Issue
The Committee reviewed this application for the first time in November 2014 and requested further information on which to base their assessment. Members are invited to consider the response from the applicant and whether it recommends authorisation of the product.

Background
1. This application from the Amino Up Chemical Company Ltd is for authorisation of Oligonol® (produced from lychee fruit and green tea extracts) as a novel food ingredient under 258/97. At November’s meeting the Committee requested further information in a number of areas:
   a) specifications
   b) analytical data
   c) production process
   d) toxicology and
   e) allergenicity

2. A letter outlining the concerns raised with the applicant is provided in Annex A. The applicant has now provided a response to the Committee’s questions Annex B and a number of appendices providing the analyses and publications requested.

   a) specifications

3. The Committee requested a more detailed specification of Oligonol®. It was viewed as important to understand the total catechin content of the final product for the risk assessment. The Committee also suggested that further characterisation of the 60% of uncharacterised polyphenols was needed.

4. The company in their response note that as a minimum specification, Oligonol® contains 10% monomeric flavan-3-ols and 70% procyanidin. In a communication the applicant explained that procyandins and the monomeric flavan-3-ols are forms of catechin and epicatechin and so approximately 93% of the product are represented by these components. The higher molecular weight procyanidin oligomers and polymers comprising 60% of Oligonol® have not been fully
characterised due to technical limitations. The company considers it is not necessary to further characterise the procyandin content because the toxicological data does not suggest an issue at the dose proposed.

b) analytical data

5. The Committee considered the quality of the analytical data made it difficult to undertake a risk assessment and be assured of the specification of Oligonol®. In response the applicant has provided further copies of the analysis information in appendix A of their response. The analyses presented in Chinese have been identified as pesticide analysis for both Oligonol® and source material extracts. Details of the AOAC method, which is the same as the Japanese official method used for fat determination, is also provided.

c) production process

This section has been removed as certain aspects of the production process of Oligonol® are commercially sensitive.

d) toxicology

NOAEL selection

6. The applicant was asked to provide further information on the choice of NOAEL selected of 1000 mg/kg bw/day. A query was raised as to why the statistically significant activated partial thromboplastin time in males at the 1000 mg/kg bw/day dose was not considered as an adverse event.

7. In their response the applicant explains that the NOAEL was established as the highest treatment dose in Fujii et al (2008) with a lack of biologically significant effects on body weight gain, food consumption, organ weight values, or on the results of the clinical chemistry, haematology, urinalysis or histopathological examination. The applicant commented that they had followed a standard approach in using the highest dose tested based on two similar studies suggesting a NOAEL of the highest dose. It is also noted that the Fujii (2008) was published and as such had been subject to peer review, Leuschner (2011) was provided as a confirmatory study.

8. The applicant recognised there was an increase in activated partial thromboplastin time in male subjects at the 1000 mg/kg bw/day. However they do not view it as an adverse event because the magnitude of the effect, while statistically significant, was small, the effect was not seen in females and was not dose dependant. The applicant also noted there was no effect on prothrombin time at any dose. In their view the conclusion that this is not an adverse event is
supported by the lack of increase in activated partial thromboplastin time seen in a second unpublished gavage study (Leuschner, 2011).

**ADME data**

9. Members requested further information to clarify how the ‘Oligonol-like’ product used for ADME analyses compares to the composition and behaviour of the novel ingredient. Information was requested to support the conclusion that the ADME properties of the two products are similar.

10. The applicant stated the toxicological data produced for the ‘oligonol like’ product is in addition to that provided for Oligonol® and as such is supplementary. The materials differ in that green tea leaves are used in Oligonol and therefore the monomeric green tea catechins would be higher relative to the ‘Oligonol like’ product. In their view neither product raised safety concerns in testing.

11. The applicant suggests the "Oligonol-like" material referred to in the dossier is very similar to Oligonol® containing procyanidins, and produced by a similar process. It contains approximately 15% monomeric polyphenols and 8 to 12% as dimers and 5-10% as trimers. Much of the remainder (~60%) is present in the form of longer chain oligomers, largely mirroring the composition of Oligonol®. The applicant states that the polyphenol content of the materials is similar and therefore the ADME characteristics are similar also.

12. The Committee also sought clarification on the comments made in relation to the kinetics of digestion and absorption of Oligonol®. The dossier had suggested that the product would have a similar ADME profile to the parent polymeric materials despite stating that Oligonol® comprised of largely monomeric flavan-3-ols and procyanidins.

13. The applicant stated that Oligonol® is comprised of at least 30% monomeric, dimeric, trimeric constituents with a further 60% containing longer procyanidin oligomers. On this basis the applicant considers that the ADME and bioavailability of the product can be assessed. The monomeric flavan-3-ols are expected to be bioavailable following ingestion. Additional phenolic content is likely to be bioavailable following degradation of oligomers by gut microflora.

14. The applicant has replied that the exact pharmacokinetics cannot be assessed as the exact nature of the high molecular weight oligomer content of the ingredient cannot be identified. They consider further analysis is not necessary as the 90 day gavage studies have verified the toxicological effect of the material.

**Genotoxic studies**

15. Members sought further reasoning on the dismissal of observed effects of increased polyploidy in the chromosome aberration test. The applicant suggests
the Chinese Hamster Lung cell line used for the test is known to have given false positives with similar substances. The line is p53 deficient and suggestion is made that p53 competence is linked to increased likelihood of polyploidy as a result of cell dysregulation. The applicant states the chromosome aberration assay did not detect chromosome aberrations at the highest concentrations that could be scored. No genotoxic activity was seen in an in-vivo mouse micronucleus test. On this basis the finding of polyploidy in their view was not considered to present evidence of genotoxic risk.

Green tea liver effects

16. The Committee highlighted the need for a specific risk assessment of the green tea catechins of Oligonol®. Members requested a more detailed discussion of the green tea associated (liver effects) toxicity. The literature review performed by the applicant was requested and is provided in Appendix E of their response.

17. The applicant summarises findings of a study undertaken by the National Toxicology programme on green tea extracts. High doses of the extract were found to be linked to liver necrosis, with some evidence of hepatotoxicity. The applicant comments that the finding of this study does not have direct relevance for the assessment of Oligonol® as there was no evidence of liver toxicity including histopathology or clinical chemistry changes seen in the two 90 day rodent toxicity tests. The green tea component in the highest doses in those studies was estimated as 120mg/kg bw/day and 150mg/kg bw/day respectively. Heavy users of Oligonol® were estimated to be exposed to green tea components equivalent to 3 mg/kg bw/day representing a greater than 100 fold safety margin on the NOAEL reported for liver toxicity in rats.

e) allergenicity

18. The Committee requested information on the lychee fruit extract used as a starting material for Oligonol®. Information was requested on whether the extract is produced from the fruit including the nut given the genetic relatedness of lychee to common allergens in the EU. LC-MS analysis of the proteins present in the lychee was also requested in order to assess allergenic risk.

19. The applicant’s response notes that the lychee fruit extract does not contain the nut. It is their view that as lychee fruit are freely available in the EU and are not listed under the EFSA report evaluating allergenic foods for labelling purposes as a food with allergenic potential, there is not a need for further analysis of allergenic lychee nut proteins.

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Public comments
20. In line with the Agency’s openness policy, the application dossier was published on the Committee’s website for a twenty one day public consultation. One public comments was received summarised in Annex C and should be considered as part of the Committee’s assessment.

Committee Action Sought

f) The Committee is asked whether the response from the applicant is sufficient to address the questions raised in November 2015.

g) If not, the Committee is asked to indicate what feedback should be given to the applicant.

Secretariat
February 2015

Appendices attached
Annex A – Letter sent to applicant following November 2014 meeting
Annex B – Applicants response
Annex C– Summary of consultation responses
## Annex C - Consultation responses

<table>
<thead>
<tr>
<th>Respondent</th>
<th>Points raised</th>
<th>How this can be taken forward in the risk assessment</th>
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<tbody>
<tr>
<td>A member of the public</td>
<td>• Information was provided from publically available sources of the nutritional content of lychee fruit and in relation to the caffeine content of green tea.</td>
<td>• The information provided was in relation to the source material. The effect of the final product has been studied in test subjects and therefore this submission does not provide additional evidence to be considered in the risk assessment.</td>
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<td></td>
<td>• A link was also provided to a study in the Journal of Nutrition(^2) that suggests there is evidence that Oligonol (a low molecular weight polyphenol from Lychee fruit) can have a protective effect against some renal complications in type 2 diabetic mice.</td>
<td>• While interesting, this source is not directly relevant to the risk assessment of the novel food ingredient.</td>
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