

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR OLIGONOL[®]

Applicant: Amino Up Chemical Company Ltd

Responsible Person: Kohei Homma

EC Classification: 2.1

Introduction

1. An application from Amino Up Chemical Company Ltd, as a novel ingredient was accepted by the Food Standards Agency in November 2014. A copy of the non-confidential version of the application was placed on the Agency's website for public consultation.
2. The applicant's Oligonol[®] is made by an oligomerisation reaction that cleaves the polyphenols present in a combined extract of lychee fruit and green tea into monomers and low molecular weight oligomers. Oligonol[®] is composed mainly of monomeric flavan-3-ols, as well as procyanidins formed from the condensation of these monomeric units.
3. The applicant proposes to incorporate Oligonol[®] into a range of different foods including dairy products, confectionery, cereals, bakery wares, non-alcoholic beverages and foods for particular nutritional uses. Oligonol[®] is intended to serve as another source of dietary polyphenols. No assessment has been made by the Committee on the efficacy of the product as this is outside the remit of the novel foods risk assessment.
4. Oligonol[®] has been classified as a complex novel food from non-GM source. The source of the novel food has a history of food use in the EU (class 2.1) according to the scheme in Commission Recommendation 97/618 (EC).

I. Specification of the novel food

5. The applicant has provided a detailed compositional analysis of three separate batches of Oligonol[®] to characterise and quantify the individual components of the novel ingredient.
6. The analysis demonstrates that Oligonol[®] is comprised mainly of monomeric flavan-3-ols and procyanidins, with sugars, protein, ash and moisture making

up the remaining components. A specification for the product is provided below. The applicant has analysed three independent batches of its Oligonol® and demonstrated that the manufacturing process produces a consistent product meeting physical, chemical and microbiological specifications.

Specification Parameter	Specification
Characteristic	Reddish-brown powder, Astringent taste
Moisture (%)	Not more than 5.0
Total Procyanidin (%)	More than 70
Monomeric Flavan-3-ols (%)	More than 10
Lead (Pb) (ppm)	Not more than 0.2
Arsenic (as As ₂ O ₃) (ppm)	Not more than 1.0
Number of bacteria (CFU/g)	Not more than 1,000
Mould and Yeast (CFU/g)	Not detected
Coliforms (CFU/g)	Not detected

***Discussion:** The Committee requested further information on the composition of the product in particular in relation to the 60% uncharacterised polyphenol component. The applicant provided further explanation that the specific phenols present had not been characterised due to technical limitations but analysis indicated that these were monomeric flavon-3-ols, procyanidin dimers and trimers. Specific structures of the monomers, dimers, and trimers contained in Oligonol® have been identified and have been presented in the dossier. No new or unique structures had been identified in the analysis. In light of the further information the Committee was content that the product had been appropriately characterised.*

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

7. The applicant has provided full details of the production processes for Oligonol® in the dossier. Oligonol® is manufactured by an oligomerisation process where the polyphenols present in a 5:1 mixture of extracts from the lychee fruit (*Litchi chinensis*.) and green tea leaves (*Camellia sinensis*) are cleaved into monomers and lower molecular weight oligomers. The applicant

states that the starting materials and processing aids used in the manufacture of Oligonol[®] meet food-grade specifications.

8. The applicant has provided information to substantiate that pesticide residues in the starting materials and end product, were not present at levels of toxicological concern. Further information has also been provided at the Committee's request on the controls that would be used during production to detect pesticides in the starting materials (extracts of lychee fruit and green tea leaf) or Oligonol[®] that would be of toxicological concern.
9. The applicant has also investigated the stability of Oligonol[®] in solutions of different pH following storage for 3 months. The applicant states that Oligonol[®] is proposed for use mainly in foods that are acidic e.g. fruit and vegetable based beverages. As such, the applicant highlights that the total polyphenol content of Oligonol[®] was not altered for the duration of storage under acidic conditions (pH 3).
10. The applicant emphasises that although Oligonol[®] will be less stable under alkaline conditions, such as in dairy based foods, these products are normally refrigerated which would reduce the extent of degradation. The applicant states there are no safety concerns anticipated with the degradation products that may be formed from Oligonol[®] under alkaline conditions and has provided further details to substantiate this.

***Discussion:** The Committee requested further information on the production process to ensure the presence of pesticides and lychee nut were managed effectively in production.*

To verify the pesticide residue analysis, information was provided by the applicant for three batches of both the lychee extract and green tea extract starting materials and the final product. Information was displayed in an accessible format and translated for ease of review. The Committee were content that this potential hazard was being appropriately managed.

Further information was provided by the applicant on the columns used to purify the product and the steps taken to ensure there was not leaching of the column. This is reflected in the updated production section of the dossier along with flow diagrams of the production of both starting materials. These indicate the steps taken to manage allergy risks from the presence of lychee nut in the starting material and controls for pesticide residues.

III. History of the organism used as a source of the novel food

11. Extracts of the lychee fruit and green tea leaves, both of which have an extensive history of consumption in the diet, are used as the starting materials for the manufacture of Oligonol[®].
12. The applicant states that the lychee fruit has a long history of cultivation in China of more than 2000 years; it is now widely grown in subtropical regions, with China, Thailand, India, South Africa, Madagascar, Mauritius, and Australia currently being the major lychee producing countries in the world. The applicant mentions that European markets import approximately 20,000 tonnes of fresh lychee annually, of which nearly 50% is imported by France, and the remainder by the UK and Germany.
13. The applicant emphasises the long history of safe consumption of tea dating back to ancient civilisation. Both black and green teas are made from the leaves of the same plant species (*Camellia sinensis*) though levels of polyphenols tend to be higher in green tea due to differences in the post-harvest processing.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

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

14. The applicant intends to incorporate Oligonol[®] in a variety of conventional foods and beverages with use levels ranging from 100 to 1150 mg/kg or mg/l. The range of foods proposed by the applicant include dairy products, confectionery, cereals, bakery wares, soups and sauces, non-alcoholic beverages and foods for particular nutritional uses. Full details can be found in Annex A.
15. Using the European Food Safety Authority (EFSA) 'Food Additives Intake Model' (FAIM) tool, the mean daily estimated intake of Oligonol[®] from the proposed uses by the EU population was estimated by the applicant to range from 3.3 to 14.3 mg/kg body weight/day in toddlers, 4.2 to 14.6 mg/kg body weight/day in children, 2.5 to 6.7 mg/kg body weight/day in adolescents, 1.7 to 8.8 mg/kg body weight/day in adults, and 1.4 to 7.0 mg/kg body weight/day in elderly individuals. High level intakes ranged from 11.1 to 27.1 mg/kg body weight/day in toddlers, 9.1 to 25.4 mg/kg body weight/day in children, 4.2 to 13.7 mg/kg body weight/day in adolescents, 3.1 to 15.5 mg/kg body weight/day in adults, and 2.8 to 12.6 mg/kg body weight/day in elderly individuals.

16. Using the reference body weights for the EU population, the applicant states that the mean daily estimated intake of Oligonol[®] from the proposed uses corresponds to 40 to 172 mg/day in toddlers, 97 to 336 mg/day in children, 108 to 288 mg/day in adolescents (10 to 14 years old), 153 to 409 mg/day in adolescents (14 to 18 years old), 119 to 616 mg/day in adults, and 98 to 490 mg/day in elderly individuals. The applicant showed that high level intakes corresponded to 133 to 325 mg/day in toddlers, 209 to 584 mg/day in children, 181 to 589 mg/day in adolescents (10 to 14 years old), 256 to 836 mg/day in adolescents (14 to 18 years old), 217 to 1,085 mg/day in adults, and 196 to 882 mg/day in elderly individuals.
17. The applicant also intends to incorporate Oligonol[®] into food supplements to provide a dose of 200 mg/day. The applicant's view is that given that Oligonol[®] food supplements are intended to serve as an alternative to foods enriched with Oligonol[®], it is highly unlikely that individuals will consume both Oligonol[®] food supplements and Oligonol[®]-containing foods.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

X Information from previous human exposure to the NF or its source

18. The applicant states that polyphenols are bioactive compounds that are present in various dietary sources, including fruit, vegetables and beverages of plant origin, such as teas.
19. Among the different classes of polyphenols, the applicant emphasises that flavonoids are one of the most common in the diet, accounting for nearly two-thirds of the total dietary intake of polyphenols. Specifically, flavan-3-ols and their polymeric condensation products (proanthocyanidins) are one of the most commonly consumed flavonoids, found in foods such as fruits, vegetables, plant-derived beverages (tea, coffee, wine, beer), and chocolate.
20. The applicant has cited literature proposing that total polyphenol intake levels of 1000 to 1100 mg/day can be expected among individuals who consume a balanced diet.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

XI. Nutritional information on the novel food

21. The applicant states that Oligonol[®] is intended as another source of dietary polyphenols, particularly the flavonoids such as monomeric flavan-3-ols and their polymeric condensation products (e.g. procyanidins). The applicant has

cited references which support that high intake of foods rich in polyphenols is associated with a lowered risk of chronic diseases, including cardiovascular disease, cancer, neurodegeneration, and chronic inflammation. It is outside the scope of this opinion to evaluate scientific evidence for potential health benefits from consuming the product.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

XII. Microbiological information on the novel food

22. The applicant has provided microbiological specifications for Oligonol[®], taking into account mould and yeast, and Coliforms. Analyses of three separate batches of Oligonol[®] reveal that all batches comply with set microbiological specifications.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

XIII. Toxicological information on the novel food

23. The applicant states that Oligonol[®] has low acute toxicity with the median lethal dose determined to be greater than 2000 mg/kg in both sexes of Sprague-Dawley rats after oral administration.

24. The applicant has evaluated the sub-chronic toxicity of orally administered Oligonol[®] in two 90 day gavage studies conducted in rats (at doses up to 1000 mg/kg body weight/day) and one 90 day feeding study in mice. The applicant states that data show there were no toxicologically relevant effects in these two 90-day studies. There were no treatment-related changes in body weight, food consumption, haematology, clinical chemistry, and urinalysis. The No Observed Adverse Effect Level (NOAEL) from these studies was determined to be 1000 mg/kg body weight/day which was the highest dose tested, for both males and females.

25. The applicant states that the results from the rat studies were further supported by a lack of toxicity in a 90 day mouse feeding study, where Oligonol[®] was administered at doses up to 200 mg/kg body weight/day.

26. The applicant states that results from a series of *in vitro* and *in vivo* assays demonstrate that Oligonol[®] is not mutagenic/genotoxic.

27. Three clinical studies are detailed by the applicant in the dossier which the applicant states show that Oligonol[®] was well tolerated, without adverse events being reported and no treatment-related changes were observed in

haematology or serum biochemistry parameters in subjects consuming 200 to 600 mg/day of Oligonol[®] for as long as 3 months.

28. The applicant states that based on a NOAEL of 1000 mg/kg body weight/day derived from 90-day oral toxicity studies in rats, the safety margin in adults is at least 114-fold for the estimated mean intakes of Oligonol[®] (1.7 to 8.8 mg/kg body weight/day), and at least 65-fold for the estimated high level intakes of Oligonol[®] (3.1 to 15.5 mg/kg body weight/day) from the proposed food uses of Oligonol[®].
29. The applicant acknowledges that Oligonol[®] is also proposed for use in food supplements and notes that there is a 54-fold safety margin for the total exposure to Oligonol[®] estimated under the worst-case scenario where Oligonol[®] food supplements are consumed at the maximum recommended levels by adults with the highest estimated high level intake of Oligonol[®] from the proposed food uses (18.4 mg/kg body weight/day). The applicant acknowledges that some safety margins are less than the generally accepted level of 100-fold, but emphasises that these safety margins are the worst-case scenario estimates and therefore are appropriately protective.
30. Although green tea has a long history of safe consumption, the applicant acknowledges there have been some safety concerns relating to liver toxicity for highly concentrated, purified forms of green tea extracts being marketed mainly as dietary supplements. The applicant has explored this issue further and concluded that, based on the results of its toxicology studies, these concerns are not relevant for Oligonol[®].

Discussion: *The Committee considered in further detail some of the findings in toxicological studies. An explanation was sought on the NOAEL selection. Further information provided supported the applicant's view that the changes in the activated thromboplastin time in the 90-day animal study conducted by Fujii et al. (2008), were not considered adverse as the results were not biologically significant.*

The Committee queried the polyploidy finding seen in the chromosome aberration test. The applicant responded explaining the limitations of the test and the rate of false positives found using this methodology. The applicant therefore suggested this was not of concern and this was supported by the lack of similar findings in the animal studies.

Information had been provided in the dossier on both Oligonol[®] and a similar related product. The applicant explained that the studies on the related product were intended to be supporting information that products rich in polyphenols were well tolerated. Information was also provided for three human studies. When

considered in detail, the Committee considered that these were supplementary evidence but did not directly contribute to the assessment of the product's safety.

The Committee also considered in detail the findings of the unpublished 90 day oral toxicity study performed in rats. The Committee sought further information on the findings that were statistically significant to provide reassurance that these were not adverse effects. The information provided verified the applicant's suggestion that the findings were statistically significant but not of biological significance given the changes in the control populations used for comparison.

Further information was sought from the applicant on the catechin content of Oligonol® and the potential for toxicity. The applicant provided a review of the evidence of catechin liver toxicity supporting their view this would not be a concern at the intake levels expected for products containing Oligonol®. Further analysis was requested by the Committee to consider the potential exposure of consumers from catechins from Oligonol® compared to the exposure from green tea. The response showed that Oligonol® at the maximum level of intake from all uses would provide some additional exposure on a per day basis but that this was less than the exposure from a single cup of green tea. The Committee was satisfied with the response received.

XIV Allergenicity

31. The applicant stated that although Oligonol® is composed mainly of polyphenols, a small amount of protein is also present (1-2%). The applicant reports that allergic reactions to lychee fruit are rare but have been documented in the literature and relevant references are cited in the dossier along with further consideration of this issue. The applicant concluded that the potential allergenicity of Oligonol® is low and highlighted that none of the participants from their human studies exhibited any symptoms of allergic reactions to Oligonol®.

Discussion:

The Committee requested further information on the lychee extract used as a starting material of Oligonol®. Concerns were raised that the lychee extract might include the nut of the fruit. It noted that while lychee nuts are not eaten, they are related to tree nuts such as cashew and pistachio which are allergenic for some people, suggesting the potential for cross reactivity. IgE-mediated individuals with latex allergy may also react to lychee fruit. The applicant confirmed that the nut is not used to produce the extract and has provided further information on the controls used to verify this and that the residual protein content of the product was so low as to pose little risk. This information is included in the update production process section of the dossier.

To verify the controls were effective a further protein analysis was requested which the applicant considered indicated that lychee nut proteins were successfully excluded from the starting material. The Committee were content that the analysis provided suggested the risk of contamination with lychee nut was low. However, given the potential severity of reactions in individuals allergic to related species such as cashew as a result of cross reactivity, the Committee suggested that risk managers should consider whether further risk management is needed to protect this group of consumers.

CONCLUSION

The ACNFP has completed its assessment of Oligonol[®] as a novel ingredient for use in a range of products including food supplements.

The Committee requested further information from the applicant on the following:

- The composition of the product
- The production process used to produce Oligonol[®] and the measures taken to reduce the risk from the presence of undesirable substances including pesticide residues and the lychee nut.
- Further information on details of the toxicological studies undertaken to verify the safety of Oligonol[®].

After reviewing the applicant's response to these issues, the Committee did not have any outstanding safety concerns. The potential risks from contamination of lychee nut in the starting materials are highlighted to risk managers for them to consider the further risk management measures needed to protect cashew nut allergic consumers.

Based on the evidence provided the ACNFP therefore concluded that Oligonol[®] used in the ways and doses proposed by the applicant, is unlikely to present a health risk to consumers.

October 2017

Annex A

Food type	Specific category	Proposed Maximum Use Level (mg/kg or mg/L)
Dairy products and analogues	Unflavoured fermented milk products, including natural unflavoured buttermilk (excluding sterilised buttermilk)	200
	Flavoured fermented milk products including heat treated products	200
	Dairy analogues, including beverage whiteners	100
Other confectionery including breath refreshing microsweets	Other confectionery with added sugar	1,150
	Other confectionery without added sugar	1,150
Chewing gum	Chewing gum with added sugar	1,150
	Chewing gum without added sugar	1,150
Cereals and cereal products	Breakfast cereals	800
Bakery wares	Fine bakery wares	800
Salts, spices, soups, sauces, salads and protein products	Soups and broths	410
Foods intended for particular nutritional uses as defined by Directive 2009/39/EC (European Parliament and the Council of the European Union, 2009)	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal	800
Non-alcoholic beverages	Fruit juices as defined by Council Directive 2001/112/EC (Council of the European Union, 2002)	420
	Flavoured drinks with sugar	420
	Flavoured drinks with sweeteners	420
	Coffee, tea, herbal and fruit infusions, chicory, and chicory extracts	420
Food supplements		200 mg/day