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SCIENTIFIC OPINION

Scientific Opinion on the safety of 'yeast *beta*-glucans' as a Novel Food ingredient[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2], [3]

European Food Safety Authority (EFSA), Parma, Italy

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 the safety of 'yeast *beta*-glucans' as a novel food ingredient in the context of Regulation (EC) No. 258/97 taking account of the comments/objections of a scientific nature raised by the Member States. 'Yeast *beta*-glucans' consists of complex, high molecular mass polysaccharides derived from the cell wall of baker's yeast *Saccharomyces cerevisiae*. This novel food application concerns both insoluble as well as soluble 'yeast *beta*-glucans'. The source, characterisation, specification and production process do not give reasons for concern. The applicant intends to market 'yeast *beta*-glucans' in food supplements at dose levels of up to 375 mg per day and in foods for particular nutritional uses (PARNUTS) at dose levels of up to 600 mg per day. It is not intended for infant formulae and follow-on formulae. In addition, the applicant intends to market 'yeast *beta*-glucans' in a variety of foods including beverages for the general population. The Panel notes that the "high intake*"* scenario for 'yeast *beta*-glucans' is grossly similar to the background intake of *beta*-glucans from other dietary sources. Data provided on (sub)acute and sub-chronic toxicity, absorption, and limited human data do not give reason for concern. The Panel considers that the allergenic risk of the 'yeast *beta*-glucans' is not higher than the risk from other products containing baker's yeast. *Beta*-glucans from other sources have already been evaluated for safety by EFSA. On the basis of the nature of 'yeast *beta*-glucans', the significant history of use of its source, the provided intake estimate and the supplementary data from human and animal studies, Panel concludes that 'yeast *beta*-glucans' is safe at the proposed conditions of use.

KEY WORDS

Yeast, *beta*-glucans, fiber, novel food, ingredient

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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 the safety of ''yeast *beta*-glucans'' as a novel food ingredient in the context of Regulation (EC) No 258/97 taking account of the comments/objections of a scientific nature raised by the Member States.

'Yeast *beta*-glucans' consists of complex, high molecular mass (100 – 200 kDa) polysaccharides derived from the cell wall of baker's yeast *Saccharomyces cerevisiae*. 'Yeast *beta*-glucans' differs from their cereal counterparts in that they contain ß-1,3- and 1,6-glucosydic bonds, compared to the cereal derivatives which contain ß-1,3- and 1,4-glucosydic bonds. This novel food application concerns both insoluble [BetaRight WGP (BWGP) and Wellmune WGP Dispersible (WGPD)] as well as soluble [Wellmune WGP soluble (WGPS)] 'yeast *beta*-glucans'. The insoluble products contain at least 70 % (BWGP) or 75 % (WGPD) carbohydrate in the form of *beta*-glucans; the soluble product (WGPS) contains at least 75 % *beta*-glucans. The characterisation, specification and production process do not give reasons for concern.

The source, baker's yeast, traditionally used for the production of bread, beer and wine, does not give reason for concern since it has a long history of use in and outside Europe.

The applicant intends to market 'yeast beta-glucans' in food supplements at dose levels of up to 375 mg per day and in foods for particular nutritional uses (PARNUTS, as specified by Directive 2009/39/EC) at dose levels of up to 600 mg per day, with the exception of infant formulae and follow-on formulae (as defined by Commission Directive 2006/141/EC). In addition, the applicant intends to market 'yeast beta-glucans' in a variety of foods including beverages for the general population.
Based on these proposed uses, the applicant has provided an intake estimate for 'yeast *beta*-glucans' for different population groups, using data from the United Kingdom National Diet and Nutrition Surveys. Of the individual population groups, male teenagers had the greatest mean and 97.5th percentile all-user intakes of 'yeast *beta*-glucans' resulting of 0.80 and 1.94 g/person per day, respectively. On a body weight basis, children were identified as having the highest mean and 97.5th percentile all-user intakes of any population group, of 49 and 105 mg/kg body weight per day, respectively. In response to a Member State request, the applicant provided an intake estimate of *beta*-glucans naturally present in foods based on the contents in foods and based on UK consumption data. For normal *beta*-glucans intake, male adults were determined to have the greatest mean and 97.5th percentile all-user intakes of *beta*-glucans at 726 and 4,673 mg/person per day (9 and 52 mg/kg bw per day), respectively. An analysis of the impact of individual food categories on the intake of *beta*-glucans by male adults revealed that the consumption of beer produced the largest individual food intakes of *beta*-glucans in this population group. Children of 1.5 – 4.5 years old had the lowest mean estimates for daily *beta*-glucans intake with values of 281 mg/person. On a body weight basis, infants/young children (1.5 - 4.5 years old) were identified as the population group having the highest mean and 97.5th percentile all-user intakes of normal *beta*-glucans at 20 and 115 mg/kg body weight per day, respectively.

The Panel notes that the "high intake*"* scenario for *beta*-glucans from BWGP, WGPD, or WGPS is grossly similar to the background intake of *beta*-glucans from other dietary sources.

Data provided on (sub)acute and sub-chronic toxicity, absorption, and limited human data do not give reason for concern. The Panel considers that the allergenic risk of the 'yeast beta-glucans' is not higher than the risk from other products containing baker's yeast. *Beta*-glucans from other sources have already been evaluated for safety by EFSA.

On the basis of the nature of 'yeast *beta*-glucans', the significant history of use of its source, the conservative intake estimates of 'yeast *beta*-glucans', which at its maximum is grossly similar to the background intake of *beta*-glucans from other sources, and the supplementary data from human and

animal studies, the Panel considers that the intake of the NFI at the proposed conditions of use, does not raise concerns. The Panel concludes that 'yeast *beta*-glucans' is safe at the proposed conditions of use.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

On 23 September 2009, the company Biothera Inc. submitted a request under Article 4 of the Novel Food Regulation (EC) No 258/97 to place on the market ''yeast *beta*-glucans'' as a novel food ingredient.

On 23 December 2009, the competent authorities of Ireland forwarded to the Commission their initial assessment report, which came to the conclusion that ''yeast *beta*-glucans'' meets the criteria for acceptance as a novel food.

On 18 January 2010, the Commission forwarded the initial assessment report to the other Member States. Several of the Member States submitted comments or raised objections.

In consequence, a Community Decision was required under Article 7, paragraph 1 of Regulation (EC) No 258/97.

The concerns of a scientific nature raised by the Member States can be summarized as follows:

- Accreditation of the test laboratories issuing test reports is not apparent. Accreditation should be according to an internationally-recognised system for analysing food. To what extent this is the case here is not clear from the documents.
- When establishing the specifications, in regard to the actually recorded values very widely selected tolerances are noticeable so that a restricted establishment of the specification seems completely appropriate. Analysis of the glucose content as another indicator in the context of the specifications has to be proven.
- The specifications for the 3 formulations should be based on appropriate batch testing. The difference between the two insoluble products WGPD and BWGP should also be made clear. From a toxicological perspective the products should also be characterised and specified regarding the distribution of molecular weight and particle size.
- Information on the presence of mannans co-extracted from the cell wall, in the form of mannoproteins should be provided. They could represent an important part of the carbohydrates. They could lead to hypersensitivity.
- The content of dietary fibre should be conducted by a recognised method (e.g., AOAC). In the dossier, the content has been determined by difference.
- There are no references to a HACCP concept or quality management or data on the shelf life of the product that is the subject of the application.
- More information on the risk of co-concentration of another molecule, for example in the lipid or albuminous fraction or trapped in the polysaccharide fraction.
- The applicant's data estimating total daily intake of *beta*-glucans from conventional food is not sufficient. Simultaneous consumption of nutritional supplements, dietary food and conventional food intended for enrichment should not be excluded. The initial test authority also takes into consideration the fact that particularly in the group of young men the projected intake amount can be further increased by consuming dietary food for athletes. An exposure estimation which includes *beta*-glucans naturally present in foods should be submitted.
- The estimated probable 97.5 percentile consumption of the applied for product for children already exceeds the highest administered dose in sub-chronic rat studies (100 mg/kg bw per day corresponds to 75 mg *beta*-glucans/kg body weight per day). In assessing the studies discussed in the section "Toxicological information", it is essential to discover whether in the human studies blood clotting and the immune system were affected. The corresponding information is not available in the submitted study.

- *Beta*-glucans are absorbed in the epithelial cells and therefore further information on the immunostimulatory effects of the ingredients and whether this has significant effects on the gut flora should be requested.
- The applicant has submitted a publication summarising the results of studies on acute and sub-chronic oral toxicity in the insoluble *beta*-glucan product „WGP® 3-6"(Babíček et al., 2007). The composition of the test substance „WGP® 3-6" does not, however, match that of the insoluble products that are the subject of the application. Moreover, with the male animals the high dose group recorded a statistically significant dose-dependent increase of blood clotting time compared to the control group (141 versus 78.3 seconds). In the opinion of the authors, this effect is not toxicologically significant since the blood clotting time in the control group was relatively high, all average values were within the historic control values and the difference at the end of a 14 day recovery phase was no longer statistically significant. A toxicological relevance cannot be excluded. A conclusive assessment on the basis of the publication is however not possible so the applicant should be asked to submit the complete study report. In addition, the applicant refers to a series of short (maximum 7 days) toxicological studies and to a chronic study (52 weeks) on rats about which nothing further is discussed since the studies likewise were not conducted with the products that are the subject of the application and also in the case of the short studies the type of administration (intravenous) is not relevant for assessing the safety of oral intake.
- The safety data presented in the application are not clearly cross-referenced to the correct product. It considered there are likely to be significant differences between 1,3- and 1,4-*beta*-glucans and therefore more information is required on which substances the safety data corresponds to.
- The 52-week study carried out using *beta*-glucans derived from *C. albicans* only reports the observation of reversible hyperplasia of the colonic mucosa at 200 mg/kg per day. The coagulation time was not determined in this study. A NOAEL of 100 mg/kg per day could therefore be defined. There is no safety margin between the NOAEL taken into account and the daily consumption specified by the petitioner (49 to 105 mg/kg per day).
- Toxicological studies on the soluble product (WGPS) should be provided to execute a complete assessment. The toxicological studies provided in the dossier have only been performed on the insoluble products.
- Although yeast allergy is rarely encountered in everyday practice, it nonetheless exists and should be taken into consideration. Therefore, the source of *beta*-glucans of these products as *Saccharomyces cerevisiae* should be given on the product label.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Food Safety Authority is asked to carry out the additional assessment for 'yeast *beta*-glucans' as food ingredient in the context of Regulation (EC) No 258/97.

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

ASSESSMENT

In accordance with the Commission Recommendation 97/618/EC, 'yeast *beta*-glucans' is allocated to Class 2.1 'a complex (non-GM derived) novel food ingredient, the source of the novel food having a history of food use in the community'. The assessment of the safety of this novel food ingredient is based on data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections of the other Member States and the responses of the applicant to these questions and those of Ireland. The data are required to comply with the information required for novel foods of Class 2.1 i.e. structured schemes I, II, III, IX, X, XI, XII and XIII. It is noted that the novel ingredient is intended by the applicant to be marketed for consumption as an ingredient as well as in food supplements and foods for particular nutritional uses. This assessment concerns only risk that might be associated with consumption and is not an assessment of the efficacy of 'yeast *beta*-glucans' with regard to any claimed benefits.

1. Specification of the Novel Food (NF)

Beta-glucans are complex, high molecular mass (100 – 200 kDa) polysaccharides, found in the cell wall of many yeasts and cereals. The chemical name for 'yeast *beta*-glucans' is (1-3),(1-6)-β-D-glucans. 'Yeast *beta*-glucans' differs from their cereal counterparts in that they contain ß-1,3- and 1,6-glucosidic bonds, compared to the cereal derivatives which contain ß-1,3- and 1,4-glucosydic bonds.

This novel food application concerns both insoluble [BetaRight WGP (BWGP) and Wellmune WGP Dispersible (WGPD)] as well as soluble [Wellmune WGP soluble (WGPS)] 'yeast *beta*-glucans', isolated from *Saccharomyces cerevisiae*. The insoluble products contain at least 70 % (BWGP) or 75 % (WGPD) carbohydrate in the form of *beta*-glucans; the soluble product (WGPS) contains at least 75 % *beta*-glucans.

The tertiary structure of the glucan cell wall of *S. cerevisiae* consists of chains of ß-1,3-linked glucose residues, branched by ß-1,6-linkages, forming a backbone to which are linked chitin via ß-1,4- bonds, ß-1,6-glucans and some mannoproteins. As the latter can be linked to ß-1,6-glucose chains through alkali-sensitive bonds, most of the protein-linked components are expected to be removed during processing which includes treatment with alkali. Small amounts of protein and lipids, as well as small amounts of ß-1,6-glucan and chitin, are also expected to be present in the final products.

The applicant gave the following specifications for the novel food ingredient (Table 1).

Table 1: Specification for 'yeast *beta*-glucans'

Specification Parameter	Insoluble 'yeast *beta*-glucans'		Soluble 'yeast *beta*-glucans' - Wellmune WGP® Soluble (WGPS)	Reference/Test Methodology; Test laboratory
	BetaRight® WGP (BWGP)	Wellmune WGP® Dispersible (WGPD)		
Physical Specifications				
Description	Fine beige/tan powder			Visual inspection
Taste	Bland			Taste
Odour	Faint/mild			Olfactory
Chemical Specifications				
Total Carbohydrate (%)	> 70	≥ 75	≥ 75	by difference [a]
beta-glucans (1,3/1,6) (%)	> 70 [b]	≥ 75 [b]	≥ 75	Internal method [c]

Protein (%)	< 10	< 3.5	< 3.5	AOAC Method 990.03
Fat (%)	< 20	< 10	< 10	AOAC Method 989.05
Ash (%)	< 5	< 3	< 4	AOAC Method 942.05
Moisture (%)		< 8		AOAC Method 930.15
Lead (mg/kg)		< 0.5		AOAC Method 984.27
Microbiological Specifications				
Aerobic Plate Count (CFU/g)	< 20,000		< 10,000	AOAC Method 966.23
Yeast and Mould (CFU/g combined)		≤ 100		U.S. FDA BAM, 7th ed.[d]
Coliforms (MPN/g)		< 3		AOAC Method 966.24
Escherichia coli		Negative [e]		AOAC Method 966.24
Salmonella spp.		Negative [f]		AOAC Method 2004.03

Abbreviations: AOAC = Association of Official Analytical Chemists; BAM = Standard Bacterial Analytical Manual

CFU = colony-forming units; MPN = most probable number;

[a] The percentage of carbohydrates is calculated by subtracting the percentages of protein, fat, ash, and moisture from 100 % [*i.e.*, 100 % - (%protein + %fat + %ash + %moisture)].

[b] The product will be designated as WGPD if it contains a *beta*-glucans content of at least 75 %, and otherwise will be designated as BWGP.

[c] Biothera's internal enzymatic and spectrophotometric method

[d] U.S. FDA. Yeasts, molds and mycotoxins. In: *Bacteriological Analytical Manual [BAM]*, 7th ed. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), College Park, Maryland; 1998.

[e] Where negative = <3 CFU/g.

[f] Where negative = Absent in 25 g.

Batch variation

As concerns batch variation, batches were analysed to demonstrate the ability to produce within these specifications. Analytical results are presented in Table 2 and Table 3 and indicate that results for the parameters tested met the specifications.

Table 2: Results from testing of five non-consecutive batches of WGPD

Insoluble 'yeast *beta*-glucans' [Wellmune WGP® Dispersible (WGPD)]

Specification Parameter	Specification	Manufacturing Lot				
		08206-01	**08139-01**	**08152-01**	**08152-02**	**08180-01**
Carbohydrate (%)	≥ 75	83.61	82.84	81.10	81.57	84.75
beta-glucans (%)	≥ 75	82.00	79.00	82.00	75.00	82.00
Protein (%)	< 3.5	2.81	2.94	2.80	2.56	2.94
Fat (%)	< 10	5.54	6.36	8.03	8.30	4.98
Ash (%)	< 3	1.23	1.27	1.49	1.32	1.47
Moisture (%)	< 8	6.81	6.59	6.58	6.25	5.86

Table 3: Results from testing of five non-consecutive batches of WGPS

Soluble 'yeast *beta*-glucans' [Wellmune WGP® Soluble (WGPS)]

Specification Parameter	Specification	Manufacturing Lot				
		Lot No. 1B	Lot No. 1C	Lot No. B3	07220-01	07227-01
Appearance	Fine beige/tan powder	Conforms	Conforms	Conforms	Conforms	Conforms
Taste	Bland	Conforms	Conforms	Conforms	Conforms	Conforms
Odour	Faint/mild	Conforms	Conforms	Conforms	Conforms	Conforms
Total Carbohydrate (%)	> 75	90.90	92.57	93.44	91.73	92.85
beta-glucans (%)	≥ 75	76	78	76	77	82
Protein (%)	< 3.5	0.60	0.60	0.71	0.60	0.64
Fat (%)	< 10	2.03	1.45	1.56	1.74	1.79
Ash (%)	< 4	2.82	2.29	1.16	2.55	2.38
Moisture (%)	< 8	3.65	3.09	3.13	3.37	2.34

The Panel notes that the values for several specification parameters of WGPD and WGPS derived from the batch testing are quite beyond the limits given by the specification, indicating very broad specifications set by the applicant.

Fatty acid composition based on data from the literature

Fatty acid composition was provided based on data from the literature for whole yeast and particulate glucan (Blagović et al., 2001; Müller et al., 1994; Šajbidor et al., 1991; Schulze, 1995; van der Rest et al., 1995;). Fatty acids comprised 10:0, capric acid, 12:0, lauric acid and 12:1, lauroleic acid, 14:0, Myristic acid and 14:1, Myristoleic acid, 16:0, Palmitic acid, 16:1, Palmitoleic acid, 18:0, Stearic acid, 18.1, oleic acid, 18:2 linoleic acid, 20:4, arachidonic acid and other higher fatty acids. Most abundant fatty acids were palmitic, palmitoleic, stearic and oleic acid.

Residues from the production process and contaminants

All foods, and hence also novel foods, have to comply with the existing legislation. The applicant provided data on contaminants (heavy metals, residues, pesticides). The Panel considers that the data presented on contaminants do not indicate a safety concern.

The Panel concludes that it has no concerns with regard to the specifications of the NFI.

2. Effect of the production process applied to the NF

The manufacturing process involves *S. cerevisiae* as a starting material in the production of insoluble *beta*-glucans, which is then processed further to yield soluble *beta*-glucans. The production process includes the use of standard food grade chemicals in the isolation and purification process. The process is presented in detail in the application dossier, and is indicated to be confidential. The manufacturing process can be summarised as follows.

Following fermentation, the manufacturing process is initiated by lysing the cells so that the *beta*-glucan components of the cell wall can be extracted and purified to produce the final ingredient. The autolysis process is initiated by heating the vessel under specified (but confidential) conditions. Following centrifugal separation, the cell wall isolate then undergoes a treatment with sodium

hydroxide. This step also removes any residual cell lipids trapped within the cell wall. Subsequently, the ingredient undergoes acid treatment with sulphuric acid, which results in the depolymerisation and deacetylation of chitin to form free glucosamine hydrochloride, and essentially results in the removal of most of the chitin in one step. Following sulphuric acid treatment, the yeast wall slurry undergoes heat treatment. The mixture is then nitrogen spray-dried at 180°C, and once dry, the powder is sieved through a #50 mesh. The *beta*-1,3-glucans product (WGPD or BWGP, depending on the *beta*-glucans content) is then packaged.

In response to a Member States' concern regarding potential concentration of undesirable substances, the applicant stressed that the physical separation (e.g., ultra-filtration, chromatographic separation) does not include concentration steps that would allow for the co-concentration of other molecules, but involves the simple washing and removal of impurities.

The differences in the compositional data related to the *beta*-glucans, protein, and fat content between WGPD and BWGP results from one additional washing step for WGPD which removes more protein and fat and leads to a higher *beta*-glucans content than compared to BWGP.

For the production of the soluble food grade ingredient (WGPS), WGPD undergoes further processing. The solubilising process includes pH adjustments, de-aeration via nitrogen, and heat treatment under specified (but confidential) conditions. Following heat treatment, the mixture is then spray-dried, sieved, and packaged. According to the applicant's response, the chemical structure of *beta*-glucan is retained in the solubilisation process.

The applicant provided the Hazard Analysis and Critical Control Point (HACCP) plans for both production sites (WGPD and BWGP in Columbia, USA; WGPS in Saskatoon, Canada).

The applicant provided data from stability studies and claims a shelf-life for *beta*-glucans products of five years when stored in bulk and for three years when packaged in gelatine capsules. The data provided indicate stability of the ingredients over at least three years.

The Panel concludes that production processes resulting in the insoluble and soluble products and their stability are sufficiently described and do not give cause for concern.

3. History of the organism used as the source of the NF

S. cerevisiae, more commonly referred to as brewer's/baker's yeast, has been used for over a thousand years as a food ingredient, and its most common present day and historical uses are in the production of bread and in the fermentation process of wine and beer. The cell wall of *S. cerevisiae* represents approximately 30 % of the dry weight of the cell, which is composed predominantly of polysaccharides (approximately 85 %) and proteins (approximately 15 %) (Nguyen *et al*., 1998).

4. Anticipated intake/extent of the use of the NF

The applicant intends to market insoluble and soluble 'yeast *beta*-glucans' derived from *S. cerevisiae* as a food ingredient in food supplements, foods for particular nutritional uses (PARNUTS, as specified by Directive 2009/39/EC[4]), and in conventional foods. The ingredient would be marketed under the trade names BWGP, WGPD, and WGPS depending on the 'yeast *beta*-glucans' content and solubility of the product. As indicated earlier, BWGP is the standard product containing 70 % insoluble (or dispersible) 'yeast *beta*-glucans', whereas WGPD has undergone further purification to yield a product containing a minimum of 75 % insoluble 'yeast *beta*-glucans'. These insoluble

[4] Directive 2009/39/EC of the European Parliament and of the Council of 6 May 2009 on foodstuffs intended for particular nutritional uses (recast). OJ L124, 20.5.2009, p. 21-29.

materials are of limited use in beverage products, and in order to overcome these restrictions, WGPS has been developed as a soluble form of WGPD containing a minimum 75 % soluble 'yeast *beta*-glucans' for use in beverages.

4.1. Intended use in food supplements

BWGP, WGPD, and WGPS are proposed for use in food supplements at levels of between 250 and 500 mg per day, delivering approximately 175 to 375 mg 'yeast *beta*-glucans' per day.

4.2. Intended use in PARNUTS foods

BWGP, WGPD, and WGPS are proposed for PARNUTS (including food intended for use in energy restricted diets for weight reduction, dietary foods for special medical purposes) at levels not exceeding 2-3 servings of 200 mg 'yeast *beta*-glucans' per day (i.e. 600 mg per day), with the exception of infant formulae and follow-on formulae (as defined by Commission Directive 2006/141/EC[5]).

4.3. Intended use in conventional foods

According to the applicant, BWGP, WGPD, and WGPS are intended for use in a range of conventional foods for the general population, such as beverages [bottled water, fruit juice, fruit-flavoured drinks (ready to drink (RTD), smoothies), non milk-based meal replacement beverages, and sports, energy and isotonic drinks], cereal and cereal products [cereal bars (crunchy, breakfast), cookies, crackers, ready to eat breakfast cereals and wholegrain and high fibre instant hot breakfast cereals], milk and milk products [fermented milk products, liquid milk drinks (including soya and other non dairy analogues), milk powders and drink mixes, milk-based meal replacement beverages, yoghurt drinks and yoghurt, fromage frais and other dairy desserts (including soya and other non dairy analogues)], miscellaneous (soups and soup mixes), sugar, preserves and confectionery (chocolate confectionery), and vegetables, potatoes and savoury snacks (soybased protein bars and powders). The proposed food uses range from 50 - 200 mg 'yeast *beta*-glucans'/serving. The intended use-levels of 50, 100, or 200 mg/serving for different foods, respectively, comprise the maximum use-level for 'yeast *beta*-glucans' obtained from each trade ingredient separately (i.e., BWGP, WGPD, or WGPS) or for combinations of the ingredients. Given that BWGP, WGPD, or WGPS contain approximately 70 or 75 % w/w 'yeast *beta*-glucans', respectively, the proposed maximum use level of 200 mg 'yeast *beta*-glucans' per serving is equivalent to approximately 270 - 290 mg/serving of each of the three commercial products (*i.e.*, BWGP, WGPD, or WGPS).

For the intake assessment, the applicant excluded the intake figures from food supplements and the PARNUTS categories, assuming that these products would be taken as replacements for other foods fortified with *beta*-glucans rather than in addition to them.

On the basis of these data, the applicant estimated the total daily intakes of 'yeast *beta*-glucans' from all proposed food-uses. Based on these proposed use levels, the applicant has estimated the anticipated daily intake of the NFI for different population groups, using data from the UK National Diet and Nutrition Surveys (NDNS). These surveys covered young children aged 1.5 to 4.5 years (UKDA, 1995), children 4 to 10 and female and male teenagers aged 11- 18 years (UKDA, 2001) and female and male adults aged 16 to 64 years (Office for National Statistics, 2005).

[5] Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. OJ L141, 30.12.2006, p. 1-33.

Of the individual population groups, male teenagers had the greatest mean and 97.5th percentile all-user intakes of 'yeast *beta*-glucans' resulting from the consumption of BWGP, WGPD, and WGPS at an absolute basis of 0.80 and 1.94 g/person per day, respectively. Female adults had the lowest mean all-user intake of 0.51 g/person per day and female teenagers and female adults had the lowest 97.5th percentile intake each of 1.33 and 1.34 g/person per day, respectively (Table 4). On a body weight basis, children were identified as having the highest mean and 97.5th percentile all-user intakes of any population group, of 49 and 105 mg/kg bw per day, respectively. Female and male adults displayed the lowest mean and 97.5th percentile all-user intakes, with values of 8 and 7 mg/kg bw per day (mean), and 20 and 21 mg/kg bw per day (97.5th percentile), respectively (Table 5). It is noted that this type of intake methodology for fortified foods is generally considered to be "high intake" as a result of several conservative assumptions made in the consumption estimates assuming that all food products within a food category contain the ingredient at the maximum specified level of use.

Table 4: Summary of the Estimated Daily Intake of 'yeast *beta*-glucans' in the U.K. from All Proposed Uses of BetaRight® WGP (BWGP), Wellmune WGP® Dispersible (WGPD), and Wellmune WGP® Soluble (WGPS) by Population Group (NDNS Data)

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (g)	Percentile (g)			Mean (g)	Percentile (g)		
					90	95	97.5		90	95	97.5
Children	1½ -4½	98.7	1627	0.69	1.08	1.24	1.37	0.69	1.08	1.25	1.39
Young People	4-10	99.6	834	0.79	1.23	1.38	1.53	0.78	1.22	1.38	1.53
Female Teenagers	11-18	97.5	435	0.59	0.96	1.16	1.32	0.59	0.96	1.14	1.33
Male Teenagers	11-18	99.5	414	0.81	1.38	1.62	1.94	0.80	1.38	1.62	1.94
Female Adults	16-64	93.5	896	0.50	0.92	1.12	1.35	0.51	0.93	1.12	1.34
Male Adults	16-64	94.4	723	0.58	1.14	1.43	1.65	0.58	1.15	1.44	1.65

Table 5: Summary of the Estimated Daily per Kilogram Body Weight Intake of 'yeast *beta*-glucans' from All Proposed Food-Uses of BetaRight® WGP (BWGP), Wellmune WGP® Dispersible (WGPD), and Wellmune WGP® Soluble (WGPS) in the U.K. by Population Group (NDNS Data).

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (mg/kg)	Percentile (mg/kg)			Mean (mg/kg)	Percentile (mg/kg)		
					90	95	97.5		90	95	97.5
Children	1½ -4½	98.7	1627	48	77	88	105	49	77	88	105
Young People	4-10	99.6	834	31	50	59	67	31	51	59	67
Female Teenagers	11-18	97.5	435	11	20	26	29	12	20	26	29
Male Teenagers	11-18	99.5	414	15	28	34	40	15	28	34	40
Female Adults	16-64	93.5	896	7	13	17	19	8	14	17	20
Male Adults	16-64	94.4	723	7	14	17	21	7	15	17	21

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

S. cerevisiae has been routinely and extensively used for many centuries in the production of yeast leavened breads and fermented beverages such as beer and wine. Yeast glucans also occur naturally in several other specific food products. In addition, *beta*-glucans occur in many other foods.

In response to a Member State request, the applicant provided an intake estimate of *beta*-glucans naturally present in foods based on the contents in foods and based on UK consumption data (UKDA, 1995, 2001; Office for National Statistics, 2005) of these foods for the same population groups.

For normal *beta*-glucans intake, male adults had the greatest mean and 97.5th percentile all-user intakes of *beta*-glucans at 726 and 4,673 mg/person per day (9 and 52 mg/kg bw per day), respectively. An analysis of the impact of individual food categories on the intake of *beta*-glucans by male adults revealed that the consumption of beer produced the largest individual food intakes of *beta*-glucans in this population group. Children of 1.5 – 4.5 years old had the lowest mean estimates for daily *beta*-glucans intake with values of 281 mg/person. On a body weight basis, infants/young children (1.5 - 4.5 years old) were identified as the population group having the highest mean and 97.5th percentile all-user intakes of normal *beta*-glucans at 20 and 115 mg/kg bw per day, respectively. This intake was largely driven by the consumption of yeast breads, buns, and rolls. Female teenagers displayed the lowest estimate for the mean all-user intake of *beta*-glucans at 6 mg/kg body weight per day, while the lowest estimate for the 97.5th percentile intake was observed to occur in male teenagers at 19 mg/kg bw per day.

It is concluded that *in a "high intake"* scenario (i.e. all foods that are intended to contain the NFI do contain the NFI), the intake of *beta*-glucans from BWGP, WGPD, or WGPS, is grossly similar to the background intake of *beta*-glucans from other dietary sources.

6. Nutritional information on the NF

The caloric value is low given that *beta*-glucans are fibres that contain indigestible carbohydrates (EFSA, 2010a). (Yeast) *beta*-glucans are not subject to intestinal digestion by human enzymes to any significant extent. The largest majority of the material is expected to travel intact through the gastrointestinal tract to the colon to be subject to fermentation by the resident microbiota. The fermentation of *beta*-glucans is well described in literature, and the metabolic products of fermentation are expected to be innocuous compounds (H_2, CO_2, CH_4, and volatile fatty acids).

On the basis of the available information it can be concluded that the novel food product is not nutritionally disadvantageous.

7. Microbiological information on the NF

The applicant provided methods, results and certificates from the microbiological testing of five batches of insoluble and five batches of soluble 'yeast *beta*-glucans' (data not shown). These did not indicate reasons for concern.

8. Toxicological information on the NF

8.1. Genotoxicity

The applicant did not conduct genotoxicity tests and could not identify traditional genotoxicity studies for 'yeast *beta*-glucans'. The Panel considers that neither the chemical nature of *beta*-glucans nor the source *S. cerevisiae* give reasons for genotoxicity safety concerns, which is in conformity with earlier EFSA opinions (EFSA, 2010b, c).

8.2. Absorption, distribution, metabolism and excretion studies of soluble and insoluble *beta*-1,3/1,6-glucans

Indigestible carbohydrate polymers are not absorbed through the gut mucosa, and thus significant systemic exposure following 'yeast *beta*-glucans' ingestion is not expected to occur. However, there are some data on absorption of *beta*-glucans from sources other than the NFI: small amounts of both soluble and insoluble *beta*-glucans particulates may enter the systemic circulation, e.g. via the Peyer's patches or through a process called "persorption" (Beier and Gebert, 1998; Hong et al. 2004; Volkheimer 1974; Yuji et al., 2006, 2007). Also small amounts of soluble *beta*-glucan polymers may be taken up *via* the Peyer's patches or via micropinocytosis by epithelial cells of the gut mucosa (Rice et al., 2005; Sandvik et al. 2007). Peak plasma levels were achieved within 1 hour and serum levels did not exceed 13 ng/mL. Elimination was rapid and serum levels approached baseline levels within 8 hours.

The applicant also provided a paper on a human study in which the tolerability and absorption of a soluble baker's yeast ß-1,3/ ß-1,6-D-glucans preparation ("SBG" provided by Biotec Pharmacon, Tromsø, Norway, i.e. a *beta*-glucans different from the NI) was investigated. Six individuals per group received doses of 100, 200 and 400 mg/person for 4 consecutive days. The authors reported that no statistical significant changes compared to baseline were found during intervention including a 4 four day follow-up period; the detection limit was 5 pg/mL (Lehne et al., 2005). The Panel considers that this study is of very limited value with respect to the safety of the novel food ingredient at the proposed use levels.

Based on the nature of the ingredient and the literature provided, the Panel considers that 'yeast *beta*-glucans' is not absorbed to a significant degree.

8.3. Animal toxicity studies

8.3.1. Acute and sub-acute toxicity studies

The applicant provided an overview of a number of acute and short-term toxicity studies on soluble and insoluble 'yeast *beta*-glucans' of up to 1000 mg/kg bw administered parenterally to mice, rats, rabbits and guinea pigs. None of these parenteral studies concerned the NFI preparation and hence are of limited value for the safety evaluation of the NFI.

The applicant also provided a single-dose toxicity study in rats to determine the potential acute toxicity of (insoluble) WGPD administered by gavage (Babíček et al., 2007), according to OECD guideline 420 at 2,000 mg of WGPD/kg bw. No indications of adverse effects were observed.

After the submission of the dossier to EFSA, the Panel identified a sub-acute 28-day oral toxicity study in rats with *beta*-glucans from barley (i.e. not the NFI of the application) of purity >75 % at dietary levels of up to 10 % (Jonker et al. 2010). High dose males had lower plasma cholesterol and phospholipids values and higher plasma urea levels, which findings were considered not of toxicological relevance. In addition, mid and high dose males exhibited caecal enlargement, which could be explained by the high amount of indigestible fiber. In this study the NOAEL was identified at 5.8 - 5.9 g/kg bw. The Panel considers that this study on a *beta*-glucans source other than the NFI is of limited relevance for the safety assessment of the NFI of this application.

8.3.2. Sub-chronic toxicity

A 91-day toxicity study was conducted in rats to assess the sub-chronic effects of daily oral administration of WGP® 3-6 (= WGPD) (Babíček, 2003; Babíček et al., 2007) in accordance with Good Laboratory Practice (GLP) and OECD Guideline 408. Groups of 10 male and 10 female SPF Fisher-344 rats received 0, 2, 33.3, or 100 mg WGPD/kg bw per day for 91 consecutive days by

gavage (approximately 0, 1.5, 25, or 75 mg *beta*-glucans/kg bw per day). In administering the test substance at the maximum flowable level, the authors stated that 100 mg/kg was the highest dose that could be administered by gavage. In addition, a 100 mg/kg bw per day recovery group for each sex was also included and maintained for an additional 14 days without treatment following the 91-day dosing period.

WGPD was well tolerated throughout the treatment period. A significant decrease in clotting time was observed in the two highest doses in male animals, unlike in females and was considered of no concern because of unusual high values in the control group; Table 6.

Table 6: Values for Blood Clotting Times from the 91-day rat study

	Control	2.0 mg/kg bw per day	33.3 mg/kg bw per day	100 mg/kg bw per day
Baseline (Day 0)	88.9 ± 24.4 s	92.5 ± 26.5	98.0 ± 24.4	85.3 ± 29.8
End of Treatment (Day 92)	141.1 ± 68.5 s	100.4 ± 24.7	93.9 ± 25.2	78.3 ± 20.9
Change from Baseline	+52.2	+7.9	-4.1	-7

A statistically significant (p=0.01) increase in MCV was also observed in females; however, the effect was modest (+ 6 %) and occurred equally in all doses. No pathological findings were present in any animals subjected to necropsy after termination of the recovery period. Based on clinical, pathological, and statistical evaluations, the authors concluded that no toxicity was observed over the 3-month repeat administration period when WGPD was administered up to a maximum deliverable oral dose of 100 mg/kg bw per day to rats. Therefore, the NOAEL was determined to be 100 mg/kg bw per day (approximately 75 mg *beta*-glucans/kg bw per day), the highest dose tested. The Panel agrees that no safety concerns arise from this study.

In addition, after the initial application the applicant conducted another 90-day study in which male and female Sprague-Dawley rats (10/sex/group) were administered 0 (control), 0.62, 1.25, or 2.50 g WGPD/kg bw per day via gavage. This study was not claimed to be done under GLP and it was not conducted according to official (OECD) guidelines. No toxicologically relevant changes in body weights, feed intake, blood biochemistry, haematology, organ weights, or macro- or microscopic observations were noted between the test and control animals. The no-observed-adverse-effect level (NOAEL) from this study was determined to be 2.50 g WGPD/kg bw per day (Biothera, 2009).

In addition, the applicant provided a 60 day study using water soluble *beta*-glucans intravenously injected in male ICR/HSD mice (Williams et al. 1988). The animals (5/group) received bi-weekly 'yeast *beta*-glucans' at doses of 0, 40, 200, or 1,000 mg/kg bw in 2 separate 30- and 60-day experiments. On days 30 and 60, statistically significant increased spleen weights were observed in the highest dose group (and some lower dose levels). Since the test substance is dissimilar to the NFI that is the subject of this study and the route of administration is intravenous, this study is of limited value only for the safety evaluation of the NFI.

The Panel considers that the two oral sub-chronic toxicity studies in rats with the NFI do not raise safety concerns. A NOAEL could be set at 100 mg/kg bw/day (approximately 75 mg *beta*-glucans/kg bw per day), the highest dose tested in a 91-day study (Babíček, 2003; Babíček et al., 2007). However, on the basis of other studies with the NFI or other *beta*-glucans, the Panel considers this NOAEL far below the real NOAEL-value. This can be illustrated by the NOAEL in the 90-day study with WGPD (NOAEL = 2.5 g/kg bw), the recent 28-day study on another *beta*-glucan (NOAEL at 5.8 g/kg-bw) (Jonker et al. 2010) and recent EFSA opinions on other chitin-*beta*-glucan (NOAEL of 7 g/kg bw) (EFSA, 2010b). The Panel considers that the chosen mode of administration in the 91-day sudy (gavage) may have hampered the administration of higher dose levels. Therefore, the 91-day

subchronic study is not considered suitable to derive a useful NOAEL, owing to its low highest dose tested.

8.3.3. Chronic toxicity

No chronic toxicity study has been carried out with the NFI.

Feletti et al. (1992) investigated the effects of chronic (52 weeks) oral 'yeast *beta*-glucans' administration at doses of 0, 50, 100, or 200 mg/kg bw per day in 160 Sprague-Dawley rats. The *beta*-glucans used in this experiment was an insoluble granulate derived from *Candida albicans* (99.4 % pure). The only finding attributed to *beta*-glucans administration was soft stools or diarrhoea and caecal enlargement in the test group receiving 200 mg *beta*-glucans granulate/kg bw per day (approximately 50% of the animals in this group), an effect that returned to normal after the cessation of treatment (recovery groups). The authors reported that these symptoms were typical for exposure to sugar alcohols (sorbitol, mannitol, and xylitol), lactose, and caramel, as well as some chemically modified food starches and synthetic polydextrose (Newberne et al., 1988). Based on observations of caecal enlargement at the highest dose, the authors determined the no-observed-effect level (NOEL) to be 100 mg/kg bw per day. Since caecal enlargement in association with polyols consumption in rodents is considered not relevant to humans (WHO, 1987), a NOAEL of 200 mg/kg bw per day, the highest dose tested, also can be determined. The Panel notes that caecal enlargement in experimental animals is not unusual with high doses of fibre and agrees with a NOAEL of 200 mg/kg bw per day in this study (on another source of *beta*-glucans).

8.3.4. Reproduction and Developmental Toxicity

No studies on reproductive and developmental toxicity were identified for orally administered *beta*-glucans.

8.3.5. Allergenicity

Positive skin prick tests to *S. cerevisiae* have been reported in as high a proportion as 70 to 94 % of patients with atopic dermatitis. Although allergy to *S. cerevisiae* occurring from food consumption is rare, confirmed cases of food allergy to baker's yeast have been reported in the literature (Pajno et al., 2005). The allergenic potential of the concerned novel food ingredient was not evaluated.

A Member State requested information on the presence of mannans co-extracted from the yeast cell wall, and expressed concerns that they could lead to hypersensitivity. According to the batch testing provided and assuming (worst case assumption) that all mannose present is not free but present as mannans 'yeast *beta*-glucans' contain approximately 0.5 % mannanes. The Panel considers that this amount does not represent a risk for hypersensitivity higher than baker's yeast itself.

The Panel expects that the allergenic risk of the NFI is not higher than the risk from other products containing baker's yeast.

8.4. Human studies

The applicant provided three studies with low levels of the NFI. A short unpublished summary report on an uncontrolled study with 20 healthy volunteers who received one capsule of WGPD (approximately 250 mg of insoluble *beta*-glucans) per day over 10 days (Biothera, Inc., 2005a). A variety of immunological, haematological and blood parameters was determined. There were no adverse events reported during the course of this clinical trial. According to the applicant, WGPD was well tolerated and blood biochemistry parameters were unaffected by *beta*-glucans treatment. Only serum TNF-alpha levels were increased 6-fold relative to baseline. According to the applicant, these

changes were not genuinely meaningful because the subjects did not demonstrate any other adverse events. The applicant further states that the blood chemistry profiles were not statistically analysed. The Panel notes the considerable limitations of this study such as the study design, the lack of a statistical analysis and the poor documentation of this study.

The applicant also provided a recent randomised placebo-controlled study with Wellmune WGPS in 100 volunteers (50 + 50). This study was aimed to review the efficacy of Wellmune WGPS (250 mg/day) to reduce frequency and severity of Upper Respiratory Tract Infection symptoms (the Panel considers this an effect beyond relevance for safety evaluation and is not further evaluated here) over 90 days. In total 97 volunteers completed the study (n = 48 Wellmune WGPS and n = 49 controls). Wellmune WGPS was well tolerated and demonstrated significant reduction in the total number of days with reported URTI symptoms; TNF-alpha levels were not different between intervention and control groups.

In addition, a short unpublished summary report was provided on a randomised, placebo-controlled study which was performed on 62 subjects receiving orally two doses of 250 mg *beta*-glucans in the form of WGPD for 10 days to assess the effect of 'yeast *beta*-glucans' on immunological parameters in subjects exposed to rhinovirus (common cold) and some safety related endpoints (Biothera, Inc., 2005b). According to the applicant, no statistically significant effects were found for safety related endpoints, WGPD was well tolerated and no adverse effects attributable to the test article were observed. There were no adverse events considered related to the study treatment. The Panel notes the considerable weaknesses of this study, such as safety endpoints were not specified, and the poor documentation of this study. The Panel considers that these two studies using low doses of the NFI are of limited value for the safety evaluation of the NFI.

An uncontrolled study with 15 free-living, obese, hypercholesterolaemic men by Nicolosi et al. (1999) investigated the cholesterol-lowering effect and gastrointestinal tolerability of a baker's yeast *beta*-glucans supplementation provided by Alpha-beta Technologies. According to the applicant, the *beta*-glucans preparation used in this study was essentially identical to WGPD of Biothera. Subjects were instructed to consume 7.5 g of *beta*-glucans (added to orange juice) twice daily for 8 weeks. Individuals were not instructed to follow a special diet. Based on questionnaires filled by the subjects, the authors reported that adverse effects typically reported with fibre consumption, such as diarrhoea, nausea, abdominal discomfort, abdominal distension, and flatulence, were minimal. According to the authors, 15 g/day of the 'yeast *beta*-glucans' preparation was well tolerated. The Panel notes the considerable weaknesses of this study such as the lack of monitoring for compliance, the uncontrolled nature of the study, the study population and the limited number of safety related endpoints. The Panel considers that this study is of limited value for the safety evaluation of the NFI.

In addition, the applicant provided two randomised placebo-controlled human trials (Babineau et al., 1994a, b) that investigated tolerability and effects of a soluble product, PGG, upon intravenous administration on reducing infections around surgery. According to the applicant, PGG (produced by Alpha-beta Technologies) is very similar to the soluble WGPS produced by Biothera. No adverse effects were found for PPG. The Panel notes the parenteral application. The Panel considers that this study is of limited value with regard to the safety of the BWGP, WGPD and WGPS.

The Panel notes that the human studies provided did not report adverse effects other than those typically reported for fibre. However the Panel notes considerable weaknesses in most of the human studies provided to demonstrate the safety of the NFI at the proposed uses and use levels, except for the recent study with Wellmune WGPD. The Panel also considers that human studies are in essence of limited value for safety evaluation since dose levels are necessarily lower than in animal studies. The Panel considers that the human studies provide supporting, albeit very limited, evidence for the safety of BWGP, WGPD and WGPS.

DISCUSSION

The applicant intends to market 'yeast *beta*-glucans' in food supplements at dose levels of up to 375 mg per day and in foods for particular nutritional uses (PARNUTS) at dose levels of up to 600 mg per day. It is not intended for infant formulae and follow-on formulae. In addition, the applicant intends to market 'yeast *beta*-glucans' in a variety of foods including beverages for the general population.
Male teenagers had the greatest 97.5th percentile all-user intakes of the NFI at 1.94 g/person per day. On a body weight basis, children were identified as having the highest 97.5th percentile all-user intake at 105 mg/kg bw per day.

It is concluded that in a "high intake*"* scenario (i.e. all foods that are intended to contain the NFI do contain the NFI), the intake of *beta*-glucans from BWGP, WGPD, or WGPS, is grossly similar to the background intake of *beta*-glucans from other dietary sources.

The characterisation, specification and production process do not give reasons for concern. The source of the NFI, *S. cerevisiae*, i.e. baker's yeast traditionally used for the production of bread, beer and wine, does not give reason for concern.

Data provided on (sub)acute and sub-chronic toxicity, absorption, and limited human data do not give reason for concern. The allergenic risk of the NFI is not higher than the risk from other products containing baker's yeast.

Beta-glucans from other sources have already been evaluated for safety by EFSA (2010b, c).

The data from sub-chronic toxicity studies with the NFI lead to an overly conservative, i.e. too low, NOAEL. Hence the Panel considers that the standard risk assessment route is not appropriate for this NFI.

Rather, on the basis of the nature of the NFI (mainly *beta*-glucan, a fibre, found in many foods), the significant history of use of the organism (baker's yeast used for over a thousand years for the production of bread, beer and wine), the unrealistic and overly "high intake" estimates of the NFI and the supplementary data from human and animal studies, the Panel considers that the intake of the NFI at proposed conditions of use, does not raise concerns.

CONCLUSIONS

The Panel concludes that 'yeast *beta*-glucans' is safe at the proposed conditions of use.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier on 'yeast *beta*-glucans' received on 07 July 2010.
2. Letter from the European Commission to the European Food Safety Authority with the request for an opinion on the safety of 'yeast *beta*-glucans'. SANCO E6/AK/bs, Ref Ares(2010)390402, 2 July 2010.
3. Initial assessment report carried out by Ireland: Safety Assessment of Insoluble and soluble yeast *beta*-glucan as a novel food ingredient under Regulation EC No 258/97.
4. Member States' comments and objections
5. Response by the applicant to the initial assessment report and the Member States' comments and objections

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GLOSSARY / ABBREVIATIONS

bw	body weight
EC	European Commission
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
NFI	Novel Food Ingredient
NOAEL	No observed adverse effect level
PARNUTS	Foods for Particular Nutritional Uses
SCF	Scientific Committee for Food
UK NDNS	UK National Dietary and Nutrition Survey