COMMITTEE PAPER FOR DISCUSSION **ACNFP/131/02**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OLIGONOL®

Issue

The Committee has reviewed the application from Amino Up Chemical Company for their product Oligonol® at a number of meetings. It was last considered at the July 2017 meeting. Further information was requested on two areas on which the applicant has responded. The Committee are asked to consider the response and whether they recommend the novel food for authorisation

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 Regulation number 258/97EC. The novel ingredient is proposed to be added to a range of foods from non-alcoholic beverages to confectionary.

2. At the last meeting further questions were raised on:

   - The protein analysis to verify the effectiveness of controls to prevent lychee nut contamination of the Oligonol starting material; and

   - The level of catechins in the novel ingredient and whether this represented a toxicological concern based on emerging evidence.

   The applicant has provided a response to the Committee on these areas and the Committee is asked whether this addresses the outstanding questions on the dossier.

3. To inform the discussion and further development of an opinion, the feedback to the applicant from the July meeting is provided at **Annex A**. The applicant's response to the points raised is provided at **Annex B.** The Secretariat has also provided a summary of the issues considered by the Committee on Oligonol® to date in **Annex C.** The draft opinion for consideration is provided at **Annex D**.

Protein analysis

4. At its April 2016 meeting, the Committee continued to seek evidence to demonstrate either that the production process effectively excluded lychee nut from the lychee starting material or that lychee nut proteins were not present in the Oligonol® final product. The applicant was encouraged to either provide

further evidence on this point or undertake an appropriate allergenicity risk assessment.

5. At the April meeting the applicant's response to these requests for further information were presented. Further protein analysis had been undertaken to verify the effectiveness of the controls in the production system. Following the discussion with members the applicant was asked to provide further details of the analysis of the proteins that was undertaken to confirm the conclusions reached.

6. The applicant has provided a response to the detailed questions raised on the methodology used to generate the information supplied and the data available for analysis.

Toxicological assessment of the catechin content of the novel ingredient

7. As part of the discussion at the last meeting, the emerging evidence from European reviews[1] on the toxic effects of catechins was highlighted. It was recognised that the toxicological studies on the Oligonol ingredient had not indicated liver toxicity; however, Oligonol would be contributing to the catechin levels in the diet. Given suggestions that high levels of catechins have been associated with liver toxicity especially when animals are in a fasted state the Committee sought further information on this component of the novel ingredient.

8. Information was sought on whether the toxicological testing on Oligonol had taken into account exposure after the animals had fasted. The applicant was also asked to assess the catechin content of Oligonol compared to the NOAELs for catechins in both the fed and fasted state to understand the margin of safety for this specific component and its contribution to the dietary exposure to catechins.

9. In response the applicant highlights that the studies showing adverse events were related to animals being given a bolus dose of food supplement in a fasted state. It was suggested the material used in these studies and their relevance to dietary exposure to these components was unclear. The applicant suggests that Oligonol would not be consumed in the fasted state as it would be a component in other foods and therefore the situation in the toxicological studies undertaken for Oligonol realistically represents the exposure of consumers from the novel food. Exposure to catechins from green tea was considered a more comparable situation to the exposure to Oligonol as a food ingredient.

10. Analysis has been provided of the intake of the catechin forms present in Oligonol at a population level from use of Oligonol in the requested food categories. This has been compared to the intake of these substances from green tea based on European intake data. Information has not been provided on the green tea exposure for all groups as in some surveys insufficient numbers of responders were present to provide an accurate estimate. The key findings of the analysis for adults are reproduced in the table below:

Table 1: Intake of monomeric flavan-3-ol from the consumption of Oligonol compared to green tea

	Oligonol			Green tea		
	Composition %	Adults		Intake from 200 ml serving (mg)	Adults	
		Highest mean intake (mg /day)	Highest heavy level intake (mg/day)		Highest mean intake (mg/day)	Highest p95 level intake (mg/day)
(-) catechin and (-) EC	8	49.3	86.8	21.6	ND	ND
(-)-EGC	--	--	--	33.4	ND	ND
(-)-ECG	2	12.3	21.7	39.5	ND	ND
(-)-ECGC	6	37.0	65.1	155.6	ND	ND
Total monomeric flavan-3-ol content	16	98.6	173.6	250.1	573.59	1250.00

11. The applicant suggest that the daily exposure to polyphenols from Oligonol used in all requested food categories would be less than present in one cup of green tea. It is argued in the response as up to 10 cups of green tea a day can be consumed without ill affect this supports the suggestion that Oligonol would be safe as proposed to be used. The response explains that in toxicological studies for green tea extracts in beagles in the fed state the NOAEL was 500mg/kg/day, significantly higher than would occur from the intake from the novel ingredient as calculated in the intake assessment.

Committee Action Sought

- The Committee is asked whether the response from the applicant is sufficient to address its concerns in regard to the issues discussed in July.
- If so, the Committee is asked, whether it is content to recommend approval of Oligonol® produced by Amino Up Chemical Company. A draft opinion is provided for consideration at **Annex D**.
- If not, the Committee is asked to indicate what further data is required and the feedback that should be given to the applicant.

Secretariat
September 2017

Annexes attached

Annex A – Feedback to the applicant from the July meeting

Annex B – Applicant's response to the further questions raised at the July meeting

Annex C – Summary of concerns raised by the Committee with Oligonol®

Annex D - Draft opinion on Oligonol®

Annex C

Summary of concerns to date on Oligonol® and the information provided by the applicant in response.

Concern raised	Evidence presented	Outcome based on Committee discussion
Specifications The Committee requested further information on the level of catechins in the product and sought characterisation of the unaccounted for polyphenols in Oligonol®.	The applicant provided a further explanation of the catechin levels and how these were calculated. The applicant highlighted the technical challenges of further characterising the remaining polyphenols.	The Committee was content that the potential concern on the catechin content of the product had been considered. The explanation of the difficulties of further characterising the polyphenols was noted. It was considered possible to characterise these further but was not felt to be essential for the risk assessment.
Analytical data Concerns were raised with the presentation of the data. Three batches of the pesticide analyses were requested along with information on whether these were compliant with EU pesticide residue requirements.	The applicant provided translation of the relevant analytical certificates to allow assessment. The applicant provided further batches of Oligonol® and the two starting materials. The applicant commented that they have included pesticide residues as part of their control process for the product.	The Committee accepted the translated certificates and felt these were adequate for assessment. The Committee was reassured by the information provided on pesticide residues at the April 2016 meeting.
Production process The Committee requested further information on the columns used in the purification step and how residues from the column were minimised. In light of concerns on pesticide residues and the potential presence of lychee nut in the starting material, production process diagrams and updated protocol to ensure these controls would be present in commercial operation were requested.	The applicant provided further information on the columns used in the purification step. Information was also provided on a pre-rinse step recommended by the column manufacturer to minimise potential residues. Revised documents outlining the production process used in production were provided as requested. This was supported by a flow diagram of the process.	The Committee was reassured that the potential for residues from the columns used in the production process had been considered and steps taken to mitigate the risk through use of a suitable quality of column and a methanol prewash step. The Committee welcomed the further information to ensure the risks identified would be managed during production.
Toxicology Members asked a number of questions in relation to the toxicology studies. These		

included: • Requests for full reports of some of the studies undertaken on Oligonol including the literature review relating to green tea associated toxicity (liver effects). • Follow up on particular outcomes of some of the studies e.g. the 90 day animal study (Leuschner et al) and whether the changes in grip strength were a concern. • Requesting further information on the human study by Walshe et al • Members requested further reasoning for dismissing the observed effects of increased polyploidy in the chromosome aberration test. • Clarification of the data generated by the Oligonol like material and its role in supporting the application.	The applicant provided the full text of the further studies and literature review requested. Clarification was given on the queries on individual toxicological studies including the NOAEL selection. On the Leuschner study further information was provided on why the applicant considered the statistical analysis was appropriate and the findings not considered adverse. The applicant explained the Walshe study was intended as supporting information and had not been published. The applicant suggested the Chinese Hamster Lung cell line used for the test is known to have given false positives with similar substances. As the chromosome aberration assay did not detect aberrations at the highest concentrations and no genotoxic activity was seen in an in-vivo mouse micronucleus test, the applicant concluded that genotoxicity is not a concern. It was clarified that the Oligonol like material was very similar to Oligonol® and the studies on this material were intended to support the information on Oligonol® in the dossier.	The Committee accepted the detailed explanations on the individual toxicological studies and therefore that the NOAEL identified could be used in identifying the dose to be used in products entering the EU market. The Committee were content that the statistically significant findings in relation to slight movements and increased activity in the Leuschner study are not of biological relevance. The Committee noted the human study and considered this as part of the wider safety assessment of the product. The applicant's explanation on the genotoxicity assessment was accepted. The Committee noted the differences between Oligonol® and the Oligonol like product and took account of this when considering their assessment of the toxicological package as a whole.
• Clarification was sought on the catechin content of Oligonol and how this related to the NOAEL for this component. This was requested in light of emerging evidence of liver toxicity associated with bolus doses of ECGC in food supplements.	The applicant under took an analysis of the exposure to catechins from the novel ingredient as proposed to be used. This was compared to the levels consumers were exposed to from green tea consumption. The applicant considered that as the exposure from Oligonol was significantly lower and toxicological studies did not suggest liver toxicity this was unlikely to be a safety concern.	Consideration ongoing - see above.

Allergenicity Members requested further details relating to the production of lychee extract, including information relating to whether the extract is prepared from the entire lychee fruit, including the nut component	The applicant has provided a number of responses to explain how lychee nut is excluded during the production of the lychee extract. This has been verified by the supplier and clarified in production documents. To demonstrate that proteins from the lychee nut are not present in Oligonol® further protein analyses have been undertaken to verify the effectiveness of the controls.	The Committee was reassured by the process when the starting material had arrived at the production plant. The Committee noted the production material was extracted with ethanol and considered this would exclude most of the allergenic material which may have been present. Further information was requested to confirm that the lychee nut protein is not found in Oligonol® - Consideration ongoing