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Safety of paramylon as a novel food pursuant to Regulation (EU) 2015/2283

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Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on paramylon as a novel food (NF) pursuant to Regulation (EU) 2015/2283. Paramylon is a linear, unbranched beta-1,3-D-glucan polymer that is isolated from the single-cell microalga *Euglena gracilis*. The NF consists of at least 95% beta-glucan and minor amounts of protein, fat, ash and moisture. The applicant proposed to use the NF in food supplements, as a food ingredient added to a number of food categories and in foods for total diet replacement for weight control. In 2019, *E. gracilis* was attributed the qualified presumption of safety (QPS) status with the qualification 'for production purposes only', which includes food products based on microbial biomass of the microalga. Based on the information provided, *E. gracilis* is not expected to survive the manufacturing process. The submitted toxicity studies did not raise safety concerns. No adverse effects were observed in the subchronic toxicity studies, up to the highest dose tested, i.e. 5,000 mg NF/kg body weight per day. In view of the QPS status of the source of the NF, supported by the manufacturing process, compositional data and lack of toxicity observed in the toxicity studies, the Panel has no safety concerns and concludes that the NF, i.e. paramylon, is safe under the proposed uses and use levels.

Keywords: novel food, paramylon, algae, *Euglena gracilis*, beta-glucan, safety

Requestor: European Commission

Question number: EFSA-Q-2019-00593

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

On 15 August 2019, the company Kemin Foods L.C. submitted a request to the European Commission in accordance with Article 10 of Regulation (EU) 2015/2283 to authorise the placing on the Union market of paramylon as a novel food.

The application requests to authorise the use of paramylon in a number of foods.

The applicant has also requested data protection under Article 26 of Regulation (EU) 2015/2283[1].

In accordance with Article 10(3) of Regulation (EU) 2015/2283, the European Commission asks the European Food Safety Authority to provide a scientific opinion on paramylon as a novel food.

The European Commission asks the European Food Safety Authority to evaluate and inform the Commission as to whether and if so, to what extent, the requirements of Article 26(2)(c) of Regulation (EU) 2015/2283 are fulfilled in elaborating its opinion on paramylon regarding the proprietary data for which the applicant is requesting data protection.

1.2. Additional information

In 2020, the Panel assessed the safety of whole cell *Euglena gracilis* of the specific strain from which paramylon is obtained as a novel food (EFSA NDA Panel, 2020). The safety of *E. gracilis* biomass was established for its use as a food supplement and as a food ingredient in a number of foods, including foods for total diet replacement for weight control as defined by Regulation (EU) 609/2013 (EFSA NDA Panel, 2020).

Subsequently, dried whole cell *E. gracilis* was authorised for the placing on the market in the European Union by Commission Implementing Regulation (EU) 2020/1820[2].

2. Data and Methodologies

2.1. Data

The safety assessment of this NF is based on data supplied in the application and information submitted by the applicant following EFSA requests for supplementary information.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469[3].

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application (EFSA NDA Panel, 2016). As indicated in the guidance, it is the duty of the applicant to provide all the available (proprietary, confidential and published) scientific data (including both data in favour and not in favour) that are pertinent to the safety of the NF.

This NF application includes a request for protection of proprietary data in accordance with Article 26 of Regulation (EU) 2015/2283. The data requested by the applicant to be protected comprise: *in vitro* fermentation studies, bacterial reverse mutation test, two *in vivo* micronucleus tests, acute toxicity study in rats, 14-day toxicity/palatability study in rats, two 90-day toxicity studies in rats, 90-day clinical trial, 'Annex C' (production process), 'Annex D' (compositional data), 'Annex E' (stability reports), 'Annex F' (intake assessment report), certificates of analysis for particle size analysis, transmission electron microscopy report.

2.2. Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications (EFSA NDA Panel, 2016) and the principles described in the relevant existing guidance documents from the

[1] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. OJ L 327, 11.12.2015, pp. 1–22.

[2] Commission Implementing Regulation (EU) 2020/1820 of 2 December 2020 authorising the placing on the market of dried *Euglena gracilis* as a novel food under Regulation (EU) 2015/2283 of the European Parliament and of the Council and amending Commission Implementing Regulation (EU) 2017/2470. OJ L 406, 3.12.2020, pp. 29–33.

[3] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 64–71.

EFSA Scientific Committee. The legal provisions for the assessment are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of Commission Implementing Regulation (EU) 2017/2469.

This assessment concerns only the risks 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.

3. Assessment

3.1. Introduction

The NF which is the subject of the application is paramylon, which is a beta-glucan polymer isolated from the single-cell microalga *Euglena gracilis*. Thus, the NF falls under Article 3(2)(a)(ii): foods consisting of, isolated from or produced from microorganisms, fungi or algae, as per Regulation 2015/2283.

The NF is proposed to be used as food ingredient in a number of food categories, as a food supplement and in foods for total diet replacement for weight control as defined by Regulation (EU) No 609/2013. The proposed target population is the general population, except for food supplements and for meal replacement beverages for which the target population is children from 1 year onwards and adults, and except for foods for total diet replacement for which the target population is adults.

3.2. Identity of the NF

The NF is paramylon, which is a linear, unbranched beta-1,3-D-glucan polymer that is produced as a storage polysaccharide by the single-cell microalga *E. gracilis*.

Paramylon is synthesised by *Euglena* species as a fibrillar high molecular weight polymer with a high level of crystallinity in its native state (approaching 90%) and is deposited in the cells as small discoid granules (Barsanti et al., 2011). It is insoluble in water and does not have gelling properties.

In order to determine the degree of polymerisation of the NF, the applicant employed chromatography techniques. The average degree of polymerisation of the NF was reported by the applicant as being 1,544.

Paramylon granules synthesised by *E. gracilis* are of high purity with nuclear magnetic resonance (NMR) spectra corresponding to 100% glucose (Barsanti et al., 2011). The applicant performed analyses of the bonds of the beta-glucan in the NF. NMR spectra data of beta-glucan isolated from *E. gracilis* were compared to published spectra. According to the applicant, the acquired spectra agreed by chemical shift, integration and coupling with those of exclusively 1,3-linked beta-glucans (Ensley et al., 1994; Kim et al., 2000; Barsanti et al., 2011). The ^{1}H and ^{13}C NMR spectra showed clean spectra with all signals accounted for by 1,3-bond configuration. Separate peaks, which would be generated by other bond types (Cui et al., 2000; Kwiatkowski et al., 2009), were not present in these spectra. According to the authors of the report, the possibility of other bonds overlapping directly with the peaks was ruled out by two-dimensional correlation spectroscopy (homonuclear correlation spectroscopy (COSY)), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple-bond correlation spectroscopy (HMBC) spectra, which corresponded to literature reports of 1,3-linkage. Signals commonly associated with branching (Kim et al., 2000; Lowman et al., 2011) were absent from the spectra.

The specific strain that is used by the applicant to produce the NF is *E. gracilis* Klebs var. *bacillaris* ATCC (American Type Culture Collection) PTA-123017. The strain is deposited in the ATCC patent depository and a certificate of deposit was provided by the applicant.

In some studies provided in the application dossier, the NF is also referred to as BetaVia™ Pure, 'beta-glucan 95 percent' and '95% beta-glucan product'.

3.3. Production process

According to the information provided, the NF is produced in line with Good Manufacturing Practice (GMP) and Hazard Analysis Critical Control Points (HACCP) principles.

The parent cell line of the *E. gracilis* strain used for the manufacturing process is maintained on agar plates stored in cool conditions in the dark. At regular intervals the algae are transferred to new plates and, as needed, to shake flasks. The reason being that microalga, including *E. gracilis*, are recalcitrant to cryogenic preservation (Day et al., 2007), and the most common procedure for conservation of microalgal cultures is perpetual maintenance (i.e. continuous culture) under controlled conditions (Lorenz et al., 2005).

For the manufacturing process of the NF, *E. gracilis* cells are transferred from the maintenance culture to shake flasks of increasing size and, subsequently, to a production fermenter, which is maintained at specified aerobic culture conditions (confidential information). A complete list of the culture media and processing aids/additives plus the respective certificates of analysis were provided (confidential information).

Once harvested, the broth is transferred to a stainless-steel holding tank and the pH of the slurry is adjusted with NaOH. The alkaline slurry is homogenised to release the beta-glucan granules. The homogenized solution is allowed to settle, and the settled granules are washed with filtered water and, subsequently, acidified and filtered. The filtered cake, containing the purified beta-glucan granules, is spread onto trays and dried until the moisture content is determined to be less than 5% by weight. Thereafter the product is milled, blended, packaged and stored under appropriate conditions until shipment.

The applicant was requested to provide information/evidence to demonstrate that *E. gracilis* does not survive the manufacturing process. In reply, the applicant elaborated on the stringent processing conditions, in particular the high pH (10.5–12), high pressure (8,000–10,000 psi) and elevated temperature during washing steps (at 60°C) and the final drying step (at 70°C) which lasts for about 20 h, which would kill *E. gracilis*. In order to substantiate this statement, the applicant submitted literature indicating that *E. gracilis* is killed after exposure to 44°C for 8 min (Khanna and Yadav, 2004) and, in addition, cannot survive a pH above 8 (Danilov and Ekelund, 2001). The Panel considers that the microalga is not expected to survive the manufacturing process.

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

3.4. Compositional data

The NF consists of at least 95% dietary fibre, which, in this case, corresponds to beta-glucan, as demonstrated by scientific literature and NMR data. The NF also contains minor amounts of protein, fat, ash and moisture.

In order to confirm that the manufacturing process is reproducible and adequate to produce on a commercial scale a product with certain characteristics, the applicant provided proximate analysis plus an analysis for total dietary fibre for five batches of the NF (Table 1).

Table 1: Proximate analysis and analysis of total dietary fibre in the NF

Parameter (unit)	Batch number					Method of analysis
	#1	#2	#3	#4	#5	
Total carbohydrates (%)	97.7	97.8	97.4	96.5	96.5	By calculation(1)
Fat (%)	0.4	0.3	0.3	0.3	0.2	By acid hydrolysis; AOAC 922.06 and 954.02
Protein (%)	0.57	0.49	0.43	1.09	0.99	Dumas method (N × 6.25); AOAC 968.06 and 992.15
Ash (%)	< 0.1	< 0.1	< 0.1	< 0.1	< 1	Residue on ignition; AOAC 923.03
Moisture (%)	1.31	1.34	1.93	2.10	2.03	AOAC 925.09 and 926.08
Total dietary fibre (%)	95.9	97.4	99.1	97.8	98.7	Enzymatic-gravimetric method; AOAC 991.43 (modified)
Calories/100 g	397	396	394	393	392	By calculation; CFR Title 21, Part 101.9, pp. 24–25

AOAC: Association of Official Analytical Chemists; CFR: Code of Federal Regulations.
(1): 100% - ash – moisture – fat – protein.

The applicant explained that the differences observed in the concentrations of total dietary fibre versus total carbohydrates are owing to the differences in the methods used for deriving those values, i.e. by calculation (for total carbohydrates) vs enzymatic-gravimetry (for total dietary fibre), and their inherent variabilities.

Analyses of heavy metals and microbiological parameters were provided for five batches of the NF (Table 2).

Table 2: Analysis of heavy metals and microbials in the NF

Parameter (unit)	Batch number					Method of analysis
	#6	#7	#8	#9	#10	
Heavy metals						
Lead (mg/kg)	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	ICP-MS (USP 233)
Cadmium (mg/kg)	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	ICP-MS (USP 233)
Mercury (mg/kg)	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	ICP-MS (EPA 7471)
Arsenic (mg/kg)	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	ICP-MS (USP 233)
Microbiological						
Aerobic plate count (CFU/g)	470	190	< 10	110	30	AOAC 966.23
Coliforms (MPN/g)	< 3	< 3	< 3	< 3	< 3	FDA-BAM Chapter 4
Yeasts and moulds (CFU/g)	< 20	< 20	< 20	< 20	< 20	FDA-BAM Chapter 18
Escherichia coli (in 10 g)	Not detected	Not detected	Not detected	Not detected	Not detected	USP Chapter 62
Staphylococcus aureus (in 10 g)	NOT detected	Not detected	Not detected	Not detected	Not detected	USP Chapter 62
Salmonella spp. (in 25 g)	Not detected	Not detected	Not detected	Not detected	Not detected	USP Chapter 62
Listeria monocytogenes (in 25 g)	Not detected	Not detected	Not detected	Not detected	Not detected	AOAC 2004.06

AOAC: Association of Official Analytical Chemists; CFU: colony forming units; EPA: United States Environmental Protection Agency; FDA-BAM: Food and Drug Administration's Bacteriological Analytical Manual; ICP-MS: inductively coupled plasma-mass spectrometry; MPN: most probable number; USP: United States Pharmacopeia.

The applicant submitted an analysis of the glycosyl composition (by gas chromatography/mass spectrometry) of the NF, in which only glucose and no other monosaccharides were detected.

The applicant also provided analyses (for five batches of the NF) for polycyclic aromatic hydrocarbons (PAHs), which were below detection limits (< 0.3 μg/kg), and for aflatoxins B1, B2, G1 and G2, which were also all below the detection limits (< 0.3 μg/kg).

As mentioned above, paramylon has high crystallinity owing to higher-order aggregates of nanofibrils, measuring 4–10 nm, composed of unbranched triple helices of beta-(1,3)-D-glucan chains (Barsanti et al., 2011). Therefore, in consideration of their insoluble and non-digestible nature, the applicant was requested to address the risk of release of nanofibrils from the NF. In reply, the applicant submitted data (for three batches of the NF) generated by transmission electron microscopy (TEM), which demonstrated the integrity of the paramylon granules in the NF (i.e. without the release of nanofibrils). As a result, the NF contains < 10% (number-based) of particles with at least one dimension smaller than 500 nm (EFSA Scientific Committee, 2021). The Panel therefore considers that there are no concerns in relation to the presence of nano-sized particles in the NF.

Information was provided on the accreditation of the laboratories that conducted the analyses presented in the application.

The Panel considers that the information provided on the composition is sufficient and does not raise safety concerns.

3.4.1. Stability

The applicant submitted two accelerated stability studies (at 40°C and 75% relative humidity (RH)) and one long-term (4 years) stability study at ambient conditions (25°C and 60% RH).

The first accelerated stability study lasted for 168 days and was performed with one batch of the NF, which was analysed for proximates, total dietary fibre content and sensory parameters (appearance and odour). Overall, there were no appreciable changes in the assessed parameters.

The second accelerated stability study lasted for 12 months and was performed with three batches of the NF. The analysed parameters were beta-glucan content, moisture, appearance, colour and odour. Apart from a slight reduction of beta-glucan content in one of the three batches, there were no changes over time.

The long-term stability study at ambient conditions (25°C and 60% RH) had a duration of 4 years and was performed with three batches of the NF. There were no appreciable changes for the parameters analysed, i.e. beta-glucan content, moisture, appearance, colour and odour.

In addition, stability of the NF was assessed when formulated in capsules (mixed with microcrystalline cellulose) at ambient conditions (25°C, 60% RH) for up to 24 months. The beta-glucan concentration was shown to remain stable throughout storage.

Stability of the beta-glucan content in the NF was also assessed after retort processing, which, according to the applicant, is commonly used for the thermal sterilisation of foods. To simulate harsh processing conditions, the NF was placed in an autoclave (for 15 min at 121°C; 15 PSI; wet) with the addition of aqueous citric acid solution (pH 2.5), to simulate the acidic environments typically found in products such as fruit juice beverages. A small reduction of the beta-glucan content of the tested samples was observed.

The applicant also determined the stability of the NF at various pH by using an in-house gravimetric assay. Beta-glucan remained stable in the NF when dispersed in suspensions at pH 3 and pH 7, which, according to the applicant, encompasses the typical pH range for most foods and beverages.

The applicant proposed a shelf life for the NF of 3 years, when stored under ambient conditions in unopened, tightly sealed containers.

The Panel considers that the data provided sufficient information with respect to the stability of the NF for 3 years.

3.5. Specifications

The specifications of the NF are indicated in Table 3.

Table 3: Specifications of the NF

Description: The NF is derived from the microalga *Euglena gracilis*. The manufacturing process includes conditions such as alkaline pH and heat treatment, which kill the microalga.	
Appearance: free-flowing white-cream powder with an odour characteristic of algae	
Parameter (unit)	**Specification**
Beta-glucan(1) (%)	≥ 95
Moisture (%)	≤ 6
Ash (%)	≤ 1
Heavy metals	
Lead (mg/kg)	≤ 0.5
Cadmium (mg/kg)	≤ 0.5
Mercury (mg/kg)	≤ 0.05
Arsenic (mg/kg)	≤ 0.02
Microbiological	
TAMC (CFU/g)	≤ 3,000
TYMC (CFU/g)	≤ 100
Coliforms (MPN/g)	≤ 30
Escherichia coli (in 10 g)	Not detected
Staphylococcus aureus (in 10 g)	Not detected
Salmonella spp. (in 25 g)	Not detected
Listeria monocytogenes (in 25 g)	Not detected

CFU: colony forming units, MPN: most probable number, TAMC: total aerobic microbial count, TYMC: total yeast and mould count.
(1): Expressed as total dietary fibre.

The Panel considers that the information provided on the specifications of the NF is sufficient and does not raise safety concerns.

3.6. History of use of the NF and/or of its source

3.6.1. History of use of the source

The source from which the NF is derived, *E. gracilis*, has a history of use as food (food ingredient and food supplements) in China, Japan and the USA.

According to information provided by the applicant, *E. gracilis* is marketed as a food ingredient (mostly in Japan) in a number of food products (e.g. Euglena bars, Euglena honey and oat, Euglena pudding, whey protein products, Euglena smoothies, noodles with added Euglena, etc.).

When assessing *E. gracilis* for its suitability for the QPS status, the BIOHAZ Panel identified information on food products containing *E. gracilis* marketed in Japan as cookies, cereal bars and nutritional drinks (Suzuki, 2017; EFSA BIOHAZ Panel, 2019).

In 2020, dried *E. gracilis* was authorised for the placing on the market in the European Union.[2] The authorisation comprised the use as food supplement and as food ingredient added to a number of foods.

3.6.2. History of use of the NF

In the USA the NF is marketed since 2019 as a food supplement and as a food ingredient. Sales figures (confidential) were provided for 2020 and 2021. In 2021, the NF was authorised to be put on the market by the Brazilian Health Regulatory Agency (ANVISA).

3.7. Proposed uses and use levels and anticipated intake

3.7.1. Target population

The target population proposed by the applicant is the general population, except for food supplements and for meal replacement beverages for which the proposed target population is children from 1 year onwards and adults, and except for foods for total diet replacement for which the target population is adults.

3.7.2. Proposed uses and use levels

The NF is proposed by the applicant to be used as a food ingredient in a number of food categories. These food categories, when attributed to categories present in the FoodEx2 hierarchy, and the respective proposed maximum use levels, are reported in Table 4.

Table 4: Food categories (according to FoodEx2) and maximum use levels as proposed by the applicant

FoodEx2 level	FoodEx2 code	Food category	Max use level (mg NF/100 g)
3	A00EY	Cereal bars	670
4	A02NE	Yoghurt	160
4	A02NQ	Yoghurt drinks, including sweetened and/or flavoured variants	100
1	A039K	Fruit and vegetable juices and nectars	60
4	A0EQN	Soft drinks with minor amounts of fruit or flavours	40
4	A03RV	Meal replacement beverages	80

NF: novel food.

As for the use of the NF in food supplements, the applicant proposed maximum amounts of 50 mg/day for young children (i.e. toddlers; from 12 to 35 months), 100 mg/day for children from 36 months to 9 years, 150 mg/day for adolescents (from 10 to 17 years) and 200 mg/day for adults (see also Table 6).

In addition, the applicant proposed the use of the NF in foods for total diet replacement for weight control as defined by Regulation (EU) No 609/2013[4], with a proposed maximum use level of 600 mg NF/day. The proposed target population for this food category is adults.

3.7.3. Anticipated intake of the NF

In order to derive refined intake estimates of the NF for all the population groups under evaluation, an intake assessment was performed by EFSA based on individual data from the EFSA Comprehensive European Food Consumption Database (EFSA, 2011) and the uses and maximum use levels as proposed by the applicant. The lowest and highest mean and 95th percentile anticipated daily intakes of the NF (on a mg/kg body weight (bw) basis), among the EU dietary surveys, are presented in Table 5.

The estimated daily intake of the NF for each population group from each EU dietary survey is available in the Excel file annexed to this scientific opinion (under supporting information).

Table 5: Intake estimates (in mg/kg bw per day) resulting from the use of the NF as an ingredient in the intended food categories at the maximum proposed use levels

Population group	Age (years)	Mean intake (mg/kg bw per day)		P95th intake (mg/kg bw per day)	
		Lowest[(a)]	Highest[(a)]	Lowest[(b)]	Highest[(b)]
Infants	< 1	0.6	23.3	3.7	104.4
Young children[(c)]	1 to < 3	6.1	28.1	19.6	72.9
Other children	3 to < 10	3.5	18.9	12.0	42.3
Adolescents	10 to < 18	1.3	6.1	5.1	14.1
Adults[(d)]	≥ 18	0.8	2.9	3.8	10.0

(a): Intakes are assessed for all EU dietary surveys available in the EFSA food consumption database on 17/3/2023. The lowest and the highest averages observed among all EU surveys are reported in these columns.
(b): Intakes are assessed for all EU dietary surveys available in the EFSA food consumption database on 17/3/2023. The lowest and the highest P95th observed among all EU surveys are reported in these columns (P95th based on less than 60 individuals are not considered).
(c): Referred to as 'toddlers' in the EFSA food consumption database (EFSA, 2011).
(d): Includes elderly, very elderly, pregnant and lactating women.

The proposed use of the NF as a food supplement and the respective daily intakes of the NF on a mg/kg bw basis are provided in Table 6.

Table 6: Proposed use of the NF as a food supplement and resulting intakes in mg/kg bw per day

Population group	Age(years)	Body weight[(a)] (kg)	Use level (mg/day)	Intake (mg/kg bw per day)[(b)]
Young children	1 to < 3	12	50	4.2
Other children	3 to < 10	23.1	100	4.3
Adolescents	10 to < 14	43.4	150	3.5
Adolescents	14 to < 18	61.3	150	2.4
Adults	≥ 18	70	200	2.9

bw: body weight.
(a): Default and average body weights for each population group as set by the EFSA Scientific committee (2012).
(b): Intake values in 'mg/kg bw per day' are calculated by considering the use levels in 'mg/day' and default body weights as set by the EFSA Scientific Committee (2012).

The combined intake estimates resulting from the uses of the NF as an ingredient and as a food supplement in the various population groups are provided in Table 7.

[4] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35.

Table 7: Combined intakes resulting from the uses of the NF as an ingredient and as a food supplement

Population group	Age (years)	Body weight[(a)] (kg)	Highest[(b)] P95th intake from the NF used as an ingredient (mg/kg bw per day)	Intake from the NF used as a food supplement (mg/kg bw per day)[(c)]	Total intake[(d)] (mg/kg bw per day)
Infants	< 1	5	104.4	–	104.4
Young children	1 to < 3	12	72.9	4.2	77.1
Other children	3 to < 10	23.1	42.3	4.3	46.6
Adolescents	10 to < 14	43.4	14.1	3.5	17.6
Adolescents	14 to < 18	61.3	14.1	2.4	16.5
Adults	≥ 18	70	10.0	2.9	12.9

NF: novel food; bw: body weight.
(a): Default and average body weights as set by the EFSA Scientific committee (2012).
(b): Intakes are assessed for all EU dietary surveys available in the EFSA food consumption database. The highest P95th observed among all surveys is reported in this column (P95th calculated based on less than 60 individuals are not considered).
(c): Intake values in 'mg/kg bw per day' are calculated by considering the use levels in 'mg/day' and default body weights as set by the EFSA Scientific Committee (2012).
(d): Total intake is the sum of the intake from the NF used as an ingredient (at the highest P95th) and from the NF used as a food supplement, for each population group.

3.8. Absorption, distribution, metabolism and excretion (ADME)

No ADME studies with the NF were submitted. The applicant indicated that the NF, which consists of at least 95% insoluble beta-glucans, can be expected to pass the human gastrointestinal tract undigested and that, therefore, no specific ADME studies would be required. The Panel concurs and considers that no further ADME testing is necessary for the safety assessment of the NF.

3.9. Nutritional information

The NF consists of at least 95% beta-1,3-glucan. The applicant provided analyses of proximates and a number of minerals in the NF, at concentrations that did not raise safety concerns.

The Panel considers that, taking into account the composition of the NF and the proposed conditions of use, the consumption of the NF is not nutritionally disadvantageous.

3.10. Toxicological information

3.10.1. Qualified presumption of safety (QPS) of the production organism

In 2019, the production organism, i.e. *E. gracilis*, was assessed by the EFSA Panel on Biological Hazards (BIOHAZ) for its suitability to be added to the list of QPS-recommended biological agents intentionally added to food or feed. The BIOHAZ Panel considered the identity, the body of knowledge and potential safety concerns of this microorganism. The extensive literature searches performed did not provide any evidence for a safety concern for human or animal health for any use of *E. gracilis*. The BIOHAZ Panel concluded that *E. gracilis* may be recommended for the QPS list with the qualification 'for production purposes only' (EFSA BIOHAZ Panel, 2019). The qualification 'for production purpose only' implies the absence of viable cells of the production organism in the final product and can also be applied for food and feed products based on microbial biomass (EFSA BIOHAZ Panel, 2018).

3.10.2. Overview of provided toxicological studies

The applicant provided four toxicological studies with the NF, i.e. an *in vivo* micronucleus test (Eurofins Advinus Limited, 2019, unpublished), a 14-day oral toxicity/palatability study (Product Safety Labs, 2015c, unpublished) and two 90-day oral toxicity studies (Product Safety Labs, 2015d; Eurofins Advinus Limited, 2020; unpublished).

In addition, the applicant submitted one acute oral toxicity study (Product Safety Labs, 2014, unpublished) and two genotoxicity studies (Product Safety Labs, 2015a,b, both unpublished), which were carried out with dried *E. gracilis* biomass (containing 58.8% beta-glucan).

These studies, which were claimed proprietary by the applicant, are listed in Table 8.

Table 8: List of provided toxicological studies (with the NF and *E. gracilis* biomass, respectively)

Reference	Type of study	Test system	Test item	Dose
Eurofins Advinus Limited (2019)	*In vivo* mammalian erythrocyte micronucleus test (GLP, OECD TG 474)	Swiss albino mice	NF	2,000 mg/kg bw per day (by gavage)
Product Safety Labs (2015c)	14-day toxicity/palatability study	Sprague–Dawley (SD) rats	NF	5% (in the feed)
Eurofins Advinus Limited (2020)	90-day repeated dose oral toxicity study with a 28-day recovery period (GLP, OECD TG 408)	Wistar rats	NF	1,250, 2,500, and 5,000 mg/kg bw per day (by gavage)
Product Safety Labs (2015d)	90-day repeated dose oral toxicity study with a 14-day recovery period (GLP, OECD TG 408)	SD rats	NF	5% (in the feed) corresponding to about 3,450 mg/kg bw per day
Product Safety Labs (2014)	Acute oral toxicity study (GLP, OECD TG 402)	SD rats	*E. gracilis* biomass	5,000 mg/kg bw per day
Product Safety Labs (2015a)	Bacterial reverse mutation test (GLP, OECD TG 471)	*S. typhimurium* TA98, TA100, TA1535 and TA1537, *E. coli* strain WP2uvrA	*E. gracilis* biomass	Up to 5,000 μg/plate (in absence and presence of S9 mix)
Product Safety Labs (2015b)	*In vivo* mammalian erythrocyte micronucleus test (GLP, OECD TG 474)	Swiss albino mice	*E. gracilis* biomass	2,000 mg/kg bw per day (by gavage)

bw: body weight; GLP: Good Laboratory Practice; OECD TG: Organisation for Economic Co-operation and Development Test Guideline.

3.10.3. Genotoxicity

For the *in vivo* mammalian erythrocyte micronucleus test (Eurofins Advinus Limited, 2019, unpublished), Swiss albino mice (5/sex and group) were administered the NF (containing 98.2% beta-glucan) at dose levels of 500, 1,000 or 2,000 mg/kg bw per day by oral gavage for two consecutive days. A control group received the vehicle (Milli-Q water) on the same schedule. In an additional group cyclophosphamide monohydrate was used as positive control. Bone marrow was collected 22–23 h following the final administration and a minimum of 4,000 polychromatic erythrocytes (PCE) per mouse were examined for the presence of micronuclei. In addition, the proportion of PCE among total erythrocytes was assessed as a measure of bone marrow toxicity. There were no differences in the incidences of micronucleated PCE between the groups that received the NF and the vehicle control group. The ratio of PCE to total erythrocytes was also comparable between the control and treatment groups indicating that there was no bone marrow toxicity. As there was no evidence of exposure to the bone marrow, the Panel considers this study as inconclusive. However, the Panel also notes that the main component of the NF (beta-glucan) is not expected to be systemically available.

In addition, the applicant submitted a reverse bacterial mutation assay (Product Safety Labs, 2015a, unpublished) and an *in vivo* mammalian erythrocyte micronucleus test (Product Safety Labs, 2015a, unpublished), which were both conducted with the dried biomass of the *E. gracilis* strain that is used to produce the NF, and which were both negative. These studies were submitted to establish the safety of a previous NF application, i.e. dried *E. gracilis*, which was assessed by the Panel and which was considered safe at the proposed conditions of use (EFSA NDA Panel, 2020).

The Panel considers that given the compositional data of the NF, the production process, the QPS-status of the production organism and the previous safety assessment of dried *E. gracilis* (EFSA NDA Panel, 2020), there are no concerns with regard to genotoxicity of the NF.

3.10.4. Acute and subacute toxicity

For the acute oral toxicity study (Product Safety Labs, 2014, unpublished study report, claimed as proprietary by the applicant) Sprague–Dawley rats were orally administered dried *E. gracilis* at a dose of 5,000 mg/kg bw. The Panel considers that, generally, acute toxicity studies are not pertinent for the safety assessment of NFs.

In the 14-day dietary toxicity/palatability study (Product Safety Labs, 2015c, unpublished study report, claimed as proprietary by the applicant), Sprague–Dawley rats (5/sex and group) were randomised to receive 0, 1.25, 2.5 or 5.0% of dried *E. gracilis* or 5.0% of the NF in the diet. As there were no changes in bodyweight, bodyweight gain, food consumption or food efficiency, it was concluded that the animals are expected to tolerate at least 5% (i.e. 50,000 mg/kg feed) of the NF in the diet.

3.10.5. Subchronic toxicity

In a 90-day oral toxicity study (Eurofins Advinus Limited, 2020, unpublished study report, claimed as proprietary by the applicant), Wistar rats (10/sex and group) were randomised to receive by gavage 0 (vehicle (Milli-Q water) control group), 1,250, 2,500 or 5,000 mg/kg bw per day of the NF (containing 99.5% beta-glucan) dispersed in water for 90 days. There were additional control and high-dose recovery groups (5/sex and group) in order to assess the reversibility of any potential effects during a subsequent 28 days recovery period. The study was conducted in accordance with OECD TG 408.

There were no clinical signs or mortality at any of the doses tested. Ophthalmological examination did not reveal any ocular abnormalities. No treatment-related neurological abnormalities were observed at any of the doses tested. There were no differences of body weights between the control and the treatment groups at any time-point. With respect to body weight gain, statistically significant differences were observed for the males in the high-dose recovery group for 2 weeks (higher gain from days 57–64 and days 90–97) and for females in the high-dose recovery dose group for 1 week (lower gain from days 15 to 22), which the Panel considers incidental.

A number of statistically significant differences were also observed for food consumption at different intervals during treatment/recovery periods between the control and treatment groups, however, without a consistent pattern (both increases and decreases observed) or dose–response relationship and without leading to differences in the body weights of the animals. Therefore, the Panel considers these findings as toxicologically not relevant.

There were no differences between control and treatment-groups for thyroid hormones nor urinalysis. In haematology and clinical chemistry, some statistically significant findings of small magnitude were observed in some treatment groups, which, in the absence of clear dose–response relationship, are considered by the Panel as not toxicologically relevant. Similarly, some isolated statistically significant differences were observed for organ weights (absolute or relative to body weight or brain weight) between the groups, which the Panel considers as incidental and not treatment related. There were no test item-related findings in gross pathology or histopathology. The Panel, therefore, considers that no adverse effects were observed up to the highest dose tested, i.e. 5,000 mg/kg bw per day.

In another 90-day oral toxicity study (Product Safety Labs, 2015d, unpublished study report, claimed as proprietary by the applicant; Simon et al., 2016), Sprague–Dawley rats (10/sex and group) were randomised to receive 0, 1.25, 2.5 or 5.0% of dried *E. gracilis* (containing 58.8% beta-glucan) or 5.0% of the NF (containing 97.1% beta-glucan) in the diet. The study was conducted in accordance with OECD TG 408. All animals survived to the end of the study period. There were no findings with respect to clinical observations, ophthalmology or behavioural analysis of the animals. There were no differences in body weight or body weight gain, food consumption or food efficiency. No changes were found for macroscopic and microscopic observations. The only statistically significant differences between the control group and the group that received the NF were a lower mean corpuscular volume (MCV) and a lower weight (absolute) of adrenal glands in the NF group (both findings in males only). However, the differences were small and were not accompanied by any other findings in haematology or histopathology. Thus, the Panel considers these findings as incidental and notes that no adverse effects were observed in this study up to the highest dose tested, i.e. 5% in feed, equivalent to 3,300 mg NF/kg body weight per day.

3.10.6. Human studies

No human studies with the NF were provided.

3.11. Allergenicity

According to the batch testing provided, the NF contains protein at a concentration of 0.4–1.1%.

The applicant performed a comprehensive literature search, which did not reveal any studies or case reports indicating potential allergenicity of the NF. In addition, the source from which the NF is isolated, i.e. *E. gracilis* biomass, has a history of use in China, Japan and the USA, without identified reports of allergenic reactions.

The Panel considers that the risk of allergic reactions to the NF for the general population is unknown but expected to be low.

4. Discussion

The NF, which is the subject of the application, is paramylon, which is a beta-glucan polymer isolated from the single-cell microalga *E. gracilis*. The Panel considers that the information provided on the composition of the NF is sufficient and does not raise safety concerns.

In 2019, *E. gracilis* was assessed by the EFSA BIOHAZ Panel and attributed the QPS status with the qualification 'for production purposes', which implies the absence of viable Euglena cells in the final product and can also be applied for food products based on microbial biomass of the microalgae. Based on the information provided, *E. gracilis* is not expected to survive the manufacturing process of the NF.

In 2020, the Panel assessed the safety of whole cell *E. gracilis* of the specific strain, from which paramylon is obtained, as a novel food and considered it safe at the proposed conditions of use. Subsequently, dried whole cell *E. gracilis* was authorised for the placing on the market in the European Union by Commission Implementing Regulation (EU) 2020/1820.

The applicant intends to market the NF, i.e. paramylon, as a food supplement, as a food ingredient added to a number of food categories and in foods for total diet replacement for weight control as defined by Regulation (EU) No 609/2013. Intake estimates for the NF were performed, based on the EFSA Comprehensive European Food Consumption Database. The highest intake estimate was calculated for infants, at 104 mg NF/kg bw per day at the 95th percentile.

The submitted toxicity studies did not raise safety concerns. No adverse effects were observed in the subchronic toxicity studies, up to the highest dose tested, i.e. 5,000 mg NF/kg bw per day. The margins of exposure between the highest dose tested and the high (95th percentile) intake estimates range from 48 (infants) to 388 (adults).

In view of the QPS status of the source of the NF, supported by the manufacturing process, compositional data and lack of toxicity in the experimental studies, the Panel has no safety concerns.

5. Conclusions

The Panel concludes that the NF, paramylon, is safe under the proposed conditions of use.

5.1. Protection of Proprietary data in accordance with Article 26 of Regulation (EU) 2015/2283

The Panel could not have reached the conclusion on the safety of the NF under the proposed conditions of use without the following data claimed as proprietary by the applicant: compositional data ('Annex D'), stability reports ('Annex E'), transmission electron microscopy report, 90-day subchronic toxicity study (Eurofins Advinus Limited, 2020, unpublished).

6. Steps taken by EFSA

1) On 23/04/2021 EFSA received a letter from the European Commission with the request for a scientific opinion on the safety of paramylon as a NF. Ref. Ares(2021)2734920.
2) On 23/04/2021, a valid application on paramylon, which was submitted by the company Kemin Foods L.C., was made available to EFSA by the European Commission through the Commission e-submission portal (NF 2019/1261) and the scientific evaluation procedure was initiated.

3) On 15/10/2021 and on 17/02/2023, respectively, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
4) On 20/12/2022 and on 15/03/2023, respectively, additional information was provided by the applicant through the Commission e-submission portal and the scientific evaluation was restarted.
5) During its meeting on 28/03/2023, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of paramylon as a NF pursuant to Regulation (EU) 2015/2283.

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Abbreviations

ADME	Absorption, distribution, metabolism and excretion
ANVISA	Brazilian Health Regulatory Agency
AOAC	Association of Official Analytical Associations
ATCC	American Type Culture Collection
BIOHAZ	Panel on Biological Hazards
bw	body weight
CFR	Code of Federal Regulations
CFU	colony forming units
COSY	homonuclear correlation spectroscopy
Da	dalton
dRI	differential refractive index
EPA	US Environmental Protection Agency
FDA-BAM	Food and Drug Administration's Bacteriological Analytical Manual
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis Critical Control Points
HMBC	heteronuclear multiple-bond correlation spectroscopy
HSQC	heteronuclear single quantum coherence
ICP-MS	inductively coupled plasma-mass spectrometry
MALS	multi-angle light scattering
MCV	mean corpuscular volume
MPN	most probable number
MW	molecular weight
NDA	Panel on Nutrition, Novel Foods and Food Allergens
NF	novel food
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
OECD TG	Organisation for Economic Co-operation and Development Test Guideline
PAHs	polycyclic hydrocarbons
PCE	polychromatic erythrocytes
QPS	qualified presumption of safety
RH	relative humidity
SD	Sprague–Dawley
SEC	size exclusion chromatograph
TAMC	total aerobic microbial count

TEM	transmission electron microscopy
TYMC	total yeast and mould count
USP	United States Pharmacopeia

Annex A – Dietary exposure estimates to the novel food for each population group from each EU dietary survey

The information provided in this Annex is shown in an Excel file (downloadable at https://doi.org/10.2903/j.efsa.2023.7995).