COMMITTEE PAPER FOR DISCUSSION **ACNFP/127/7**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

TONGKAT ALI ROOT EXTRACT: RESPONSE FROM THE APPLICANT

Issue

At the September 2016 meeting the Committee reviewed the dossier submitted in support of the application for authorisation of Tongkat Ali Root Extract under the Novel Foods Regulation (EC) 258/97. The Committee requested further information from the applicant and the response from the applicant has now been received. The Committee is asked whether the available data now provides an adequate basis for a risk assessment, and if it recommends authorisation of this novel ingredient.

Background

1. The comments from the Committee were conveyed to the applicant in the letter attached at Annex A. Biotropics Malaysia's response is attached to this paper as Annex B and includes a number of annexes some of which contain confidential information.
2. At the September meeting Members requested further information in a number of areas
    a) Specifications
    b) Allergenicity
    c) Toxicology
    d) Target population for the novel ingredient and intakes
    e) Potential for consumers to be misled by the novel food
    f) Sustainability of production and source of the novel food
3. A summary of each comment/request from the Committee and the response from the applicant are given below.

Specifications

4. The Committee commented that the data presented for the compositional analysis was not accurate or robust enough to allow the NI to be fully characterised. The single peak HPLC traces shown were not properly labelled and interpretation of the data was poor. These points need to be addressed.

5. The applicant has responded by including data from a previous study using high performance liquid chromatography (HPLC) followed by analysis using Mass Spectrometry, UV diode array detection and evaporative light scattering detection. However, the data is all qualitative and no quantitative data has been generated. This is summarised in the response and the full study included as annex 1 (see Annex B1 to this paper).
6. The Committee noted that the compositional analysis of three batches of the NI should be repeated using appropriate robust analytical methods. The batches should be representative of the product to be placed on the EU market.
7. In their response the applicant has presented no new data but has presented a re-analysis of one of the batches included in Table I.C.2-1 (proximate analysis) which brings the protein content closer to the other two batches. The applicant has also included the certificates of analysis for the proximate analyses as annex 2 to the response (see annex B2 to this paper).
8. The Committee was concerned that the application contained no substantial data on the glycosaponin component, which makes up 40-60% of the material in the NI. The Committee requested that at least an HLPC analysis of the glycosaponins present in the NI be carried out.
9. The applicant states that there are currently, no suitable glycosaponin standards for the specific glycosaponin component in the Tongkat Ali extract to perform accurate HPLC analysis. They then state that such information will be presented as soon it is available. The Secretariat continues to liaise with the applicant on this point.

Allergenicity

10. In the Committee's view the two different protein detection methods used has rendered the allergy risk difficult to determine, particularly given the high level of protein in the novel ingredient. More appropriate methods of protein analysis should be used and the possibility that the NI may be allergenic should be given proper consideration.
11. The applicant has not directly addressed the criticism of the methods used for the protein analysis and has provided sales figures for Tongkat Ali from 2009 to 2015 while stating that there have been no reports of side effects or allergy risk during that time.

Toxicology

12. The Committee had commented previously that the data presented in the toxicological studies shows that bioavailability of the NI is low and there is evidence of liver enlargement and also effects on testosterone levels, points that were not addressed in the dossier. It was also considered that the 12 month study was inadequate and a longer study should possibly have been undertaken.

13. In response the applicant has provided a summary of the 12-month study (Gohel, 2015) which was previously provided to members for the September 2016 meeting. A complete copy of the study report (including all appendices) has now been provided on CD and is available to members on request.

14. The applicant has provided counter-argument to the points raised by the Committee regarding liver enlargement and testosterone levels. They have also defended the adequacy, applicability and quality of the 12 month study by Gohel (2015).

15. The Committee questioned why the NOAEL used in the dossier was not the lowest figure obtained. It was also suggested that a more robust stability test of the NI should be undertaken.

16. The applicant argues that the chosen NOAEL is justified by the majority of studies carried out. Clarification is needed as to whether stability testing refers to the batches used experimentally or those used to establish the stability of the product itself.

Target consumers for the product and intakes

17. The committee raised concerns that the NI was being targeted at women as well as men in the application whereas in Malaysia, where it is already consumed, it is marketed primarily for men. The product is also claimed to be pharmacologically active and the Committee was concerned that the dossier made no reference to this issue. The Committee requested further information on the physiological effects of consumption of the NI.

18. The applicant's response has not addressed the question regarding the targeting of women. They do refer to the MHRA review of the available evidence in the published literature which concluded there was little or no credible data that indicated a physiological effect of TA on testosterone levels.

Potential for consumers to be misled by the novel food

19. The Committee raised concerns that there was the potential for consumers to be misled in relation to claims etc. which are made on the internet for the benefits of the novel ingredient. This impression was reinforced by inconsistencies between how the dossier presents the product verses how it is presented on the applicant's website.

20. The applicant's response has referred to the previous arguments presented regarding internet claims and expanded on these in the response. They have also removed the article containing the text referred to by the ACNFP from their website to "demonstrate their commitment to the application."

21. The Committee had expressed concern that the range of foods the applicant is proposing to include the novel ingredient in was very broad and some of these (e.g. confectionary) were very likely to be consumed by under age groups.

22. Due to the Committee's concerns regarding the potential consumption of foods containing Tongkat Ali by under age groups the applicant has removed the proposed use categories for the NI in chocolate bars and candy. All other uses and use levels remain as in the original application. An updated food use table is provided in the response and the exposure assessments have been recalculated.

Sustainability of production and source of the novel food

23. The Committee noted that Tongkat Ali was currently obtained from the wild plant which may not be sustainable if production of the NI increases. It was concerned that if domestic cultivars were used to meet demand the specification of the NI might be compromised. The wild plant reproduces by sexual reproduction giving a range of plant genotypes. If the production is to be properly regulated full information on the characteristics of the cultivar(s) used and how they vary will be required and data obtained to ascertain that the information in the application was valid for any domestic cultivar used in the future production of the NI.

24. The applicant states in their response that it currently uses material from wild plants to produce the NI, but has provided information on a number of programmes and initiatives within Malaysia at both national and local level designed to increase and render the supply of raw material sustainable. The applicant has also incorporated a sustainability program as part of its supply chain to ensure seedling replenishment during harvesting. The applicant refers to a study that differentiates between cultivars from different geographical locations using PCR-RAPD analysis.

25. The Committee considered that, given the development of the production of the novel food, whole genome sequencing of the plant would provide invaluable information for comparative analysis and/or characterisation of the material used to produce the NI.

26. The applicant claims to be keeping the specification of the NI consistent by comparison with the Malaysian Monograph (on the plant) and also the Malaysian Standard (MS2409:2011) for the preparation of Tongkat Ali extract via standardisation of the stipulated four marker compounds.

27. The applicant also refers to a published study on a partial chloroplast sequence from the leaves of Eurycoma longifolia which is attached to the response as annex 3 (annex A3 to this paper). The applicant has also found that molecular studies of the plant available in the literature have used plants from Asian countries other than Malaysia.

Committee action sought

28. The Committee is asked to consider whether the data now available 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.

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

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

Secretariat
February 2017

Annexes

Annex A: Letter to the Applicant Tongkat Ali 14Sept16 Letter to Applicant ACNFP Comments

Annex B: Tongkat Ali Root Extract EU Novel Food Response to ACNFP Initial Questions

Annex B1: Additional Characterisation Report

Annex B2: Certificates of Analysis (Proximate Analysis)

Annex B3: FRIM *Eurycoma longifolia* isolate 1301 tRNA Leu (trnL) gene