Scientific Opinion on the safety of alginate-konjac-xanthan polysaccharide complex (PGX) as a novel food pursuant to Regulation (EC) No 258/97

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Safety of alginate-konjac-xanthan polysaccharide complex (PGX) as a novel food pursuant to Regulation (EC) No 258/97

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Marco Vinceti, Peter Willatts, Karl-Heinz Engel, Rosangela Marchelli, Annette Pöting, Morten Poulsen, Josef Rudolf Schlatter, Emanuela Turla and Henk Van Loveren

Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on alginate-konjac-xanthan polysaccharide complex (PGX) as a novel food (NF) submitted pursuant to Regulation (EC) No 258/97. The NF is an off-white granular powder composed of three non-starch polysaccharides: konjac glucomannan, xanthan gum and sodium alginate. The information provided on the composition, the specifications, the batch-to-batch variability and the stability of the NF is sufficient and does not raise safety concerns. The production process is sufficiently described and does not raise concerns about the safety of the NF. The applicant intends to add the NF to a variety of foods as well as to market the NF in capsules. The recommended maximum daily intake of the NF from fortified foods and food supplements is 15 g. The target population proposed by the applicant is adults from 18 to 64 years of age. Considering the no observed adverse effect level of 1.8 g/kg body weight (bw) per day in a subchronic toxicity study with PGX and the highest mean and 95th percentile anticipated daily intake of NF from fortified foods, the margin of exposure (MoE) is 12 and 6, respectively, whereas the MoE for the NF from food supplements is 9. The Panel concludes that the safety of the novel food, PGX, for the intended uses and use levels as proposed by the applicant, has not been established.

Keywords: PGX, konjac glucomannan, xanthan gum, sodium alginate, novel food, ingredient, safety

Requestor: European Commission following an application by InovoBiologic Inc.

Question number: EFSA-Q-2015-00469

Correspondence: nda@efsa.europa.eu

Panel members: Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Dominique Turck, Henk Van Loveren, Marco Vinceti and Peter Willatts.

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Summary

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on alginate-konjac-xanthan polysaccharide complex (PGX) as a novel food (NF) submitted pursuant to Regulation (EC) No 258/97 of the European Parliament and of the Council. The assessment follows the methodology set out in Commission Recommendation 97/618/EC. The assessment is based on the data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections of a scientific nature raised by the other Member States and the responses of the applicant.

The NF is an off-white granular powder composed of three non-starch polysaccharides (NSP): konjac glucomannan, xanthan gum and sodium alginate. These NSP are mixed in a specific ratio, which has been claimed proprietary and confidential by the applicant, and processed by a proprietary process. The information provided on the composition, the specifications, the batch-to-batch variability and the stability of the NF is sufficient and does not raise safety concerns. The production process is sufficiently described and does not raise concerns about the safety of the NF.

The applicant intends to add the NF to a variety of foods such as yoghurt, breads, biscuits, cereals, pasta and juices. The applicant also intends to market the NF in capsules (750 mg NF per capsule). The recommended maximum daily intake of the NF from fortified foods and food supplements is 15 g. The target population proposed by the applicant is adults from 18 to 64 years of age.

By using individual data from the European Union (EU) dietary surveys and the maximum proposed use levels for the NF, the mean and 95th percentile anticipated daily intake of the NF were estimated (range of mean: 0.06–0.15 g/kg body weight (bw) which corresponds to 4.2–10.5 g/day based on an adult bw of 70 kg; range of 95th percentile: 0.16–0.30 g/kg bw which corresponds to 11.2–21 g/day based on an adult bw of 70 kg). The Panel notes that the estimate of the 95th percentile anticipated daily intake of the NF from fortified foods would exceed the recommended maximum daily intake as proposed by the applicant (15 g/day). However, the Panel notes that this intake estimate is based on the conservative assumption that all proposed food items from all food categories consumed by an individual actually contain the NF at the maximum proposed level of use. The recommended maximum intake of the NF from food supplements is 13.5 g/day (which corresponds to 0.19 g/kg bw per day for an adult bw of 70 kg).

Based on the nature of the NF, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

Owing to its high water-holding capacity, when consumed with foods or beverages, the NF is able to increase the volume and viscosity of gastric content, thereby affecting how material passes through the digestive tract. A human study and an *in-vitro* study on PGX indicate that the NF is fermented by the human intestinal microbiota.

Considering the nature of the NF, the Panel considers that the information provided does not raise concerns with respect to genotoxicity of the NF.

A subchronic toxicity study in Sprague–Dawley rats, which received a diet containing 0% (control), 1.25%, 2.5% or 5% of PGX for 13 weeks showed statistically significant increases in serum activities of alanine transaminase (ALT) and aspartate transaminase (AST) in females in the high-dose group. These effects, which indicate a toxic effect on the liver, were considered critical by the Panel. Therefore the mid-dose, i.e. 2.5% PGX in the diet corresponding to 1.8 g/kg bw per day, was set as the no observed adverse effect level (NOAEL) for this study.

Based on the results of repeated dose toxicity studies with the individual NSP of PGX as well as with other types of fibre, the Panel considers that it is not possible to conclude whether or not increases in ALT and AST activity in rats (as observed in the provided 90-day repeated-dose toxicity study with PGX) are related to the three individual NSP of PGX or other fibre in general or to exclude that the increases in ALT and AST activity in rats are specific to the NF.

Two double-blind, placebo-controlled intervention studies in adults, who were randomised to consume PGX (at doses up to 10 and 15 g/day) or placebo for 3 or 14 weeks, respectively, reported minor within-group increases in AST and ALT levels in the PGX group at week-3 and week-6 as compared to baseline, respectively. Although the Panel considers that the magnitude of increases in AST and ALT levels observed in these two human studies are not clinically relevant, the human data are not sufficient to draw conclusions on the effect of chronic consumption of PGX at the proposed maximum use levels on liver enzymes.

Considering the NOAEL of 1.8 g/kg bw per day and the highest mean and 95th percentile anticipated daily intake of NF from fortified foods the margin of exposure (MoE) is 12 and 6, respectively, whereas the MoE for the NF from food supplements is 9.

The Panel considers that the MoE for the NF at intended uses and use levels is not sufficient for the target population.

The Panel concludes that the safety of the novel food, PGX, for the intended uses and use levels as proposed by the applicant, has not been established.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

On 11 September 2014, the company InovoBiologic Inc. submitted a request under Article 4 of the Novel Food Regulation (EC) No 258/97[1] to place on the market alginate-konjac-xanthan polysaccharide complex (PGX) as a novel food (NF).

On 20 February 2015, the competent authority of Ireland forwarded to the Commission its initial assessment report, which came to the conclusion that alginate-konjac-xanthan polysaccharide complex (PGX) meets the criteria for acceptance of a NF defined in Article (3)1 of Regulation (EC) No 258/97.

On 2 March 2015, the Commission forwarded the initial assessment report to the other Member States (MS). Several MS submitted comments or raised objections.

The concerns of a scientific nature raised by the MS can be summarised as follows:

- In the specifications, the content for mercury was set above the maximum level permitted in food supplements according to Regulation (EC) No 1881/2006.
- The specifications should include the identification and quantification of PGX complex and impurities.
- Clarifications were needed whether the NF was tested in laboratories which were accredited under an internationally recognised system.
- A MS considered insufficient that the stability data only reported viscosity. No information is provided on whether the NF remains stable over 24 months in the food matrices to which the NF is added.
- Some MS expressed their concerns that the consumption of the NF, especially as a food supplement, on top of the consumption of fibre from the diet, would result in exceeding the EFSA recommended daily intake of fibre (25 g/day).
- Concerns were expressed that some food categories to which the NF is proposed to be added, are likely to be consumed by children (e.g. dairy desserts, puddings and biscuits).
- Concerns were raised on the lack of data on consumption of the NF in amounts greater than 15 g/day.
- The proposed use levels of the NF would lead to exceed the permissible use level of konjac as food additive (1% in foods as indicated in Regulation 231/2012; acceptable daily intake of 3 g/day as recommended by the Scientific Food Committee).
- Concerns were expressed about absorption, distribution, metabolism and excretion of the NF and the potential of the NF to affect absorption of nutrients such as minerals and vitamins.
- In the subchronic oral toxicity study by Matulka et al. (2009), statistically significant differences in some haematological, chemical and urine parameters were reported in the high-dose group as compared with the control group. Some effects were dose-dependent and could not be adequately explained. The high-dose tested in this subchronic toxicity study was applied to humans without the use of an uncertainty factor.
- Potential undesirable effects (such as clumping) in the stomach and intestine should be described.
- Considering the increase in the serum levels of vitamins D and C in the study by Carabin et al. (2009), which lasted 21 days with a dose of 10 g/day of PGX, concerns were expressed on long-term effects of the NF at the maximum proposed use levels.
- The choking risk posed by the NF is difficult to assess, owing to the unknown relative proportion of the three constituents of the NF. The management of choking risk when the NF is added to foods has not been addressed.

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[2], the European Food Safety Authority (EFSA) is asked to carry out the additional assessment for PGX as a NF in the context of Regulation (EC) No 258/97.

[1] Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.

[2] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

EFSA is asked to carry out the additional assessment and to consider the elements of a scientific nature in the comments raised by the other MS.

2. Data and methodologies

2.1. Data

The assessment of the safety of this NF is based on data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections of a scientific nature of the other MS and the responses of the applicant.

In accordance with Commission Recommendation 97/618/EC[3], PGX is allocated to Class 2.1, i.e. 'complex Novel Food from non-genetically modified source, which has a history of food use in the Community'. The data are required to comply with the information required for NF of Class 2.1, i.e. structured schemes I, II, III, IX, X, XI, XII and XIII of Commission Recommendation 97/618/EC. In the current scientific opinion, these structured schemes are listed in Sections 3.1–3.9. The intention is to add the NF to foods and to market the NF as a food supplement. This assessment concerns only risk that might be associated with consumption of the NF under the proposed conditions of use, and is not an assessment of the efficacy of the NF with regard to any claimed benefit.

2.2. Methodologies

The assessment follows the methodology set out in Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. Assessment

3.1. Specification of the Novel Food (NF)

The NF is an off-white granular powder which is composed of three non-starch polysaccharides (NSP): konjac glucomannan, xanthan gum and sodium alginate. Upon EFSA's request, the applicant confirmed that the three NSP are mixed in a specific ratio, which has been claimed proprietary and confidential, and processed by a proprietary process. The alginate-konjac-xanthan polysaccharide complex is named PGX (IUPAC name: α-D-glucurono-α-D-manno-β-D-manno-β-D-gluco), (α-L-gulurono-β-D-mannurono), β-D-gluco-β-D-mannan; CAS: 1189143-55-2). Other names for PGX are: PolyGlycopleX/alginate-konjac-xanthan polysaccharide complex (USP/FCC); polysaccharide complex of konjac glucomannan (konjac), sodium alginate and xanthan gum (polysaccharide complex KAX) (FDA); polysaccharide complex (glucomannan, xanthan gum, sodium alginate) (Health Canada). The NSP in PGX are authorised as food additives in the European Union (EU): konjac glucomannan as (E425 ii), xanthan gum as E 415 and sodium alginate as E 401.

Several patents have been granted for PGX (e.g. in USA, Canada, Australia, Russia, China).

Proximate analysis of one batch of the NF is presented in Table 1.

[3] Commission Recommendation 97/618/EC: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council. OJ L 253, 16.9.1997, p. 1–36.

Table 1: Proximate analysis of the NF

Parameter	Method reference	Result
Total calories	Atwater factors	362 kcal/100 g
Carbohydrates	Calculation	89.7 g/100 g
Total dietary fibre	AOAC 985.29	89.7 g/100 g
Total fat	AOAC 996.06	< 0.10 g/100 g
Protein	AOAC 992.23	0.80 g/100 g
Ash	AOAC 950.14A	6.06 g/100 g
Moisture	AOAC 925.09	4.14 g/100 g

AOAC: Association of Official Analytical Chemists.

The applicant claimed that PGX is a 'novel complex' rather than a mixture of the three NSP. In this respect, different parameters have been compared between PGX and the three NSP: sedimentation, precipitation, viscosity and macromolecular interactions (Abdelhameed et al., 2010; Harding et al., 2011, 2012; Smith et al., 2014).

In the study by Abdelhameed et al. (2010), sedimentation velocity, which was tested with an analytical ultracentrifugation technique, was increased for both PGX and the untreated mixture of the NSP as compared to the single NSP. These observations indicate an interaction within the mixture of the three NSP. This paper reports that there was a considerable amount of unreacted material, particularly at low sedimentation coefficients.

Harding et al. (2011) investigated the structure of each single NSP and the non-covalent intermolecular interactions in the mixture of the three NSP unprocessed or processed with EnviroSimplex® (TM1 and PGX, respectively) by using several analytical techniques (GC/MS, HPAEC/PAD and ^{1}H NMR). There were no changes, which might have occurred during the manufacturing process, in the primary structure of the polysaccharides. The formation of a complex by intermolecular interactions in aqueous solutions was indicated by the flow behaviour of TM1 and PGX solutions, and supported by the rheological behaviour of solutions of ternary mixtures containing variable alginate content, which was enhanced by heat treatment. Sedimentation coefficient distribution analysis from analytical ultracentrifugation supports these observations, showing a clear shift to higher sedimentation coefficients in the heat-treated solutions of ternary mixtures as compared to the unheated material. In another experiment, the addition of Ca^{2+} ions to either TM1 or PGX solutions did not induce precipitation of calcium alginate, which implied that alginate is less accessible to Ca^{2+} ions owing to alternative interactions with the other NSP. The authors concluded that the rheological measurements confirmed that non-covalent interactions occur in aqueous solutions of PGX.

Harding et al. (2012) reported that the intrinsic viscosity of PGX, which was measured with analytical ultracentrifugation, was higher than the predicted value for the unprocessed mixture of the three NSP. The authors concluded that there is a synergistic interaction among the three NSP in PGX, which is sensitive to the ionic strength of the solvent.

Smith et al. (2014) investigated viscosity development over time for PGX and a blend of the three NSP in aqueous solution. This study reported that the rate of dissolution and viscosity development could be controlled by the EnviroSimplex® process, which is used to produce PGX.

According to the applicant, the studies above showed that PGX is a novel complex, in which the primary structure of the NSP was unchanged and non-covalent intermolecular interactions among the NSP occurred, which led to an increase in viscosity as compared to the single NSP.

The applicant also claimed that PGX develops a delayed viscosity as compared to the single NSP. This delayed viscosity makes for a palatable product compared to konjac, which potentially can lead to choking hazards due to rapid viscosity development.

The Panel raised safety concerns on the ability of PGX to form gels (in terms of capacity to absorb water and rate at which viscosity develops) when PGX is consumed. In this respect, the applicant clarified that it takes approximately 25 min for PGX's viscosity to start rising rapidly. The applicant commented that in this time-period a person would consume a food in which PGX has been incorporated and dispersed, and thus avoid problems of oesophageal obstructions.

The non-reversibility of PGX into the three single NSP has not been demonstrated.

PGX specifications

In response to comments from MS and EFSA's requests for clarifications, the applicant revised the specifications for PGX by including parameters on viscosity over time, pesticide residue and residual solvents (ethanol). The applicant clarified that PGX was tested for ethanol as ethanol was used when processing konjac glucomannan. The maximum limit for mercury was reduced to 0.1 ppm. The specifications for the NF with the relative methods of analysis are presented in Table 2. The applicant indicated that the specifications of the NF are in line with the USP/FCC monograph for PGX. Test results for three batches of PGX show compliance with the proposed specifications (Table 3). The applicant provided the certificates of analysis of the starting materials (konjac glucomannan, xanthan gum and sodium alginate), which showed compliance with the specifications for the respective food additives as laid down in the Commission Regulation 231/2012. In particular, the certificate of analysis for xanthan gum showed the absence of *Xanthomonas campestris* in the NF. The applicant indicated that the laboratories where PGX was tested met the requirements in North America.

Table 2: Specifications of the NF

Parameter	Method	Specification
Appearance	Visual	Powder
Colour	Visual	Off-white
Particle size	USP<786>	Monitor
Loss on drying	135°C oven – FCC 9th Ed. 3rd suppl.	NMT 10%
Identification		
Test A (absence of konjac glucomannan)	FCC 9th Ed. 3rd suppl.	Conforms
Test B (absence of sodium alginate)	FCC 9th Ed. 3rd suppl.	Conforms
Test C (absence of xanthan gum)	FCC 9th Ed. 3rd suppl.	Conforms
Test D (viscometric characterisation)	FCC 9th Ed. 3rd suppl.	Conforms
Viscosity[(a)] over time		
10 min	5 g in 350 mL H_2O – FCC 9th Ed. 3rd suppl.	800–10,900 cP
60 min	5 g in 350 mL H_2O – FCC 9th Ed. 3rd suppl.	16,400–42,200 cP
120 min	5 g in 350 mL H_2O – FCC 9th Ed. 3rd suppl.	22,700–45,000 cP
Contaminants		
Lead	ICP	NMT 0.6 ppm
Mercury	ICP	NMT 0.1 ppm
Cadmium	ICP	NMT 0.4 ppm
Arsenic	ICP	NMT 0.6 ppm
Pesticide residue	USP<561>	Meets USP limits
Residual solvents: ethanol	USP<467>	NMT 5,000 ppm
Microbiological parameters		
Standard plate count	USP<61>	NMT 3,000 CFU/g
Yeast and mould	USP<61>	NMT 300 CFU/g
Escherichia coli	USP<61>[(b)]	Negative
Salmonella spp.	USP<61>[(b)]	Negative
Staphylococcus aureus	USP<61>[(b)]	Negative
Pseudomonas aeruginosa	USP<61>[(b)]	Negative

CFU: colony forming units; cP: centipoise; ICP: inductively coupled plasma; min: minutes; NMT: not more than; ppm: parts per million; suppl.: supplement; USP/FCC: United States Pharmacopeia/Food Chemicals Code.
(a): Viscosity is measured on a Brookfield type rotational viscometer at room temperature.
(b): The average microbial counts obtained for the total aerobic count and the total yeast and mould count, must be ≥ 50% and ≤ 200% of those obtained from the positive control inoculum plates.

Table 3: Analysis of three batches of the NF

Parameter	Specification	Batch analysis results		
		Lot number 902310	**Lot number 902870**	**Lot number 903023**
Appearance	Powder	Conforms	Conforms	Conforms
Colour	Off-white	Conforms	Conforms	Conforms
Particle size	Monitor	Not reported	Not reported	Not reported
Loss on drying	NMT 10%	5	5	4
Identification				
Test A (absence of konjac glucomannan)	Conforms	Conforms	Conforms	Conforms
Test B (absence of sodium alginate)	Conforms	Conforms	Conforms	Conforms
Test C (absence of xanthan gum)	Conforms	Conforms	Conforms	Conforms
Test D (viscometric characterisation)	Conforms	Conforms	Conforms	Conforms
Viscosity over time				
10 min	800–10,900 cP	3,500	8,000	8,400
60 min	16,400–42,200 cP	20,700	41,900	41,400
120 min	22,700–45,000 cP	27,500	42,300	43,200
Contaminants				
Lead	NMT 0.6 ppm	0.5	0.5	0.4
Mercury	NMT 0.1 ppm	< 0.1	< 0.1	< 0.1
Cadmium	NMT 0.4 ppm	0.1	0.08	0.07
Arsenic	NMT 0.6 ppm	0.3	0.3	0.5
Pesticide residue	Meets USP limits	Conforms	Conforms	Conforms
Residual solvent: ethanol	NMT 5,000 ppm	Not detected	236	311
Microbiological parameters				
Standard plate count	NMT 3000 CFU/g	1,100	300	100
Yeast and mould	NMT 300 CFU/g	< 20; 20	< 20; < 20	< 20; < 20
Escherichia coli	Negative	Negative	Negative	Negative
Salmonella spp.	Negative	Negative	Negative	Negative
Staphylococcus aureus	Negative	Negative	Negative	Negative
Pseudomonas aeruginosa	Negative	Negative	Negative	Negative

CFU: colony forming units; cP: centipoise; ppm: parts per million; NMT: not more than.

The Panel considers that the information provided on the composition, the specifications and the batch-to-batch variability of the NF is sufficient and does not raise safety concerns.

3.1.1. Stability of the NF

PGX is claimed by the applicant to be stable for 2 years from the date of manufacture when stored in tight containers under a cool, dry environment at room temperature between 15°C and 30°C, away from direct sunlight.

The applicant provided the results on viscosity for two batches of PGX up to 24 and 54 months, respectively. Upon EFSA's request for clarifications on the high and variable viscosity over time for these two batches, the applicant commented that the variability of viscosity was probably due to the analysis being performed by different operators with different instruments.

Based on the data provided and the low water content, the Panel considers that the NF is sufficiently stable.

3.1.2. Stability under the intended conditions of use

No information has been provided by the applicant on the stability on the NF when added to foods.

Upon EFSA's request for clarification on viscosity when PGX is added to foods, the applicant commented that it is not feasible to test PGX in the variety of food matrices to which it is expected to be added.

The Panel considers that no conclusions can be drawn on the stability of the NF when added to foods.

3.2. Effect of the production process applied to the NF

PGX is produced in accordance with Good Manufacturing Practice. Konjac glucomannan, xanthan gum and sodium alginate are tested for compliance to specifications. The NSP are mixed in a specific proprietary ratio, which has been claimed confidential by the applicant. The mixture is placed in the EnviroSimplex® agglomerator (a fluidised bed reactor) with 30–60% wt/wt water at no more than 110°C, for about 20 min. No processing aids are used. The material then passes through several chambers until the product reaches room temperature after a further 40 min retention time in the EnviroSimplex® agglomerator. The resulting complexed polysaccharide is evaluated by Quality Control, packaged and then placed into storage. The final product is available as an off-white granular powder.

Upon EFSA's request for clarifications, the applicant indicated that PGX is packaged in two different particle sizes, one being used for meal replacement in Canada and USA (PGX100), and the other one (PGX300) that is intended to be marketed in EU and has been used in clinical trials.

The Panel considers that the production process is sufficiently described and does not raise safety concerns.

3.3. History of the organism used as a source of the NF

The three NSP which constitute PGX (konjac glucomannan, xanthan gum, sodium alginate) have been authorised as food additives in the EU.

Konjac glucomannan, which is obtained from the tuber of the perennial plant *Amorphophallus konjac*, is a water-soluble high-molecular-weight polysaccharide, consisting of D-mannose and D-glucose units which are connected by β(1-4)-glycosidic bonds. Konjac flour, the unpurified raw product from which glucomannan is isolated, has been used for centuries in traditional Eastern Asian cooking. Both konjac flour and konjac glucomannan are used as food additives. For this purpose, konjac flour (INS No 425) has been evaluated by the Joint FAO/WHO Committee on Food Additives (JECFA) (JECFA, 1993a, 1997). In the EU, the Scientific Committee for Food (SCF) has evaluated konjac glucomannan (E 425 ii) and konjac gum (E 425 i), which is another product derived from konjac flour (SCF, 1997). The Committee could not derive an acceptable daily intake (ADI) for either konjac glucomannan or konjac gum but considered their use, e.g. as a thickener, emulsifier, stabiliser and gelling agent, up to 1% in food acceptable, provided that the total intake from all sources does not exceed 3 g/day. Konjac glucomannan or konjac gum should not be used to produce dehydrated foodstuffs intended to rehydrate on ingestion. Consumption of glucomannan may cause serious choking if used with insufficient fluid (Health Canada, 2010). Konjac glucomannan, which is used as a starting material to produce PGX, meets the specifications for the food additive E425 ii as laid down in the Commission Regulation (EU) No 231/2012.

Xanthan gum is a high-molecular-weight polysaccharide produced by the bacterium *Xanthomonas campestris,* which has been recommended by EFSA to be included in the qualified presumption of safety list of biological agents (EFSA BIOHAZ Panel, 2015). Xanthan gum is an acidic polymer constituted by a cellulose backbone, which has trisaccharide side-chains of mannose-glucuronic acid-mannose linked to every second glucose unit in the main chain. Xanthan gum (INS No 415) was evaluated by JECFA, and the Committee accepted the use as food additive without derivation of a numerical ADI (ADI 'not specified') (JECFA, 1987). The ADI 'not specified' was later endorsed by the SCF (1992). Xanthan gum is used for example as an emulsifier, stabiliser and thickener in foods. Xanthan gum, which is used as starting material to produce PGX, meets the specifications for the food additive E 415 as laid down in the Commission Regulation (EU) No 231/2012.

Sodium alginate is a salt of alginic acid, a polysaccharide extracted from brown seaweed (particularly kelp). The chemical structure consists of blocks of (1,4) linked-β-D-polymannuronic acid, (1,4) linked-α-L-polyguluronic acid and alternating blocks of the two uronic acids. Sodium alginate (INS No 401) has been evaluated by JECFA together with alginic acid and its ammonium, calcium and potassium salts, and the Committee allocated a group ADI 'not specified' (JECFA, 1993b). In the EU, alginic acid and alginates were evaluated by the SCF, which endorsed the JECFA assessment for alginic acid and its sodium, potassium and calcium salts (SCF, 1994). Sodium alginate is used as a gelling

agent, stabiliser and thickener in foods. Sodium alginate, which is used as a starting material to produce PGX, meets the specifications for the food additive E 401 as laid down in the Commission Regulation (EU) No 231/2012.

3.4. Anticipated intake/extent of use of the NF

The applicant intends to add the NF to a variety of foods: Table 4 presents the uses and maximum use levels of the NF. The applicant also intends to market the NF as a food supplement (capsules; 750 mg NF per capsule).

The recommended maximum intake of the NF from all sources (i.e. from fortified foods and food supplements) is 15 g/day. The Panel notes that the consumption of glucomannan in the NF exceeds 3 g/day (SCF, 1997).

The target population proposed by the applicant is adults from 18 to 64 years of age.

Consumers will be instructed to drink 375–500 mL of fluids immediately after the consumption of the NF, whether added to foods/beverages or taken as a food supplement, in order to reduce the risk of bowel obstruction.

The applicant indicates that final products will be labelled to be consumed by low-fibre consumers and not to be consumed by children.

Table 4: Proposed uses and maximum use levels of the NF

Food category	Maximum use level of the NF (g per 100 g)
Yoghurt	1.1
Dairy desserts and puddings (e.g. ice cream, ice cream bars, frozen yoghurt)	0.67
Breads (white and whole wheat)	5
Milkshakes	1.04
Biscuits/cookies	8.3
Cereals (e.g. flaked cereal)	8.3
Cereal bars (breakfast bars, granola type bar)	6.25
Noodles	1.79
Pasta	3.9
Cereal beverage	1.04
Fruit juices and fruit smoothie-type drinks	1.04
Vegetable juices	1.04
Canned fruit	1.79
Single serve combination meals (e.g. Teriyaki chicken, lasagne)	1.0

3.4.1. Anticipated intake from fortified foods

Based on the data from the UK National Diet and Nutrition Survey (NDNS) for 2000–2001 (Hoare et al., 2004) and the proposed maximum use levels, the applicant estimated the daily intake of the NF for adults. The applicant calculated the 97.5th percentile daily intake of the NF by doubling the mean of the daily intake of the NF. The Panel considers that this is not an appropriate method to estimate a high-level of intake.

A detailed assessment to estimate the daily intake of the NF at the maximum proposed use levels, using individual data from EU dietary surveys was performed (EFSA, 2011). Among the EU dietary surveys, the mean anticipated daily intake of the NF for adults ranges from 0.06 to 0.15 g/kg bw (4.2–10.5 g/day based on an adult bw of 70 kg), whereas the 95th percentile anticipated daily intake ranges from 0.16 to 0.30 g/kg bw (11.2–21 g/day based on an adult bw of 70 kg).

The Panel notes that the estimate of the 95th percentile anticipated daily intake of the NF from fortified foods would exceed the recommended maximum daily intake as proposed by the applicant (15 g/day). However, the Panel notes that this intake estimate is based on the conservative assumption that all proposed food items from all food categories indicated in Table 4 consumed by an individual actually contain the NF at the maximum proposed level of use.

3.4.2. Anticipated intake from food supplements

The applicant indicated that the maximum intake of the NF from food supplements is 13.5 g/day (6 capsules of 750 mg of the NF per meal, for a total of 18 capsules per day), which corresponds to 0.19 g/kg bw per day for an adult bw of 70 kg (EFSA Scientific Committee (2012).

3.4.3. Combined intake from fortified foods and foods supplements

Based on the 95th percentile of the anticipated daily intake of the NF from fortified foods, the combined intake of the NF from fortified foods and food supplements would range from 24.7 to 34.5 g/day. The Panel notes that the combined anticipated daily intake of the NF would exceed the recommended maximum daily intake as proposed by the applicant (15 g/day).

3.4.4. Intake of fibre from the background diet

The Panel notes that consumers of the NF would also be exposed to fibre from their background diet. In adults, average fibre intakes from the diet range from 15 to 30 g/day; ranges of fibre intake vary from 6 to 9 g/day (5th percentile) to 39–51 g/day (95th percentile) (EFSA, 2010)).

3.5. Information from previous exposure to the NF or its source

PGX has been sold in Canada and USA since 2004 (as food supplements or added to foods). A total of 58 million single servings of PGX-containing products have been sold. Approximately 1,800 adverse events have been reported (Carabin et al., 2010). The majority of the reported adverse events (around 43%) were related to gastrointestinal symptoms (e.g. heartburn, nausea, abdominal pain/cramps).

3.6. Nutritional information on the NF

Although the NF is a mixture of NSP and as such may be considered as fibre, the applicant suggests an energy conversion factor of 15 kJ/g (3.6 kcal/g) (see Table 1). This assumes that all the ingested NF will be fermented by the colonic microbiota and that resulting degradation products will be absorbed and fully energetically available. The Panel notes that the energy conversion factor used for fibre is 2 kcal/g.[4]

In response to a comment from a MS on the potential effect of the NF on the bioavailability of nutrients, the applicant indicated that consuming PGX is not different from consuming other fibre and referred to the study by Rattan et al. (1981).

The Panel notes that there is little evidence that a high intake of dietary fibre as part of an overall healthy diet will produce significant deleterious effects in healthy people (Wisker et al., 1991; Greenwood et al., 2003; IOM, 2005) and that a tolerable upper intake level is not set for dietary fibre.

The applicant provided publications on animal and human studies on effects of soluble fibre (e.g. cellulose, guar gum, oligofructose, konjac glucomannan meals) on mineral absorption. The Panel considers that no conclusions can be drawn from these studies on an effect of the NF on the bioavailability of minerals.

With regard to concerns raised by MS that the NF might impact bioavailability of minerals and vitamins, the applicant referred to a double-blind, placebo controlled intervention study by Carabin et al. (2009), in which 54 healthy subjects (aged 18–55 years) were randomised to consume either PGX (n = 27, 14 males) or placebo (skimmed milk powder; n = 27, 11 males) with cereals and yoghurt for 3 weeks. After an initial dose of 5 g/day of PGX in the first week, participants consumed 10 g/day of PGX in the second and third week. This study reported plasma levels of sodium, potassium, chloride, calcium, magnesium, zinc, vitamin A, B_1, B_6, B_{12}, E, K, C and 1,25-dihydroxyvitamin D.

Despite the limited value of some of these biomarkers for assessing nutritional status, the Panel considers that the study provided does not raise concerns.

Based on the nature of the NF, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

[4] Regulation (EC) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. OJ L 304/18, 22.11.2011, p. 1–46.

3.7. Microbiological information on the NF

To ensure the absence of contaminating microorganisms, PGX is tested for *Escherichia coli*, *Salmonella*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, yeast and mould as described in the specifications (Table 2).

Xanthan gum, one of the NSP used in PGX, is produced by a pure-culture fermentation of carbohydrates with the bacterium *Xanthomonas campestris*. Upon a request for clarification from EFSA, the applicant provided a certificate of analysis for xanthan gum that indicated the absence of *Xanthomonas campestris* in the NF.

The Panel considers that the microbiological information provided does not raise safety concerns.

3.8. Toxicological information on the NF

3.8.1. Absorption, distribution, metabolism and excretion

The NF is a complex of water-soluble NSP with a very high water-holding capacity. When consumed with foods or beverages, the NF is able to increase the volume and viscosity of gastric content, thereby affecting how material passes through the digestive tract.

In a randomised, double-blind, placebo-controlled study, Reimer et al. (2012a) examined faecal short-chain fatty acids (SCFA) concentrations in healthy subjects on a low-fibre background diet (approximately 10 g/day) who were allocated to consume either 5 g/day of PGX in a first week and 10 g/day during the following 2 weeks (PGX group, n = 27), or a placebo consisting of skimmed milk powder (control group, n = 27). Acetate decreased over time in the control but not in the PGX group, which resulted in higher concentrations of acetate in the PGX group at the final visit as compared to the control group ($p = 0.018$). There were no differences in propionate, butyrate, valerate, caproate or lactate concentrations between the groups. Repeated-measures analysis of variance showed a significant treatment effect ($p = 0.03$) for total SCFA, which was higher in the PGX group vs control subjects.

In another study, Reimer et al. (2014) investigated the fermentability (through NaOH consumption) and production of SCFA (acetate, propionate, butyrate) and branched chain fatty acids (BCFA) of PGX as compared to fructo-oligosaccharide (FOS) and cellulose in an *in vitro* model which simulates the human large intestine. This study reported that NaOH consumption for PGX was higher as compared to cellulose, whereas it was lower as compared to FOS. Acetate and butyrate production were higher for PGX as compared to cellulose, whereas they were not different as compared to FOS. Propionate production was higher for PGX as compared to cellulose and FOS. Total BCFA production with PGX was lower than cellulose, but higher than FOS. The authors concluded that PGX is fermented by the colonic microbiota.

The Panel notes that one study in human subjects and one *in-vitro* model on the human large intestine indicate fermentability of the NF by human intestinal microbiota.

3.8.2. Genotoxicity

The applicant provided a publication on two studies on the potential mutagenicity of PGX (Marone et al., 2009). According to the authors, these studies were conducted in compliance with the Organisation for Economic Co-operation and Development (OECD) principles of good laboratory practice (GLP) (OECD, 1998b) and according to the OECD test guideline for the bacterial reverse mutation test (test guideline No 471; OECD, 1997a) and the mammalian erythrocyte micronucleus test (test guideline No 474; OECD, 1997b), respectively.

In the bacterial reverse mutation assay (Ames test) using *Salmonella* Typhimurium strains TA 98, TA 100, TA 1535, and TA 1537 and the *Escherichia coli* strain WP2 uvrA, PGX was tested in the presence or absence of a metabolic activation system (S9-mix), using the plate-incorporation and pre-incubation methods. Due to solubility problems, only doses up to 100 μg/plate could be tested. At the tested dose levels, PGX did not cause relevant increases in revertant colony numbers in any of the five strains with or without metabolic activation system. This study thus showed no mutagenicity of PGX up to the highest tested dose level of 100 μg/plate.

For the mammalian erythrocyte micronucleus test, a cottonseed oil extract of PGX was prepared and administered intraperitoneally to NMRI mice (five/sex per group) at dose levels designated 100%, 50% and 20% extract. Owing to the bulk properties of PGX, a cottonseed oil extract of PGX was used in this study. The highest tested dose (100% extract) produced signs of toxicity in a preliminary

experiment. In the main experiment, toxicity symptoms (e.g. reduction of spontaneous activity, rough fur, prone position, palpebral closure, and constricted abdomen) were observed at the highest dose level; weak or moderate toxicity symptoms were observed at the lower dose levels. Peripheral blood was taken 44 hours after the administration from animals of each treatment group, the negative and the positive control groups, and 68 hours after the administration from animals of the negative control group and a second high-dose group. Blood cell populations were discriminated using specific antibodies and analysed by flow cytometry. The percentage of polychromatic (immature) erythrocytes (PCE) relative to total erythrocytes (= relative PCE) as well as the ratio of micronucleated PCE to total PCE were determined. Treatment with the PGX extract did not cause an increase in the incidence of micronucleated PCE compared with the negative control group. All mean values were within the range of the historical control data of the laboratory. The positive control cyclophosphamide induced the expected statistically significant increase. According to the author, the relative PCE was statistically significantly reduced in males at the 44 h time point, indicating that the target tissue was exposed. However, the Panel notes some inconsistencies regarding the information on statistical significance in the publication. Despite this and another limitation in data reporting (no individual animal data were shown), the Panel concludes that the study provided no indications of clastogenicity and/or aneugenicity of the tested PGX extract.

Considering the nature of the NF, the Panel considers that the information provided does not raise concerns with respect to genotoxicity of the NF.

3.8.3. Repeated dose toxicity studies

A repeated dose subchronic toxicity study with PGX was provided by the applicant. In addition, publications on animal studies with PGX using specific disease models, publications on studies with the three individual NSP of PGX or with other fibre have been considered in this section.

Subchronic toxicity study with PGX

The applicant provided a subchronic toxicity study, which was conducted in compliance with the OECD principles of GLP and in accordance with OECD Test Guideline No. 408 (OECD, 1998a,b). Sprague–Dawley rats (ten/sex per group, housed singly; 7–8 weeks of age) were fed a standard rodent diet containing 0% (control group), 1.25%, 2.5% or 5% PGX for 92 days (Eurofins, Product Safety Laboratories, 2008; Matulka et al., 2009). The test and control diets, as well as water, were provided throughout the study to ensure *ad libitum* feeding. The mean overall daily intake of PGX in males and females, respectively, was calculated to be approximately 0.8 and 0.9 g/kg bw in the 1.25% group, 1.6 and 1.8 g/kg bw in the 2.5% group, 3.2 and 3.8 g/kg bw in the 5% group.

Upon EFSA request for clarification, the applicant indicated that the test material used in the 90-day study had been produced in the same way as the NF using the same proprietary ratio of the three NSP. The Panel considers that the test material is representative of the NF.

There were no mortalities during the treatment period. Detailed clinical observations of the animals conducted weekly revealed transient clinical signs including light brown faeces for one female in the 2.5% group (day 57), all 5% group males (days 57 and 64) and two (day 57) and six (day 64) females in the 5% group. One male and one female in the 5% PGX group were found emaciated on day 57 and day 92, respectively; these findings were not considered test substance-related, by the authors of the study. In the case of the male animal, it was attributed to a faulty valve in the water supply. No such reason could be identified for the female animal. Additional findings in this animal were reduced body weight, body weight gain, food consumption, food efficiency, reduced absolute and relative thymus weights, as well as slight atrophy of the thymus in histopathological examinations. Therefore, in view of the Panel, it cannot be excluded that this effect is due to application of the test substance.

In ophthalmoscopic examinations before the start and at the end of the treatment period, the animals' eyes were considered normal. Results from 'Functional Observational Battery' (FOB) and motor activity tests in rats fed PGX showed no relevant differences when compared to those of the control group.

Mean body weights, body weight gains, feed consumption and feed efficiency in the groups administered PGX were comparable to those in the control group.

Relevant findings observed in the study by Matulka et al. (2009) are presented in Table 5. Male rats fed a diet with 5% PGX showed a statistically significant decrease in red blood cell count (3.7%; $p < 0.05$) compared with the control group. In the absence of significant changes in other haematology and coagulation parameters in males and females, this slight change is not considered toxicologically relevant. Clinical chemistry analysis showed a statistically significant increase in the

serum albumin concentration in male rats of the high-dose group (6.5%; $p < 0.05$). Since there were no significant differences in other clinical chemistry parameters in male animals, this slight change is not considered toxicologically relevant. For high-dose females, statistically significant increases were noted in serum aspartate aminotransferase (AST) activity (20%), alanine aminotransferase (ALT) activity (69%) and triglyceride (TG) concentration (36%). The increase in TG concentration (and a non-significant increase in cholesterol concentration) may be regarded as an effect on liver function and general metabolism, which does not necessarily constitute an adverse effect. However, the magnitude of the effect on transaminases and the pattern of these changes (ALT > AST), which is typical for liver toxicity raise concerns regarding liver toxicity. Significant decreases in serum electrolyte levels, i.e. sodium (5%), potassium (6%) and chloride levels (4%) ($p < 0.05$), also occurred. These changes may be attributable to increased fluid loss, which is accompanied by other urinalysis findings, i.e. increased urine volume (> +110% in both sexes), and reduced gravity and protein content in high-dose females (and males). The authors of the publication argued that the diet was provided in powder form, and the high oral viscosity of PGX may have increased water intake. However, water intake of the animals was not measured in this study. A statistically significant decrease in the inorganic phosphorous concentration (16.9%) was found only in mid-dose females and is thus considered an incidental finding. Upon EFSA's request for additional information, the applicant provided historical control data for those parameters, which showed statistically significant differences. The Panel notes the broad range of values for the historical control data, which were collected over a period of 10 years, and considers that the data are not suitable to overrule the concerns raised from this study.

At necropsy, no gross abnormalities attributable to the test material were identified. Incidental findings included fluid-filled uteri in some females in all groups, and a light brown encapsulated firm mass, anteriomedial of the right testis in one male of the mid-dose group, for which there were no corresponding histological findings. Organ weight determinations showed no statistically significant differences in absolute or relative organ weights (relative to body and brain weight) between PGX-treated groups and the control group. Microscopic analysis of selected organs and tissues (including liver and kidneys) found that the histopathological changes were of a type commonly observed in control laboratory rats, and occurred with comparable incidence in the control and high dose groups.

The Panel considers the increased serum activities of ALT and AST in females in the high-dose group (i.e. 5% PGX in the diet), which indicate a toxic effect on the liver, as critical effects. Therefore, the mid-dose, i.e. 2.5% PGX in the diet corresponding to 1.8 g/kg bw per day, is regarded as the no observed adverse effect level (NOAEL).

Table 5: Relevant findings observed in the study by Matulka et al. (2009)

Dose group	Mean daily intake of PGX (mg/kg bw per day)	RBC count (× 10^6/μL)	AST (U/L)	ALT (U/L)	SDH (sorbitol dehydrogenase) (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dL)	TG (mg/dL)	Total protein (g/dL)	Albumin (g/dL)	P (mg/dL)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Urine volume (mL)	Specific gravity	pH	Total protein (mg/dL)	Liver weight (g)	Relative liver weights to body weight
MALES																				
Control	**0**	**9.12**	**107**	**50**	**8.4**	**107**	**0.12**	**36**	**6.2**	**3.1**	**6.9**	**144.2**	**5.39**	**102.4**	**3**	**1.074**	**6.2**	**876**	**11.11**	**27.01**
SD	0	0.32	32	16	2.7	30	0.01	11	0.2	0.2	0.4	5.6	0.28	4	1.5	0.02	0.3	683	1.1	1.06
1.25%	**805.6**	**8.98**	**82**	**43**	**8.3**	**112**	**0.12**	**45**	**6.2**	**3.1**	**7**	**145.5**	**5.39**	**103.4**	**4**	**1.06**	**6.4**	**808**	**11.12**	**26.87**
SD	49.02	0.32	7	7	3	32	0.01	19	0.2	0.1	0.7	4.8	0.4	3.3	1.7	0.017	0.3	279	0.89	1.56
2.50%	**1617.2**	**9.04**	**85**	**46**	**8.2**	**96**	**0.12**	**44**	**6.2**	**3.2**	**7.1**	**145**	**5.44**	**102.9**	**6.3**	**1.054**	6.6(*)	**745**	**11.62**	**28.31**
SD	72.22	0.29	15	9	2	13	0.02	16	0.3	0.1	0.6	4.8	0.23	2.9	4.6	0.025	0.3	412	1.29	1.99
5%	**3218.9**	**8.78(*) (diff: −3.7%)**	**92**	**48**	**8.3**	**113**	**0.13**	**44**	**6.2**	**3.3(**) (diff: +6.4%)**	**7.5**	**145.6**	**5.34**	**102.9**	**6.4(**) (diff: +113%)**	**1.045(*) (diff: −2.7%)**	**7.1(*)**	**457**	**11.76**	**29.05**
SD	81.34	0.18	13	7	2	25	0.02	10	0.2	0.1	1	6.2	0.46	4.1	3.3	0.018	0.5	346	0.68	1.46
FEMALES																				
Control	**0**	**8.21**	**84**	**32**	**10**	**87**	**0.16**	**25**	**6.5**	**3.5**	**5.9**	**143.5**	**5.02**	**104.9**	**2.9**	**1.055** (from 8 animals)	**6** (from 7 animals)	**258**	**6.34**	**26**
SD	0	0.13	13	3	2	31	0.03	5	0.3	0.2	0.5	5.8	0.28	4	3.3	0.026	0	245	0.58	1.66
1.25%	**917.5**	**8.19**	**86**	**38**	**9.2**	**97**	**0.16**	**31**	**6.5**	**3.5**	**5.5**	**141**	**4.88**	**102.3**	**4** (from 9 animals)	**1.042** (from 8 animals)	**6.2** (from 8 animals)	**196** (from 9 animals)	**6.7**	**26.54**
SD	51.1	0.22	6	4	1.7	18	0.02	8	0.2	0.2	0.6	6.9	0.25	5.1	2.7	0.017	0.4	374	0.84	2
2.50%	**1827.6**	**8.17**	**88**	**40**	**10.3**	**89**	**0.16**	**29**	**6.5**	**3.5**	4.9 (*) (diff: 17%)	**143.4**	**4.89**	**104.8**	**1** (from 8 animals)	**1.07** (from 6 animals)	**6.1** (from 5 animals)	**111** (from 7 animals)	**6.51**	**26.17**
SD	115.44	0.26	10	7	2.2	25	0.02	8	0.3	0.2	0.4	5.6	0.25	3.4	1	0.011	0.2	66	0.4	1.6
5%	**3798.8**	**8.24**	**101(**) (diff: +20%)**	**54(**) (diff: +69%)**	**10.4**	**103**	**0.18**	**34(**) (diff: +36%)**	**6.4**	**3.5**	**5.4**	**136.6(*) (diff: −4.8%)**	**4.71(*) (diff: −6.2%)**	**100.4(*) (diff: -4.2%)**	**6.8(**) (diff: +134%)**	**1.027(*) (diff: −2.6%)**	**6.9(**)**	**61(**) (diff: −76.3%)**	**6.5**	**27.25**
SD	104.82	0.4	18	14	2	24	0.02	8	0.3	0.2	0.7	5.1	0.25	3.6	2.9	0.008	0.2	46	0.38	1.81

*: Statistically significant different than control at $p < 0.05$ Dunnett/Tambane–Dunnette test.
**: Statistically significant different than control at $p < 0.05$ Dunn's test.

Studies with disease models

The applicant has also referred to studies which investigated the effect of 5% PGX in disease models for type II diabetes. In the studies by Grover et al., (2011a,b) and Reimer et al. (2012b), Zucker diabetic rats were used, whereas in the study by Reimer et al. (2011) Sprague–Dawley rats, which consumed a diet with 65% sucrose, were used. Study durations ranged from 6 up to 43 weeks, the latter occurring in the study with the high sucrose-diet. Control groups received the same amount of cellulose or inulin, to identify specific effects of PGX in comparison to other fibre. Food intake was decreased in all studies, compared to the other fibre, in some studies accompanied also by lower body weight or body weight gain. No adverse effects were reported with respect to cholesterol, TG, ALT, AST, alkaline phosphatase, bilirubin, histopathology of the kidney or liver.

Repeated dose toxicity studies with three individual NSP of PGX or other fibre

In order to evaluate whether the effect on liver enzymes in rats in the subchronic toxicity study by Matulka et al. (2009) is compound related or incidental, the Panel analysed data on the three constituents based on the reviews by JECFA and the SCF (JECFA, 1987, 1993a,b, 1997, SCF, 1992, 1994, 1997). No increases in ALT plus AST activities in rodent toxicity studies were observed. The Panel notes that the more recent publication by Hagiwara et al. (2004) on a 90-day study with xanthan gum reported an increase in ALT activity in a 90-day female F344 rats. However, the increase was not dose-related and statistically significant only at the mid-dose level.

Furthermore, to determine whether liver findings may be a general effect of fibre, the applicant was requested to retrieve studies on the effect of fibre on liver in rats. In its reply, the applicant indicated that among around 400 articles which were retrieved on the effects of fibre in rats, only three studies reported similar effects as those observed in the study by Matulka et al. (2009), i.e. the study by Kotkoskie and Freeman (1998) on ethylcellulose, by Lina and Bär (2004) on β-cyclodextrin, and by Doi et al. (2006) on gum Arabic.

The Panel considers that it is not possible to conclude whether or not increases in ALT and AST activity in rats (as observed in the provided 90-day repeated-dose toxicity study with PGX) are related to the three individual NSP of PGX or other fibre in general or to exclude that the increases in ALT and AST activity in rats are specific to the NF.

3.8.4. Human studies

The applicant provided 13 articles on human studies with the NF.

Six of these studies investigated the effect of single doses of PGX, up to 7.5 g, consumed as capsules or granules dissolved in water or added to foods, on glycaemic index of starchy foods or on post-prandial glucose levels, satiety, food intake or palatability in healthy adults or adolescents (Vuksan et al., 2009; Brand-Miller et al., 2010, 2012; Jenkins et al., 2010a,b; Solah et al., 2014). These studies did not observe or report adverse effects. The Panel considers that no conclusions on the safety of the NF can be drawn from these studies due to low and single doses investigated.

In the double-blind, cross-over study by Kacinik et al. (2011) on appetite ratings, 45 overweight and obese women were randomised to consume PGX (15 g/day) or placebo in a low calorie diet for three days. The Panel considers that no conclusions on the safety of the NF can be drawn from this study owing to the short duration of consumption of the NF.

Obese and overweight adults consumed PGX, up to 15 g/day, together with meal replacements for 12 weeks in the single-arm (no control group) studies by Reichert et al. (2013a,b). Changes from baseline in anthropometric parameters were investigated. These studies did not record adverse effects. The Panel considers that no conclusions on the safety of the NF can be drawn from these uncontrolled studies.

In the double-blind, controlled intervention study by Lyon et al. (2011), 59 obese or overweight adults were randomised to consume either PGX (n = 29) or inulin (n = 30) with yoghurt for 15 weeks. The daily dose of 6 g of PGX in the first week was increased to 10 g/day during the second week and then to 15 g/day from the third week up to week-15. There was no between-group difference with regard to TG, whereas a decrease in total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol was observed only in females in the PGX group as compared to females in the inulin group. No between-group difference was reported in the number of participants with at least one adverse effect of gastrointestinal origin. No serious adverse events were reported. The Panel notes that this study was not designed for assessing safety and did not include a placebo group, however,

the Panel considers that this study provides no indications that consumption of 15 g PGX for 3 months would raise safety concerns.

Twenty-nine overweight or obese adults (6 men) were included in a clinical weight-loss programme at the Canadian Centre for Functional Medicine (Lyon and Reichert, 2010). Participants consumed 10–15 g of PGX per day for 14 weeks. A total of 32% of participants experienced mild gastrointestinal side effects (e.g. gas, bloating, constipation, loose stools) which did not lead to discontinuation of the study. Sixty-eight per cent of these gastrointestinal symptoms resolved within approximately the first 3 weeks of the study. The Panel considers that no indications for safety concerns can be inferred from this study.

In the double-blind, placebo-controlled intervention study by Carabin et al. (2009), 54 healthy subjects (aged 18–55 years) were randomised to consume either PGX (n = 27, 14 males) or placebo (skimmed milk powder; n = 27, 11 males) with cereals and yoghurt, for 3 weeks. The initial dose of 5 g/day of PGX in the first week was followed by a dose of 10 g/day in the second and third week. ANOVA or Mann–Whitney–Wilcoxon test were used to compare data between groups.

No statistically significant between-group differences were reported in AST and ALT serum levels. Upon request by EFSA, the applicant provided AST and ALT serum levels at baseline, at week-1 and week-3 for each group and conducted a post-hoc power analysis for AST and ALT levels. A within-group analysis showed that in the PGX group, there was a small, statistically significant increase of 10% in AST (20.3 ± 4.4 IU/L vs 22.4 ± 5.2 IU/L, change 2.1 ± 4.2 IU/L, p = 0.039) and a non-significant increase of 14% in ALT serum levels (16.4 ± 6.4 IU/L vs 18.7 ± 10.0 IU/L, change 2.3 ± 7.3 IU/L, p = 0.063) at week-3 as compared to baseline. The Panel notes that the changes in AST and ALT levels were within normal range values.

No between-group difference was reported in the other parameters investigated (stool, urinary, haematological, biochemical parameters; gastrointestinal discomfort symptoms), except for total and LDL cholesterol, gamma-glutamyl transpeptidase and uric acid levels which had a greater decrease in the PGX group as compared to the placebo group. No serious adverse events were reported.

The Panel considers that this study in 54 volunteers provides no indication that the consumption of PGX up to 10 g/day for 3 weeks would raise safety concerns. No conclusions can be drawn from this study with regard to possible adverse effects associated with long-term consumption of PGX at the maximum use level proposed by the applicant (i.e. 15 g/day).

In the double-blind, placebo-controlled intervention study by Reimer et al. (2013), 64 overweight Japanese adults (28 men) were randomised to consume either PGX (n = 32) or placebo (rice flour; n = 32) with yoghurt for 14 weeks. The initial PGX daily dose of 5 g was increased to 10 g at day 4, and then to 15 g from day 8 until week-14.

Fifty-six participants completed the study and were included in the analysis (n = 28 in each group). One participant in the PGX group withdrew from the study owing to diarrhoea. Repeated measures ANOVA was used to compare data between groups.

No statistically significant between-group differences were reported in AST and ALT levels. Upon request by EFSA, the applicant provided AST and ALT levels at baseline, at week-6 and week-14 for each group and conducted a post-hoc power analysis for AST and ALT parameters. A within-group analysis showed that at week-6, ALT was 30.5 ± 16.2 IU/L, which is still within the reference range, but was significantly higher than the baseline value of 23.9 ± 13.0 IU/L, for a change of 6.7 ± 10.0 IU/L in the PGX group (p = 0.003), whereas the increase in the placebo group was non-significant (2.2 ± 8.9 IU/L). This within-group analysis also showed that in the PGX group at week-14, the increases of 7% in AST levels and 20% in ALT levels were non-significant as compared to baseline.

No between-group difference was reported in the other blood or urine parameters investigated, which included red blood cells, TG, sodium, potassium, chloride, albumin, and urine pH. Faecal bile acids and SCFA were not altered (except for butyrate which was decreased).

A total of 30 and 28 adverse events were reported in the PGX and in the placebo group, respectively. The most common adverse events were abdominal symptoms (n = 9 in PGX; n = 6 in the placebo) and common cold.

Although the Panel considers that the magnitude of increases in AST and ALT levels observed in the above-mentioned studies by Carabin et al. (2009) and by Reimer et al. (2013) are not clinically relevant, the human data are not sufficient to draw conclusions on the effect of chronic consumption of PGX at the proposed maximum use levels on liver enzymes.

3.9. Allergenicity

The applicant performed a scientific literature review to address the topic of allergy/allergic reaction to the components of PGX following oral consumption. No references to published studies describing an allergenic response to the oral consumption of konjac glucomannan, sodium alginate or xanthan gum have been retrieved. Furthermore, the applicant indicated that approximately 800 million single servings of PGX have been sold with no reports of allergenicity.

The Panel considers that the likelihood of allergic reactions to the NF is low.

4. Discussion

The NF is an off-white granular powder composed of three NSP: konjac glucomannan, xanthan gum and sodium alginate. These NSP are mixed in a specific ratio, which has been claimed proprietary and confidential by the applicant, and processed by a proprietary process. The information provided on the composition, the specifications, the batch-to-batch variability and the stability of the NF is sufficient and does not raise safety concerns. The production process is sufficiently described and does not raise concerns about the safety of the NF.

The applicant intends to add the NF to a variety of foods such as yoghurt, breads, biscuits, cereals, pasta and juices. The applicant also intends to market the NF in capsules (750 mg NF per capsule). The recommended maximum daily intake of the NF from fortified foods and food supplements is 15 g. The target population proposed by the applicant is adults from 18 to 64 years of age.

By using individual data from EU dietary surveys and the maximum proposed use levels for the NF, the mean and 95th percentile anticipated daily intake of the NF were estimated (range of mean: 0.06–0.15 g/kg bw which corresponds to 4.2–10.5 g/day based on an adult bw of 70 kg; range of 95th percentile: 0.16–0.30 g/kg bw which corresponds to 11.2–21 g/day based on an adult bw of 70 kg). The Panel notes that the estimate of the 95th percentile anticipated daily intake of the NF from fortified foods would exceed the recommended maximum daily intake as proposed by the applicant (15 g/day). However, the Panel notes that this intake estimate is based on the conservative assumption that all proposed food items from all food categories consumed by an individual actually contain the NF at the maximum proposed level of use. The recommended maximum intake of the NF from food supplements is 13.5 g/day (which corresponds to 0.19 g/kg bw per day for an adult bw of 70 kg).

Based on the nature of the NF, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

Owing to its high water-holding capacity, when consumed with foods or beverages, the NF is able to increase the volume and viscosity of gastric content, thereby affecting how material passes through the digestive tract. A human study and an *in vitro* study on PGX indicate that the NF is fermented by the human intestinal microbiota.

Considering the nature of the NF, the Panel considers that the information provided does not raise concerns with respect to genotoxicity of the NF.

A subchronic toxicity study in Sprague–Dawley rats, which received a diet containing 0% (control), 1.25%, 2.5% or 5% of PGX for 13 weeks showed statistically significant increases in serum activities of ALT and AST in females in the high-dose group. These effects, which indicate a toxic effect on the liver, were considered critical by the Panel. Therefore, the mid-dose, i.e. 2.5% PGX in the diet corresponding to 1.8 g/kg bw per day, was set as the NOAEL for this study.

Based on the results of repeated dose toxicity studies with the individual NSP of PGX as well as with other types of fibre, the Panel considers that it is not possible to conclude whether or not increases in ALT and AST activity in rats (as observed in the provided 90-day repeated-dose toxicity study with PGX) are related to the three individual NSP of PGX or other fibre in general or to exclude that the increases in ALT and AST activity in rats are specific to the NF.

Two double-blind, placebo-controlled intervention studies in adults, who were randomised to consume PGX (at doses up to 10 and 15 g/day) or placebo for 3 or 14 weeks, respectively, reported minor within-group increases in AST and ALT levels in the PGX group at week-3 and week-6 as compared to baseline, respectively. Although the Panel considers that the magnitude of increases in AST and ALT levels observed in the above-mentioned studies by Carabin et al. (2009) and by Reimer et al. (2013) are not clinically relevant, the human data are not sufficient to draw conclusions on the effect of chronic consumption of PGX at the proposed maximum use levels on liver enzymes.

Considering the NOAEL of 1.8 g/kg bw per day and the highest mean and 95th percentile anticipated daily intake of NF from fortified foods the margin of exposure (MoE) is 12 and 6, respectively, whereas the MoE for the NF from food supplements is 9.

The Panel considers that the MoE for the NF at intended uses and use levels is not sufficient for the target population.

5. Conclusions

The Panel concludes that the safety of the novel food, PGX, for the intended uses and use levels as proposed by the applicant, has not been established.

Documentation provided to EFSA

1) Letter from the European Commission to the European Food Safety Authority with the request for a scientific opinion on the safety of 'alginate-konjac-xanthan polysaccharide complex (PGX)' as a novel food ingredient. SANTE/E6/SS/ks Ref. Ares(2015)3221121, dated 31 July 2015.
2) Dossier on 'alginate-konjac-xanthan polysaccharide complex (PGX)' received by EFSA on 6 August 2015, which was submitted by InovoBiologic Inc.
3) Upon a request by EFSA for missing information, on 5 October 2015 EFSA received the missing information as submitted by the applicant.
4) Initial assessment report carried out by the Food Safety Authority of Ireland: 'Safety Assessment of alginate-konjac-xanthan polysaccharide complex (PGX)'.
5) Member States' comments and objections.
6) Response by the applicant to the initial assessment report and the Member States' comments and objections.
7) On 17 February 2016 and on 1 June 2016, EFSA sent requests to the applicant to provide additional information.
8) On 5 April and on 28 July 2016, EFSA received additional information as submitted by the applicant. Further clarifications and additional information were also received on 1 December 2015 and on 20 May 2016.
9) During its meeting on 4 April 2017, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of alginate-konjac-xanthan polysaccharide complex (PGX) as a novel food pursuant to Regulation (EC) No 258/97.

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Abbreviations

ADI	acceptable daily intake
ALT	alanine transaminase
AOAC	Association of Official Analytical Chemists
AST	aspartate transaminase
BCFA	branched chain fatty acids
bw	body weight
CFU	colony forming unit
FOB	functional observational battery
FOS	fructo-oligosaccharide

GC/MS	gas chromatography/mass spectrometry
GLP	good laboratory practice
^{1}H NMR	proton nuclear magnetic resonance
HDL	high-density lipoprotein
HPAEC/PAD	high-performance anion exchange chromatography with pulsed amperometric detection
ICP	inductively coupled plasma
JECFA	Joint FAO/WHO Committee on Food Additives
LDL	low-density lipoprotein
MS	Member State
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NDNS	National Diet and Nutrition Survey
NF	novel food
NOAEL	no observed adverse effect level
NSP	non-starch polysaccharides
OECD	Organisation for Economic Co-operation and Development
PCE	polychromatic erythrocytes
PGX	alginate-konjac-xanthan polysaccharide complex
RKM	refined konjac meal
SCF	Scientific Committee for Food
SCFA	short-chain fatty acids
TG	triglycerides
USP/FCC	United States Pharmacopeia/Food Chemicals Code