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Safety of cranberry extract powder as a novel food ingredient pursuant to Regulation (EC) No 258/97

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Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on 'cranberry extract powder' as a novel food (NF) submitted pursuant to Regulation (EC) No 258/97 of the European Parliament and of the Council. The NF contains about 55–60% proanthocyanidins (PACs). The Panel considers that the information provided on the composition, the specifications, batch-to-batch variability and stability of the NF is sufficient and does not raise safety concerns. Cranberry extract powder is produced from cranberry juice concentrate through an ethanolic extraction using an adsorptive resin column to retain the phenolic components. The Panel considers that the production process is sufficiently described and does not raise concerns about the safety of the novel food. The NF is intended to be added to beverages and yogurts to provide 80 mg PACs per serving. The target population is the adult general population. The mean and 95th percentile estimates for the all-user intakes from all proposed food-uses are 68 and 192 mg/day, respectively, for female adults, and 74 mg/day and 219 mg/day, respectively, for male adults. Taking into account the composition of the novel food and the intended use levels, the Panel considers that the consumption of the NF is not nutritionally disadvantageous. While no animal toxicological studies have been conducted on the NF, a number of human clinical studies have been conducted with cranberry products. Considering the composition, manufacturing process, intake, history of consumption of the source and human data, the Panel considers that the data provided do not give reasons for safety concerns. The Panel concludes that the cranberry extract powder is safe as a food ingredient at the proposed uses and use levels.

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Keywords: cranberry extract powder, proanthocyanidins, novel food, ingredient, safety

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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 an opinion on 'cranberry extract powder' as a novel food (NF) ingredient submitted pursuant to Regulation (EC) No 258/97¹ of the European Parliament and of the Council, taking into account the comments and objections of a scientific nature raised by Member States. The assessment, which follows the methodology set in Commission Recommendation 97/618/EC is based on the data supplied in the original application, the initial assessment by the competent authority of France, the concerns and objections of the other Member States and the responses of the applicant.

The NF is prepared from the juice concentrate of sound, mature berries of the cranberry cultivar (*Vaccinium macrocarpon*). According to the specification, the NF contains 55–60% proanthocyanidins (PACs) as measured by OSC-DMAC (colorimetric analysis using dimethylaminocinnamaldehyde (DMAC) with isolated cranberry PACs as a standard compound). Other main constituents of the NF are anthocyanins, other phenolic compounds such as flavonols, sugars and organic acids. The Panel considers that the information provided on the composition, the specifications, batch-to-batch variability and stability of the NF is sufficient and does not raise safety concerns.

Cranberry extract powder is produced from cranberry juice concentrate through an ethanolic extraction using an adsorptive resin column to remove sugars and organic acids and to retain the phenolic components which are eluted, concentrated and spray-dried to yield the powder. Silicon dioxide is added as a flow agent and maltodextrin as a carrier. The manufacturing process is performed according to good manufacturing practice (GMP). About 66 mL of pure (7.5 Brix) cranberry juice is needed to produce 145 mg of cranberry extract containing 33–36 mg PACs (about 80 mg measured by OSC-DMAC) and this amount approximately corresponds to a 240 mL serving of Ocean Spray's 27% 'cranberry juice classic' currently on the market. The Panel considers that the production process is sufficiently described and does not raise concerns about the safety of the novel food.

The NF is intended to be added to fruit-flavoured drinks (regular and low calorie), isotonic drinks (including electrolyte types), tea drinks (ready-to-drink, iced), vitamin enhanced waters, yogurts and yogurt drinks with the intention to provide 80 mg PACs per serving (based on OSC-DMAC method). According to the applicant, the target population is the adult general population and the NF is not intended to be marketed to children.

When assuming that 240 mL of 27% cranberry juice contains on the average 156 mg PACs, the mean and 95th percentile of an adult female consumer is about 200 and 1,200 mL, respectively, cranberry juice per day. The corresponding mean and 95th percentile intakes of PACs from cranberry juice would be about 130 and 780 mg PACs per day for adult females, and 108 and 246 mg for adult males. For female adults, the mean and 95th percentile estimates for the all-user intakes of PACs from all proposed food-uses of the NF were 68 mg/day and 192 mg/day, respectively. The mean and 95th percentile estimates for the all-user intakes for male adults of PACs from all proposed food-uses also were 74 and 219 mg/day, respectively.

Taking into account the composition of the novel food and the intended use levels, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

While no animal toxicological studies have been conducted on the NF, a number of human clinical studies have been conducted with cranberry products other than the NF. None of these studies have indicated adverse effects caused by cranberry consumption. In addition, three clinical studies have been conducted with the NF. The Panel notes that the PACs dose of these clinical studies is high as compared to the conditions of use of the NF. The Panel considers these studies do not raise safety concerns of the NF.

Based on the data provided, and considering the composition, manufacturing process, anticipated intake, history of consumption of the source and human studies, the Panel considers that the consumption of the cranberry extract powder under the proposed conditions of use does not raise safety concerns.

The Panel concludes that the cranberry extract powder is safe as a food ingredient at the proposed uses and use levels.

¹ Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients (OJ L 43, 14.2.1997, p. 1). <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1997R0258:20090120:EN:PDF>

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1. Introduction

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

On 20 September 2011, the company Ocean Spray Cranberries Inc. submitted a request in accordance with Article 4 of the Novel Food Regulation (EC) No 258/97 to place on the market cranberry extract powder as a novel food (NF) ingredient.

On 11 December 2014, the competent authority of France forwarded to the Commission its initial assessment report, which came to the conclusion that cranberry extract powder meets the criteria for acceptance of a NF defined in Article (3) 1 of Regulation (EC) No 258/97.

On 16 January 2015, the Commission forwarded the initial assessment report to the other Member States. Several Member States submitted comments or raised objections.

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

- The specification of the product is incomplete. In particular, the application and the documents submitted subsequently contain discrepancies in the information on the concentration of proanthocyanidins (PACs) and intake amounts.
- There are no studies in children on the safety and tolerance of PACs intake at the 95th percentile of the anticipated intake.
- The cumulative intake of polyphenols from the NF for children between 1 and 3 years of age together with other sources of polyphenols in a child's diet would bring total exposure to polyphenols to a level 2–7 times higher than that of adults. Given that there are known adverse effects related to the overconsumption of polyphenols, reassurance is required that daily levels of total polyphenols exposure inclusive of the intakes from the NF would be safe for children.
- Possible side effects can be observed from long-term elevated polyphenol intake, for example inhibition of iron and folic acid absorption, interaction with other food components in the stomach, such as inhibiting triglyceride absorption by restricting pancreatic lipase (Sugiyama et al., 2007), interaction with carrier proteins (Faria et al., 2006), potential interaction with warfarin (Pham and Pham, 2007).
- Information on the protein content is needed to confirm that an allergy risk is unlikely.

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority (EFSA) to provide a scientific opinion by carrying out the additional assessment for cranberry extract powder as a novel food ingredient in the context of Regulation (EC) No 258/97.

2. Data and methodologies

2.1. Data

The assessment of the safety of this novel food ingredient (NFI) is based on data supplied in the original application, the initial assessment by the competent authority of France, the concerns and objections of the other Member States and the responses of the applicant. The data are required to comply with the information required for novel foods of Subclass 2.1: 'the source of the novel food has a history of food use in the Community', i.e. structured schemes I, II, III, IX, X, XI, XII and XIII of Commission Recommendation 97/618/EC. In the current opinion, these structured schemes are listed in Sections 3.1–3.9. The intention of the applicant is to add 'cranberry extract powder' to beverages, milk and other dairy products. The target population is the general population. This assessment concerns only risk that might be associated with consumption under the proposed conditions of use, and is not an assessment of the efficacy of the NF with regard to any claimed benefit.

2.2. Methodologies

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

3. Assessment

3.1. Specification of the Novel Food (NF)

The NF is prepared from the juice concentrate of sound, mature berries of the cranberry cultivar (*Vaccinium macrocarpon*). The NF is a fine, free-flowing deep red powder obtained from spray drying of chromatographically isolated Cranberry Extract Liquid – Type R, standardised to the PACs content with maltodextrin as a carrier and silicon dioxide as a flow agent (Table 1).

Table 1: Specifications proposed by the applicant

Parameters	Range	Method of Measurement
Moisture (% w/w)	≤ 4	Gravimetric, loss of drying (CEM microwave oven or equivalent)
PACs (% DWB)		
OSC-DMAC method ^{(a),(c)}	55.0–60.0	OSC-DMAC (25 EtOH wash) using cranberry extract response factor. BL-DMAC using procyanidin A2 standard
BL-DMAC method ^{(b),(c)}	15.0–18.0	
Total phenolics (GAE, % DWB) ^(c)	> 46.2	Folin–Ciocalteu using gallic acid standard
Solubility	100%, with no visible insoluble particles	Powder should dissolve completely in 2 min with agitation
Ethanol content (mg/kg)	≤ 100	AOCS Official method Ca 3b-87, hexane residues in fats and oils, or equivalent
Screen analysis	100% through 30-mesh screen	Rotap with hammer, 5 min
Appearance & aroma; as powder	Free-flowing, deep red colour. Earthy aroma with no burnt character	Sensory
Heavy metals		
Arsenic (ppm)	< 3	EPA 200.8
Lead (ppm)	< 2	EPA 200.8
Cadmium (ppm)	< 10	EPA 200.8
Mercury (ppm)	< 1	EPA 200.8
Microbiology		
Yeast	< 100 cfu/g	Microbiological methods as described by AOAC ^(d) , APHA ^(e) or BAM ^(f) (FDA)
Mould	< 100 cfu/g	
Aerobic plate count	< 1,000 cfu/g	
Coliforms	< 3 mpn/g or < 10 cfu/g	
<i>Escherichia coli</i>	< 3 mpn/g or < 10 cfu/g	
<i>Salmonella</i>	Absent in 375 g composite sample	

PAC: proanthocyanidin; DWB: dry weight basis; GAE: gallic acid equivalent; cfu: colony forming unit; mpn: most probably number.

(a): OSC-DMAC method (J. Agric. Food Chem. 1998).

(b): BL-DMAC method (J. Agric. Food Chem. 2010).

(c): The different values for these three parameters are due to the different methods used.

(d): AOAC (Association of Official Analytical Chemists or Association of Analytical Communities).

(e): APHA American Public Health Association).

(f): BAM (Bacteriological Analytical Manual, FDA).

Regarding heavy metals, the applicant provided information on the testing of three batches which gave the following ranges: arsenic 71.9–95 ppb, cadmium < 10 ppb, mercury < 10 ppb and lead 42.3–110 ppb.

The applicant notes that the NF must comply with regulatory limits for pesticides, herbicides, heavy metals, growth regulators and mycotoxins. In this regard, the applicant points out that the berry juice concentrate used for the manufacture of the product in question complies with the maximum levels of contaminants laid down in Regulation (EC) No 1881/2006. Tests were carried out on at least three different production batches for PACs and the total phenolic content as well as for the content of residual heavy metals (including As, Cd, Hg and Pb) and ethanol, and the content of the flow agent SiO₂.

According to the specification, the NF contains 55–60% PACs as measured by OSC-DMAC (colorimetric analysis using dimethylaminocinnamaldehyde (DMAC) with isolated cranberry PACs as a standard compound). The PACs content was also analysed using the BL-DMAC method (colorimetric analysis using DMAC with the procyanidin dimer A2 as a standard compound) with a content of 15–18%. Analytical data on the distribution of the PACs monomers, dimers, trimers and larger polymers in the NF was provided.

Additional information provided by the applicant indicates that the NF also contains 3.2% anthocyanins, 4.8% sugars and 6.0% organic acids. The residual protein content of the NF is 1.16% as measured by the Dumas method with a limit of quantitation of 1 g/kg.

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

3.1.1. Stability of the NF

Based on the analysis of the PAC content, of anthocyanins and total phenolics, the results of stability tests demonstrate that the cranberry extract powder is stable for 30 months when stored in dry conditions at 25°C. The applicant also provided results (PACs and total phenolic analyses) indicating that cranberry extract powder is stable as incorporated at a level of 45 mg PAC per portion (240 mL) into diet- or water-type beverages for up to 22 weeks at room temperature. Additional stability testing of water-type beverages containing 70 mg PACs (measured by OSC-DMAC) per portion (240 mL) stored at 32°C showed no appreciable change in PACs content during a 12-week period.

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

3.2. Effect of the production process applied to the NF

Typically, cranberry juice contains sugars, organic acids and phenolic compounds (including flavonols, flavan-3-ols, anthocyanins and PACs). Of the solid material in cranberry juice, 90% are organic acids and sugars (Ocean Spray Cranberries internal compositional cranberry juice database). These phenolic compounds are selectively isolated from the other components of cranberry juice to yield cranberry extract.

The applicant provided a detailed description of the production process including a flowchart. Cranberry extract powder is produced from cranberry juice concentrate through an ethanolic extraction using an adsorptive resin column to remove sugars and organic acids, and to retain the phenolic components which are eluted, concentrated and spray-dried to yield the powder. Silicon dioxide is added as a flow agent and maltodextrin as a carrier. The material is packaged in two polyethylene bags, each with a twist tie, and placed in a standard fibre drum. The outer bag contains one desiccant sachet. A second desiccant sachet is placed at the top of the drum, outside the outer bag. Each drum contains about 22.7 kg powder net.

The manufacturing process is performed according to good manufacturing practice (GMP). The material shall be processed under sanitary conditions in accordance with GMP regulations FDA 21 CFR Part 110. Additionally, a HACCP plan shall be documented, reviewed, and implemented.

In response to an EFSA request to provide information on the production yield (i.e. how much cranberry juice is needed to produce a defined amount of the NF), the applicant informed that 66 mL of pure (7.5 Brix) cranberry juice is needed to produce 145 mg of cranberry extract containing 33–36 mg PACs (about 80 mg measured by OSC-DMAC) and that this amount approximately corresponded to a 240 mL serving of Ocean Spray's 27% 'cranberry juice classic' currently on the market.

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

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

The source of the NF is cranberry (*Vaccinium macrocarpon*) juice. According to ANSES (2013), cranberry juice has a history of food use in European Union (EU).

According to the applicant, cranberry juice products are sold globally and are marketed without limitations on their consumption.

The provided consumption data concern exclusively for the US. According to the US Agricultural Marketing Resource Center, the annual consumption of cranberries per person is about 1 kg cranberries, almost entirely in the form of juice or juice blends (AGMRC, 2016).

The estimated mean per-user daily intake of cranberries by male and female adults in the US is 23.6 and 42.1 g, respectively, and the estimated 90th percentile per-user daily intake of cranberries is 69.3 and 103.9 g/day, respectively (CDC, 2006). These intake estimates are based on food consumption data included in the National Center for Health Statistics' (NCHS), National Health and Nutrition Examination Surveys (NHANES) (survey data from years 2003–2004, 2005–2006).

According to the NHANES of 2005–2008, the mean per-user daily intake consumption of cranberry juice (100% cranberry juice, cranberry juice cocktail, low-calorie cranberry juice cocktail and blended cranberry drinks) was 221 mL. Duffey and Sutherland (2013) considered that the amount of cranberry juice in products to be around 27% due to the astringency of cranberry juice. The applicant concurs with the assumption that 'cranberry juice' consumption as recorded by NHANES represents beverages with about 27% cranberry juice and not the pure juice.

In response to a request by EFSA, the applicant provided data on the adults' consumption of cranberry beverage in the US NHANES (2013–2014), presented in Table 2 (per consumer only) and Table 3 (per kg body weight (bw), consumer only). Following a request from EFSA regarding data on cranberry juice consumption by children and regarding the target population, the applicant provided intake estimates also for children, but confirmed that children are not the target group.

Table 2: Estimated daily intake of cranberry beverage in the US by adults

Population group	Age group (years)	Consumer-only Intake (mL/day)					
		%*	n	Mean	90th percentile	95th percentile	97.5th percentile
Female Adults	≥ 20	2.1	60	203	310	1,201	1,201
Male Adults	≥ 20	1.5	30	166	314	379	521

Source: 2013–2014 NHANES Data.

*Percentage of consumers among survey population.

Table 3: Estimated daily per kilogram body weight intake of cranberry beverage in the US by adults

Population group	Age group (years)	Consumer-only Intake (mL/kg bw per day)					
		%*	n	Mean	90th percentile	95th percentile	97.5th percentile
Female adults	≥ 20	2.1	60	2.2	5.0	7.4	7.4
Male adults	≥ 20	1.5	30	1.9	2.8	6.4	7.2

Bw: body weight. Source: 2013–2014. NHANES Data.

*Percentage of consumers among survey population.

The applicant proposed to establish the safety of the NF on the basis of the history of consumption of its source (cranberry juice), along with the provided compositional data on the source and on the NF. Table 4 presents a comparison between the composition of pure (100%, 7.5 brix) and 27% cranberry juice, cranberry juice cocktail and the contents of cranberry extract powder constituents at the intended use level of the NF in beverages.

According to the applicant, 8 oz (\approx 240 mL) of 100% unsweetened cranberry juice contain 576 mg PACs, 736 mg phenolics and 53 mg anthocyanins (Table 4). These values present the mean of 64 samples over several years. A mean PACs content of 156 mg/240 mL has been calculated by EFSA for 27% cranberry juice (27/100 of 576 mg PACs). To confirm this figure, the applicant referred to analyses over the shelf-life of cranberry juice cocktail samples have resulted to a range of PACs content from 70 to 140 mg/240 mL.

Table 4: Constituents of existing cranberry juice products and of beverages based on proposed use levels of cranberry extract powder and naturally occurring constituents provided by the applicant

Constituents (mg/240 mL ^(a))	Cranberry beverage products			Proposed uses in beverages
	100% cranberry juice (unsweetened)	27% cranberry juice ^(c)	Cranberry juice Cocktail	
Cranberry extract powder	0	0	0	144 ^(d)
Proanthocyanidins	576 ^(b) (481–916)	156	90 (70–140)	76.8 ^(d)
Phenolics	736	199	211	61
Anthocyanins	53	14	12	12
Quinic acid	2,304	623	648	0.1
Malic acid	1,872	506	504	0.4
Citric acid	2,520	681	672	0.4
Quercetin	–	–	3	0.4
Galacturonic acid	–	–	288	–
Dextrose	7,512	2,030	16,372	0
Fructose	1,824	493	12,408	0
Sucrose	120	32	1,512	0
Ascorbic acid	Not provided	–	69.6	–
Water (mL)	222	–	207	–

(a): 240 mL \approx 8 oz which is the amount considered as one portion size by the applicant.

(b): Mean and range on the basis of 64 samples over several years.

(c): These values are calculated on the basis of the provided figures for pure (100%) cranberry juice and does not consider any addition other than water, noting that existing 27% cranberry juices on the market may contain higher amounts of some of these constituents deriving from other fruit/vegetable juice used for blending.

(d): Calculated on the basis of a level equivalent to 150 mg cranberry extract powder and 80 mg PACs (by OSC-DMAC) per 250 mL beverage.

When assuming that 240 mL of 27% cranberry juice contains on average 156 mg PACs (0.65 mg/mL) (Table 4, measured by the OSC-DMAC method), and that the mean and 95th percentile of an adult female consumer is about 200 and 1,200 mL, respectively, cranberry juice per day (according to Table 2), then the resulting estimated mean and 95th percentile PACs intake from cranberry juice products would be about 130 and 780 mg PACs per day. The mean and 95th percentile daily PACs per kg bw for adult females were 2.2 and 7.4 mL (Table 3) which would correspond to a PACs intake of 1.43 and 4.81 mg/kg bw per day, respectively. For male adults, the mean and 95th percentile intakes of PACs from cranberry juice would be 108 (1.24 mg/kg bw) and 246 mg (4.16 mg/kg bw) per day, respectively.

3.4. Anticipated intake/extent of use of the NF

3.4.1. Uses and use levels

Cranberry extract powder is intended to be added to fruit-flavoured drinks (regular and low calorie), isotonic drinks (including electrolyte types), tea drinks (ready-to-drink, iced), vitamin-enhanced waters, yogurts and yogurt drinks with the intention to provide 80 mg PACs per serving (based on OSC-DMAC method). In order to achieve this level, the proposed food-uses and corresponding use levels for cranberry extract powder are provided in Table 5.

The target population is the adult general population. Upon request from EFSA, the applicant confirmed that the cranberry extract powder is not intended to be marketed to infants, toddlers and children of below 19 years of age.

Table 5: Summary of proposed individual food uses and use of cranberry extract powder in the European Union (NDNS data)

Food category	Proposed food-uses	Cranberry extract powder (mg/portion) ^(a)	Portion (g or mL) ^(b)	Level of use of cranberry extract powder (%)
Beverages	Fruit-flavoured beverages (regular) ^(c)	150	250	0.06
	Isotonic beverages (including those containing electrolytes)	150	250	0.06
	Low-calorie fruit-flavoured beverages	150	250	0.06
	Tea beverages (ready-to-drink, iced) ^(d)	150	250	0.06
	Vitamin waters	150	330	0.045
Milk and dairy products	Yogurts	150	125	0.12
	Yogurt drinks	150	200	0.075

(a): The quantity of cranberry extract powder was calculated on the basis of a level equivalent to 80 mg (by OSC-DMAC) proanthocyanidins/portion (approx. 55–60% of PACs are present in cranberry extract powder).

(b): The portions are based on the UK's 'Food Portions Sizes' handbook. Food Standards Agency (3rd edition; FSA, 2002).

(c): Not low-calorie beverages.

(d): As the NDNS databases (1992–1993, 1997, 2000–2001) do not include food codes for tea drinks (ready-to-drink, iced) specifically, food codes for herbal teas (ready-to-drink) were used as surrogates.

Table 4 (last column) provides also information on the contents of cranberry extract powder constituents (PACs, phenolics, anthocyanins and organic acids) at the intended use level of the NF in beverages. The Panel notes that when the NF is added to 150 mL beverages or yogurts at the intended use levels, the resulting contents of PACs per mL would be within the range reported for cranberry juice cocktail or below the content in 27% cranberry juice.

3.4.2. Consumption data

For estimating intakes of the NF under the proposed uses and use levels for the target population (i.e. adults), the applicant used the following UK surveys: United Kingdom Data Archive (UKDA) for the NDNS: Adults Aged 16–64 years collected in 2000–2001 (NDNS 2000–2001) (Office for National Statistics, 2005) and 1992–1993 (NDNS 1992–1993) (UKDA, 1995). Estimates for the intake of cranberry extract powder by the UK population were generated and collated by computer, using consumption data from individual dietary records, detailing food items ingested by each survey participant on each of the survey days. Estimates for the daily intake of cranberry extract powder represent projected 7-day averages for each individual of NDNS data. The distribution from which mean and percentile intake estimates were produced was comprised of these average amounts.

The applicant also provided exposure calculations based on data from the EFSA Comprehensive Food Consumption Database. Intake of cranberry extract powder was calculated for total population and users only (either fermented milk products or soft drinks).

3.4.3. Intake estimate for cranberry extract powder

Table 6 summarises the estimated total intake of cranberry extract powder (mg/person per day) from all proposed food-uses in the EU by population group. Table 7 presents this data on a per kilogram body weight basis (mg/kg bw per day). When all-user consumers (mean and 95th percentile) were assessed, the estimates for the intakes of cranberry extract powder from adult food-uses were determined to be at 123 and 366 mg/day for male adults and at 114 and 319 mg/day for female adults, respectively. On a body weight basis, the all-user mean and 95th percentile intake estimates of cranberry extract powder for adults were at 1.5–1.7 and 4.3–4.7 mg/kg bw per day, respectively (Table 7).

Table 6: Estimated daily intake of cranberry extract powder from all proposed food categories in the EU by adults (1992–1993, 2000–2001 NDNS Data)

Population group	Age group (years)	% user	All-person consumption			All-users consumption		
			Mean (mg)	Percentile (mg)		Mean (mg)	Percentile (mg)	
				90th	95th		90th	95th
Female adults	16–64	60.8	76	206	278	114	243	319
Male adults	16–64	54.3	72	208	298	123	281	366

Table 7: Estimated daily per kilogram body weight intake of cranberry extract powder from all proposed food categories in the EU by adults (1992–1993, 2000–2001 NDNS Data)

Population group	Age group (years)	% user	All-person consumption			All-users consumption		
			Mean (mg/kg)	Percentile (mg/kg)		Mean (mg/kg)	Percentile (mg/kg)	
				90th	95th		90th	95th
Female adults	16–64	60.8	1.0	2.9	3.8	1.7	3.6	4.7
Male adults	16–64	54.3	0.8	2.4	3.6	1.5	3.4	4.3

Using the EFSA Comprehensive Food Consumption Database, estimated total intake levels of cranberry powder extract were highest in adults, with a range of 167–885 mg/day at the 95th percentile. Among users of fermented milk products only, the estimated intake levels were also highest with adults, with a range of 135–717 mg/day at the 95th percentile. Among users of soft drinks only, estimated intakes were highest in adults, with a range of 198–819 mg/day at the 95th percentile. The applicant maintained that the intake levels using the EFSA Database are likely to overestimate as compared to the intake levels derived using the UK NDNS database. This is because the exposure assessment conducted in the UK NDNS survey was specified at a food-code level, thereby allowing a more specific matching of the fortified food-use concentration data, whereas the EFSA Database uses a food category level.

3.4.4. Intake estimate for PACs of cranberry extract powder

Cranberry extract powder contains a maximum of 60% PACs (Table 1). The total estimated daily all-person and all-user adult intakes of PACs from all proposed uses of cranberry extract powder are presented in Table 8 and Table 9 on an mg/day and mg/kg bw per day basis, respectively. It should be noted that only the all-user intake results will be discussed in detail.

For female adults, the mean and 95th percentile estimates for the all-user intakes of PACs from all proposed food-uses were 68 mg/day (1.0 mg/kg bw per day) and 192 mg/day (2.8 mg/kg bw per day), respectively. The mean and 95th percentile estimates for the all-user intakes for male adults of PACs from all proposed food-uses also were 74 mg/day (0.9 mg/kg bw per day) and 219 mg/day (2.6 mg/kg bw per day), respectively.

Table 8: Estimated daily intake of PACs resulting from all proposed food-uses of cranberry extract powder in the adult EU population (1992–1993, 2000–2001 NDNS Data)

Population group	Age group (years)	% user	All-person consumption			All-user consumption		
			Mean (mg)	Percentile (mg)		Mean (mg)	Percentile (mg)	
				90th	95th		90th	95th
PACs (OSC-DMAC)								
Female adult	16–64	60.8	46	123	167	68	146	192
Male adult	16–64	54.3	43	125	179	74	168	219

Table 9: Estimated daily per kilogram body weight intake of PACs resulting from all proposed food-uses of cranberry extract powder in the adult EU population (1992–1993, 2000–2001 NDNS Data)

Population group	Age group (years)	% user	All-person consumption			All-user consumption		
			Mean (mg/kg bw)	Percentile (mg/kg bw)		Mean (mg/kg bw)	Percentile (mg/kg bw)	
				90th	95th		90th	95th
PACs (OSC-DMAC)								
Female adult	16–64	60.8	0.6	1.8	2.3	1.0	2.2	2.8
Male adult	16–64	54.3	0.5	1.4	2.2	0.9	2.1	2.6

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

According to the applicant, cranberry juice and cranberry cocktails are widely consumed throughout Europe. Marketing data indicates that, from 2010, the European consumption of the applicant's cranberry juice cocktail equated to 200 million litres. Recent market data from the European Juice Industry (AIJN, 2012 – Liquid Fruit Market Report) further estimated the import of cranberry concentrate to be equivalent to consumption of cranberry juice cocktail of 300 million litres. In addition, many different cranberry food supplement products are available in Europe.

The applicant estimated the intake of PACs from consumption of Ocean Spray's cranberry extracts to be 17.1% (analysed using BL-DMAC method) using adult data set from the Netherlands which was found to be the Member State with the highest intake of Ocean Spray's cranberry extract. The mean and 95th percentile intakes for PACs were 74.4 and 162.2 mg/day (when using the OSC-DMAC method the reported PACs content was about 60% which would result in approximately three times higher PACs intakes).

3.6. Nutritional information on the NF

In response to Member State concerns, the applicant provided literature data on polyphenols from different food matrices and folic acid transport (Martel et al., 2010; Couto et al., 2012), iron absorption (Bentivegna and Whitney, 2002; Yamakoshi et al., 2002; Erdman et al., 2007; Fujii et al., 2008; Hurrell and Egli, 2010; Ma et al., 2011), absorption of lipids including triglycerides (Erdman et al., 2007; Sugiyama et al., 2007; Toyoda-Ono et al., 2007; Bladé et al., 2010; Chen et al., 2011; Jakobek, 2015), possible interaction with carrier proteins (Faria et al., 2006; Yang and Pan, 2012; Jakobek, 2015), and potential interaction with warfarin (Greenblatt et al., 2006; Grenier et al., 2006; Lilja et al., 2007; Zikria et al., 2010). The Panel notes that nutritional information is available for foods other than cranberry PACs. The Panel considers that, based on the available literature on polyphenols, there is no reason to assume that consumption of cranberry PACs would lead to dissimilar nutritional consequences in comparison to consumption of other polyphenol containing foods.

Taking into account the composition of the novel food and the intended use levels, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

3.7. Microbiological information on the NF

The Panel considers that the microbiological information provided (Table 1) does not raise safety concerns.

3.8. Toxicological information on the NF

In absence of toxicological studies on the NF, the applicant provided toxicological information on other source of PACs, namely grape seed extract (GSE) and on phenolic acids (e.g. chlorogenic acid) as supporting evidence for the safety of the NF. The Panel notes, however, that the types of PACs in the NF are not the same as in GSE (with differences in the composition of monomeric, dimeric, trimeric, oligomeric and polymeric PACs and the A-type linkages typical to cranberries). The Panel considers that these studies are not pertinent for assessing the safety of the NF.

3.8.1. Absorption, distribution, metabolism and excretion

The toxicokinetic properties of PACs have not been extensively evaluated. However, it has been demonstrated that only the PACs with a low degree of polymerisation (i.e. dimers) can be absorbed, and that the extent of their absorption is low (Cos et al., 2003; Prior and Gu, 2005). *In vitro* studies suggest that PAC polymers could be degraded into monomers under the acidic conditions of the stomach, although this is not thought to occur readily in humans (Manach et al., 2005). Rather, it has been proposed that oligomeric and polymeric PACs are transported to the large intestine where they undergo degradation by the colonic microbiota into simple phenolic acids which can then be subsequently absorbed (Manach et al., 2005; Prior and Gu, 2005).

3.8.2. Genotoxicity

Lack of genotoxicity with three different commercial cranberry products with low doses of phenolics was reported in the Palikova et al. (2010) rat study. However, the Panel considers that this study is not pertinent for assessing the genotoxicity of the NF. The Panel considers that the genotoxicity risk related to the consumption of the NF is not higher than the risk related to the consumption of cranberry juice.

3.8.3. Subacute and subchronic toxicity studies

No data was provided on the NF.

3.8.4. Subchronic toxicity studies

In its 2011 comments, ANSES asked the applicant to conduct a 90-day study in accordance with OECD guidelines as well as a mutagenicity study on the product in this application. In its response of 17 September 2012, the applicant noted that 'these studies were not considered to be necessary since safety has been demonstrated through history of consumption and pre-clinical and clinical data using cranberry products with a similar PAC content'.

Instead, the applicant referred to one controlled 14-week study with male Wistar rats fed with three different commercial cranberry products (Palikova et al., 2010). The Panel notes that this study was not performed according to the respective OECD Guidance. The Panel also notes the low dose tested (i.e. up to 0.60 mg PACs/kg bw per day). The Panel considers that this study is of no relevance for the safety of the NF at the proposed uses and use levels.

3.8.5. Human studies

While no animal toxicological studies have been conducted on the Ocean Spray product, a number of human clinical studies have been conducted with cranberry juice cocktails containing 30% concentrates (30–300 mL/day), or cranberry capsules (400–7,500 mg/day) (Jepson et al., 2008). None of these studies have indicated adverse effects caused by cranberry consumption. Although the phenolic composition of the test articles were not specified in these studies, the applicant assumes from the BL-DMAC analysis of several different cranberry extract products provided above that the PACs values used in the studies would be similar to that of the Ocean Spray product with added cranberry extract (meaning the NF).

ANSES published an opinion on the potential effects of cranberry on community-acquired urinary tract infection, which included an evaluation of the safety of cranberry juices and supplements based on data from these published clinical trials (ANSES, 2011). The opinion noted that side effects associated with the consumption of cranberry products were predominantly gastrointestinal in nature (such as gastroesophageal reflux, nausea and digestive disorders), and were observed particularly when large amounts of cranberry beverage were consumed for prolonged periods. No adverse findings or alterations in haematological and clinical biochemistry parameters were observed in one study where 65 healthy females consumed 400 mg/day (PACs content not reported) of a cranberry juice extract for 8 weeks (Valentova et al., 2007). ANSES concluded that 'in the current state of knowledge, there is no safety concern related to the consumption of cranberry by the general population' (ANSES, 2011).

In addition to the clinical study evaluated within the ANSES opinion (2011), three clinical studies have been conducted with Ocean Spray's cranberry extract powder. In these randomized, double-blind, placebo-controlled trials 54–140 adults received cranberry extract providing 36 mg or 72 mg PACs (measured by using the BL-DMAC method; when using the OSC-DMAC method the reported PACs

content would result to approximately three times higher values) daily for 10–12 weeks (Nantz et al., 2009; Juturu et al. 2015, manuscript; one unpublished report). Neither difference in the numbers of adverse effects was noted nor adverse effects on blood biochemistry or haematology. The Panel notes that the PACs dose of these studies is high as compared to the conditions of use of the NF. The Panel considers these studies do not raise safety concerns of the NF.

3.9. Allergenicity

No cases of an allergic reaction to cranberries or cranberry extract have been identified in the scientific literature. As stated earlier, the level of residual protein in the NF is 1.16%.

The Panel considers that the allergenic risk of the novel food is not dissimilar as of other cranberry products.

4. Discussion

The applicant provided sufficient information regarding the composition, production, stability and the estimated intake of the cranberry extract powder.

The NF is prepared from the juice concentrate of the cranberry cultivar (*Vaccinium macrocarpon*), and contains 55–60% PACs as measured by OSC-DMAC. During the manufacturing process, these phenolic compounds are selectively isolated from the other components of cranberry juice (e.g. sugars and organic acids) to yield cranberry extract. The amount of the cranberry juice needed to produce a defined amount of the NF corresponds to a 240 mL serving of Ocean Spray's 27% 'cranberry juice classic' currently on the market. The source has a history of human consumption.

The NF is intended to be added to fruit-flavoured drinks (regular and low calorie), isotonic drinks (including electrolyte types), tea drinks (ready-to-drink, iced), vitamin enhanced waters, yogurts and yogurt drinks with the intention to provide 80 mg PACs per serving (based on OSC-DMAC method). According to the applicant, the target population is the adult general population and the NF is not intended to be marketed to children.

The mean and 95th percentile volume consumption of a 27% cranberry juice drink for an adult female is about 200 and 1,200 mL, respectively. Assuming that 240 mL of 27% cranberry juice contains on average 156 mg PACs, the corresponding mean and 95th percentile intakes of PACs from cranberry juice would be about 130 and 780 mg PACs per day for adult females and 108 and 246 mg for adult males.

For female adults, the mean and 95th percentile estimates for the all-user intakes of PACs from all proposed food-uses of the NF were 68 mg/day and 192 mg/day, respectively. The mean and 95th percentile estimates for the all-user intakes for male adults of PACs from all proposed food-uses also were 74 mg/day and 219 mg/day, respectively.

Taking into account the composition of the novel food and the intended use levels, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

While no animal toxicological studies have been conducted on the NF, a number of human clinical studies have been conducted with cranberry products other than the NF. None of these studies have indicated adverse effects caused by cranberry consumption. In addition, three clinical studies have been conducted with the NF. The Panel notes that the PACs dose of these clinical studies is high as compared to the conditions of use of the NF. The Panel considers these studies do not raise safety concerns of the NF.

Based on the data provided, and considering the composition, manufacturing process, anticipated intake, history of consumption of the source, and human studies, the Panel considers that the consumption of the cranberry extract powder under the proposed conditions of use does not raise safety concerns.

5. Conclusions

The Panel concludes that the cranberry extract powder is safe as a food ingredient at the proposed uses and use levels.

Documentation provided to EFSA

- 1) Letter from the European Commission to the European Food Safety Authority with the request for a scientific opinion on the safety of cranberry extract powder a novel food ingredient. Ref. Ares(2016)1870715, dated 20 April 2016.

- 2) On 28 April 2016, EFSA received the following documentation: dossier 'cranberry extract powder', which was submitted by Ocean Spray Cranberries Inc.; initial assessment report carried out by the French Agency for Food, Environmental and Occupational Health regarding the evaluation of an application for authorisation to market a novel ingredient: 'cranberry extract powder' under Regulation (EC) No 258/97 concerning novel foods; Member States' comments and objections; response by the applicant to the initial assessment report.
- 3) On 14 June 2016, EFSA sent a request to the applicant to provide missing information to accompany the application.
- 4) On 20 July 2016, EFSA received the missing information as submitted by the applicant. After checking the content of the full dossier, including the missing information, EFSA considered the application valid as of 24 August 2016.
- 5) On 25 October and 7 December 2016, and 11 January 2017, EFSA sent requests to the applicant to provide additional information to accompany the application.
- 6) Additional data were provided by the applicant on 14 November and 19 December 2016, and 13 January 2017.
- 7) During its meeting on 4–6 April 2017, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of 'cranberry extract powder' as a novel food pursuant to Regulation (EC) No 258/97.

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Abbreviations

AOAC	Association of Official Analytical Chemists
APHA	American Public Health Association
BAM	Bacteriological Analytical Manual
BL-DMAC	Brunswick Laboratories - 4-dimethylaminocinnamaldehyde
bw	bodyweight

cfu	colony forming units
DWB	dry weight basis
FDA	(US) Food and Drug Administration
GAE	gallic acid equivalent
GMP	good manufacturing practice
GSE	grape seed extract
HAACP	hazard analysis and critical control point
MOE	margin of exposure
mpn	most probably number
NF	novel food
NFI	novel food ingredient
OECD	Organisation for Economic Co-operation and Development
OSC-DMAC	Ocean Spray Cranberries-4-dimethylaminocinnamaldehyde
NCHS	National Center for Health Statistics
NDNS	National Diet and Nutrition Survey
NHANES	National Health and Nutrition Examination Surveys
PACs	proanthocyanidins
UKDA	United Kingdom Data Archive