugar, cane sugar, confectioners' sugar, granulated sugar, dextrose, white sugar, corn syrup and corn syrup solids, molasses, honey, and all types of syrups such as maple syrup, table syrups, and pancake syrup*" (Bowman *et al*., 2013a,b).

Part 4. §170.240 Self-Limiting Levels of Use

Ingredion's Bioligo™ IMOs will be added to foods only at levels needed to achieve its functions as a general-purpose sweetener and bulking agent, in order to achieve the desired texture and/or flavor profile in the final product. The addition of Bioligo™ IMOs will be self-limiting for technological reasons, as excessively high levels can lead to attributes (*e.g.,* excessive sweetness) that could negatively impact consumer acceptability.

Part 5. §170.245 Experience Based on Common Use in Food Before 1958

Not applicable. The GRAS status of the notified substance, Bioligo™ IMOs, for its intended uses in foods is established through scientific procedure.

Part 6. §170.250 Narrative on Safety

6.1 Introduction

IMOs (*e.g.*, isomaltose, panose, isomaltotriose) have a history of safe consumption in humans, being present in honey and certain fermented foods such as miso, sake, and soy sauce (White and Hoban, 1959; Hondo and Mochizuki, 1979; Nishino *et al*., 1981; Nunokawa, 1981; Tungland and Meyer, 2002). Commercially available preparations of IMOs have also been marketed as components of foods in the U.S. and other countries globally. Similar to many of these preparations, Ingredion's Bioligo™ IMOs are produced from the enzyme-catalyzed transglycosylation of hydrolyzed food-grade, edible starch. As described in Part 2.2.1, all of the enzymes that are used in the production of Ingredion's IMO preparations are safe and suitable for such purposes.

The safety of IMOs is largely supported then by the fact that they are hydrolyzed food starches (*i.e.*, glucose syrups) wherein a proportion of the α-(1,4)-glycosidic linkages has been converted to α-(1,6)-forms. Even so, a number of preclinical and clinical studies have been conducted with IMO preparations, which demonstrate the safety and tolerability of these materials. The saccharide composition of the test articles used differs across these studies, reflecting the variability in the composition of the IMO preparations that are available on the market.

Nevertheless, while there are quantitative differences in the relative proportions of the individual "isomalto-" and "malto-" oligosaccharides in the IMO preparations, qualitatively, it is the same saccharide components that are present. While such differences could potentially influence digestibility, they are not expected to have any significant impact on the overall safety profiles of the IMO preparations, as discussed further below.

To identify the information relevant to the safety of Ingredion's Bioligo™ IMOs and its IMO components, comprehensive and detailed searches of the published scientific literature were conducted through August 2018. All of the pivotal data and information used to establish the safety of Ingredion's Bioligo™ IMOs under their intended conditions of use as a general-purpose sweetener and bulking agent in foods are "generally available" (*i.e.*, in the public domain), and none are exempt from disclosure under the Freedom of Information Act. A listing of the data and information discussed herein is provided in Part 7 of the GRAS notice.

6.2 Digestibility and Tolerability of IMOs

6.2.1 Considerations Regarding the Digestibility of IMOs

The metabolic fate of starch carbohydrates has been well established. The digestion of starch first begins in the mouth by the action of salivary amylases and continues to occur in the small intestines through the action of pancreatic amylases (IOM, 2005; Barrett *et al*., 2010; Hall, 2011). Dietary starch typically consists of a mixture of amylose [*i.e.*, linear chains of glucose joined by α-(1,4)-linkages] and amylopectin [*i.e.*, amylose chains with α-(1,6)-linked side branches] (Barrett *et al*., 2010; Flint *et al.*, 2012). Salivary and pancreatic amylases readily hydrolyze the α-(1,4)-linkages of the starch polysaccharides, but not α-(1,6)-linkages or the terminal α-(1,4)-linkages (Barrett *et al*., 2010). As a result, amylase digestion of starch results in the formation of α-limit dextrins [*i.e.*, polymers containing approximately 8 glucose units with 1 or more α-(1,6) linkages], as well as smaller disaccharides (*e.g.*, maltose) and trisaccharides (*e.g.*, maltotriose) (IOM, 2005; Barrett *et al*., 2010). The starch derivatives are further digested by enzyme complexes, such as sucrase-isomaltase, maltase-glucoamylase, and α-limit dextrinase that are bound to the brush border membranes of the enterocytes lining the villi of the small intestines (IOM, 2005; Barrett *et al*., 2010; Abumrad *et al.*, 2016). These enzymes are responsible for degrading the α-limit dextrins, as well as the di- and trisaccharides, into their glucose constituent for uptake and utilization (IOM, 2005; Barrett *et al*., 2010; Hall, 2011). Any carbohydrates that escapes digestion in the upper gastrointestinal tract will ultimately pass through into the colon where they can undergo fermentation by the local microflora to release gases (hydrogen, carbon dioxide, and methane) and short-chain fatty acids (acetate, propionate, and butyrate) (Cummings and Macfarlane, 1991; Flint *et al.*, 2012; den Besten *et al.*, 2013).

The digestibility of any given IMO constituent will likely vary depending on factors such as its configuration of glycosidic linkages and its size (*i.e.*, DP). For instance, using the rat jejunum loop method, Kaneko *et al.* (1995) reported that IMOs with increasing molecular weight became increasingly indigestible, but that the digestibility of the disaccharide component (*i.e.*, isomaltose) is similar to those of sucrose or maltotriose. The ability of rat intestinal mucosa enzymes to hydrolyze IMOs has been demonstrated using an *in vitro* model of digestion, though hydrolysis appears to occur at a markedly lower rate than that of maltose or isomaltose (Kaneko *et al.*, 1992). Studies in humans also suggest that IMO preparations are at least partly digestible. In 6 healthy male subjects, Kohmoto *et al*. (1992) have estimated that a ^{13}C-labeled IMO mixture delivered 70 to 80% of the calorific value of maltose. As described further in Part 6.2.2, it has been demonstrated that Bioligo™ IMOs produces similar post-prandial glycemic and insulinemic responses as a dextrose control providing equivalent amounts of carbohydrates, suggesting that the IMOs in Ingredion's product are in fact digestible and caloric (Gourineni *et al*., 2018). Similar findings have also been reported for other IMO preparations (FSA, 2012; Madsen *et al.*, 2017; Lowery *et al.*, 2018).

Overall, it is generally recognized that IMO preparations are a mixture of carbohydrates comprising both digestible and digestion-resistant saccharides (FSA, 2012; Health Canada, 2012; FSANZ, 2017a,b). There is evidence to suggest that some IMO preparations may contain digestion-resistant fractions that remain available for fermentation by the colonic microflora [*e.g.*, reviewed by Goffin *et al*. (2011) and Sorndech *et al.*, (2018)]. However, ingestion of Bioligo™ IMOs did not result in any increase in breath hydrogen excretion in comparison to the dextrose control (described further in Part 6.2.2), suggesting that colonic fermentation did not occur (Gourineni *et al*., 2018). Together with the results of the post-prandial glycemic and insulinemic response assessments, these data provide support that the saccharides in Bioligo™ IMOs are largely digestible, and accordingly, they are unlikely to reach the large intestines and undergo fermentation.

6.2.2 Clinical Studies Conducted with Bioligo™ IMOs

Ingredion has conducted 2 randomized, double-blinded, placebo-controlled, cross-over clinical studies in which the glycemic and insulinemic responses were examined following the ingestion of Bioligo™ IMOs. One of these studies also included an assessment of gastrointestinal tolerability. The Bioligo™ IMOs employed as test articles in these studies are the preparations with the content of IMOs[3] in the high-end of the specification range (*i.e.*, 50 to 70% on a dry weight basis). The results of these studies have been recently published by Gourineni *et al*. (2018) and are summarized below.

In 1 study, 26 healthy adult men and women (mean age: 39.9±1.9 years) consumed either 54.7 g of dextrose (control) or 68.5 g of the Bioligo™ IMOs syrup (Gourineni *et al*., 2018). The 2 test articles were matched to contain a total carbohydrate content of 50 g, and the Bioligo™ IMOs used in the study provided approximately 25 g of IMOs on a dry weight basis[4]. The test articles were mixed in 237 mL water and consumed as a single bolus dose on 2 separate occasions with a 1-week washout period in between. Blood samples were collected for serum glucose and insulin measurements *via* an indwelling venous catheter or venipuncture 15 minutes prior to the ingestion of the test articles (fasted state), and at 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes post-ingestion. Additionally, a breath sample was collected for evaluation of hydrogen excretion at 8, 12, and 24 hours following ingestion of the test articles. The samples at 8 and 12 hours were collected by the participants at home, while the 24-hour collection was conducted at the clinic. The participants were given a standardized lunch (low fiber/low dairy), snack, and dinner on the test days. To assess gastrointestinal (GI) tolerability, the participants completed a questionnaire where they were asked to rate the frequency of occurrence for 6 selected GI symptoms (nausea, GI rumblings, abdominal pain, bloating, flatulence, and diarrhea) over the 24-hour period following administration of the test article. The GI symptoms were scored as follows: 0 = none, 1 = no more than usual, 2 = somewhat more than usual, and 3 = much more than usual. A composite score was also calculated as the sum of the 6 individual GI symptom ratings, for a total possible score of 0 to 18.

[3] The IMO content is defined by Ingredion to include the IMO components ranging from DP2 to DP7 (isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose, and isomaltoheptaose).

[4] The Bioligo™ IMOs test article used in this study contains an IMO content of approximately 50% on a dry weight basis.

The incremental area-under-the-curve (iAUC) for postprandial glucose or insulin from 0 to 4 hours following the consumption of Bioligo™ IMOs was generally comparable to the dextrose control. The iAUC from 0 to 4 hours for glucose was slightly lower for Bioligo™ IMOs when compared to dextrose (194.8±20.1 *vs.* 230.0±22.8; p = 0.058), which appears to be driven by the significantly lower iAUC from 2 to 4 hours (5.9±3.1 *vs*. 18.6±7.2; p = 0.008). Moreover, the peak blood glucose concentrations achieved and time to reach this maximum was comparable between the 2 groups. No significant differences were observed in the 24-hour breath hydrogen excretion following the ingestion of Bioligo™ IMOs when compared to the dextrose control, suggesting the saccharides in Bioligo™ IMOs did not undergo colonic fermentation. With regard to GI tolerability, there was no statistically significant difference in the mean composite score between the control and Bioligo™ IMOs treatment (1.42 *vs.* 1.38, respectively). Moreover, the proportion of individuals with scores ≥2 ("somewhat more than usual" and "much more than usual") for each of the 6 GI symptoms rated did not significantly differ between groups. Therefore, a single bolus dose of Bioligo™ IMOs (68.5 g of the syrup) was well tolerated.

In the second study, 10 healthy adult men and women (mean age: 33.9±3.5 years) consumed either 54.7 g of dextrose (control), 66.3 g of Bioligo™ IMOs syrup, or 66.0 g of the Bioligo™ IMOs syrup which has undergone an additional chromatographic separation step to remove the mono- and di-saccharides (Gourineni *et al*., 2018). The test articles were all matched to contain a total carbohydrate content of 50 g. The Bioligo™ IMOs syrup, and the version that has been filtered, provided approximately 25 g and 35 g of IMOs on a dry weight basis, respectively[5]. The test and control products were mixed in 250 mL water and consumed as a single bolus dose on 3 separate days over a period of 2 to 3 weeks, with at least 1 day in between tests. Two fasting blood samples were collected by finger-prick, and samples were obtained again at 15, 30, 45, 60, 90, and 120 minutes following consumption of the test articles. As with the first study described in the publication, the iAUC values for glucose from 0 to 2 hours following the ingestion of the 2 Bioligo™ IMOs syrups were comparable to those observed in the dextrose control. The results of the post-prandial glycemic and insulinemic responses from these 2 clinical studies suggest that the Bioligo™ IMOs are digestible and caloric.

[5] The Bioligo™ IMOs test article (unfiltered) used in this study contains an IMO content of approximately 50% on a dry weight basis, while the preparation that has undergone chromatographic separation to remove the mono- and disaccharides contains an IMO content of approximately 70% on a dry weight basis.

6.2.3 Clinical Studies on the Tolerability of Other IMO Preparations

Several clinical studies have been conducted where other IMO preparations were administered to human subjects for durations ranging from 7 days to as long as 8 weeks. These studies have been extensively reviewed and discussed in the previous GRAS notices submitted for IMOs (GRN 246; GRN 674) (BioNeutra Inc., 2008, 2016; U.S. FDA, 2009, 2017), and by authoritative bodies during their safety assessment of IMOs, including Health Canada, the Food Standards Australia New Zealand (FSANZ), and the Advisory Committee on Novel Foods and Processes (ACNFP) of the Food Standards Agency in the United Kingdom (see Part 6.4 of this GRAS notice). The main outcomes of these studies, as they relate to gastrointestinal tolerability, are summarized in Table 6.2.3-1. The study conducted by Ingredion on their Bioligo™ IMOs is also included for comparison.

Oku and Nakamura (2003) has reported that administration of an IMO preparation at up to 40 g as a single bolus dose was well tolerated, with none of the subjects reporting any adverse gastrointestinal symptoms. These same authors have also cited an earlier reference (Oku and Okazaki, 1999) where the maximum single bolus dose of IMOs that can be consumed without causing transitory osmotic diarrhea was derived as >1.5 g/kg body weight (Oku and Nakamura, 2002; Oku and Nakamura, 2003). For a 70-kg individual, this corresponds to approximately 105 g of IMOs. In another study conducted to investigate the glycemic response, ingestion of whey protein bars containing IMOs (up to 50 g IMOs) as a single bolus dose did not result in any significant differences in the subjective ratings of hypoglycemia, dizziness, headache, fatigue, or stomach upset when compared to an equivalent dose of the dextrose placebo (up to 50 g) (Grubic *et al.*, 2018). For comparison, as described in Part 6.2.2, a single bolus dose of Ingredion's Bioligo™ IMOs syrup at 68.5 g, which provided approximately 50 g carbohydrates (or approximately 25 g of IMOs on a dry weight basis), was also well tolerated (Gourineni *et al*., 2018).

In repeated-dose studies, administration of IMO preparations at up to 30 g/day was generally well tolerated, with no adverse gastrointestinal symptoms (including diarrhea) reported (see Table 6.2.3-1). In an unpublished study conducted by BioNeutra which was described in GRN 674 (BioNeutra Inc., 2016; U.S. FDA, 2017), the incidence of diarrhea occurring at any point of the 4-week study was higher (but not statistically significant) in the group administered the highest dose of the Vitasugar™ IMO preparation of 54 g/day taken as 3 divided daily doses, when compared to the control group (*i.e.*, 7 out of 19 subjects *vs*. 2 out of 19 subjects). It was further noted that there was a significant increase in the severity of diarrhea among the group receiving 54 g/day of the IMO preparation at Week 1 when compared against baseline, but this did not occur at Weeks 2 through 4. However, it was stated in the GRAS notice that:

"*The authors determined that the results of the study suggest a threshold dose of 36 g/day based on the increased severity of diarrhea in the 54 g/day dose group. This is conservative since severity of diarrhea is subjective, only occurred during week 1, and was only significantly different from baseline and not from controls. This increase in severity of diarrhea in the 54 g/day dose group is unlikely to be related to the dose of IMO and the true threshold for tolerability of IMO may be 54 g/day under the conditions of this study*".

Overall, these clinical studies demonstrate that IMO preparations in general are well tolerated, thereby further supporting that the intended uses of Bioligo™ IMOs as a general-purpose sweetener and bulking agent in foods would not be associated with adverse effects.

Table 6.2.3-1 Summary of the Safety and Tolerability Related Outcomes Assessed in Clinical Trials Conducted with IMO Preparations

Reference	IMO Dose Level[a]	Duration of Intervention	Study Population	Safety-Related Outcomes
Gourineni *et al*. (2018)	IMO: 68.5 g of **Bioligo™ IMOs** Placebo: dextrose Matched for carbohydrate content (50 g)	Single bolus dose with 1-week washout period	26 healthy adults (M & F; mean age 39.9±1.9 y)	• NSD in mean composite GI tolerance scores • NSD in the proportion of individuals with frequency scores of ≥2 ("somewhat more than usual" or "much more than usual") for each of the 6 individual GI symptoms assessed (nausea, bloating, rumblings, flatulence, abdominal pain, and diarrhea)
Oku and Nakamura (2003)	IMO: 10, 20, or 40 g FOS and GS were also tested (10 or 20 g)	Single bolus dose, 4- to 7-day washout period in between doses	38 healthy adults (9 M & 29 F; mean age: ~23 to 26 y)	• None of the subjects experienced gastrointestinal symptoms following ingestion of IMOs (10, 20, or 40 g)
Grubic *et al.* (2018)	IMO: Whey protein bar containing 25 g IMO Placebo: 25 g dextrose	Single bolus dose, 7- to 10-day washout period in between doses	20 healthy adults (10 M & 10 F; mean age: 24.3±4.2 y)	• NSD in subjective ratings of hypoglycemia, dizziness, headache, fatigue, or stomach upset
	IMO: 2 servings of a whey protein bar containing 25 g IMO each (50 g IMO total) Placebo: 50 g dextrose	Single bolus dose, 7- to 10-day washout period in between doses	10 healthy adults (6 M & 4 F; mean age: 26.3±3.2 y)	• NSD in subjective ratings of hypoglycemia, dizziness, headache, fatigue, or stomach upset

Table 6.2.3-1 Summary of the Safety and Tolerability Related Outcomes Assessed in Clinical Trials Conducted with IMO Preparations

Reference	IMO Dose Level[a]	Duration of Intervention	Study Population	Safety-Related Outcomes
Bouhnik *et al*. (2004)	IMO: 10 g/d Placebo: 10 g/d (contained 50% sucrose and 50% digestible maltodextrin) Taken as 2 divided daily doses	7 days	8 healthy adults (M & F)	• None of the subjects experienced diarrhea. NSD in the subjective ratings of GI symptom intensity.
Kohmoto *et al*. (1988)	IMO: 20 g/d No placebo control group included	10 days	6 healthy adults (M only; 26 to 48 y)	• None experienced diarrhea. • Transient ↑ in flatulence in 2/24 subjects.
		14 days	18 healthy adults (5 M, 13 F; 50 to 93 y)	
Kaneko *et al*. (1993)	IMO: 10 or 15 g/d No placebo control group included	3 weeks	31 healthy adults, some with a history of constipation (9 M, 22 F; mean age: ~27 to 30 y)	• No gastrointestinal disturbances.
Wang *et al*. (2001)	IMO: 30 g/d in 2 divided daily doses No placebo control group included	28 days	20 adults on hemodialysis with constipation (8 M, 12 F; ~64 y)	• 5% of patients reported diarrhea, 10% abdominal distention, 10.5% tormina,6.1% from borborgymi, and 4.5% from abdominal spasm. None dropped out from the study as a result of these GI symptoms. • No changes in clinical chemistry of concern. Changes to lipid profile, hemoglobin and hematocrit were considered to be beneficial effects by the study authors.
Chen *et al*. (2001)	Control: low-fiber diet Test: low-fiber control diet, but with IMO added to afternoon dessert. IMO dose ↑ from 8 to 24 g/d (3.3 to 10 g of "active" IMOs[b]) during the first 10 days	30 days	7 elderly constipated patients in a nursing home (M only; ≥60 y)	• No complaints of diarrhea and bloating.

Table 6.2.3-1 Summary of the Safety and Tolerability Related Outcomes Assessed in Clinical Trials Conducted with IMO Preparations

Reference	IMO Dose Level[a]	Duration of Intervention	Study Population	Safety-Related Outcomes
Yen *et al.* (2011)	Placebo: fructose syrup Test: IMO consumed as an afternoon beverage. Dose ↑ from 11 to 22 g/day (5 to 10 g/day of "active" IMOs[c]) during the first 7 days	8 weeks	13 elderly adults with constipation in a nursing home (5 M, 8 F; mean ± SEM age: 82.5±1.9 y)	• NSD in bw, plasma albumin, glucose, triglyceride, HDL-Ch, urea nitrogen, creatinine, and ALT. • Evidence of improved laxation during IMO intervention (SS ↑incidence of spontaneous defecation; SS ↑ wet and dry fecal mass)
BioNeutra's unpublished study on Vitasugar™ (cited in GRN 674)	Placebo: 36 g/d of dextrose Test: 36 g and 54 g/d of IMO preparation Taken as 3 divided daily doses	4 weeks	60 healthy adults (18 to 65 y)	• NSD in bw, vital signs, hematology or clinical chemistry parameters between groups. • No changes in bowel habits (ease of defecation, # of bowel movements per day) • ↑ incidence of diarrhea in the high-dose group than in the controls (7 out of 19 *vs*. 2 out of 19); SS ↑ severity of diarrhea in high-dose group at Week 1 *vs*. baseline • NSD in frequency of subjects reporting an AE; no serious AEs reported during the study

AE, adverse event; ALT, alanine aminotransferase; bw, body weight; F, females; FOS, fructo-oligosaccharide; g/d, grams per day; GI, gastrointestinal; GRN, Generally Recognized as Safe (GRAS) notice; GS, galactosyl-sucrose; HDL-Ch, high-density lipoprotein cholesterol; IMO, isomalto-oligosaccharide; M , males; NSD, no statistically significant differences; SEM, standard error of the mean; SS, statistically significant; y, years of age

[a] Some of the studies may have also administered other carbohydrate test articles. Only the IMO test article and the placebo control (if one was included in the study) are described in this table.

[b] Active components were described by the study authors as isomaltose, panose, isomaltotriose, isomaltotetraose, and dextrin.

[c] The test article contained 45% w/w of the "active" components, including isomaltose (11.7%), panose (26.2%), isomaltotriose (1.95%), and isomaltotetraose (5.15%).

6.3 Toxicological Studies

A number of preclinical studies have been conducted which demonstrate that IMOs in general do not pose any concerns for systemic toxicity. The preclinical dataset available on various IMO preparations have been extensively reviewed and discussed elsewhere (ACNFP, 2008; GRN 246 – BioNeutra Inc., 2008; U.S. FDA, 2009; GRN 674 – BioNeutra Inc., 2016; U.S. FDA, 2017; FSANZ, 2017a), and a summary is provided herein.

Kaneko *et al.* (1990) has conducted a series of toxicological testing on an IMO preparation. No evidence of mutagenicity was reported for the IMO preparation when it was tested using the Ames assay in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA, in either the presence or absence of metabolic activation (Kaneko *et al*., 1990). Additionally, IMOs did not induce chromosome aberrations in Chinese hamster lung cells in either the presence or absence of metabolic activation (Kaneko *et al*., 1990). IMOs are also not acutely toxic, with Kaneko *et al*. (1990) reporting the median lethal dose (LD_{50}) to be greater than 44 g/kg body weight in male Wistar rats following gavage administration of an IMO mixture. In this study, following an overnight fast, the animals (6/dose) were administered a 60% w/w solution of the IMO mixture in water at doses of 14.5, 22.0, 31.1, or 44.0 g IMO/kg body weight. The animals were observed for 14 days after dosing. Two of the 6 animals receiving 44 g/kg body weight of IMOs died within 24 hours of dosing in this study, and other clinical signs observed at the high-dose group included diarrhea, decrease of voluntary movements, prone position, and changes in respiration. The study authors indicated that these effects were not specific to the administration of IMOs as they are also frequently observed when a large amount of hypertonic sugar solution is administered. Similarly, in their assessment of this study, FSANZ noted that:

> "*The clinical signs described are consistent with the very large dose of IMO causing death by a physical rather than a toxicological mechanism. The highest administered dose in rats (44 g/kg bw) would be the equivalent of a 70 kg human receiving a bolus dose of 3 kg directly into the stomach*" (FSANZ, 2017b).

Additionally, Kaneko *et al.* (1990) concluded that no adverse effects were observed in male Wistar rats receiving IMOs in their drinking water for 12 months. In this study, the animals (32/group) received either drinking water alone (control), or drinking water containing 3% of an IMO preparation, which provided approximately 3 to 5 g IMO preparation/kg body weight/day. The animals were 5 weeks old at the start of the study, and they had *ad libitum* access to commercially available rat feed. Body weight was assessed at 1, 3, 6, 9, and 12 months. At 1, 3, 6, and 12 months, 8 rats from each group were terminated. Blood samples were collected for the analysis of serum biochemistry and hematology parameters, and histopathological examination was conducted at necropsy. There was a slight reduction in body weight (<4%) in the IMO group during months 1, 3, and 6 (statistical significance not reported), but no remarkable differences were observed for the remainder of the study. There were a few statistically significant differences in the levels of some of the serum biochemistry and hematology parameters among the animals receiving the IMO preparation when compared to controls. These were limited to a decrease in the levels of hemoglobin, hematocrit, and alanine aminotransferase

(ALT) at study completion, a decrease in blood urea nitrogen at the 1-month endpoint, and higher lymphocyte counts (total and individual subsets) during the first 3 months. However, no abnormalities were observed upon gross and histopathological examination, and the findings were not correspondingly observed at later time points, suggesting that they are not toxicologically relevant. Overall, the study authors concluded that "*it is considered that toxicity is very low in long term consumption of isomaltooligosaccharide*".

A number of other repeated-dose studies have been conducted where IMO preparations were administered in animal models (*e.g.*, Kaneko *et al*., 1992; Ohta *et al.*, 1993; Ly *et al.*, 1999; Chai and Rhee, 2001; Day and Chung, 2004; Sung *et al.*, 2004; Ketabi *et al.*, 2011). Although only a limited number of endpoints relevant to safety were assessed in these studies, administration of IMOs were reported to be without any overt signs of toxicity.

6.4 Safety Assessments Conducted by Authoritative Bodies

In addition to the "no questions" responses issued by the U.S. FDA on the GRAS status of other IMO preparations (GRN 246; GRN 674) (BioNeutra Inc., 2008; U.S. FDA, 2009, 2017; BioNeutra Inc., 2016), commercially available IMO preparations are accepted for use as an ingredient in foods in various countries globally. The safety assessments that have been conducted by several major authoritative bodies on the use of IMO preparations as food ingredients are summarized below as representative examples. These assessments help to further support that the safety of IMOs is well established.

6.4.1 Canada

Health Canada has indicated that they had no objections to the use of BioNeutra's IMO preparation (VitaFiber™) as a novel food (Health Canada, 2012). According to its listing in Health Canada's inventory of approved novel foods, the IMO preparation contains less than 5% glucose and more than 90% isomaltose and oligosaccharides. IMOs may be added to a variety of foods including, but not limited to, baked goods and baking mixes, beverages and beverage bases, condiments, salad dressings, frozen dairy desserts and mixes, gravies, sauces, hard and soft candies, jams, meat and nut products, processed fruits and vegetables, sugar substitutes, sweet sauces, and toppings[6]. It was concluded that "*there are no toxicological issues with IMO at the proposed maximum intake of 30 g/person/day for the general population*".

[6] Excluding foods for which a standard exists in the Food and Drug Regulations unless the standard provides for the addition.

6.4.2 European Union

IMOs are authorized as novel foods in the European Union. The specification requirements and conditions of use for IMOs are generically set forth under *Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods* (the "Union List") (EU, 2017). The provisions for IMOs in the Union List originate from an application submitted by BioNeutra to gain approval for the use of their IMO preparation, "Vitasugar-IMO", as a novel food under the now repealed *Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients*. The application was accepted by the United Kingdom Food Standards Agency in 2009 (ACNFP, 2008). In the initial assessment report by the ACNFP, it was concluded that there were no safety concerns related to IMOs when it is added to foods at use levels ranging from 5 to 97%, which provides up to 15.6 g/serving (FSA, 2012). Under these proposed uses, it was estimated that the daily intake will not exceed 31.2 g/day, based on the assumption that a person will consume no more than 2 servings per day.

Under the current novel food regulations, the authorization of novel foods are generic approvals. The conditions of use approved for IMOs under the Union List, which includes various specified food categories at levels ranging from 5 to 97%, apply to preparations that meet the specification requirements set forth therein (*e.g.*, glucose ≤5,0% dry basis; isomaltose + DP3 to DP9 ≥90% dry basis). According to the Union List, foods containing IMOs must be labeled as "a source of glucose", though no other warning statements (*e.g.*, with regard to laxative effects at high doses, or avoidance by certain sub-groups) are required.

6.4.3 Australia/New Zealand

IMOs have been generically approved for use as a novel food in Australia/New Zealand, following the submission of an application by COFCO Corporation. In their risk assessment, FSANZ made the following conclusions:

> "*There is no evidence of adverse gastrointestinal effects (e.g. diarrhoea) in healthy humans up to a single bolus dose of 40 g, and IMO did not cause any abdominal symptoms (e.g. laxative effects) in any subjects at this level. In the absence of any identifiable hazard, an Acceptable Daily Intake (ADI) 'not specified' is considered appropriate. However, it is anticipated that IMO will be poorly tolerated by certain individuals with congenital or acquired sucrase-isomaltase deficiency*" (FSANZ, 2017b).

The conclusion that a single bolus dose of 40 g will be well tolerated is based upon the study conducted by Oku and Nakamura (2003). As part of their risk assessment, FSANZ conducted an estimation of the dietary exposure to IMOs, wherein it was assumed that IMOs would replace 50% of added sugars in all foods, excluding infant formula products, infant foods and formulated supplementary foods for young children. Although the daily intake by some high-consumers could exceed 40 g of IMOs under such a scenario, it was recognized that conservative assumptions were made in the assessment to model the "worst-case" estimates, and thus are unlikely to reflect normal consumption patterns of IMO-containing foods. Based on their risk assessment, FSANZ decided that mandatory advisory labeling statements about possible laxative effects were not warranted for foods containing IMOs (FSANZ, 2017a). Additionally, while FSANZ recognized that IMOs will be poorly tolerated by individuals with congenital or acquired sucrase-isomaltase deficiency, it was determined that risk management strategies will be in place (*i.e.*, ingredient declaration on product labels) to help such individuals identify and avoid food products containing added IMOs (FSANZ, 2017a,b).

Following FSANZ's assessment, Schedule 25 (Permitted novel foods) of the Australia New Zealand Food Standards Code ("the Code") has since been amended to include an entry for IMOs. The only restriction on the conditions of use for IMOs is that they must not be added to infant formula products, food for infants, and formulated supplementary food for young children. The IMOs sold as permitted novel foods in Australia/New Zealand are also required to meet the specification requirements set forth in Schedule 3 (Identity and purity) of the Code, which includes, for instance, a limit for glucose (not more than 5% dry weight), oligosaccharides (not less than 55% with a DP of 3 or more), and IMO content[7] (not less than 90% for powder, and not less than 75% syrup).

6.4.4 China, Japan, and South Korea

IMO preparations are accepted as general food ingredients[8] in countries in Southeast Asia such as China, Japan, and South Korea. Each of these countries have established their own unique regulatory definition and specification requirements for IMOs. The compositional requirements for IMOs in these jurisdictions are summarized in Table 6.4.4-1 below. As mentioned, Ingredion manufactures their Bioligo™ IMOs in South Korea, and these preparations meet the regulatory definitions for IMOs as defined in the *Standards and Specification for Food* in that country.

[7] It is not further indicated how IMO content should be determined or which components should be included in the derivation of this value. However, the specification for IMOs in Schedule 3 indicates that "*IMO is a mixture of glucose oligomers with α 1→6 glycosidic linkages that include isomaltose, panose, isomaltotriose, isomaltopentaose and various branched oligosaccharides*".

[8] IMOs can be added to general foods without restrictions on its use, unless its use specifically requires provisions to exist within a certain food standard or regulation.

Ingredion's Bioligo™ IMOs have been marketed in South Korea as a general-purpose sweetener and bulking agent in foods for more than 25 years (personal communications).

Table 6.4.4-1 Compositional Characteristics for IMO Preparations as Defined in China, Japan, and South Korea

Jurisdiction	Description	IMO Content (dwb)	Distribution of IMO (dwb)	Reference
China	IMO is a starch sugar. The main component is oligosaccharides with α-1,6- glycosidic bonds, such as isomaltose, panose, isomaltotriose, and tetrose (or greater).	IMO-50: ≥50%[b] IMO-90: ≥90%[b]	**Sum of isomaltose, isomalto-triose and panose**: ≥35% (for IMO-50); ≥45% (for IMO-90)	GB/T 20881-2007
Japan	IMO is the resulting substance when starch is reacted by enzymes (α-amylase, β-amylase, α-glucosidase) and its main constituents are the sugars with α-1,2-, α-1,3-, and α-1,6- glycosidic bonds with DP 2 to 6.	NLT 37%[a]	**Isomaltose (DP2)**: 10 to 27% **Isomaltotriose (DP3)**: 5 to 15%	FOSHU specification monograph for IMO
South Korea	Oligosaccharides are liquid sugar linked by less than 10 monosaccharides and are produced from sugar-rich raw material *via* enzymatic reactions.	Oligosaccharide content (for IMOs): ≥10%[c]	Not specified.	*Standards and Specification for Foods*[d]

DP, degree of polymerization; dwb, dried weight basis; FOSHU, Food for Specified Health Uses; IG2, isomaltose; IG3, isomaltotriose; IG4, isomaltotetraose; IG5, isomaltopenaose; IMO, isomalto-oligosaccharide; KB, kojibiose; NG, nigarose; NLT, not less than; P, panose

[a] Refers to the sum of IG2+KB+NG+P+IG3+IG4+IG5.

[b] Refers to the sum of IG2+P+IG3+Gn.

[c] Refers to the sum of IG2+KB+NG+P+IG3+IG4+IG5+IG6+IG7.

[b] As per the monograph for "Oligosaccharides", which includes IMOs.

6.5 Summary of Safety and Basis for GRAS Conclusion

The totality of evidence summarized herein demonstrates that Ingredion's Bioligo™ IMOs mixture is safe for its intended uses as a general-purpose sweetener and bulking agent in foods in the U.S. The raw materials (*i.e.*, corn starch) and processing aids that are used to produce the Bioligo™ IMOs, including all enzymes used to catalyze the hydrolysis and transglycosylation of starch, are food-grade and suitable for use for such purpose. The resulting Bioligo™ IMOs syrup is predominately composed of carbohydrates (*i.e.,* approximately 74 to 75% total solids), with a minimum IMO content of 14% on a dry weight basis. The IMO content is derived by Ingredion as the summation of the levels of "isomalto-" components with DP ranging from 2 to 7 (*i.e.*, isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose,

and isomaltoheptaose). The remaining components are represented by monosaccharides (glucose) and the "malto-" forms of the glucosyl oligosaccharides that are present.

Hydrolyzed starch (*i.e.*, glucose syrups) are widely consumed in the diet, and Ingredion's Bioligo™ IMOs are preparations of hydrolyzed starch in which a proportion of the α-(1,4)-glycosidic linkages have been enzymatically converted to α-(1,6)-forms. Such mixtures of starch carbohydrates do not pose concerns for systemic toxicity, as supported by the results of preclinical toxicological studies that have been conducted on IMOs (Kaneko *et al.*, 1990). Nonetheless, excessive consumption of poorly digested carbohydrates can produce gastrointestinal symptoms among sensitive individuals, such as flatus, abdominal cramps, bloating, borborygmi, and even watery stools and diarrhea (Livesey, 2001; Hammer and Hammer, 2012). IMO preparations are generally considered to be a mixture of carbohydrates comprising both digestible and digestion-resistant saccharides (FSA, 2012; Health Canada, 2012; FSANZ, 2017a,b). The extent of digestibility of an IMO preparation will likely vary depending on factors such as the configuration of glycosidic linkages and size (DP) of its saccharide constituents. Clinical studies conducted by Ingredion indicate the Bioligo™ IMOs syrup, including the formulation in which the mono- and di-saccharide fractions have been removed, will be digestible given that they elicited a comparable post-prandial glycemic and insulinemic response as an equivalent dose of dextrose matched for the carbohydrate content (Gourineni *et al*., 2018). Likewise, no increase in 24-hour breath hydrogen excretion was observed following the ingestion of Bioligo™ IMOs syrup when compared to dextrose, suggesting colonic fermentation did not occur (Gourineni *et al*., 2018). A single bolus dose of Ingredion's Bioligo™ IMOs syrup at 68.5 g (as consumed), which provided approximately 50 g carbohydrates (or approximately 25 g of IMOs on a dry weight basis), was also well tolerated and did not produce any adverse gastrointestinal effects (Gourineni *et al*., 2018). Studies in the published literature further support that IMO preparations are well tolerated materials. For instance, a single bolus dose of IMO at up to 40 g did not produce adverse gastrointestinal symptoms (Oku and Nakamura, 2003). The same authors have also suggested the maximum bolus dose of IMOs that can be consumed without causing transitory osmotic diarrhea to be >1.5 g/kg body weight, which is equivalent to approximately 105 g of IMOs for a 70-kg individual (Oku and Nakamura, 2003; Oku and Nakamura, 2002).

Ingredion's Bioligo™ IMOs are intended for use as a table-top sweetener, and as a general-purpose sweetener in processed food products. The mean and 90th percentile daily intake of added sugars among the U.S. population has been estimated at 67 g and 122 g, respectively (NCI, 2018). The intake of Bioligo™ IMOs is expected to be less than these estimates given that they will not completely replace all of the added sugars that are currently in the food supply. For comparison, BioNeutra's IMO preparation (Vitasugar™) has been concluded GRAS under its

intended conditions of use as an alternative sweetener in specified foods at a maximum use level of 15 g/serving (GRN 246) (BioNeutra Inc., 2008; U.S. FDA, 2009). Considering that Ingredion's Bioligo™ IMOs will be used for similar purposes as Vitasugar™, the exposure to Bioligo™ IMOs in the U.S. is expected to be in comparable ranges (*i.e.*, 30 g/person/day). While some individuals, namely those with acquired or congenital sucrase-isomaltase deficiency, may not be able to tolerate IMOs (FSANZ, 2017b), such individuals will know to avoid consuming food products containing added IMOs.

Based on the data and information presented herein, Ingredion concludes that the intended uses of their Bioligo™ IMOs mixture as a general-purpose sweetener and bulking agent in foods (except for infant formula and meat and poultry products regulated by the FSIS of the USDA), at levels determined by current Good Manufacturing Practices, are GRAS based on scientific procedures.

Part 7. §170.255 List of Supporting Data and Information

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Table of CFR Sections Referenced (Title 21—Food and Drugs)

Part	Section §	Section Title
Subchapter B—Food for Human Consumption		
170—Food additives	170.30	Eligibility for classification as generally recognized as safe (GRAS)
172—Food additives permitted for direct addition to food for human consumption	172.892	Food starch-modified

Table of CFR Sections Referenced (Title 21—Food and Drugs)

Part	Section §	Section Title
184—Direct food substances affirmed as generally recognized as safe	184.1372	Insoluble glucose isomerase enzyme preparations

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Richard E. Bonnette, M.S.
Center for Food Safety and Applied Nutrition
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U.S. Food and Drug Administration

July 25, 2019

Dear Mr. Bonnette,

Re: GRAS Notice for Isomalto-oligosaccharides (GRN No. 818)

In an email dated July 17, 2019, the Agency noted that the GRAS notice for isomalto-oligosaccharides (IMOs) did not include batch analyses confirming compliance with the listed food grade specifications. As requested, the analytical data for representative batches of the Bioligo™ IMOs are provided in the accompanying Attachment 1. The corresponding Certificates of Analysis are provided in Attachment 2.

Ingredion Incorporated manufactures 5 different preparations of their Bioligo™ IMOs syrup product, which are designated internally as Bioligo™ IL5040, IH200, IS300, IL7010, and IS850. The conclusion of GRAS status applies to all of these preparations, which are all manufactured according to the process described in Section 2.2 of the GRAS notice for Bioligo™ IMOs. Depending on the end use (*e.g.*, desired level of sweetness), slight variations in the production process may be applied, which results in products that differ in their saccharide profiles. For instance, Ingredion may apply a chromatography step to remove the mono- and di-saccharides, which would increase the IMO content within the preparation.

Despite these variations in the production steps, the end products will all meet the specifications defined in GRN 818 (table 2.3-2), as demonstrated by the batch analysis data presented in Attachment 1. Collectively, the 5 preparations of IMO meet the specification of 14% minimum IMO content on a percent dry basis, however, as noted on the certificates of analysis the minimum IMO content ranges from 14% to 70%.

The different preparations of Bioligo™ IMOs are all intended for use as a table-top sweetener, and as a partial or complete replacement for general-purpose sweeteners and bulking agent that are added to various processed foods (excluding infant formula or meat and poultry products regulated by the FSIS of the USDA). As explained in Part 6 of the GRAS notice, the intended conditions of use for Bioligo™ IMOs do not pose any safety or tolerability concerns considering that the syrup is simply composed of carbohydrates, either in the form of IMOs, which are considered by Ingredion as the summation of the level of the "isomalto-" components with degree of polymerization ranging from 2 to 7 (*i.e.,* isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose, and isomaltoheptaose), or otherwise as monosaccharides (glucose) and the "malto-" forms of the glucosyl oligosaccharides.

We would like to thank the Agency for the opportunity to respond to their query. We hope that the information provided herein sufficiently addresses the FDA's request.

Yours sincerely,

(b) (6)

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ATTACHMENT 1

Table 1 Batch Analysis Data for Bioligo™-IL5040						
Parameter	**Specification**	**422610 5/9/19**	**424889 5/28/19**	**426048 06/06/19**	**427239 06/17/19**	**428251 6/25/19**
Appearance	Colorless or light yellow, transparent syrup	Pass	Pass	Pass	Pass	Pass
Brix	Min. 75.0	75.5	76.4	76.2	75.6	76.2
IMO content[a] (% dry basis)	Min. 50.0	53.2	52.0	53.2	51.8	53.0
pH	4.5 to 7.0	5.2	5.0	5.2	5.0	5.0
Ash (sulfated %)	Max. 0.3	0.1	0.1	0.1	0.1	0.1
Lead (ppm)	Max. 0.1[b]	Not detected[c]	Not detected[c]	Not detected[c]	Not detected[c]	Not detected[c]
Standard Plate Count (cfu/g)	Max. 1,000	70	60	60	40	50
Yeast and Mold (cfu/g)	Max. 100	Negative	Negative	Negative	Negative	Negative
Escherichia coli (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative

cfu, colony-forming units; IMOs, isomalto-oligosaccharides; Max., maximum; Min., minimum; ppm, parts per million; ppb, parts per billion

[a] IMO content defined as IMO components from DP2 to DP7 (isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose, and isomaltoheptaose).

[b] Max on COAs provided is listed as 1 ppm according to Korean FDA regulations, however, product manufactured for the United States will have a lead limit of 0.1 ppm

[c] Detection Limit is 3 ppb

Table 2 Batch Analysis Data for Bioligo™-IH200						
Parameter	**Specification**	**423075 5/14/19**	**426224 6/8/19**	**428537 6/27/19**	**430093 7/9/19**	**430339 7/10/19**
Appearance	Colorless or light yellow, transparent syrup	Pass	Pass	Pass	Pass	Pass
Brix	Min. 75.0	76.2	76.0	76.4	75.6	76.2
IMO content[a] (% dry basis)	Min. 14.0	15.5	14.8	15.3	15.0	14.9
pH	4.5 to 7.0	5.1	5.2	5.2	4.9	5.0
Ash (sulfated %)	Max. 0.3	0.1	0.1	0.1	0.1	0.1
Lead (ppm)	Max. 0.1[b]	Not detected[c]	Not detected[c]	Not detected[c]	Not detected[c]	Not detected[c]
Standard Plate Count (cfu/g)	Max. 1,000	100	60	80	70	50
Yeast and Mold (cfu/g)	Max. 100	Negative	Negative	Negative	Negative	Negative
Escherichia coli (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative

cfu, colony-forming units; IMOs, isomalto-oligosaccharides; Max., maximum; Min., minimum; ppm, parts per million; ppb, parts per billion

[a] IMO content defined as IMO components from DP2 to DP7 (isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose, and isomaltoheptaose).

[b] Max on COAs provided is listed as 1 ppm according to Korean FDA regulations, however, product manufactured for the United States will have a lead limit of 0.1 ppm [c] Detection Limit is 3 ppb

Table 5 Batch Analysis Data for Bioligo™-IS850						
Parameter	**Specification**	**424098 5/21/19**	**425645 6/3/19**	**427561 6/19/19**	**430438 7/11/19**	**430764 7/15/19**
Appearance	Colorless or light yellow, transparent syrup	Pass	Pass	Pass	Pass	Pass
Brix	Min. 75.0	75.6	76.0	76.0	76.0	75.5
IMO content[a] (% dry basis)	Min. 15.0	16.5	17.0	16.3	15.8	16.2
pH	4.5 to 7	5.1	5.4	4.9	5.2	5.0
Ash (sulfated %)	Max. 0.3	0.1	0.1	0.1	0.1	0.1
Lead (ppm)	Max. 0.1[b]	Not detected[c]	Not detected[c]	Not detected[c]	Not detected[c]	Not detected[c]
Standard Plate Count (cfu/g)	Max. 1,000	30	20	30	10	30
Yeast and Mold (cfu/g)	Max. 100	Negative	Negative	Negative	Negative	Negative
Escherichia coli (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative

cfu, colony-forming units; IMOs, isomalto-oligosaccharides; Max., maximum; Min., minimum; ppm, parts per million; ppb, parts per billion

[a] IMO content defined as IMO components from DP2 to DP7 (isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, isomaltohexaose, and isomaltoheptaose).

[b] Max on COAs provided is listed as 1 ppm according to Korean FDA regulations, however, product manufactured for the United States will have a lead limit of 0.1 ppm

[c] Detection Limit is 3 ppb

ATTACHMENT 2

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL5040(Isomalto-oligosaccharide)

Manufactured Date : May 09, 2019

Expired Date : May 08, 2021

Batch No. : 422610

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.5	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 50.0	53.2	By HPLC
pH	4.5~7.0	5.2	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	70	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL5040(Isomalto-oligosaccharide)

Manufactured Date : May 28, 2019

Expired Date : May 27, 2021

Batch No. : 424889

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.4	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 50.0	52.0	By HPLC
pH	4.5~7.0	5.0	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	60	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL5040(Isomalto-oligosaccharide)

Manufactured Date : June 06, 2019

Expired Date : June 05, 2021

Batch No. : 426048

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 50.0	53.2	By HPLC
pH	4.5~7.0	5.2	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	60	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL5040(Isomalto-oligosaccharide)

Manufactured Date : June 17, 2019

Expired Date : June 16, 2021

Batch No. : 427239

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.6	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 50.0	51.8	By HPLC
pH	4.5~7.0	5.0	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	40	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL5040(Isomalto-oligosaccharide)

Manufactured Date : June 25, 2019

Expired Date : June 24, 2021

Batch No. : 428251

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 50.0	53.0	By HPLC
pH	4.5~7.0	5.0	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	50	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IH200(Isomalto-oligosaccharide)

Manufactured Date : May 14, 2019

Expired Date : May 13, 2021

Batch No. : 423075

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 14.0	15.5	By HPLC
pH	4.5~7.0	5.1	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	100	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IH200(Isomalto-oligosaccharide)

Manufactured Date : June 08, 2019

Expired Date : June 07, 2021

Batch No. : 426224

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.0	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 14.0	14.8	By HPLC
pH	4.5~7.0	5.2	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	60	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IH200(Isomalto-oligosaccharide)

Manufactured Date : June 27, 2019

Expired Date : June 26, 2021

Batch No. : 428537

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.4	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 14.0	15.3	By HPLC
pH	4.5~7.0	5.2	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	80	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IH200(Isomalto-oligosaccharide)

Manufactured Date : July 09, 2019

Expired Date : July 08, 2021

Batch No. : 430093

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.6	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 14.0	15.0	By HPLC
pH	4.5~7.0	4.9	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	70	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IH200(Isomalto-oligosaccharide)

Manufactured Date : July 10, 2019

Expired Date : July 09, 2021

Batch No. : 430339

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 14.0	14.9	By HPLC
pH	4.5~7.0	5.0	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	50	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS300(Isomalto-oligosaccharide)

Manufactured Date : June 26, 2019

Expired Date : June 25, 2021

Batch No. : 428530

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	17.0	By HPLC
pH	4.5~7.0	5.1	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	50	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS300(Isomalto-oligosaccharide)

Manufactured Date : June 28, 2019

Expired Date : June 27, 2021

Batch No. : 428699

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.5	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	15.8	By HPLC
pH	4.5~7.0	5.3	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	80	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS300(Isomalto-oligosaccharide)

Manufactured Date : July 03, 2019

Expired Date : July 02, 2021

Batch No. : 429349

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.4	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	16.8	By HPLC
pH	4.5~7.0	4.9	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	50	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS300(Isomalto-oligosaccharide)

Manufactured Date : July 04, 2019

Expired Date : July 03, 2021

Batch No. : 429597

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.8	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	16.4	By HPLC
pH	4.5~7.0	5.1	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	30	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS300(Isomalto-oligosaccharide)

Manufactured Date : July 05, 2019

Expired Date : July 04, 2021

Batch No. : 429705

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.0	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	16.0	By HPLC
pH	4.5~7.0	5.1	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	10	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL7010(Isomalto-oligosaccharide)

Manufactured Date : March 15, 2019

Expired Date : March 14, 2021

Batch No. : not commercialized

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 70.0	70.5	By HPLC
pH	4.5~7.0	5.2	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	100	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL7010(Isomalto-oligosaccharide)

Manufactured Date : April 19, 2019

Expired Date : April 18, 2021

Batch No. : not commercialized

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.8	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 70.0	71.0	By HPLC
pH	4.5~7.0	5.0	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	80	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL7010(Isomalto-oligosaccharide)

Manufactured Date : May 24, 2019

Expired Date : May 23, 2021

Batch No. : not commercialized

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 70.0	70.8	By HPLC
pH	4.5~7.0	4.8	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	120	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL7010(Isomalto-oligosaccharide)

Manufactured Date : June 14, 2019

Expired Date : June 13, 2021

Batch No. : not commercialized

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.2	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 70.0	71.2	By HPLC
pH	4.5~7.0	5.1	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	110	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IL7010(Isomalto-oligosaccharide)

Manufactured Date : July 19, 2019

Expired Date : July 18, 2021

Batch No. : not commercialized

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.6	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 70.0	70.6	By HPLC
pH	4.5~7.0	5.3	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	60	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS850(Isomalto-oligosaccharide)

Manufactured Date : May 21, 2019

Expired Date : May 20, 2021

Batch No. : 424098

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.6	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	16.5	By HPLC
pH	4.5~7.0	5.1	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	30	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS850(Isomalto-oligosaccharide)

Manufactured Date : June 03, 2019

Expired Date : June 02, 2021

Batch No. : 425645

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.0	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	17.0	By HPLC
pH	4.5~7.0	5.4	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	20	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS850(Isomalto-oligosaccharide)

Manufactured Date : June 19, 2019

Expired Date : June 18, 2021

Batch No. : 427561

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.0	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	16.3	By HPLC
pH	4.5~7.0	4.9	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	30	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS850(Isomalto-oligosaccharide)

Manufactured Date : July 11, 2019

Expired Date : July 10, 2021

Batch No. : 430438

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	76.0	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	15.8	By HPLC
pH	4.5~7.0	5.2	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	10	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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Certificate of Analysis

Date : July 25, 2019

Commodity : Bioligo-IS850(Isomalto-oligosaccharide)

Manufactured Date : July 15, 2019

Expired Date : July 14, 2021

Batch No. : 430764

Quantity :

Item	Specification	Result	Remarks
Appearance	Colorless or light yellow, transparent syrup	pass	Sensory
Brix	Min 75.0	75.5	Refractometer, at 20℃
Isomaltooligosaccharide (%DB)	Min 15.0	16.2	By HPLC
pH	4.5~7.0	5.0	10% solution
Ash(sulphated %)	Max 0.3	0.1	Korea Food Codex
Lead (ppm)	Max 1.0	Not detected	Korea Food Codex (detection limit: 3ppb)
Standard Plate Count (cfu/g)	Max 1,000	30	Korea Food Codex
Yeast & Mold (cfu/g)	Max 100	Negative	Korea Food Codex
E-coli	Negative	Negative	Korea Food Codex
Salmonella	Negative	Negative	Korea Food Codex

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From:	Debra Levine
To:	Bonnette, Richard
Subject:	RE: Extension of review timeframe for GRN 818 - Isomalto-oligosaccharides
Date:	Monday, December 09, 2019 12:23:36 PM
Attachments:	image001.png

Richard,

At the time we prepared the GRAS dossier, the corn starch and all processing aids met the 10th edition of the FCC specs. We monitor all FCC revisions to ensure continued compliance, and can confirm that we currently meet the 11th edition of FCC specs.

I look forward to hearing from you shortly.
Regards,
Debbie

From: Bonnette, Richard <Richard.Bonnette@fda.hhs.gov>
Sent: Monday, December 09, 2019 8:22 AM
To: Debra Levine <debra.levine@ingredion.com>
Subject: [External] RE: Extension of review timeframe for GRN 818 - Isomalto-oligosaccharides

Debbie,
Your email reminds me that I do have a (very) quick question regarding this submission. Page 8 notes that the corn starch and all processing aids meet FCC specs. Which edition of the FCC?
Thanks,
Richard

From: Debra Levine <debra.levine@ingredion.com>
Sent: Friday, December 06, 2019 5:41 PM
To: Bonnette, Richard <Richard.Bonnette@fda.hhs.gov>
Subject: RE: Extension of review timeframe for GRN 818 - Isomalto-oligosaccharides

Hello,
I'd like to request an update on the status of FDA's review of GRN 818.
Thank you very much.
Debbie

From: Debra Levine
Sent: Thursday, August 15, 2019 2:06 PM
To: Bonnette, Richard <Richard.Bonnette@fda.hhs.gov>
Subject: RE: Extension of review timeframe for GRN 818 - Isomalto-oligosaccharides

Richard,
Thank you very much for letting me know.
I look forward to hearing from you soon.