

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES**ISOMALTO-OLIGOSACCHARIDE****ISSUE**

An application has been submitted to the UK Competent Authority for authorisation of isomalto-oligosaccharide under the novel foods regulation (EC) No 258/97. The Committee is asked to advise whether the available data provide an adequate basis for a safety assessment of this novel ingredient, and if it recommends authorisation of the product.

Background

1. An application has been submitted by a Canadian company, Bioneutra, Inc., for authorisation of isomalto-oligosaccharide as a novel ingredient in the EU. The application was accepted by the UK Competent Authority on 5 January 2009. In accordance with Article 6(3) of Regulation (EC) No 258/97, the UK has 3 months to prepare an initial assessment report on the application. The initial assessment will then be circulated for review by the Competent Authorities in the other member States.
2. Isomalto-oligosaccharides (IMO) are mixtures of glucose oligomers with alpha-(1-6) linkages such as isomaltose, panose, isomaltotriose, isomaltopentose and higher branched oligosaccharides. The novel ingredient (NI) from Bioneutra is composed of mono- and di-saccharides (15-20%), oligosaccharides of three to six degrees of polymerisation (70-80%) and larger oligomers of seven to nine glucose units (up to 10%).
3. The applicant intends to incorporate the NI (powder and syrup forms) into a range of food products as a nutritive sweetener and prebiotic dietary fibre. Other disaccharides have previously been considered 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 recently agreed new 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;"

4. The present application for authorisation of the NI was prepared pursuant to Commission Recommendation (97/618/EC) of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. The NI has been classified as a complex novel food from non-GM source, the source of the novel food has no history of food use in the EU (class 2.2). The requirements for a submission for this class are as follows:

I	Specification of the NF	X	<i>VIII</i>	<i>Ability to survive in and colonise the human gut</i>	-
II	Effect of the production process applied to the NF	X	IX	Anticipated intake/extent of use of the NF	X
III	History of the organism used as the source of the NF	X	<i>X</i>	<i>Information from previous human exposure to the NF or its source</i>	-
<i>IV</i>	<i>Effect of the genetic modification on the properties of the host organism</i>	-	XI	Nutritional information on the NF	X
<i>V</i>	<i>Genetic stability of the GMO</i>	-	XII	Microbiological information on the NF	X
<i>VI</i>	<i>Specificity of expression of novel genetic material</i>	-	XIII	Toxicological information on the NF	X
<i>VII</i>	<i>Transfer of genetic material from GM microorganisms</i>	-			

The information presented in the dossier is structured accordingly and is considered below under these schemes.

5. The application dossier is attached as Annex 1, and contains eight appendices (A-H). A non-confidential version of the application dossier has been placed on the FSA website to allow the public to contribute to the assessment and the deadline for replies is 10 February. Any comments received will be tabled at the meeting

I. Specification of the novel food

Annex 1, p 9-14

6. The applicant proposes to market the NI 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 NI is prepared so that the content of isomaltose and larger oligosaccharides (with 3-9 degrees of polymerisation) is not less than 90% while glucose content is no more than 5%. The NI does not contain any detectable levels of heavy metals. Microbiological specifications are summarised in paragraph 22.
7. Batch on batch variation was assessed by analyses of different lots of the NI from the same starch source (3 separate lots of syrup and 2 separate lots of

powder), Annex 1, p 13-14. 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 NI, as set out in Tables 1.7.2-1 to -4 of the dossier.

8. Members should note that 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 (see paragraph 17 below).

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

Annex 1, p 15-23

9. The NI is produced via enzyme-catalysed hydrolysis of food grade starch from different cereal crops. A series of downstream processes are employed to remove impurities. Following concentration by evaporation, syrup manufacture is complete, whereas an additional spray drying process is employed to produce the powder.

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

Annex 1, p 25-28

10. The unmodified food-grade starch used as a raw material for the production of the NI is obtained from a wide variety of different commonly available crops.
11. 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 to be placed on the Foods for Specified Health Use (FOSHU) ingredient list and it is now estimated that more IMO are now consumed in Japan from formulated foods than traditional food sources. In the US, Bioneutra's IMO product has been incorporated into foods (energy bars and beverages) for the last two years.

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

Annex 1, p 29-35

12. The applicant intends to incorporate the NI 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 the NI 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. The applicant offers no evidence to support this assumption. A list of products and the proposed food uses and levels can be found below.

Summary of the individual proposed food-uses, use-levels, and amount per serving of Bioneutra's IMO in the E.U.

Food Category	Proposed Food-Uses	Serving Size (grams)	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	5.0	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

13. Intakes were estimated for a range of population groups using information from the most recent NDNS surveys available to the public. The table below provides a breakdown of the NDNS results as supplied by the applicant.

Summary of the Estimated Daily Intake of IMO from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)

Population Groups	Age Group (years)	% Users	All-Person Consumption				All-Users Consumption			
			Mean (g)	Percentile (g)			Mean (g)	Percentile (g)		
				90th	95th	97.5th		90th	95th	97.5 th
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 Daily per Kilogram Body Weight Intake of IMO from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)

Population Groups	Age Group (years)	% Users	All-Person Consumption				All-Users Consumption			
			Mean (g/kg)	Percentile (g/kg)			Mean (g/kg)	Percentile (g/kg)		
				90 th	95 th	97.5 th		90 th	95 th	97.5 th
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

14. On an all-user basis, the highest mean and 97.5th percentile intakes of the NI 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 the NI 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 the NI at the levels given in the above table.

XI. Nutritional information on the novel food

Annex 1, p 36-57

15. 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 (Annex 1, p 51). The applicant does not view the compositional differences (due mainly to differences in proportions of various oligomers) to be a concern and states that since production of IMO mixtures occurs via natural enzymatic processes, some compositional variability between different products is expected. The dossier highlights that Bioneutra affirmed in March 2007 that their product is GRAS (generally regarded as safe, as defined in US legislation). A formal notification has been made to the FDA in December 2007 and the applicant is awaiting the FDA's response. Further details can be found in Annex 1, p 72-73 and Appendix H.

16. The applicant advises that the NI has a calorific value of 1.5-2 kcal/g based on typical values for non-digestible and poorly digestible carbohydrates compared to 4 kcal/g for fully digestible carbohydrates (Annex 1, p 57). Members may wish to note that EC Directive 90/496/EEC on nutrition labelling has recently been amended to include a definition of "fibre", which will contribute 2 kcal/g to the stated energy content of foods. "Fibre" is defined as

"carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine and belong to the following categories:

- edible carbohydrate polymers naturally occurring in the food as consumed;
- edible carbohydrate polymers which have been obtained from food raw material by physical, enzymatic or chemical means and which have a beneficial effect demonstrated by generally accepted scientific evidence;
- edible synthetic carbohydrate polymers which have a beneficial effect demonstrated by generally accepted scientific evidence"

This definition will be implemented in each Member State before 31 October 2009 and it is possible that the NI would fall into the second of the three categories.

17. The applicant describes that the NI functions as a prebiotic dietary fibre and is closely related to fructo-oligosaccharide (FOS) in terms of functional benefits. The applicant advises that the NI is a poorly digestible carbohydrate which is resistant to digestion in the human stomach and small intestine but can be partially broken down in the colon by bacterial species (mainly Bifidobacteria and lactobacilli).
18. Although not of direct relevance to a safety evaluation, the applicant has submitted evidence of 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 (Annex 1, p 41-44 and p 53). 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.
19. The applicant also details studies investigating the fermentation of IMO 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 produced varied and there was no evidence of butyrate production (Annex 1, p 44-45). 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 intestine. However, one human study (Oku and Nakamura, 2003) suggested that IMO was not subject to extensive fermentation in the large intestine.

XII. Microbiological information on the novel food

Annex 1, p 13-14

20. Microbiological specifications are summarised below. All batches of the NI analysed met the following specifications.

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)

XIII. Toxicological information on the novel food

Annex 1, p 61-79

21. The applicant has provided an explanation relating to the metabolism and fate of IMO (Annex 1, p 61-63) and concludes that given the sequential hydrolysis of the smaller oligomers in IMO to glucose, combined with a lack of systemic absorption of the larger oligosaccharides, no toxicologically significant adverse effects related to the administration of the IMO mixture are expected.
22. Mutagenicity and genotoxicity studies: Bacterial reverse mutation assays with and without metabolic activation did not reveal any significant increases in IMO-induced revertant colonies. Likewise, IMO did not significantly increase the number of chromosome aberrations in Chinese hamster lung cells (with and without metabolic activation).
23. Reproductive and developmental studies: The applicant states that no studies investigating the reproductive and developmental toxicity of IMO mixtures have been identified but reassures that given the explanation in paragraph 24 above, systemic toxicity including any adverse effects on reproduction or development are not expected.
24. Subchronic and chronic studies: A summary of oral subchronic and chronic animal studies can be found below; the studies are described in more detail in Annex 1, p 64-67.

Species (Strain, sex, No./group)	Duration	Concentrations (Dose levels)	Results ¹	Reference
Rat (Sprague-Dawley, male, 8/group)	35 days	0 (corn starch) or 20% in diet (~20 g/kg bw/day)	↓ in FUE and TG; No Δ in body weight, body weight gain, food intake, cecal contents, and relative organ weights (stomach, small intestine, cecum, colon, liver, kidney, retroabdominal adipose tissue); No Δ in serum and liver total Ch and PL, and serum HDL-Ch and NEFA.	Kaneko <i>et al.</i> (1992)
Rat (Sprague-Dawley; male; 5-6/group)	42 days	0 (Purina rat chow), 5, 10, or 20% in diet (~0, 5, 10, and 20 g/kg bw/day, respectively)	↑ in weight of cecum at 10 and 20%; ↓ (dose-dependent) in abdominal fat gain (normalized for food intake); No Δ in food intake, body weight gain, and absolute heart, spleen, kidneys, lungs, and brown and white adipose tissue weight.	Day and Chung (2004)
Rat (Wistar, males, 8/group)	365 days (1 year)	0 or 3% in drinking water (~0 and 3-5 g/kg bw/day, respectively)	No Δ in body weight gain and body weights, AST, ALP, LDH, Cre, BUN (↓ 1 st month), UA, T-Ch, TG, WBC, and RBC; ↓ in serum Hb, Ht, and ALT; No gross or histopathological abnormalities. ↑ in <i>Lactobacillus</i> count and <i>Bifidobacterium</i> frequency of occurrence; ↓ <i>Clostridium</i> .	Kaneko <i>et al.</i> (1990)

¹Study-end results unless otherwise indicated; Results are provided for test animals relative to controls.

No Δ = No variations between test and control animals; ALP = alkaline phosphatase; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; BUN=Blood urea nitrogen; Ch=Cholesterol; Cre=Creatinine; FUE=Food utilization efficiency; Hb=Haemoglobin; HDL-Ch=High-density lipoprotein cholesterol; Ht=Haematocrit; LDH=Lactate dehydrogenase; NEFA=non-esterified fatty acids; PL=Phospholipids; RBC=Red Blood Cell count; TG=Triglycerides; UA=Uric acid; WBC=White Blood Count;

25. Human tolerance studies: A summary of human tolerance studies can be found below and further details in Annex 1, p 67-79.

Study Population and study design	Duration	Daily Dose Levels	Results	Reference
9 healthy males (~26 years old) and 29 females (~23 years old)	Single dose	10, 20, or 40 g	No GI disturbances.	Oku and Nakamura (2003)
81 healthy males and 119 females (~30 years old) (8 ingested IMO mix); double-blind placebo-controlled study	7-day run-in and 7-day treatment period	0 (placebo) or 10 g/day (2 equal portions)	↑ (slight) in excess flatus, bloating, borborygmi, and abdominal pains (all mild symptoms) vs. run-in period; however, No Δ in any of the GI symptoms vs. placebo control; None of the subjects experienced diarrhoea.	Bouhnik <i>et al.</i> (2004)
6 healthy males (26-48 years old)	10 days	20 g/day	None of the subjects experienced diarrhoea; only transient increase in flatulence in 2/24 subjects.	Kohmoto <i>et al.</i> (1988)
18 older subjects (5 males and 13 females; 50-93 years old)	14 days			
20 healthy females and 11 males (22 subjects w/ history of constipation) (~27 – 30 years old)	21 days (total) ²	10 or 15 g	No GI disturbances. ↑ Defecation frequency in constipated subjects w/ 15 g IMO mix vs. 1 st week.	Kaneko <i>et al.</i> (1993)
8 male and 12 female hemodialysis patients (~64 years old)	14-day run-in and 28-day treatment period	30 g/day (2 equal portions)	↑ in severity of distension (10%) ¹ , tormina (10.5%), borgorgymi (6.1%), spasms (4.5%) and in bowel movements; No Δ in diarrhoea (5%). <u>Clinical Chemistry</u> ↑ in Hb, Ht, and HDL-Ch vs. run-in; ↓ in Tg, Ch; No Δ in glucose, albumin, total protein; BUN, Cre, Ca ²⁺ , P, and LDL-Ch.	Wang <i>et al.</i> (2001)
7 elderly males w/ history of constipation (~75 years old)	30-day run-in and 30-day treatment period	↑ from 8 to 24 g (1 st 10 days)	↑ in defecation frequency and wet and dry faecal weight per day and stool sample; no reports of GI disturbances. <u>Clinical Chemistry</u> ↑ in Na ⁺ ; No Δ glucose, total protein, albumin, TG, Ch, HDL-Ch, Ca ²⁺ , P, and K vs. run-in.	Chen <i>et al.</i> (2001)

No Δ = No change; BUN = Blood urea nitrogen; Ca²⁺⁺=Calcium; Cre=Creatinine; Ch=Cholesterol; GI=Gastrointestinal; HB=Haemoglobin; HDL-Ch=High-density lipoprotein cholesterol; Ht=Haematocrit; LDL-Ch=Low density lipoprotein cholesterol; K=Potassium; Na⁺=Sodium; P=Phosphorus; TG=Triglycerides.

¹ Percent in parentheses indicates percent of patients experiencing GI symptoms.

² 1st week run-in period; 2nd and 3rd week IMO mix ingestion; 4th week break; 5th week IMO mix ingestion.

26. Although not all studies revealed GI symptoms following ingestion of IMO, mild GI symptoms (not including diarrhoea) have been observed at IMO doses as low as 10g/day. In response to a request by the Secretariat to further clarify this, the applicant states that

“mild GI upset at doses of 10-30g/day is possible in some individuals but not in general, as the maximum dose of IMO that does not cause diarrhoea is estimated at 1.5g/kg body weight, which is higher than for any other sugar substitute” (Oku, 2002, Annex 2) Annex 1, p 32-22, 40 and 77)

The applicant proposes that a product label warning of possible GI effects will address the possibility of susceptibility by certain individuals.

27. The applicant highlights that their GRAS expert panel considered that 30g/day of the NI is expected to be well tolerated (Appendix H, p 14 and 16). The applicant also makes reference to food products containing the NI which have been marketed in the US for over one year (with the recommendations of no more than 30g/day), and states that no public health related issues have been reported to the manufacturing company to date (Annex 1, p 28).

Allergenicity

Annex 1, p 72

28. The applicant views that allergenicity issues are unlikely to be a concern as the NI 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.

Labelling

29. The applicant proposes to label the NI to warn of the possibility of GI effects in susceptible individuals (paragraph 29 above). The applicant has provided other general labelling details in Annex 1, Appendix G. Members should note that EU legislation requires all products derived from wheat to be labelled to indicate their origin unless a specific exemption has been given, following advice from EFSA on the absence of wheat allergens and gluten.

Consumer access and choice

30. The Secretariat has considered the issues of access and choice in relation to the NI. If authorised, the NI would be available for use in products across the UK and subsequently in other EU Member States. In practical terms, access to products containing the NI could be limited by a high price or by limited

geographic distribution, which are both driven by commercial considerations that cannot be predicted at this stage.

31. It is envisaged that the introduction of products containing the NI will increase existing consumer choice. The consumer would be aware of the presence of the NI through the ingredient list and, most likely through special marketing that highlights its contribution to the nutrient composition of foods.

COMMITTEE ACTION REQUIRED

32. The Committee is asked whether the available data provide satisfactory basis for evaluating the safety of this novel food ingredient.
33. If so the Committee is asked whether it is content to recommend approval of Bioneutra's isomalto-oligosaccharide preparation as an ingredient in the foodstuffs listed in paragraph 14.
34. If not, the Committee is asked to indicate what additional data would be required.

**Secretariat
February 2009**

Annex attached:

Annex 1- (Confidential version) Application for the approval of Isomalto-oligosaccharide (IMO).

A non-confidential version of the application dossier is available via the ACNFP website www.acnfp.gov.uk

Annex 2- Reference paper (Oku and Nakamura, 2002): Digestion, absorption, fermentation, metabolism of functional sugar substitutes and their available energy.