Food Standards Agency
food.gov.uk

Andreas Klepsch
European Commission, DG SANCO
Brussels B-1049
sent by email

7 December 2012

Dear Mr Klepsch

INITIAL OPINION: ISOMALTO-OLIGOSACCHARIDE AS A NOVEL FOOD INGREDIENT

In February 2009, an application was accepted by the UK Competent Authority from Bioneutra Inc. for authorisation of Isomalto-oligosaccharide as a novel ingredient in accordance with Article 4 of Regulation (EC) 258/97.

The Advisory Committee on Novel Foods and Processes (ACNFP) reviewed this application and their opinion is attached.

In view of the ACNFP's opinion, the UK Competent Authority considers that Isomalto-oligosaccharide, for use in the foods proposed by the applicant at levels between 5 and 15.6 g/serving, meets the criteria for acceptance of a novel food, as set out in Article 3(1) of Regulation 258/97.

Yours sincerely,
(By email only)

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ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR ISOMALTO-OLIGOSACCHARIDE

Applicant:	**Bioneutra Inc.**
Responsible Person:	**Mohammed Qureshi**
EC Classification:	**2.2**

Introduction

1. An application was submitted to the Food Standards Agency in February 2009 by Bioneutra Inc. for the authorisation of isomalto-oligosaccharide (IMO) as a novel ingredient in the EU. A copy of the application was placed on the Agency's website for public consultation in 2009.

2. IMO preparations generally consist of glucose oligomers with degrees of polymerisation of 3 to 10, depending on the method of production, along with variable amounts of monomeric and dimeric material.

3. The applicant's dossier refers to the intended use of IMO as a prebiotic dietary fibre. In subsequent correspondence the applicant clarified that they are seeking authorisation of their IMO as a general food ingredient and any references to fibre and prebiotic effects are not intended to be claims (see Section XIV below)

4. Other disaccharides have previously been considered and authorised under Regulation (EC) 258/97 which also have a sweet taste (tagatose, trehalose, isomaltulose) during which time their status as a sweetener and/or novel ingredient has been questioned. However, the regulatory framework for food additives now clarifies this issue. Article 3 of Regulation (EC) No 1333/2008 on food additives states:

   "The following are not considered to be food additives: monosaccharides, disaccharides or oligosaccharides and foods containing these substances used for their sweetening properties;"

5. IMO has been classified as a complex novel food from non-GM source, the source of the novel food has a history of food use in the EU (class 2.2) according to the scheme in Commission Recommendation 97/618 (EC).

Specification of the novel food

Information on this aspect is provided on p. 9-14 of the application dossier

6. The applicant proposes to market IMO in powder and syrup forms. The powder form is white and crystalline, while the syrup is a, pale yellow liquid. Both forms are approximately 50% as sweet as sucrose. On a dry basis, the IMO is prepared so that the content of isomaltose and larger oligoosaccharides (with 3-9 degrees of polymerisation) is not less than 90% while glucose content is no more than 5%. The IMO does not contain any detectable levels of heavy metals.

7. Batch on batch variation was assessed by analyses of different lots of IMO from the same starch source (3 separate lots of syrup and 2 separate lots of powder). The results of these analyses indicated a narrow range of variation in composition and contaminants and showed that all batches analysed met the required specification criteria for the IMO, as set out in Tables 1.7.2-1 to -4 of the dossier.

8. A number of other companies also manufacture IMO preparations, not for sale in the EU, which differ in the proportions of mono, di, tri, oligo and polysaccharide constituents.

***Discussion**: The Committee did not have any concerns relating to the general specifications of IMO. It was noted however, that the applicant had originally provided safety data based on IMO from other sources rather than its own product. The Committee highlighted that IMO preparations are variable and the data provided by the applicant were of limited value for a safety assessment. This aspect will be discussed further below under the appropriate sections.*

II. Effect of the production process applied to the novel food

Information on this aspect is provided on p 15-24 of the application dossier

9. The applicant's IMO is produced via enzyme-catalysed hydrolysis of food grade starch from different cereal crops. Details are provided in the confidential dossier.

10. The applicant has provided confidential details of the specifications and regulatory status of the enzymes used in the production of its IMO in

Appendix D of the dossier along with details of all other raw materials used.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

III. History of the organism used as a source of the novel food

Annex 1, p 25-28

11. The unmodified food-grade starch used as a raw material for the production of IMO is obtained from commonly available cereal crops such as barley, corn, oats, rice and other starch sources such as cassava, potato and pulses (peas, beans and lentils).

12. The applicant has advised that IMO are naturally present in foods such as honey, soy sauce, sake and miso and have been ingested by humans for hundreds of years particularly in Japan and other Asian countries. IMO have been approved in Japan for use in Foods for Specified Health Use (FOSHU) and it is now estimated that Japanese consumers intake of IMO from formulated foods now exceeds that from traditional food sources. In the US, Bioneutra's IMO product has been incorporated into foods (energy bars and beverages) for over two years.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

IX. Anticipated intake/extent of use of the novel food

Information on this aspect is provided on p 29-35 of the application dossier

13. The applicant intends to incorporate IMO into a variety of conventional foods and also certain foods for particular nutritional uses (meal replacement bars and milk based meal replacements). The applicant states that IMO will be added to foods at maximum levels of up to 15.6 g/serving and the applicant suggests that a daily intake will not exceed 31.2g/day, assuming that a person will consume no more than two servings per day. A list of products and the proposed food uses and levels can be found below.

Summary of the individual proposed food uses, maximum use-levels, and amounts per serving of Bioneutra's IMO in the EU

Food category	Proposed food uses	Serving size (g)	Maximum use level (%)	IMO per serving (g/serving)
Beverages	Regular Soft Drinks	240	5	12
	Energy-Reduced Soft Drinks	240	6.5	15.6
	Energy Drinks	240	5	12
	Sports & Isotonic Drinks	240	6.5	15.6
	Fruit Juices	140	5	12
	Processed Vegetables and Vegetable Juices	100	5	12
Cereals products	Cereals Bars	50	10	5
	Cookies, Biscuits	40	20	8
	Breakfast Cereal Bars	50	25	12.5
Sugar confectionery	Hard Candies	10	97	9.7
	Soft Candies/Chocolate Bars	30	25	8.2
Nutritionally complete and fortified foods	Meal Replacement Bars	40	20	8
	Milk based Meal Replacement	40	20	8

14. Intakes were estimated for a range of population groups using information from the most recent publicly-available data from National Diet and Nutrition Surveys (NDNS). The tables below provide a breakdown of these estimates, as supplied by the applicant.

Summary of the estimated intake of IMO from all proposed food categories in the UK by population group (NDNS Data)

Population Groups	Age Group (years)	% Users	All-Person Consumption (g/day)				All-Users Consumption (g/day)			
			Mean	Percentile			Mean	Percentile		
				90th	95th	97.5th		90th	95th	97.5th
Children	1½ - 4½	98.3	15.3	29.5	35.3	38.3	14.2	21.6	26.8	28.3
Young People	4-10	99.6	26.7	44.8	51.8	62.1	26.7	44.8	51.8	62.1
Female Teenagers	11-18	99.3	24.8	45.5	53.7	63.3	24.9	45.5	53.9	63.3
Male Teenagers	11-18	99.5	33.4	59.5	69.2	86.7	33.5	39.5	69.2	86.7
Female Adults	16-64	88.1	8.1	19.3	25.8	34.3	9.2	20.7	26.5	36.7

Male Adults	16-64	85.3	9.0	22.5	33.1	40.8	10.6	24.4	35	41.5

Summary of the estimated intake per kilogram body weight intake of IMO from all proposed food categories in the UK by population group (NDNS Data)

Population Groups	Age Group (years)	% Users	All-Person Consumption (g/kg bw/day)				All-Users Consumption (g/kg bw/day)			
			Mean	Percentile			Mean	Percentile		
				90th	95th	97.5th		90th	95th	97.5th
Children	1½ - 4½	98.3	0.8	1.1	1.7	1.9	0.9	1.2	1.6	1.8
Young People	4-10	99.6	0.9	1.3	1.8	2.1	0.9	1.6	2.0	2.5
Female Teenagers	11-18	99.3	0.4	0.8	0.9	1.1	0.4	0.8	0.9	1.3
Male Teenagers	11-18	99.5	0.6	1.1	1.4	1.6	0.6	1.1	1.4	1.6
Female Adults	16-64	88.1	0.08	0.3	0.4	0.5	0.1	0.3	0.4	0.5
Male Adults	16-64	85.3	0.08	0.2	0.4	0.6	0.1	0.3	0.5	0.6

15. On an all-user basis, the highest mean and 97.5th percentile intakes of IMO by the UK population from proposed food uses in the EU were observed in male teenagers and estimated to be 33.5 and 86.7 g/person/day, respectively. Young people (age 4-10) consumed the greatest amount of IMO on a body weight basis with the highest mean and 97.5th percentile all-user intakes of 0.9 and 2.5 g/kg body weight/day, respectively. These are “worst-case” estimates, based on the assumption that all possible foods contain IMO at the maximum levels given in the table above.

Discussion*: The Committee did not raise any issues with this section of the dossier.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p 36-57 of the application dossier

16. The dossier reports the results of nutritional and toxicological studies conducted with IMO preparations from different manufacturers. The applicant has provided information on the composition of Bioneutra’s product compared to IMO from other sources (p 51 of the dossier). The applicant did not view the compositional differences (due mainly to

differences in proportions of various oligomers) to be a concern and stated that since production of IMO mixtures occurs via natural enzymatic processes, some compositional variability between different products is expected.

17. The applicant stated in the dossier that IMO has a calorific value of 1.5-2 kcal/g based on typical values for non-digestible and poorly digestible carbohydrates compared with 4 kcal/g for fully digestible carbohydrates.

18. The applicant stated in its dossier that its IMO functions as a prebiotic dietary fibre and is closely related to fructo-oligosaccharide (FOS) in terms of functional benefits[1]. The applicant mentioned that its IMO is poorly digestible as it is resistant to digestion in the human stomach and small intestine, but it can be partially broken down in the colon by bacterial species (mainly bifidobacteria and lactobacilli).

19. Although not of direct relevance to a safety evaluation, the applicant described several studies illustrating the prebiotic effects of various IMO preparations (from other manufacturers). The majority of studies reveal that IMO consumption is associated with a significant increase in gut bifidobacteria and lactobacilli. The lowest effective dose of IMO to function as a prebiotic was reported to be 8-10g/day, compared to 1g/day for the prebiotic action of FOS.

20. The applicant also provided details of published studies investigating the fermentation of IMO (from other manufacturers) by gut bacteria. Fermentation of non-digestible oligosaccharides in the colon by gut bacteria can produce short chain fatty acids (SCFA) such as acetate, propionate and butyrate, generally thought to be beneficial to gut health, although there is conflicting evidence relating to the effects of butyrate production in the lower sections of the GI tract. Data presented in the dossier shows that SCFA were produced as a result of IMO administration in some studies but the types and amounts of SCFA varied and there was no evidence of butyrate production. Additional data to evaluate the nutritional quality of IMO are presented in the dossier. Animal studies generally support the partial hydrolysis of IMO in the upper intestine, with the remaining proportion passing into the lower

[1].The Committee disputed this statement, noting that IMO is chemically and structurally different to FOS and its microbiological effects in the gut are likely to be different.

intestine. However, one human study (Oku and Nakamura, 2003) suggested that IMO was not subject to extensive fermentation in the large intestine.

21. The applicant subsequently provided additional analytical data to show that approximately 70% of its IMO is in the form of oligosaccharides that are resistant to digestion in the small intestine. The applicant also provided a letter from Health Canada stating that the applicant's IMO has an available energy value of 2.4 kcal/g. Health Canada has also advised that approximately 80% of the applicant's IMO is digestion resistant and that IMO is regarded as a source of dietary fibre. (The applicant has explained that this 80% value was obtained by considering IMO preparations from a range of manufacturers, while the 70% value mentioned above relates solely to the applicant's IMO.)

22. In response to a request from the Committee, the applicant conducted a four week human tolerance study with their IMO preparation. Adults were given doses of 36g or 54g per day in three divided doses. No serious adverse effects were reported during the study and there were no significant changes in the frequency of bowel movements, although seven out of nineteen subjects in the high dose group reported diarrhoea. No statistically significant differences were observed relating to clinical chemistry parameters or biochemistry. The applicant concluded that the dose of 36 g/day was well tolerated, safe and did not contribute to worsening of GI symptoms.

23. The new study also investigated glucose/insulin responses to the applicant's IMO. The data indicated that IMO produces a similar blood glucose profile and insulin response to the glucose control. The study also indicated that IMO had a prebiotic effect, as determined by increases in numbers of bifidobacteria and lactobacilli in faeces ($p=0.049$ and $p=0.058$ respectively), although there were no significant changes in faecal levels of volatile fatty acids.

***Discussion**: Given the variability of IMO preparations from different manufacturers, the Committee asked the applicant to provide data from human studies on its own product in order to determine the extent of absorption and to investigate tolerance. The Committee also asked the applicant for information on the effects of its IMO preparation on serum glucose/insulin levels, bearing in mind the potential to mislead diabetics*

who might consume the product because they have perceived it to be a prebiotic dietary fibre rather than a mixture of carbohydrates that may be largely or fully absorbed.

The Committee noted that plasma glucose/insulin responses following administration of the applicant's IMO were almost identical to those following the same dose of glucose, which is inconsistent with the applicant's claim that the majority of the oligosaccharides in IMO are resistant to digestion.

The applicant argues that, in order to assess the metabolic behaviour of IMO, it is essential to consider not only the glucose/insulin profiles but also the other observations in the new human study e.g. IMO administration exhibited a prominent prebiotic effect and resulted in increased short chain fatty acid production and other factors such as increased defecation frequency, indicating that part of the dose ended up in the colon for fermentation by gut microbiota,

The applicant has acknowledged that its IMO preparations are partly digestible, being a mixture of partially digestible and digestion resistant short chain carbohydrates, and an increase in blood glucose and insulin levels would be expected to occur following intake of IMO. As a significant proportion of IMO is absorbed as glucose, the applicant agreed that IMO will not be marketed as suitable for diabetics.

Based on the data provided by the applicant, the Committee was not convinced that this product has a significantly reduced energy content, compared with other digestible carbohydrates.

XII. Microbiological information on the novel food

Information on this aspect is provided on p.14, p58-59 of the application dossier

24. Microbiological specifications for IMO are presented below:

Specification parameter	**Specification**
Total aerobic plate count (CFU/g)	<10, 000
Yeast (CFU/g)	< 100
Escherichia coli (MPN/g)	< 10
Salmonella (CFU/g)	Absent (i.e. <1 CFU per gram or ml)

25. Analyses of five different batches of IMO showed that all batches complied with set specifications.

***Discussion**: The Committee did not raise any concerns or questions on this aspect of the application.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p. 60-79 of the application dossier

26. The applicant's dossier summarised a series of data relating to toxicological tests and human tolerance of IMO (from other manufacturers). A summary of these data can be found at Annex A.

***Discussion**: The Committee did not raise any toxicological concerns relating to IMO products in general, but did request that the applicant investigates human tolerance to its own IMO preparation which the applicant has addressed as above. The Committee was satisfied that the data from the applicant's new human study provide reassurance that there are no concerns relating to tolerance at the proposed intake levels.*

XIV. Allergenicity and labelling

Information on this aspect is provided on p.72 of the application dossier

27. The applicant has stated that allergenicity issues are unlikely to be a concern as IMO is subjected to extensive purification (including filtration and cation and anion exchange chromatography) as part of the production process to minimise the possibility of contamination with residual enzymes, other proteins or yeast.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier. The Committee's assessment focuses on safety and labelling, it does not address any nutrition or health benefits that may be claimed for the novel ingredient or for foods that contain it. Nutrition or health claims may only be made if they are specifically authorised under EU Regulation (EC) No 1924/2006. IMO will need to be labelled in accordance with requirements for food allergens if it is derived from one of the allergenic crops identified in EU labelling legislation,[2] unless a specific exemption is obtained following an evaluation by EFSA.*

[2] Directive 2000/13/EC and Regulation (EU) 1169/2011.

CONCLUSION

The Committee concluded that there were no safety concerns relating to IMO, provided that it is labelled as unsuitable for diabetics.

The Committee noted that there are conflicting data on the digestibility of IMO preparations. The most recent clinical study, which was conducted with the applicant's product, showed that plasma glucose and insulin responses were very similar to those for glucose, which suggests that the product is well digested in the small intestine.

While the Committee did not regard this as a safety issue, it will have implications for the labelling of products containing IMO, particularly for the energy value of the product, and for any claims that it functions as a dietary fibre or prebiotic. The EU has adopted specific criteria for claims that a food is a "source of fibre" and the labelling of any foods containing IMO will need to comply with this legislation (i.e. Regulation 1924/2006 on nutrition and health claims). According to the same Regulation, prebiotic claims can only be made when they have been validated by the European Food Safety Authority and specifically authorised at EU level.

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