Citizen Petition

BioNeutra™

BioNeutra North American Inc.

May 2019

Contents

Cover Letter

BioNeutra

BioNeutra North America Inc.

9608 25 Ave NW, Edmonton, Alberta, T6N 1J4

Pioneer in Multifunctional Oligosaccharides

May 3, 2019

Division of Dockets management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: CITIZEN PETITION TO INCLUDE ISOMALTOOLIGOSACCHARIDE IN THE LIST OF DIETARY FIBERS

In accordance with 21 CFR § 10.30, BioNeutra North America Inc. wants to respectfully submit a citizen petition to include Isomaltooligosaccharide (IMO) in the 21 CFR 101.9 (c)(6)(i) list of dietary fibers. Enclosed please find the petition along with full-length copies of the relevant articles for both the FDA (Appendix-A (for FDA)) and public release (Appendix-A (Public-Release)) for your review.
I trust that the enclosed petition is acceptable to FDA. Should you have any questions or concerns regarding the petition, please do not hesitate to contact me at any time during the review process.

Thanks for your consideration.

Sincerely,

Dr. Jianhua Zhu
President/CEO

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BioNeutra™

CITIZEN PETITION

May 3, 2019

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD
20852

The undersigned, BioNeutra North America Inc. (BioNeutra), respectfully submits this new citizen petition under the United States (U.S.) Food and Drug Administration's (FDA) implementing regulation at 21 CFR §10.30 to request the Commissioner of Food and Drugs to amend 21 CFR §101.9(c)(6)(i) so that it includes "isomalto-oligosaccharides" in the list of dietary fibers that meet the definition of dietary fiber.

A. ACTION REQUESTED

21 CFR §101.9(c)(6)(i) (U.S. FDA, 2016a) states the following:

> *"Dietary fiber": A statement of the number of grams of total dietary fiber in a serving, indented and expressed to the nearest gram, except that if a serving contains less than 1 gram, declaration of dietary fiber is not required or, alternatively, the statement "Contains less than 1 gram" or "less than 1 gram" may be used, and if the serving contains less than 0.5 gram, the content may be expressed as zero. Dietary fiber is defined as non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health. Except as provided for in paragraph (f) of this section, if dietary fiber content is not required, and as a result not declared, the statement "Not a significant source of dietary fiber" shall be placed at the bottom of the table of nutrient values in the same type size. The following isolated or synthetic non-digestible carbohydrate(s) have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber: [beta]-glucan soluble fiber (as described in 101.81(c)(2)(ii)(A)), psyllium husk (as described in 101.81(c)(2)(ii)(A)(6)), cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose. The manufacturer must make and keep records in accordance with paragraphs (g)(10) and (11) of this section to verify the declared amount of dietary fiber in the label and labeling*

of food when a mixture of dietary fiber, and added non-digestible carbohydrate(s) that does not meet the definition of dietary fiber, is present in the food.

BioNeutra is requesting that 21 CFR §101.9(c)(6)(i) be amended, as indicated below in **bold font**, so that it includes the additional mention of "isomalto-oligosaccharides" in the list of dietary fibers that meet the dietary fiber definition:

The following isolated or synthetic non-digestible carbohydrate(s) have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber: [beta]-glucan soluble fiber (as described in 101.81(c)(2)(ii)(A)), psyllium husk (as described in 101.81(c)(2)(ii)(A)(6)), cellulose, guar gum, pectin, locust bean gum, ~~and~~ hydroxypropylmethylcellulose, **and isomalto-oligosaccharides**.

The FDA has determined that the 7 isolated or synthetic non-digestible carbohydrates listed in 21 CFR §101.9(c)(6)(i)–*i.e.,* [beta]-glucan soluble fiber, psyllium husk, cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose–have beneficial physiological effects on human health to warrant their inclusion in the calculation of the amount of "dietary fiber" stated on Nutrition and Supplement Facts labels (U.S. FDA, 2018c). In addition, rulemaking is in progress to add the following 8 non-digestible carbohydrates to the above list of dietary fibers appearing in 21 CFR §101.9(c)(6)(i): mixed plant cell wall fibers, arabinoxylan, alginate, inulin and inulin-type fructans, high amylose starch (resistant starch 2), galactooligosaccharide, polydextrose, and resistant maltodextrin/dextrin (U.S. FDA, 2018c).

A citizen petition was submitted by BioNeutra to the FDA in 2016 (the 2016 citizen petition); the petition was denied by the FDA in 2018 (2018 letter), who concluded that there was insufficient evidence demonstrating that isomalto-oligosaccharides (IMO) have a beneficial physiological effect to human health (U.S. FDA, 2018a). BioNeutra has since translated three relevant non-English human studies to English (Liu et al., 1994; Lee et al., 2003; Lin et al., 2005) that were identified in the previous citizen petition. Furthermore, Bioneutra is now submitting scientific evidence to support the relationship between IMO consumption and blood cholesterol levels.

Based on the science review provided below, BioNeutra is requesting that IMO be recognized as having beneficial physiological effects and thus be added to the list of dietary fibers stated in 21 CFR §101.9(c)(6)(i) (U.S. FDA, 2016a).

B. STATEMENT OF GROUNDS

B.1 Legal Grounds

The definition of dietary fiber is stated in 21 CFR §101.9(c)(6)(i) as:

> *Dietary fiber is defined as non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health.*

Per the FDA's Final Rule on Food Labeling (U.S. FDA, 2016b), the FDA has identified the existing citizen petition process described in 21 CFR §10.30 as an avenue to request a regulatory amendment to the definition of dietary fiber [21 CFR §101.9(c)(6)(i)] (U.S. FDA, 2016a,b). In fact, in their Final Rule on Food Labeling (U.S. FDA, 2016c), the FDA specifically states, "*Any interested person may seek to amend the listing of added fibers through the existing citizen petition process in 21 CFR §10.30*".

Since IMO are an "isolated or synthetic non-digestible carbohydrate (with 3 or more monomeric units)", whether evidence exists to support their beneficial physiological effect in humans needs to be determined by the FDA. This citizen petition describes the results of human intervention studies that evaluated the relationship between IMO consumption and laxation and/or blood cholesterol levels. The FDA has affirmed that an improvement in laxation, described as the elimination of fecal waste/fecal output, is a beneficial physiological effect of dietary fiber (U.S. FDA, 2018b). Importantly, of the studies evaluated by BioNeutra, endpoints specifically stated by the FDA to be appropriate indicators of laxation were measured, namely defecation frequency (number of stools/day) and fecal weight per day (based on stool collections over multiple days), as well as subjective symptoms related to laxation.

B.2 Factual Grounds

Overview of Isomalto-oligosaccharides

IMO are a mixture of glucose oligomers enzymatically produced from starch and modified through transglycosylation reaction (Health Canada, 2017). The glucose oligomers contain α-(1, 4) and non-digestible α-(1, 6) glucosidic linkages (EFSA, 2010). Since α-(1, 6) glucosidic linkages are resistant to digestion, IMO are resistant to digestion in the upper gastrointestinal tract. IMO are partially digested by enzymes residing in the small intestine and multiple studies have shown that residual IMO are then fermented in the large intestine by colonic bacteria (Kohmoto *et al.*, 1988; Kaneko *et al.*, 1993; Chen *et al.*, 2001; Yen *et al.*, 2011; BioNeutra Inc., 2012 [unpublished]). Multiple studies have shown that fecal bifidobacteria and short chain fatty acids (SCFAs) are increased following the consumption of IMO, indicating that IMO stimulate the growth and activity of beneficial gut microbes (Kohmoto *et al.*, 1991; Kaneko *et al.*, 1993, 1994; Chen *et al.*, 2001; Yen *et al.*, 2011). IMO can be quantified in foods by established methods (EFSA, 2010). IMO naturally occur in fermented foods such as rice, miso, soy sauce, and sake (Hondo and Mochizuki, 1979; Nishino *et al.*, 1981; Nunokawa, 1981; Tungland and Meyer, 2002; taken from BioNeutra Inc., 2012 [unpublished]).

BioNeutra manufactures an IMO, marketed as VitaFiber™, which is produced from the starch of various cereal crops *via* enzymatic conversion. VitaFiber™ is primarily composed of oligo-saccharides with a degree of polymerization ranging from 3 to 9 glucose units. BioNeutra intends to incorporate VitaFiber™ into a variety of food categories, including baked goods, confectionary, breakfast cereals, sauces/dressings/ condiments, dairy, meat, dairy and meat analogs, nuts, processed fruits/vegetables, beverages, fruit/vegetable juices, snack foods, and soups. Levels of incorporation of VitaFiber™ are intended to range from 1.5 to 15 g per serving, depending on the food/food category.

Scientific Evidence on Isomalto-oligosaccharides and Laxation and cholesterol

Literature Search Methods

To retrieve relevant literature (*i.e.,* human intervention studies) on the health effects of IMO, 15 literature databases were searched using the electronic search tool ProQuest Dialog™. The databases that were searched, as well as the search terms used, are listed in Tables 1 and 2, respectively. To increase the relevance and specificity of the literature search, the search terms were selected to reflect the dietary fiber of interest (IMO) and health outcomes of interest (i.e., laxation and blood cholesterol levels). No other limitations were placed on the literature search with respect to the publication date, language, and the "fields"[1] searched within the publication.

Table 1. Electronic Databases Used to Retrieve Literature

Electronic Database	Date Range	Update Frequency
Adis Clinical Trials Insight	1990 to present	Weekly
AGRICOLA	1970 to present	Monthly
AGRIS	1975 to present	Monthly
Allied & Complementary Medicine™	1985 to present	Monthly
BIOSIS® Toxicology	1969 to present	Weekly
BIOSIS Previews®	1926 to present	Weekly
CAB ABSTRACTS	1910 to present	Weekly
Embase®	1947 to present	Daily
Foodline®: SCIENCE	1972 to present	Stopped updating April 2016; previously twice weekly
FSTA®	1969 to present	Weekly
Gale Group Health Periodicals Database	1983 to present	Daily
Global Health	1910 to present	Weekly
MEDLINE®	1946 to present	Daily
NTIS: National Technical Information Service	1964 to present	Weekly
ToxFile®	1900 to present	Daily

[1] All applicable "fields" were searched which for most databases included the: titles, abstracts, subject, descriptors, category, notes, keywords, and the full-length article (if available in ProQuest Dialog™).

Table 2.

Keywords Used to Retrieve Literature[a,b]

Exposure	Isomaltooligosaccharide* or Isomalto-oligosaccharide*
Health Outcome	stool or feces or faeces or fecal or faecal or defecation or transit time or laxation or bowel or evacuation or bulk or colon* or bifidobacter* or bifidogenic or lactobacill* or bacteroid* or faecalibacter* or eubacter* or roseburia or clostridium or acetate or propionate or butyrate

[a] The symbol "*" indicates a truncation so as to not place a limitation on the word ending (*e.g.*, "isomaltooligosaccharide*" would have resulted in the identification of "isomaltooligosaccharide" and "isomaltooligosaccharides").
[b] Keywords used for the exposure were searched for in combination with keywords used for the health outcome.

Once the search strategy was implemented and the publication titles were retrieved, the relevance of the publications was determined at 3 stages using the titles, abstracts, and the full-text of publications. At each stage, the inclusion/exclusion criteria listed in Table 3 were applied to determine literature relevance. The 3 stages are outlined below in greater detail.

Stage 1: Titles of articles were reviewed, and abstracts of titles determined to be potentially relevant were retrieved.

Stage 2: Abstracts were reviewed, and full-length articles of abstracts determined to be potentially relevant were retrieved.

Stage 3: Full-length articles were reviewed, and those determined <u>not</u> to meet all of the inclusion criteria or to meet any of the exclusion criteria specified in Table 3 were excluded.

Table 3 Inclusion and Exclusion Criteria Used to Filter the Identified Literature

<u>Inclusion Criteria</u>

- A full-length article published in a peer-reviewed journal or an unpublished full study report
- A human intervention study (± randomization and ± a control group)
- The food/food constituent studied was IMO
- The independent effects of IMO on the outcomes of interest could be isolated
- The duration of IMO intake was reported and was at least 1 week for laxation and 3 weeks for cholesterol provided for the same duration as the control group
- IMO was orally consumed in any matrix (food or dietary supplement)
- The study population was comprised of subjects with no symptoms of constipation or subjects with occasional or chronic constipation
- Bowel-related outcomes were measured (*e.g.*, defecation frequency, fecal weight, transit time, stool consistency, subjective symptoms related to laxation) or total and/or LDL cholesterol
- Statistical analyses conducted between the treatment and control group and statistical results reported

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Table 3 Inclusion and Exclusion Criteria Used to Filter the Identified Literature

Exclusion Criteria

- A full-length article published in a non-peer-reviewed source (*e.g.*, website, magazine, *etc.*)
- Published in abstract form only or as a short communication (*e.g.*, letter to the editor, commentary, *etc.*)
- If unpublished, the full study report was not available
- A research synthesis study (*e.g.*, narrative review, systematic review, meta-analysis, *etc.*)
- An *in vitro* or animal study
- A human observational study
- The food/food constituent studied was not IMO
- The independent effects of IMO could not be isolated (*e.g.*, IMO was co-consumed with another dietary fiber)
- The duration of IMO intake was not reported or the duration of IMO intake was less than 1 week
- The outcomes measured were not bowel-related
- Statistical analyses not conducted between the treatment and control group and/or statistical results not reported
- The study was a duplicate record in the literature search
- The study results were reported in a kin publication[a]

IMO = isomalto-oligosaccharides.
[a] Kin publications are those in which results for the same study population are reported. Where kin publications were identified, preference was given to the most recent publication, unless a sound rationale existed for choosing the older or both publications (*e.g.*, if different but complimentary and relevant outcomes were assessed across the kin publications, both were included).

Laxation

Literature Search Results

Using a similar process for identifying relevant studies that was used for the 2016 citizen petition (Figure B.2.2.3-1), a total of ten human studies were identified that evaluated the relationship between IMO consumption and bowel function. Scientific conclusions could not be drawn from five of these studies for the following reasons: (1) the study lacked an appropriate control group or statistics were not reported between treatment and control groups (Liu et al., 1994; Qing et al., 2003; Wang et al., 2001; Lee et al., 2003); and/or (2) the study did not measure the rate of laxation but rather the number of days of constipation (Lin et al., 2005). While two studies were not previously considered by FDA due to enema use (2018 letter), discussion is provided below on the validity of these two studies (Chen et al., 2001; Yen et al., 2011).

Discussion of Relevant Human Studies

BioNeutra Inc. (2012) [unpublished]

As described by FDA in the 2018 letter to BioNeutra, "Healthy adults were randomized into one of the following three treatment groups (n = 19 per group) in a double-blind, randomized,

placebo-controlled, parallel study: 36 grams (g)/day of IMO; 54 g/day of IMO; or dextrose (control). The study subjects were provided sachets of IMO or the dextrose placebo and were instructed to dissolve the substances completely in water and to consume them three times per day. The study subjects recorded their daily bowel habits. At the end of four weeks, there was no statistically significant difference in the number of bowel movements per day between the IMO and the control groups ($P > 0.05$)." IMO did not significantly improve subjective symptoms of laxation (*i.e.*, straining to start defecation, straining to stop defecation, or feeling of incomplete defecation) compared to the placebo control.

Bouhnik et al. (2004)

As discussed by FDA in the 2018 letter, "In a randomized parallel, double-blind, placebo-controlled study, 64 healthy adults consumed their usual diet for 14 days. On days 8 to 14, their diets were supplemented with seven different non-digestible carbohydrates, including IMO, or a placebo (50% sucrose/50% fully digestible waxy maize-derived maltodextrins) (n = 8 per group; 5 g twice daily). The study subjects were asked to exclude fermented milk and food products containing any of the non-digestible carbohydrates in the study from their diets. The study subjects reported gastrointestinal symptoms using daily charts, which included noting stool frequency. There was no statistically significant effect of IMO consumption on the number of stools compared to the control ($P > 0.05$; data not reported)."

Kaneko et al. (1993)

As discussed by FDA in the 2018 letter, "Men and women were included in a five-week, free-living study in which the subjects consumed their usual diets. IMO was not provided during the first week. The second and third weeks included daily supplementation of IMO, the fourth week served as a washout period without IMO, and the fifth week included daily IMO consumption. The appropriate control periods that were considered included periods without IMO consumption that were the same duration as the treatment periods. Therefore, the comparisons used were Week 2 (one week of IMO) versus Week 1 (one week of control) and Week 5 (one week of IMO) versus Week 1. Week 3 was not used because it represented two weeks of IMO consumption, and there was not an appropriate control period to which it could be compared (i.e., two weeks without IMO consumption). The subjects used study questionnaires to classify themselves as either constipated or not constipated. Groups A (n = 9; not constipated) and B (n = 10; constipated) consumed 10 g/day of IMO. Group C (n = 12; constipated) consumed 15 g/day of IMO. There was no statistically significant effect on self-reported defecation frequency per five days in Groups A and B after Week 2 or Week 5 ($P > 0.05$). In Group C, the self-reported defecation frequency was also not statistically significantly different after Week 2 or Week 5 compared with Week I ($P > 0.05$). There was no statistically significant effect of IMO on self-reported fecal weight in any of the groups after week 2 or Week 5 ($P > 0.05$) compared to the

control phases of the study. There also was no statistically significant effect on fecal weight in a subset of individuals from Group A and B who collected fecal samples ($P > 0.05$; n = 7)."

"The study authors also reported results from a subgroup analysis of individuals in Groups B (10 g/day) and C (15 g/day) who had defecation frequency of three times or less per five days. In the subset of Group B (n = 5), defecation frequency was statistically significantly higher after Week 2 compared with Week I ($P < 0.05$). However, there was no statistically significant difference when comparing Week 5 with Week I ($P > 0.05$). In the subset of Group C (n = 7), there was no statistically significant difference when comparing Week 2 with Week I ($P > 0.05$). However, defecation frequency was significantly higher when comparing Week 5 with Week I ($P < 0.01$)."

Yen et al. (2011)

In a single-arm, double-blind, placebo-controlled intervention study (run-in period[2], 4-week placebo period, two 4-week IMO supplementation periods, 4-week post-IMO period–i.e., IMO-free period), Yen et al. (2011) investigated the effect of a daily intake of 10 g IMO[3] on "spontaneous" defecation frequency (recorded daily) and fecal weight (stools collected over the last 7 days of each period[4]) in 13 elderly (5 males and 8 females) with a mean age of 82.5 years and with chronic constipation (not defined). The subjects lived in a nursing home in Taiwan. During the 1-month run-in period and throughout the study, the subjects were prescribed a "low-fiber diet" (mean intake of dietary fiber was 12.0 ± 0.2 g/day over the placebo and IMO intake periods) of typical Chinese foods (via a 7-day rotating menu). Consumption of supplements or foods containing lactic acid bacteria or other oligosaccharides was not permitted throughout the study. Once the placebo period (3 mL fructose syrup mixed with 100 mL water) was completed, subjects received an incremental dose of IMO that increased from 5 to 10 g/day in 100 mL water over the course of 1 week. The dose of 10 g/day was then maintained for the remaining 7 weeks.

Although enema use was not strictly controlled (i.e., enemas were administered upon subject request or if a bowel movement had not occurred within 3 days), there was no significant difference in the use of enemas (number/week) between the placebo (1.9 ± 0.2), IMO intake periods (1.7 ± 0.1 and 1.6 ± 0.1 for the first and second IMO intake periods, respectively), or post-IMO (1.8 ± 0.1) intake periods[5]. An expert review of the study by Dr. Levinus Dieleman, submitted as part of the Top Health Ingredients citizen petition (Docket number FDA-2019-P-

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[2] Subjects consumed a prescribed low-fiber diet (12 g dietary fiber/day) for 1 month prior to study start; this same diet was consumed during the course of the study.
[3] Subjects received an incremental dose of IMO that increased from 5 to 10 g/day over the course of 1 week. The dose of 10 g/day was then maintained for the remaining 7 weeks.
[4] Stools were individually collected in plastic bags and sent to the laboratory immediately.
[5] Ten subjects were also permitted to be treated for constipation with laxatives (*i.e.*, magnesium oxide, bisacodyl, or sennoside).

1640), stated that "The subjects, for both Control as well as Test treatments, were treated with enemas if spontaneous defecation did not occur in 3 days, or if requested. Though requests were allowed, for both Test and Control subjects, exactly the same criteria were used to provide enemas. Thus, this in combination with the data showing that there was no statistical difference in the number of enemas used regardless of diet, demonstrates that the enema use did not have an impact on the laxation findings of the study."

Although there was no statistically significant change in defecation frequency after the first 4 weeks of IMO supplementation *versus* the placebo period, defecation frequency significantly increased by 67% in the second 4-week IMO supplementation period *versus* the placebo period (2.0 ± 0.3 *versus* 1.2 ± 0.4 defecations/7 days, respectively; $P < 0.05$), which represents an increase of close to 1 additional defecation (+0.8) over a 1-week time period. Defecation frequency in the post-IMO period (*i.e.*, IMO-free period) was not significantly different from the placebo period, demonstrating that the discontinuation of IMO supplementation unfavorably mitigated the increases in defecation frequency attained during IMO supplementation.

Wet fecal weight frequency (g/week) significantly increased by 24% following the first and second 4-week IMO intervention periods as compared to the placebo period ($P < 0.05$), resulting in an increase in fecal weight of 0.92 g/day per gram of IMO consumed. Dry fecal mass (g/week) significantly increased by 16 and 12% after the first and second 4-week IMO intervention periods, respectively, compared to the placebo period ($P < 0.05$). Wet and dry fecal mass were not significantly different in the post-IMO period compared to the placebo period, demonstrating that the discontinuation of IMO supplementation unfavorably mitigated the increases in fecal weight established during IMO supplementation.

Chen et al. (2001)

In a non-randomized sequential study, nursing home residents (n=7) with a history of chronic constipation consumed a low-fiber background diet (14.8 g/day) for two 30-day periods. The first phase of the study excluded IMO (control) and the second phase included IMO. The IMO source was provided in a dessert and intake was gradually increased from 8 g/day (representing 3.3 g of IMO) to 24 g/day (representing 10 g IMO) during the first ten days of the treatment period. While the subjects were taking enemas, an expert review of the study by Dr. Levinus Dieleman, submitted as part of the Top Health Ingredients citizen petition (Docket number FDA-2019-P-1640), stated that "Analysis demonstrates that there is no statistical difference in the number of enemas used by subjects on Control vs. Experimental diets (Table 3)." "In these studies, enemas did not affect the conclusions that can be drawn on comparing the laxation effects of test diets in comparison to control diets."

During the 8-week study period, subjects consumed a prescribed, low-fiber diet (mean intakes of 11.2 ± 0.7 to 11.6 ± 0.5 g/day in the reference and IMO intake periods, respectively) that

consisted of Chinese foods (3-day rotating menu). During the 4-week IMO period, subjects received, daily, an afternoon dessert supplemented with IMO. The IMO concentration was gradually increased from 3.3 to 10 g IMO/day over a period of 10 days, and then maintained at 10 g per day for the remainder of the IMO period. Bowel-related endpoints evaluated in the control and IMO periods were "spontaneous" defecation frequency (recorded daily) and wet and dry fecal weight (stools were collected over the last 5 days of each period[6]). The authors clearly stated that "spontaneous defecation" did not include the bowel movement induced by enema (enema use was permitted when spontaneous defecation was incomplete or if defecation did not occur within 3 days).

Spontaneous defecation frequency significantly and favorably increased 3-fold during the IMO period compared to the reference period (1.5 ± 0.4 *versus* 0.5 ± 0.2 defecations/5 days, respectively); $P < 0.05$. Subjects consuming IMO experienced, on average, one additional defecation (+1.0) over a 5-day period as compared to the reference period. Concomitantly, average daily wet fecal weight and wet fecal weight per stool significantly increased in the IMO period compared to the reference period; $P < 0.05$. The authors report that, compared to the reference period, during the IMO period, the wet fecal weight increased by 3.34 ± 0.54 g/day (mean ± SEM) per gram of IMO consumed. Average daily dry fecal weight and dry fecal weight per stool also increased significantly in the IMO period compared to the reference period; $p<0.05$. Importantly, there were no statistically significant changes in enema use (times/5 days) between the reference and IMO periods (2.3 ± 0.9 and 1.1 ± 0.6, respectively).

Summary of Findings

Of the five studies from which scientific conclusions could be drawn, all five measured the defecation rate and one of the studies also measured rate of defecation of wet and dry stools. Three of the five studies included heathy subjects who were not constipated (BioNeutra, 2012; Bouhnick et al., 2004; Kaneko et al., 1993). No beneficial effect was observed in these three studies. The two studies that were conducted using constipated subjects showed that IMO consumption significantly increased the rate of laxation when compared to the control (Chen et al., 2001; Yen et al., 2011). Furthermore, Yen et al. (2011) demonstrated that there was an increase in both the defecation rate for wet and dry stool weights. Based on these findings, IMO consumption is beneficial in improving laxation in constipated subjects. Constipation is a common problem and affects up to 28% of the general population (McCrea et al., 2009). Therefore, the health benefits of IMO in improving laxation in the constipated population is of relevance to a significant portion of the general US population. Being relevant to not all, but a significant portion, of the US population is not different than FDA's decision to make the labeling of iron mandatory on the food label because of iron deficiency concerns only in women (U.S. FDA, 2014).

[6] Stools were stored at 4°C and weighed within 8 hours of collection.

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Blood Cholesterol Levels

Literature Search Results

Using a similar process for identifying relevant studies that was used on the 2016 petition (Figure B.2.2.3-1), five studies were identified that evaluated the effect of IMO consumption on blood cholesterol levels.

Discussion of Relevant Human Studies

BioNeutra Inc. Report (2012)

In a double-blind, randomized, placebo-controlled, parallel study, healthy adults were provided on of the following three treatment groups (n = 19 per group): 36 g/day of IMO; 54 g/day of IMO; or dextrose (control). The study subjects were instructed to completely dissolve the sachets of IMO or dextrose in water and to be consumed three times per day. After completion of the four-week intervention, there was no statistically significant difference in total or LDL cholesterol levels between the control and two IMO groups ($P > 0.05$).

Chen et al. (2001)

In a non-randomized sequential study, nursing home residents (n=7) with a history of chronic constipation and normal blood cholesterol levels consumed a low-fiber background diet (14.8 g/day) for two 30-day periods. The first phase of the study excluded IMO (control) and the second phase included IMO. The IMO source was provided in a dessert and intake was gradually increased from 8 g/day (representing 3.3 g of IMO) to 24 g/day (representing 10 g IMO) during the first ten days of the treatment period. There was no significant difference in the subjects' total cholesterol or LDL cholesterol levels between the control and IMO periods ($P > 0.05$).

Wang et al. (2001)

Twenty hemodialysis patients with chronic constipation and uremic dyslipidemia consumed 30 g/day of IMO in a parallel design study, following a two-week run-in period. The control group consisted of 30 age- and sex-matched hemodialysis patients who did not consume IMO. The subjects in the treatment group were instructed to dissolve the IMO syrup in warm water and to consume it after meals. The recommended dose was 15 g twice daily, but the patients were permitted to increase the dose of IMO according to their bowel movements. Baseline values were reported for the treatment and control groups, but statistical comparisons of the baseline

values between the groups was not reported. While adequate statistical analyses were not provided in the paper, the Top Health Ingredients citizen petition (Docket number FDA-2019-P-1640) had statistical analyses conducted on the baseline data and showed that the control and IMO groups were not significantly different. Furthermore, it was determined in this analysis that IMO significantly reduced total and LDL cholesterol levels with IMO consumption compared to the control ($P < 0.05$).

Yen et al. (2011)

In a single-arm, double-blind, placebo-controlled intervention study (run-in period[7], 4-week placebo period, two 4-week IMO supplementation periods, 4-week post-IMO period–*i.e.,* IMO-free period), Yen *et al.* (2011) investigated the effect of a daily intake of 10 g IMO[8] on "spontaneous" defecation frequency (recorded daily) and fecal weight (stools collected over the last 7 days of each period[9]) in 13 elderly (5 males and 8 females) with a mean age of 82.5 years and with chronic constipation (not defined). The subjects lived in a nursing home in Taiwan. During the 1-month run-in period and throughout the study, the subjects were prescribed a "low-fiber diet" (mean intake of dietary fiber was 12.0 ± 0.2 g/day over the placebo and IMO intake periods) of typical Chinese foods (*via* a 7-day rotating menu). Consumption of supplements or foods containing lactic acid bacteria or other oligosaccharides was not permitted throughout the study. Once the placebo period (3 mL fructose syrup mixed with 100 mL water) was completed, subjects received an incremental dose of IMO that increased from 5 to 10 g/day in 100 mL water over the course of 1 week. The dose of 10 g/day was then maintained for the remaining 7 weeks.

The study compared the control phase of the study at four weeks to the IMO1 treatment phase at four weeks and the IMO1 phase to the washout phase (four weeks). The IMO2 treatment phase was not considered because it represented eight consecutive weeks of treatment, which was not the same duration as the control periods (four weeks of placebo and four weeks of post treatment washout). A refined diet was used as the background diet throughout the study. IMO was consumed with 100 mL of water as an afternoon snack. The IMO dose gradually increased from 11 g/day (5 g of the active component) to 22 g/day (10 g of the active component) in the first seven days of the IMO1 phase. Compared with the control phase, total cholesterol and LDL-cholesterol levels were significantly lower after the IMO1 phase of the study (10% and 8%, respectively) ($P < 0.05$). Total cholesterol and LDL-cholesterol levels were not significantly different when comparing the IMO1 phase and the four-week washout period ($P > 0.05$).

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[7] Subjects consumed a prescribed low-fiber diet (12 g dietary fiber/day) for 1 month prior to study start; this same diet was consumed during the course of the study.
[8] Subjects received an incremental dose of IMO that increased from 5 to 10 g/day over the course of 1 week. The dose of 10 g/day was then maintained for the remaining 7 weeks.
[9] Stools were individually collected in plastic bags and sent to the laboratory immediately.

Lin et al. (2005)

Forty-two Taiwanese men and women (average age 17 years) with hypercholesterolemia participated in a double-blind, parallel design study. Subjects were randomly assigned to consume chiffon cake that contained 68 g sucrose (control) (n=20) or 71 g IMO syrup (10 g active ingredient) (n=22) for 6 weeks along with their normal diet. The study involved a 1-week run-in period followed by a 6-week experimental period. After the 6-week period, a significant reduction in total and LDL cholesterol was observed ($P < 0.05$).

Summary of Findings

There were five studies on IMO consumption and blood cholesterol levels. Two of these studies showed no effect of IMO consumption on blood cholesterol (BioNeutra, 2012; Chen et al., 2001). One study provided mixed results based on the order of receiving the IMO and control (Yen et al., 2011). Two studies showed that IMO consumption significantly reduced total and LDL cholesterol levels (Wang et al., 2001; Lin et al., 2005). These two studies had the largest sample size (n= 20-30 per group) of the five studies and presented both normal and hypercholesterolemic individuals. Therefore, the health benefits of IMO in reducing blood cholesterol levels is of relevance to the entire US population.

C. ENVIRONMENTAL IMPACT

An environmental impact assessment is not provided since this citizen petition relates to an action that is categorically excluded from environmental impact considerations [21 CFR 25.32(p) – U.S. FDA, 2016d][10].

D. ECONOMIC IMPACT

In accordance with 21 CFR 10.30, an economic impact assessment will be submitted only if requested by the Commissioner after the citizen petition has been reviewed (U.S. FDA, 2016b).

[10] 21 CFR §25.32(p) states the following: *"Issuance, amendment, or revocation of a regulation in response to a reference amount petition as described in 101.12(h) of this chapter, a nutrient content claim petition as described in 101.69 of this chapter, a health claim petition as described in 101.70 of this chapter, or a petition pertaining to the label declaration of ingredients as described in 10.30 of this chapter."*

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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