COMMITTEE PAPER FOR DISCUSSION **ACNFP/113/3**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

(*R*)-3-HYDROXYBUTYL (*R*)-3-HYDROXYBUTYRATE

Issue

The Committee is invited to consider whether the response provided by the applicant addresses the concerns raised at the September meeting, and whether this provides sufficient information for the Committee to conclude its evaluation of this novel food application.

Background

1. This application, submitted to the UK by TdeltaS Limited (University of Oxford), is for food supplements containing (*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate, referred to as D-β-hydroxybutyrate ester, which is a novel food in the EU.
2. When the Committee considered this application at its meeting in September Members highlighted the following issues:
    a) The absence of mutagenicity and genotoxicity tests.
    b) Some changes in clinical chemistry parameters in the 28 day rat study were apparently treatment-related and the Committee queried whether these findings should have resulted in a follow up 90 day study to confirm their significance.
    c) Whether circulating levels of ketone bodies (including hydroxybutyrate) seen under certain physiological conditions were a relevant comparator when considering the safety of D-β-hydroxybutyrate ester as a food supplement.
    d) No investigation of the long term effects of consuming relatively large amounts of D-β-hydroxybutyrate ester as a supplement and whether this may have a deleterious effect on an athlete's digestive system.
    e) The human studies do not investigate whether D-β-hydroxybutyrate ester supplementation can lead to adverse gastrointestinal effects in athletes, who often have a highly specific and controlled diet, and whether its consumption could interfere with other nutrients.
    f) The perceived pronounced short term effect of D-β-hydroxybutyrate ester supplements may tempt consumers to exceed the stated dose.

3. The Secretariat contacted the applicant regarding concerns (letter attached at **Appendix 1**). The applicant's response is attached at **Appendix 2** and is summarised below.

   a) The applicant is of the view that there is no need to carry out mutagenicity and genotoxicity studies on D-β-hydroxybutyrate ester because the starting materials are highly purified and have previously been evaluated by the European Food Safety Authority and neither was regarded to be mutagenic. D-β-hydroxybutyrate ester will also be completely hydrolysed in the gut and there are no structural alerts for ketone esters to suggest that the esterification of D-β-hydroxybutyrate would give rise to a mutagen.

   b) The applicant does not regard any of the clinical chemistry parameters that are statistically different to the controls to be biologically or clinically significant, noting that only one (lactate dehydrogenase, LDH) is outside the normal laboratory range for the age and strain of rat studied. For LDL, the applicant notes that it is not routinely assessed in preclinical studies as it lacks hepatic specificity and other enzymes that are used as markers for hepatocellular injury were present at normal levels. The applicant suggests that the raised level seen may be an artefact of the study design, as LDL levels are known to be effected by 'extrahepatic' factors, such as handling and blood collection, and the level of D-β-hydroxybutyrate ester present in the animal diets is high. The applicant also highlights extensive studies carried out on 1,3-butanediol, including a 2 year rat feeding study, as further evidence that it is unnecessary to commission a 90 day study for D-β-hydroxybutyrate ester.

   c) The applicant highlights a the absence of adverse effects during ketosis, Atkins diets and the low carbohydrate, ketogenic, diet of the Inuit as evidence that raising the level of D-β-hydroxybutyrate will not have any acute or long term effects.

   d,e) The applicant has stressed that, in order to obtain any meaningful effect, consumption of as D-β-hydroxybutyrate ester should only be consumed by high performance athletes during times of extremely strenuous exercise (e.g rowing for 30min to exhaustion) and, as D-β-hydroxybutyrate ester has no effect building body mass, consumption would be restricted to times of intense muscular activity during competition rather than as an aid to training (Annex 2 Fig. 2). The applicant suggests that these periods could not coincide with meal times and there is therefore no potential for as D-β-hydroxybutyrate ester to interfere with the absorption of nutrients. The applicant also points to a study carried out on athletes consuming a sugar rich energy drink (with and without as D-β-hydroxybutyrate ester) as evidence that it did not interfere with glucose absorption.

e,f) The applicant accepts that the cost and taste of as D-β-hydroxybutyrate ester are not an inevitable barrier to consumption of excessive quantities. However the applicant reiterates the lack of benefit, except to a small group of high performance athletes who are undergoing intense muscular activity, as sufficient reassurance that consumption will not exceed the stated dose. Following the type of extreme exertion where the novel ingredient can provide a significant energy boost, individuals would be exhausted and unable to exercise further for a prolonged period and would therefore not need to consume additional supplements containing the novel ingredient. The applicant also provides data to indicate that a beneficial effect is only seen during periods of the most extreme muscular activity noting that an individual cycling for 60 min at 75% of maximum power would not benefit from supplementation, whereas rowing for 30min to exhaustion would (cf figs 3 and 5 of Annex 2).

Committee Action Sought

9. The Committee is asked whether the response from the applicant is sufficient to complete the risk assessment.

10. If not, the Committee is asked to indicate what additional information would be required.

Secretariat
November 2013

Appendices attached

Appendix 1 Letter to applicant setting out Committee concerns

Appendix 2 Response from applicant