**COMMITTEE PAPER FOR DISCUSSION** **ACNFP/126/01**

**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

# TONGKAT ALI ROOT EXTRACT

## Issue

An application has been submitted to the UK Competent Authority for authorisation of Tongkat Ali Root Extract under the Novel Foods Regulation (EC) 258/97. The Committee is asked to advise whether the available data provides an adequate basis for a risk assessment, and if it recommends authorisation of this novel ingredient.

## Background

1. The company Biotropics Malaysia Berhad has submitted an application for the authorisation of the dried, ground root chips of *Eurycoma longifolia,* hereinafter referred to as Tongkat Ali Root Extract (TA) as an ingredient in conventional foods and food supplements
2. Due to internet claims of aphrodisiac properties the Secretariat consulted the MHRA at an early stage regarding its potential medicinal status. The MHRA reviewed the available evidence regarding its physiological effects, but concluded that there was little or no reliable data to substantiate the claims that TA has aphrodisiac properties. On this basis and the lack of medicinal claims they did not consider the product as medicinal.
3. As there was no evidence of TA having a physiological effect and there was little information in the dossier about the reasons for adding TA to foods the application of the criterion that a novel food must not be misleading for consumers was considered. To address this, the Secretariat wrote to the applicant (letter attached as Annex A) asking them to provide further information on the following issues: (1) Why use TA in foods, (2) Intended claims for food products containing TA and (3) Warning labels for children. The response from the applicant (attached as Annex B) is discussed in the relevant sections of the paper below.
4. The UK Competent Authority accepted the application on 17 August 2016. In accordance with Article 6(3) of Regulation (EC) No 258/97, the UK has 3 months to prepare an initial assessment report on the above application. The European Commission will then circulate this initial assessment to the Competent Authorities in the other Member States for comment.
5. The present application for authorisation of the NI was prepared pursuant to Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. The NI has been classified as a complex novel food from a non-GM source (class 2.2). The requirements for a submission of this class are as follows:

| | | |
|---|---|---|
| **I** | **Specification of the NF** | **X** |
| **II** | **Effect of the production process applied to the NF** | **X** |
| **III** | **History of the organism used as the source of the NF** | **X** |
| IV | Effect of the genetic modification on the properties of the host organism | **-** |
| V | Genetic stability of the GMO | **-** |
| VI | Specificity of expression of novel genetic material | **-** |
| VII | Transfer of genetic material from GM microorganisms | **-** |

| | | |
|---|---|---|
| VIII | Ability to survive in and colonise the human gut | **-** |
| **IX** | **Anticipated intake/extent of use of the NF** | **X** |
| **X** | **Information from previous human exposure to the NF or its source** | **X** |
| **XI** | **Nutritional information on the NF** | **X** |
| **XII** | **Microbiological information on the NF** | **X** |
| **XIII** | **Toxicological information on the NF** | **X** |

6. The information presented in the dossier (attached as Annex C) is structured accordingly and where necessary is considered below.
7. The Committee will wish to note that the application dossier has been published on the Agency's website for public consultation. Any comments received will be presented at the next meeting.

**I Specification of the Novel Ingredient (NI)**

8. TA is a standardised water extract obtained from dried, ground root chips of the plant *Eurycoma longifolia*. The resulting product is a fine, light brown powder.
9. The applicant explains in the dossier that the physical and chemical specifications for the product are based on the standardisation parameters outlined in the Malaysian Standard's 'phyto-pharmaceutical aspects of dried water extract from Tongkat Ali roots.' Details of the in-house methods of analysis are available in Appendix A of the dossier.
10. The applicant suggests that the characteristic component of TA is eurycomanone (a quassinoid compound), comprising between 0.8 to 1.5% of the extract. TA can be further characterised by chromatographic methods: HPLC for eurycomanone (Figure I.A.4-2) and MALDI-TOF for peptide components.
11. The applicant presents results of the analysis of 3 non-consecutive batches of TA. The applicant suggests the results indicate that the manufacturing process for TA yields a product that complies with the established physical and chemical specifications. The NI has also been analysed for the heavy metals lead, mercury arsenic and cadmium and these are well within the acceptable safety levels
12. The applicant has also provided proximate analysis data on three batches of the NI (for energy, fat, carbohydrate, protein and total dietary fibre content. The results show the NI contains negligible levels of fat and is comprised mainly of carbohydrates and proteins.

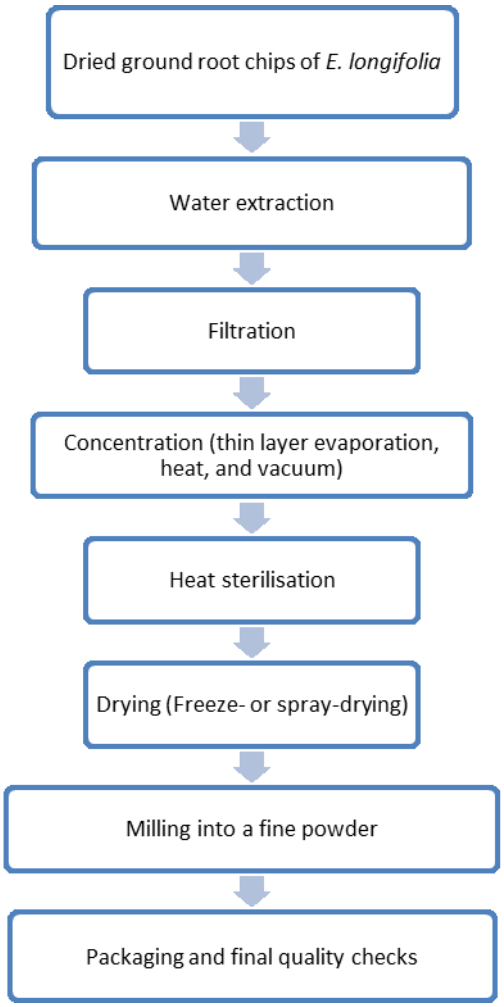
13. The applicant presents the results of real-time and accelerated stability testing conducted on 2 independent batches of TA. The results indicate that TA conforms to the physical and microbial specifications established for the NI for at least the recommended shelf life of 24 months and possibly up to 36 months.

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

14. Dried root chips of *E. longifolia* meeting raw material specifications (for identity, colour, odour, flavour, and free from extraneous material) serve as the source material. Purified water is the solvent used for extraction and no excipients or diluents are used in the preparation of the novel ingredient.

15. TA is prepared using traditional drying, water extraction and grinding methods that are typical of the food industry. The manufacturing process is conducted according to Good Manufacturing Practice (GMP) and is compliant with ISO 22000:2005 and Hazard Analysis and Critical Control Points (HACCP) principles.

**Figure II.A.2-1: Flowchart schematic of the manufacturing process of Tongkat Ali Root Extract**



**Identification of Potential Toxicological and Nutritional Hazards Arising from the Production Process**

16. The applicant does not anticipate that any toxicological, nutritional, or microbiological hazards will arise from the production process. The raw material must meet the specifications set and is checked for microbiological quality before its use as the source material for the ingredient. No organic solvents are used in the production process and the results of regular analyses for heavy metal and microbiological parameters provide reassurance for the absence of deleterious compounds originating from the production process.

**Presence of Micro-organisms of Adverse Health Significance**

17. The applicant highlights three stages in the manufacturing process where microbiological contamination is minimised. (1) The raw material must meet microbiological standards prior to its use. (2) After the extraction and filtration process, the concentrate is subject to heat sterilisation. (3) Microbiological specifications have been established to ensure the absence of deleterious amounts of total bacteria, yeast and mould, salmonella, *Escherichia coli, Staphylococcus aureus* and bile-tolerant gram-negative bacteria. The results of batch analyses and stability testing presented by the applicant in their view demonstrate the absence of such microbiological contaminants.

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

18. Biotropics' TA ingredient is produced from the dried roots of *Eurycoma longifolia* a flowering shrub of the family Simaroubaceae, native to Indonesia, Malaysia and other South East Asian countries. The plant is a medium-sized slender shrub that is verified and authenticated with accompanying specimen vouchers from the Universiti Putra Malaysia.

19. Several publications describing the history of the consumption of *Eurycoma longifolia* as a herbal remedy in South East Asia are available. Consumption of *E. longifolia* is prevalent in South-East Asian countries including Malaysia, Indonesia, and Vietnam, with most of the parts of the plant having a history of consumption. In particular, an extract of the root has been used by indigenous men and women.

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

20. Table IX.A-1 (reproduced below) provides a summary of the proposed food uses and use levels for TA in the EU. The applicant has indicated that the novel ingredient will be presented in a form which is similar to many botanical ingredients, such as ginseng which is used in tonic-type and food supplements in the EU. They have suggested that while there are internet claims for products containing TA as an aphrodisiac the applicant only intends to make a claim of general well-being not of aphrodisiac properties.

21. The applicant states that all products containing TA will be labelled as intended for adult males and females and not for children under the age of 18, pregnant, or lactating women. All products containing TA will be labelled as intended for adults and not for children under the age of 18.

| Table IX.A-1 Summary of the Individual Proposed Food Uses and Use Levels for Tongkat Ali Root Extract in the European Union | | | | | |
|---|---|---|---|---|---|
| **FCS L2[a]** | **Food Category** | **Proposed Food-Uses** | **Serving Size[b] (g or mL)** | **Use Level (mg/serving)** | **Use Level (mg/100g)** |
| A.01.06 | Breakfast cereals | Cereal bars | 40 | 50 to 75 | 125 to 187.5 |
| A.10.03 | Chocolate (Cocoa) products | Chocolate bars | 40 | 50 to 75 | 125 to 187.5 |
| A.10.04 | Confectionery (non-chocolate) | Candies (for adults)[c] | 40 | 50 to 75 | 125 to 187.5 |
| A.13.02 | Tea (Infusion) | Tea-based drinks | 190 | 50 to 75 | 26.3 to 39.5 |
| A.13.03 | Coffee (beverage) | Coffee-based drinks | 190 | 50 to 75 | 26.3 to 39.5 |
| A.18 | Products for special nutritional use (unspecified) | Nutrition bars | 40 | 50 to 75 | 125 to 187.5 |
| A.18.03 | Food for sports people (labelled as such) | Energy bars | 40 | 50 to 75 | 125 to 187.5 |
| A.18.03 | Food for sports people (labelled as such) | Sports and energy drinks | 500 | 50 to 75 | 10 to 15 |

a Based on the Commission Regulation Food Classification System, Level 2.

b Serving sizes are based on the UK Food Portion Sizes Handbook (FSA, 2002).

c Tongkat Ali Root Extract is proposed for use in candies conspicuously labelled for adults; however, for the purposes of generating conservative estimates of intakes, it is noted that all candies were selected in the assessment below.

## IX.B Anticipated Daily Intakes of TA in the EU

22. To assess the potential consumption of TA in the EU, estimates were generated based on food consumption data from the European Food Safety Authority (EFSA) Comprehensive Database utilising the EFSA Food Additive Intake Model (FAIM) Tool. It was acknowledged that this would produce a conservative overestimate of exposure due to the use of very broad food categories and is not considered further here.

23. A further and more detailed intake assessment was conducted by the applicant using the most recent data from the United Kingdom (UK) National Diet and Nutrition Survey (NDNS) rolling programme 2008-2012 (Department of Health, 2014; UKDA, 2014). Calculations for the mean and high-level (95th percentile) all-person and all-user intakes, and percentage consuming were performed for each of the individual proposed food-uses for TA. Similar calculations were used to determine the estimated total intake of TA from all proposed food-uses combined.

24. A full description of the methodology used for the intake assessments and a detailed discussion of the results are provided in Appendix F of the dossier.

### IX.B.2 Intake Estimate Based on the UK National Diet and Nutrition Survey (UK NDNS)

25. Adults represent the target population for food products containing Tongkat Ali Root Extract; however, intake data for teenagers (aged 11 to 18 years) are

included below as a worst-case scenario in which this population group may incidentally consume foods containing this ingredient. Greater than 41.5% of all population groups consisted of users of those food products in which TA is currently proposed for use.

**Table IX.B.2-1 Summary of the Estimated Daily Intake of Tongkat Ali Root Extract from All Proposed Food Categories in the UK by Population Group (NDNS Data, 2008-2012)**

| Population Group | Age Group (Years) | Total n | All-Person Consumption (mg/day) | | All-Users Consumption (mg/day) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | 95th Percentile | % | n | Mean | 95th Percentile |
| Teenagers | 11-18 | 884 | 40.3 | 135.6 | 74.2 | 655 | 54.4 | 150.1 |
| All adults | 19-64 | 1,655 | 31.6 | 128.0 | 56.0 | 918 | 56.4 | 165.9 |
| Female Adults | 19-64 | 945 | 27.4 | 116.6 | 54.6 | 521 | 50.2 | 152.1 |
| Male Adults | 19-64 | 710 | 35.7 | 130.3 | 57.4 | 397 | 62.3 | 187.2 |
| Elderly | ≥65 | 428 | 19.9 | 77.4 | 41.5 | 176 | 47.9 | 161.7 |

Abbreviations: NDNS = National Diet and Nutrition Survey; UK = United Kingdom.

26. In the target population of adults, the mean and 95th percentile intakes among the user population were 0.75 and 2.26 mg/kg body weight/day, respectively. With the worst-case scenario that foods consumed by teenagers would contain TA at the maximum intended use level, the mean and 95th percentile intakes on a body weight basis were the highest in this population group at 0.99 and 3.01 mg/kg body weight/day, respectively. However, the applicant notes that teenagers are not the intended target population and this data is presented for information purposes only and is not intended to model actual exposures.

**Table IX.B.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Tongkat Ali Root Extract from All Proposed Food Categories in the UK by Population Group (NDNS Data, 2008-2012)**

| Population Group | Age Group (Years) | Total n | All-Person Consumption (mg/kg bw/day) | | All-Users Consumption (mg/kg bw/day) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | 95th Percentile | % | n | Mean | 95th Percentile |
| Teenagers | 11-18 | 853 | 0.74 | 2.72 | 74.1 | 631 | 0.99 | 3.01 |
| All adults | 19-64 | 1,545 | 0.43 | 1.71 | 57.1 | 873 | 0.75 | 2.26 |
| Female Adults | 19-64 | 878 | 0.41 | 1.67 | 55.7 | 493 | 0.73 | 2.34 |
| Male Adults | 19-64 | 667 | 0.45 | 1.76 | 58.5 | 380 | 0.77 | 2.21 |
| Elderly | ≥65 | 393 | 0.28 | 1.21 | 42.4 | 165 | 0.65 | 2.09 |

Abbreviations: bw = body weight; NDNS = National Diet and Nutrition Survey; UK = United Kingdom.

### IX.B.3 Food Supplements

27. TA is also intended to be an ingredient in food supplements marketed to adults. The proposed use level of TA in supplements is up to 200 mg/day, equivalent to approximately 2.86 mg/kg body weight/day for a 70 kg adult. Food supplements

containing TA would be consumed as an alternative source to that in conventional foods and the applicant states that supplements will be conspicuously labelled to indicate this fact, therefore they do not expect individuals to consume both supplements and foods containing TA.

### IX.B.4 Conclusions Regarding Intakes of TA

28. The more refined intake assessment was conducted using data from the UK NDNS. The all-user mean and 95$^{th}$ percentile calculations for the target population (adults) resulted in intake estimates of 56.4 and 165.9 mg/day, respectively (equivalent to 0.75 and 2.26 mg/kg body weight/day). The results of the assessment indicate that the 95$^{th}$ percentile TA intakes for the non-target teenager population group was up to 150.1 mg/day (equivalent to 3.01 mg/kg body weight/day on a per kilogram body weight basis).
29. The applicant has not attempted to relate the intakes data to the no effect levels estimated from the various toxicological studies carried out with TA.

## X. Information from previous human exposure to the novel ingredient

30. Although there is only limited evidence of consumption of the ingredient in the Community (dating back approximately 15 years), Biotropics Malaysia Berhad's Tongkat Ali Root Extract has been distributed in various international markets including Canada, USA, Japan, and Russia.
31. The applicant states that, to date, they are not aware of any reports of adverse effects following consumption of Biotropics Malaysia Berhad's TA ingredient. The total global circulated volume for TA in 2014 was approximately 3,015.66 kg (equivalent to 15.0 million servings of 200 mg or 60.31 million servings of 50 mg).

## XI Nutritional information on the novel food

32. The applicant indicates that TA is not nutritionally equivalent to other foods and is not intended to replace other foods or food ingredients currently on the market in the EU. Based on the proximate analysis data and composition of the NI as presented in the dossier, TA is not anticipated to impact on the quality of the diet nor play any role in the diet of individuals consuming the NI. TA is also not anticipated to modulate the nutritional properties of the foods to which it is to be added.

## XII. Microbiological information on the novel food

33. The microbiological specifications and batch analyses are presented by the applicant. They consider the results confirm that the production process does not introduce a potential for microbiological contamination and the final TA ingredient is free from microbial contaminants, even after 36 months of storage.

## XIII. Toxicological information on the novel food

34. The toxicological data and studies on TA presented in the dossier are summarised below.

## XIII.A Absorption, Distribution, Metabolism, and Elimination (ADME)

35. The bioavailability and pharmacokinetics of the characteristic component of TA, eurycomanone, was evaluated in rats using a validated high-performance liquid chromatography (HPLC) assay (Low *et al.*, 2005). A purified preparation of eurycomanone was prepared and singly administered to male Sprague-Dawley rats (5/group) by intravenous injection (in saline) at a dose of 1.96 mg/kg body weight.

36. Blood samples were obtained from the rats at baseline (pre-dose), and at various intervals up to 8 hours post-dose. Following a two-week washout period, the same rats were administered the eurycomanone preparation by feeding needle at 9.8 mg/kg body weight and blood samples were obtained at various time points post-administration. The plasma was analysed using a validated HPLC method.

37. In the study Eurycomanone exhibited low bioavailability following oral administration which is anticipated to be due to pre-systemic metabolism or the first-pass effect prior to reaching the systemic circulation. Eurycomanone also exhibits a short half-life in the systemic circulation as evidenced by the half-life of approximately 1 hour following intravenous administration.

## XIII.B Toxicological Studies

### XIII.B.1 Acute Toxicity Studies

38. The acute oral toxicity of TA was evaluated in Wistar rats according to OECD Test Guideline 420 (Choudhary *et al.*, 2012). The oral median lethal dose ($LD_{50}$) of TA was determined to be greater than 2,000 mg/kg body weight, which suggests that TA is not an acute oral toxicant.

### XIII.B.2 Repeated Dose Toxicity Studies

XIII.B.2.I/II 28 and 90 Day Repeat Dose Oral Toxicity Studies

39. A sub-acute 28 day repeat dose oral toxicity study was conducted with TA in accordance with OECD Guideline 407 (Choudhary *et al.*, 2012) and a 90 day sub-chronic repeat dose oral toxicity study was conducted with TA in accordance with OECD Guideline 408 (Choudhary *et al.*, 2012). No adverse findings related to the test substance were found in either study.

40. Based on the results of these studies, a no-observed-adverse-effect level (NOAEL) of 1,000 mg/kg body weight/day, the highest dose tested, was established for both male and female rats.

XIII.B.2.3 12-Month Repeat Dose Oral Toxicity Study

41. A chronic repeat dose oral toxicity study was conducted with TA in accordance with OECD Guideline 452 (Gohel, 2015 [unpublished]). Wistar rats (25/sex/group) were administered TA at doses of 0 (control), 250, 500, or 1,000 mg/kg body weight/day for 12 months by oral gavage.

42. No mortality or morbidity was observed in females, and no treatment related mortality or morbidity was observed in males. No toxicological relevant or treatment

related clinical signs of toxicity, ophthalmological abnormalities, or clinical and neuro-behavioural observations were reported. Minor changes in haematological, clinical chemistry, urinalysis, and organ weight parameters were observed.

43. None of these changes were associated with histological lesions and the authors of the study are of the opinion that these effects are adaptive responses to the test substance and are not adverse reactions

44. Based on the results of this study, the NOAEL for TA was confirmed as 1,000 mg/kg body weight/day, the highest dose tested, for male and females.

### XIII.B.3 Developmental and Reproductive Toxicity

45. The reproductive and developmental toxicity of TA was evaluated in a reproductive and developmental toxicity screening study conducted in accordance with OECD Testing methods 421 (Takawale, 2011 [BSL Bioservice Study No. 103437]).

46. Clinical signs noted in rats receiving 500 and 1,000 mg/kg body weight/day included the following: piloerection, aggressive behaviour, moving the bedding, salivation, and nasal discharge (statistical significance not reported). None of the clinical signs observed occurred consistently or on consecutive days, but were sporadic and only observed on a limited number of occasions and no adverse effects on overall health were observed in the study. These clinical signs were, therefore, not considered to be of toxicological significance by the authors of the study.

47. Significant increases and decreases in food consumption were observed in males and females receiving 250, 500 and 1,000 mg/kg body weight/day at different times during the experiment, which were correlated with the changes in body weight during these periods. Due to a lack of consistent effect and no dose related relationship, no toxicological relevance was attributed to these findings by the study authors. No remarkable findings were noted upon necropsy and gross and/or histopathological examination of the males, females, and pups in the study.

48. Based on the results of the study, the NOAEL for reproductive and developmental toxicity of TA was determined to be 1,000 mg/kg body weight/day, the highest dose tested.

#### XIII.B.3.2: Effects on the Male Reproductive System

49. The effect of TA on sperm was evaluated in Sprague-Dawley rats. Male rats (14/group) were administered TA at doses of 0 (control), 200, or 800 mg/kg body weight/day for 14 days by oral gavage (Solomon *et al.*, 2014). Animals were monitored for overt signs of toxicity and body weights were recorded during the treatment period. At the end of the treatment period samples were obtained to determine a number of parameters associated with the male reproductive system.

50. No overt signs of toxicity were observed during the treatment period. An increase in serum testosterone was observed in rats provided 800 mg/kg body weight/day (+30.2%; from 0.86 ng/mL in controls to 1.12 ng/mL in high-dose rats); however, the increase was not statistically significant following ANOVA trend analysis. Values remained within high normal ranges for this strain of rats.

51. No significant differences in the absolute organ weights of the male reproductive organs were observed in rats administered TA compared to the controls. With respect to semen parameters, there were significant increases in sperm concentration, motility and vitality, but no significant changes in mitochondrial membrane potential (MMP) or acrosomal status; which the study authors considered was suggestive of no deleterious effect on sperm function.

52. Statistically significant decreases in body weight and omentum fat observed in animals receiving 800 mg/kg body weight/day were attributed to be a possible secondary effect to the increase in serum testosterone concentration. Overall, the study authors conclude that there were no adverse effects noted following administration of the TA at doses of up to 800 mg/kg body weight/day (equivalent to 56 g/day for a 70 kg individual).

### XIII.B.4 Mutagenicity and Genotoxicity

XIII.B.4.1 In vitro Assessments of Genotoxicity

53. A bacterial reverse mutation assay conducted in accordance with OECD Testing Guideline 471 was undertaken to evaluate the genotoxic potential of TA (Ming *et al.*, 2014). In this experiment, *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were exposed to TA using the standard plate incorporation method at concentrations of 0.005, 0.01, 0.03, 0.05, 0.3, 1.0, 3.0, or 5.0 mg/plate in the presence and absence of metabolic activation (S9 mix).

54. No significant differences in the numbers of revertant colonies were observed at any concentration compared to the negative controls. Based on the results, it was concluded that Tongkat Ali Root Extract was not mutagenic under the conditions of the assay.

55. The genotoxic potential of TA was further evaluated in an *in vitro* mammalian cell gene mutation test in L5178Y mouse lymphoma cells (Verbaan, 2013 [unpublished]). The study was conducted in accordance with OECD Testing Guideline 476. L5178Y mouse lymphoma cells were exposed to TA at concentrations of 800, 1,000, or 3,000 µg/mL in the presence or absence of metabolic activation (S9 mix). It was noted that precipitation was observed at concentrations of 1,250 µg/mL and above.

56. In the absence of metabolic activation (S9), TA induced a 2.6- to 4.5-fold statistically significant increase in mutation frequency at a concentration of 3,000 µg/mL. However, no statistically significant increases in mutation frequency were observed at 800 and 1,000 µg/mL. Similarly, no increases in mutation frequency were observed in the presence of metabolic activation. Taken together, the increase in mutation frequency was noted to occur only at severely toxic and precipitating dose levels, and thus, the increases were considered “not biologically relevant” by the study authors. It is well-recognised that high and precipitating testing concentrations may produce false positive responses (EFSA, 2012) and therefore, TA is not considered to be mutagenic under the conditions of the assay. However, a follow-up *in vivo* assessment of genotoxicity was undertaken as per EFSA Guidelines (see following section).

XIII.B.4.2 In vivo Assessment of Genotoxicity

57. A mouse erythrocyte micronucleus assay was conducted with TA in accordance with OECD Testing Guideline 474 (Ming *et al.*, 2014). NMRI mice (5/sex/group) were administered a single dose of 0 (negative control), 100, 250, or 500 mg/kg body weight by intraperitoneal injection. An additional group received 40 mg/kg body weight of cyclophosphamide as a positive control. Animals were sacrificed 24 hours post-administration and erythrocytes collected for analysis.

58. No significant differences in the ratios of polychromatic erythrocytes to normochromatic erythrocytes were observed between groups. No increases in the frequency of micronucleated polychromatic erythrocytes were observed compared to the negative control, whereas the positive control produced the expected response. Therefore, the results of the study suggest that TA is not genotoxic.

**XIII.B.5 Carcinogenicity**

59. The applicant states that studies evaluating the carcinogenic potential of TA are not available.

**XIII.C Human Studies**

60. The effects of oral administration of TA on supporting men's health have been evaluated in several studies; The applicant provided more detailed information on one the safety of Biotropics' TA (meeting the standardisation criteria described in this dossier).

61. In a randomised, double-blind, placebo-controlled, parallel designed study conducted in accordance with Good Clinical Practice, 109 healthy men or those with stable chronic medical illnesses[1] (aged 30 to 55 years) were provided with capsules containing 75 mg of TA (31.75% total protein, 41.08% glycosaponin, and 1.604% eurycomanone) or placebo, to be taken 4 times a day (for a total dose of 300 mg/day or placebo) for 12 weeks (Ismail *et al.*, 2012). Safety parameters included a quality of life questionnaire, adverse event monitoring, physical examination, recording of clinical and laboratory measurements, as well as efficacy parameters related to sexual function and physical fitness were recorded.

62. At the end of the study, no adverse effects on quality of life parameters compared to placebo were observed. There were statistically significant changes in some laboratory parameters, but these were observed in both the TA and the placebo groups and thus were not deemed to be clinically significant. A total of 32 adverse events in 26 subjects were reported; all of which were deemed "unlikely" to be related to the test substance (except one, a headache). In conclusion, the study authors considered that the daily dose of 300 mg TA for 3 months was well-tolerated and safe compared to placebo.

63. Details of a comparative study of a number of physically active older men and women are given, but as this study was not placebo-controlled the effect of TA itself is difficult to determine and it is not considered further here.

---

[1] These included subjects with controlled diabetes mellitus and/or hypertension on mono-therapy or low dose combination therapy.

### XIII.C.2: Other Studies

64. In addition to the safety study summarised above, TA has been evaluated in a number of other published studies primarily examining efficacy endpoints. These studies do not measure safety parameters, but the applicant claims they lend further support to the conclusion that no adverse effects are anticipated from the consumption of TA at doses up to 300 mg/day for up to 12 weeks.

65. No studies appear to be available for what the applicant refers to as non-target groups (teenagers, the elderly and pregnant women).

### XIII.D Allergenicity

66. Studies specifically examining the allergenic potential of this ingredient have not been conducted; however, the applicant suggests the results of 3-month studies in humans do not suggest a potential for the development of sensitivities to this ingredient.

### Committee action sought

67. The Committee is asked to consider whether the available data are adequate to determine whether the NI complies with the criteria for acceptance under the novel food regulation, namely:

    - It does not present a danger to the consumer
    - It does not mislead the consumer
    - It is not nutritionally disadvantageous compared with foods which it might replace.

68. If so, the Committee is asked whether it is content to recommend approval for the NI to be used in the proposed food products.

69. If not, the Committee is invited to identify what further data should be provided.

**Secretariat**
**September 2016**

### Annexes

Annex A: Letter to the applicant on purpose of the novel ingredient

Annex B: Response from the applicant (5 attachments available on request)

Annex C: Application dossier (Appendices A – F)

Appendix A: Methods of Analysis
Appendix B: Certificates of Analysis
Appendix C: Contaminant Analysis
Appendix D: Results of Stability Testing
Appendix E: Specimen Vouchers for *Eurycoma longifolia*
Appendix F: Detailed Intakes Report for Tongkat Ali Root Extract in the EU