Safety Assessment of Alginate-Konjac-Xanthan Polysaccharide Complex (PGX)

Name of Applicant: InnovoBiologic Inc., Canada

Contact person: Simon Wood, Consultant

Introduction

An application for the authorisation of Alginate-Konjac-Xanthan Polysaccharide Complex (hereafter referred to as PGX) as a novel food was submitted to the Food Safety Authority of Ireland (FSAI) by InnovoBiologic Inc. of Canada in accordance with *Article 4* of the novel food Regulation (EC) No. 258/97. The application was accepted by the FSAI on September 5th of 2014.

The novel ingredient is a viscous, water soluble complex of three non-starch polysaccharides, each of which is currently authorised as a food additive in the EU; sodium alginate (E401); konjac-mannan flour (E425) and xanthan gum (E415). PGX is intended for use in a range of foods (including dietary supplements) as a source of dietary fibre. The purported benefits of the complex include a level of viscosity when hydrated that is greater than that for the individual polysaccharides (or simple mixtures) and delayed viscosity development compared to that for konjac which reduces the choking risk.

Dietary fibre is often defined as non-digestible carbohydrates, oligosaccharides, lignin and polysaccharides derived from edible plant material. It is generally resistant to absorption but may be partially or wholly metabolised during fermentation by bacteria in the large intestine. Dietary fibre is considered beneficial for human health with several physiological effects including laxation and lowering of blood cholesterol.

The applicant classes the ingredient as novel based on the altered viscosity of the agglomeration relative to the individual polysaccharides or simple mixtures. While not specified in the dossier, the ingredient could be classed as novel based on *Article 1.2(d) and (e)* of the novel food Regulation (EC) No 258/97 as the individual poly saccharides are derived from plant, microbial and algal sources. The application dossier was prepared pursuant to Class 2 of Commission Recommendation 97/618/EC; "Complex novel food from a non-GM source", and sub-class (1); "the source of the novel food has a history of food use in the Community".

I. Specification of the novel food

PGX consists of three ingredients that are currently authorised in the EU as additives: sodium alginate (E401), konjac-mannan flour (E425) and xanthan gum (E415). The novel ingredient is produced by mixing the individual polysaccharides (predominantly konjac-mannan) under controlled conditions. It is a water soluble, off-white granular powder which is stable for 24 months in a dark and dry environment at room

temperature. The applicant asserts that while the primary structures of the individual polysaccharides remain unchanged, secondary and tertiary non-covalent interactions within the complex result in an increased and delayed viscosity compared to the individual polysaccharides. Studies on physicochemical and rheological properties including sedimentation velocity, selective ^{1}H NMR, flow behaviour and selective precipitation would appear to confirm this assessment. Detailed specifications are provided which include viscosity measurements as well as heavy metal and microbial data.

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

Details of the production process are provided which is carried out in accordance with good manufacturing practices. The production process involves mixing defined proportions of the individual poly saccharide ingredients with water in a fluidised bed reactor at controlled temperatures. The process is entirely mechanical without the use of any chemicals and the final product clarified on the basis of particle size before packaging.

III. History of the source organism

The novel ingredient is a viscous, water soluble complex of non-starch polysaccharides derived from plants, bacteria and seaweed. The individual polysaccharides that make up the PGX complex are currently authorised food additives in the EU; sodium alginate (E401), konjac-mannan flour (E425) and xanthan gum (E415).

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

The applicant intends to market PGX as a source of dietary fibre in a range of foods and beverages as well as in dietary supplements, with a recommended daily intake of 15 g PGX/day (equivalent to 13.5g fibre). This intake recommendation is based on purported health benefits associated with a high fibre diet observed during clinical trials of PGX and provides a level of fibre that is within the 25 g/day of dietary fibre which EFSA concluded was adequate for normal laxation in adults. However, it exceeds the “safe intake” of 13g of PGX/day for a 60kg individual proposed by the applicant in supplementary information provided during the assessment. A worst case scenario where an individual in the total population consumed many of the foods containing PGX at the upper level of intakes (P97.5) along with food supplements could result in the EFSA value of 25 g/day of dietary fibre being exceeded, though this is an unlikely occurrence and therefore not of significant concern. Information was not provided in relation to intakes for users (consumers only). For food groups with large user percentages within a population group (e.g. bread), this would have had little impact and would lead to similar intake results for the total population. However, for food groups with smaller user percentages within a population group, intake estimates are likely to be higher than reported here (e.g. yogurts, cereals, juices, deserts).

The applicant does not identify a target population that would specifically benefit from the consumption of dietary fibre in the form of PGX, but instead proposes labelling advice for certain sub-populations that should not consume it or consume it only under medical supervision. While there is little cause for concern about the potential for over-exposure to PGX, the anticipated intake and extent of use of the novel food is not well defined, possibly due to the combination of theoretical and empirical North American and UK consumption data. Nevertheless, the data provided does provide sufficient assurance that the use of PGX as proposed will provide a safe source of dietary fibre for the EU population.

X. Information from previous human exposure to the novel food or its source

The applicant concludes that while the individual polysaccharides have a history of consumption in the EU as food additives, the specific polysaccharide complex that constitutes PGX does not have a history of consumption in the EU. Food supplements and meal replacements containing PGX are currently on the market in the USA and Canada.

XI. Nutritional information on the novel food

The nutritional value of PGX is limited, with the predominant constituent being carbohydrate in the form of soluble dietary fibre. Dietary fibre is indigestible in the small intestine with any appreciable metabolism carried out by gut microflora in the large intestine. PGX does not contain phytates, oxalates or tannins which are considered to be responsible for the reduced mineral bioavailability sometimes associated with high fibre diets.

XII. Microbiological information on the novel food

The microbiological status of the novel ingredient is controlled by product specifications and supported by test results.

XIII. Toxicological information on the novel food

Konjac glucomannan jelly sweets have been implicated in several choking deaths around the world and have been banned in the EU since 2003. The delayed viscosity of PGX should help to mitigate this risk as will the provision of PGX in dietary supplement form, where the outer casing would shield the fibre from water before it reaches the stomach.

(i) Absorption, distribution, metabolism and excretion (ADME)

Though specific details on the fate of PGX in the GI tract are limited, it is not digestible and any metabolism is limited to fermentation by the microbial population in the large intestine, with the higher molecular weight metabolites and unfermented material excreted in the faeces. The by-products of fermentation in the large intestine include short chain fatty acids, primarily acetate, propionate, butyrate, and lactate, which can be absorbed across the intestinal wall and used as a source of energy by intestinal mucosal cells. The component soluble fibres of PGX are also indigestible

and pass through the small intestine virtually intact, undergoing partial digestion by the microbial flora in the large intestine. Sodium alginate and xanthan gum show limited fermentation in the large intestine but konjac glucomannan is degraded almost completely and undergoes extensive fermentation by the action of gut microbial enzymes.

(ii) Acute and Short-term toxicity

Acute dose or short term preclinical studies conducted on PGX have not been identified. Acute oral intake studies of the component polysaccharides of PGX are limited by their viscous nature rather than by any toxicological effects. However, their consumption does not appear to cause toxicity, with any reduction in bodyweight gain likely occurring as a consequence of reduced calorific intake.

The PGX complex has distinct physical and rheological properties compared to those of the individual polysaccharides, either individually or simply mixed together. The sugar components making up each polysaccharide ingredient are not chemically altered in the PGX agglomeration and though the precise fate of PGX in the gastrointestinal tract is unclear, it is still useful to consider the toxicological information available for the three individual components.

Konjac glucomannan (konjac flour)

Konjac flour has been extensively evaluated and information regarding the safety of konjac flour can be found under the World Health Organisation (WHO) Food Additive Series No 32 and 37. The no-observed-adverse-effect level (NOAEL) of konjac flour is based on 1%, which is equivalent to an intake of 500 mg/kg body weight/day. Konjac flour has been used in traditional East Asian cooking for several hundred years and it continues to be a popular food ingredient and food additive in condiments, pasta, soups and other foods. Significant doses of konjac in animal and human studies (2,000 – 3,000 mg/day in obese children) had no adverse effects on mineral metabolism or absorption or the health status of the individuals.

Sodium Alginate

Safety data for sodium alginate can be found in the WHO Food Additive Series No 5 and 30. An analysis of the research shows that alginic acid and its salts, inclusive of sodium alginate, have an estimated acceptable daily intake for human consumption of 25 mg/kg body weight, though higher doses have been evaluated. Sodium alginate at high levels (175 – 200 mg/kg bw/day) was not found to cause adverse effects other than some mild gastrointestinal upset in some individuals.

Xanthan gum

Safety data for xanthan gum can be found in the WHO Food Additive Series No 21, where several human studies indicated no adverse effects at levels up to 10 – 13 g daily (30th Report of the Joint FAO/WHO Expert Committee, 1987). The ingestion of xanthan as a pre-hydrated gel has been shown to act as a bulking agent in terms of its effects on faecal wet and dry weight and intestinal transit time, with no adverse dietary or physiological effects in tested subjects.

(iii) Repeated dose Toxicity

PGX was tested in a 90-day feeding study in Sprague-Dawley rats at up to 5% of the diet with no evidence of adverse effects on body weight, food consumption, organ weights, histopathology, or clinical pathology reported when compared with the control diet. The NOAEL for PGX was determined as 5% of the diet (3,219 and 3,799 mg/kg of bw/day for male and female rats, respectively). In general, studies and literature on PGX or its components indicate a lack of toxicity at high doses evaluated in long-term feeding studies.

(iv) Genotoxicity and Carcinogenicity

Genotoxicity

An Ames study and an *in vivo* Mammalian Erythrocyte Micronucleus test (MMA) were conducted on PGX according to GLP and OECD 471 (1997) and OECD 474 (1997) respectively (Marone *et al.* 2009). PGX could only be evaluated at up to 100 µg/plate due to solubility constraints in the test system. No biologically relevant increases in revertants were observed in any of the microbial strains, with or without metabolic activation.

The genotoxicity of PGX was also assessed using the micronucleus assay and a biologically relevant increase of micronuclei was not identified at either the 44hr or 68hr time points. A slight statistically significant reduction ($P < 0.05$) in the number of cells with micronuclei was noted in the PGX-dosed groups (males only, 44hr) and the positive control performed as expected, demonstrating the validity of the assay. PGX did not induce structural or numerical chromosomal damage in the immature erythrocytes of the mouse test system.

In general, the published data indicates that PGX and its constituent polysaccharides lack genotoxic activity at the concentrations tested.

Carcinogenicity

There are no carcinogenicity studies available for PGX, though EFSA concluded in 2010 that dietary fibre in general was important for the health of the lower intestine and might reduce the risk of colon cancer.

Two chronic studies and one sub-chronic study investigating the effects on carcinogenesis from sodium alginate and konjac did not reveal evidence of carcinogenic potential.

(v) Reproductive toxicity

There are no reproductive/developmental studies available for PGX, while limited data from animal studies on xanthan gum and sodium alginate did not identify any adverse effects on reproduction.

(vi) Clinical trials

Clinical trials studying the effect of PGX on satiety, glucose control, insulin sensitivity, weight management and metabolic response demonstrated that PGX is well tolerated in humans, with no toxicological or adverse side effects evident.

(vii) Allergenicity

The consumption of the component polysaccharides of PGX as food additives has not been associated with any concerns related to allergenicity. A literature study did not identify any evidence of an allergenicity threat posed by PGX. Therefore, allergenicity arising out of the low protein content of PGX is not a significant concern.

Conclusions

PGX represents a novel source of fibre that purports to delay the transit and digestion of food in the gut while adding little calorific value to foods or supplements containing it. Its existence on the North American market along with a positive safety record of the individual polysaccharide components as food additives in the EU provides a level of assurance as to the safety of the novel ingredient. Safety concerns relating to a possible choking hazard are mitigated by the delayed viscosity facilitated by the agglomeration of individual polysaccharides in the PGX complex, while in supplement form the encapsulated novel ingredient is protected from water during the early part of digestion.

The applicant proposes a number of advice or warning statements on products that contain PGX so that groups such as children and people with swallowing difficulties can avoid them, while diabetics, people on cholesterol lowering medication and pregnant or breast feeding women would consume them only after medical consultation. Such warnings are considered necessary for consumer protection but may need to be simplified if they are to be practical and effective. In addition, a more targeted marketing approach (e.g. a reduction in the number of food categories selected for PGX supplementation) in conjunction with warning labels may help to further reduce the risk of consumption by people who do not need to increase their fibre intake. For example, potential snack foods such as “Dairy desserts and puddings” (ice cream, milkshakes frozen yoghurts) and biscuits are more likely to be consumed by children relative to other food categories.

Recommendation

On the basis of the information provided by the applicant, along with subsequent clarifications, the Food Safety Authority of Ireland has not identified any safety concerns with the consumption of foods or food supplements containing PGX at the proposed use levels. Adequate advice should be provided to consumers to help avoid consumption by people who do not need to increase their fibre intake or those who should only consume PGX after medical consultation.
Therefore, the FSAI considers that this novel ingredient, produced by InnovoBiologic Inc. of Canada meets the criteria for novel food set out in *Article 3.1.* of the novel food Regulation (EC) No 258/97.