

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Conjugated Linoleic Acid (CLA)-Rich Oil

**Issue**

The Spanish Competent Authority has prepared an initial opinion on an application for the authorisation of CLA-rich oil derived from safflower oil as a novel food ingredient (NI) under the Novel Food Regulation (EC) No. 258/97. The Committee is asked whether it agrees with the conclusions of the Spanish CA and whether it has any further comments or objections to make on the application. The Committee's advice will form the basis for the UK's formal response.

**Introduction**

1. On 31 July 2008, the European Commission forwarded the Spanish Competent Authority's (CA) initial assessment report on an application made by Cognis Deutschland GmbH under Article 4(1) of Regulation (EC) 258/97, for the authorisation of Tonalin®TG-80, an oil that is rich in conjugated linoleic acid triglycerides, as a novel food ingredient (NI). The Spanish report identifies a number of issues arising from the dossier and concludes that the application requires further assessment. Under the time scales set out in the regulation, the UK and other Member States have until 29 September 2008 to provide comments and/or reasoned objections to the initial opinion.
2. The Initial Assessment Report is attached as **Annex 1** (restricted). The dossier provided by the applicant is attached as **Annex 2** (restricted).

**Background**

3. This application from Cognis Deutschland is for the placing on the market of CLA-rich oil derived from safflower oil. The NI has been previously consumed in the EU as a food supplement in weight management products since 1996, however its use in food products is considered novel and requires a pre-market safety assessment.

4. The ACNFP has recently considered an application for a similar CLA-rich oil from a different producer, Lipid Nutrition BV (paper ACNFP/89/2). On that occasion the Committee considered a positive initial assessment from the Irish authorities and raised a number of concerns that formed the basis for the UK's reasoned objections. The Committee's concerns were as follows:
- Intake: Lipid Nutrition intended that consumers should obtain a daily dose of 3.0 g of CLA by consuming 2 servings of any of a wide range of foods. The Committee was concerned that consumers could habitually consume more than this amount, and that the food products containing the ingredient would be consumed significantly by children and teenagers. Consuming the recommended amount of CLA over one year could potentially result in the additional intake of 1.8 kg of fat, which may require further consideration in light of the increased risk of obesity in the population.
  - Stability/oxidative Stress: An additional daily intake of 3 to 6 g CLA would have a significant effect on the population intake of n-6 polyunsaturated fatty acids and appears to contradict existing UK advice. The applicant did not consider the potential adverse effect of oxidative stress due to CLA e.g. peroxidation of unsaturated lipids in the artery wall. The Committee was also concerned about the potential for oxidation in the products itself during normal use, particularly in dry products with a longer shelf life such as powdered drinks.
  - Animal studies: The Committee did not agree with the applicant's suggestion that adverse outcomes of animal studies could be dismissed because fat deposition differs in humans and animals, noting that there are numerous mouse and rat models of human obesity where very high levels of fat deposition are observed.
5. In accordance with Commission Regulation 258/97 and Commission Recommendation 97/518/EC, which sets out the guidelines for novel food applications, the applicant considers that the NI falls within Class 1: Pure chemicals of simple mixtures from non-GM sources. The requirements for a submission for this class are as follows:

<b>I</b>	<b>Specification of the NF</b>	<b>X</b>
<b>II</b>	<b>Effect of the production process applied to the NF</b>	<b>X</b>
<b>III</b>	<b>History of the organism used as the source of the NF</b>	<b>X</b>
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	-
<b>IX</b>	<b>Anticipated intake/extent of use of the NF</b>	<b>X</b>
<b>X</b>	<b>Information from previous human exposure to the NF or its source</b>	<b>X</b>
<b>XI</b>	<b>Nutritional information on the NF</b>	<b>X</b>
<b>XII</b>	<b>Microbiological information on the NF</b>	<b>X</b>
<b>XIII</b>	<b>Toxicological information on the NF</b>	<b>X</b>

6. The dossier and the assessment report are structured accordingly and the key issues for consideration are presented below under these headings.

### **I. Specification of the novel food**

Annex 2, p.14-18

7. The NI is a modified oil derived from safflower oil (see section II below). A detailed specification is set out in Table 2 (Annex 2, p141). The fatty acid composition of the oil consists of isomers of CLA (minimum 78%) with smaller amounts of oleic acid (10-20%), palmitic acid (up to 4%), stearic acid (up to 4%) and linoleic acid (up to 3%). CLA is predominantly present as a 50:50 mixture of the *c9, t11* and the *t10, c12* isomers. Specifications for the raw materials have been provided along with analytical reports for five individual batches of the NI. These analyses demonstrated that all batches of the NI were within specification.
8. The Spanish CA has commissioned analysis of additional batches provided by the applicant and their results (not shown) indicated that the levels minor CLA isomers exceeded the limits in the specification. They also detected low levels (70-770 ppm) of rapeseed sterols and the applicant has explained that this is due to crossover in the production facility, which also processes phytosterols.

9. The applicant regularly analyses for contaminants such as benzo(a)pyrene, heavy metals, dioxins and aflatoxins, in line with EU legislation on contaminants in food.
10. The applicant provided stability data for the NI when stabilised with 0.1% natural mixed tocopherols. These showed that the NI in bulk form is stable for at least 24 months with only minimal oxidation observed. The applicant noted that the small amount of oxidation observed was within typical ranges seen for other foods containing high amounts of unsaturated fatty acids.
11. The applicant also provided additional information on the stability of the NI in a range of food matrices. These data indicate that when added to products such as orange juice, milk, yoghurt and nutrition bars, the food matrix has no effect on the stability of the NI within usual best before time-frames. The applicant concluded that there was no indication of isomerisation of the NI, and as a consequence no new isomers were formed. Additional studies showed that stability of the NI (contained within milk products) was not affected by pasteurisation or ultrahigh temperature treatment.
12. The Spanish CA concluded that the industrial process did not guarantee uniformity of the resulting product and that the tolerance of minor fatty acids were excessively large. Also, they considered that the cross-contamination with phytosterols to be unacceptable, although they noted that this was not a safety concern.
13. The Spanish CA noted that the stability of the NI in bulk ingredient form was of limited relevance, and although additional studies were carried out using food matrices, these were restricted to the analysis of fatty acid profiles, and were also limited to a small number of food types.

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

Annex 2, p.19-22

14. The applicant provided an overview of the production process in Figure 2 (Annex 2, p.169) which is essentially the same process as used by Lipid Nutrition to manufacture the previous product. The raw material is food grade safflower oil, which is rich in linoleic acid. The oil undergoes the following processing stages:

transesterification with ethanol; isomerisation to convert linoleic acid ethyl esters to the *cis* isomers; hydrolysis; and re-esterification with glycerol.

15. The process is controlled by HACCP and the relevant control parameters are described in Figure 3 and Table 13 (Annex 2, p170 and pp157-9).

### **III. History of the source organism**

Annex 2, p. 23

16. The applicant regards their product as a chemical mixture and therefore considers that the history of the source organism (safflower seed) is not relevant. As described in ACNFP/89/2, safflower (*Carthamus tinctorius L*) has been cultivated as a source of food oil that is widely used throughout the world.

### **IX. Anticipated intake/extent of use of the NI**

Annex 2, p.24-34

17. The ingredient is intended for use in foods such as milk-type products, yoghurt-type products and fruit-juice-type products. The applicant stresses that this is not intended to be an exhaustive list. However, the ingredient is considered to be unsuitable for use in foods that undergo extensive heating, due to its polyunsaturated fat content.

18. The level of addition would be controlled so as to provide a daily intake of 3.5 g of CLA glycerides, corresponding to 4.5 g of the ingredient, by restricting its use to foods that can be readily divided into daily portions containing up to 3.5 g CLA (if the recommendation is for one portion per day) or a correspondingly smaller amount if the recommendation is for 2 or 3 portions per day.

19. The applicant has not provided intake estimates based on the current consumption of the relevant foods but suggests that clear instructions on food labels will prevent excessive consumption, drawing a parallel with the current situation for food supplements that currently contain the same ingredient.

20. The applicant considers it unlikely that consumers will consume multiple products containing the ingredient and refers to German research on food supplements which found that no more than 0.5% of the population consumed two or more products containing the same active ingredients (vitamin C and magnesium). In

addition, they suggest that the higher cost of foods containing the NI is likely to be a disincentive to over-consumption.

21. The Spanish CA concluded that the list of food uses should be made more specific and that it could not assess the use of the NI in foods where its stability has not been expressly demonstrated. In addition, they were unable to assess total intake of the NI and could not agree whether labelling would be an effective means of avoiding excessive intake.

## **X. Information from previous human exposure to the novel food or its source**

Annex 2, p.26-27 and p.35-36

22. The applicant provides information on levels of CLA isomers occurring naturally in foods like milk and meat in Tables 16 and 18 (Annex 2, p163 and p165) and estimates that average CLA intake is around 0.1 – 0.3 g/day, which is low in relation to the recommended intake of the novel ingredient.

23. The applicant confirms that their ingredient has been marketed in the form of food supplements since before 1997 and states that it may also be used as a food ingredient in other parts of the world (Switzerland, USA and Korea). However, there is no information about adverse effects associated with previous exposure to the ingredient.

24. The Spanish CA noted that there was established consumption of various CLA isomers in the EU diet, both as natural constituents of existing products and in supplements containing the NI.

## **XI. Nutritional information on the novel food**

Annex 2, p.37-38

25. The applicant notes that CLA is also a naturally occurring polyunsaturated fatty acid with two isomers *c9, t11* and *c10, t12* isomers being the major forms. CLA is found in dairy products and ruminant meat (see Table 18 for an overview).

26. The applicant is of the view that it is not an essential nutrient (and there is no consequence of CLA deficiency), but that there are a number of physiological effects that are attributed to its consumption which are perceived to be beneficial. In this regard the applicant highlights the effect that CLA has in the reduction of

adipose tissue mass in vertebrates either by increased energy expenditure or by minimising the accumulation of triglycerides in adipocytes. The applicant also points to CLA reducing body mass fat by altering the key enzymes of lipid storage mobilisation and oxidation. The applicant concludes by noting that the biochemical effects are not fully understood.

27. The Spanish CA notes that the isomeric distribution of the NI are such that it cannot be compared, for nutritional purposes, with those found in foods.

28. As the NI is also currently being considered under EU Health Claims legislation, Members are asked to limit any comments to those of significance to the safety assessment, and not comment on the validity of claims that might be made in relation to perceived health benefits. The Secretariat is of the view, however, that the safety assessment requires special attention to be paid to the implications of the postulated mechanisms for the weight loss effect that is attributed to consumption of CLA.

## **XII. Microbiological information on the novel food**

Annex 2, p.39

29. The applicant notes that fatty products have a low water content and are not subject to microbial contamination, and supplies a standard list of criteria that are used for internal quality control purposes. The Spanish CA accepted this view.

## **XIII. Toxicological information on the novel food**

Annex 2, p.40-80

30. The toxicological data provided by the applicant reports is largely the same published data set that was presented in the previous application. Given the two products are also largely the same, the Secretariat has not provided a summary of the toxicological studies as this was provided for the Lipid Nutrition product reviewed at the last meeting (paper ACNFP/89/2). However, Members may wish to note that whilst the Spanish CA is broadly content that the toxicological studies provide adequate reassurance that the NI is safe, they highlighted insulin resistance amongst prediabetic and type 2 diabetic individuals as a potential cause for concern. The applicant reports this as of borderline statistical significance, noting also that the substance that was administered was solely  $\alpha$ 10

112 CLA (Publications attached at **Annex 3**). The Spanish CA are of the view that, based on these findings it may be prudent to ensure that there are appropriate measures in place to ensure that the product can be avoided by at risk groups (Annex 1, 16)

31. The Spanish CA advised that it is not appropriate to calculate an ADI or a margin of exposure based on the animal data and that the assessment should be based on the clinical studies that have been reported. They concluded that no adverse effects are to be expected at doses of 3 g of the NI per day (equivalent to 2.4 g CLA per day), with the possible exception of diabetic patients (see above). This is with the proviso that the NI is used in specific foods where the specifications are complied with and NI is present in a stable form.

32. **Allergenicity:** The application dossier does not address allergy issues, and the ACNFP raised no concerns over allergenicity in its previous discussion of CLA-rich oil. As explained in the previous paper, no significant protein is expected in the final product given the high temperature, highly lipophilic environment and the purification steps in the production process. No allergenic proteins are reported to be associated with safflower oil, which is a recognized food oil. There have also been no reports of allergenicity in over 30 clinical trials conducted on the NI.

### **Overall conclusion**

Annex 1, p.15-18

33. The overall conclusion from the initial assessment report is that this ingredient has not been shown to meet the criteria for approval of a novel ingredient and further assessment is required. As indicated above, the applicant is seeking clearance for their ingredient to be added to any food or beverage and the Spanish CA's concerns are that the NI may not be stable in all food matrices and that labelling may not be effective in avoiding excessive intake. (The Secretariat notes that, in its consideration of the previous application for a similar CLA-rich oil, the ACNFP was also concerned about stability and the potential for excessive intake).

### **Committee Action Required**

34. The Committee is asked

- whether it agrees with the initial opinion from the Spanish CA that there is no cause for concern regarding the safety of this novel ingredient at doses up to 3g/day (equivalent to 2.4 g CLA per day) but that further assessment is required in relation to stability and the range of food uses; and
- whether it wishes to make any additional comments on the application.

**Secretariat  
August 2008**

**Annexes attached:**

**Annex 1** – Spanish Competent Authority's initial assessment report on CLA. (RESTRICTED)

**Annex 2** - Application dossier submitted by Lipid Nutrition B.V for the approval of CLA-rich oil as a novel food ingredient. (RESTRICTED)

**Annex 3** – Scientific Papers reporting of possible effects amongst prediabetic and Type 2 diabetes individuals



**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

Spanish Competent Authority's Initial Assessment Report

**Secretariat  
August 2008**



**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

**RESTRICTED**

Application dossier submitted by Cognis Deutschland for the approval of CLA-rich oil as a novel food ingredient.

**Secretariat  
August 2008**

**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

**RESTRICTED**

**Scientific Papers reporting of possible effects amongst prediabetic and Type 2 diabetes individuals**

Riserus *et al*, (2002, a, b)

Moloney *et al*, (2004

**Secretariat  
August 2008**