

ADVISORY COMMITTEE ON NOVEL FOOD AND PROCESSES

CALCIUM L-METHYLFOLATE

Issue

The Irish Competent Authority has prepared an initial assessment report on an application for the authorisation of calcium L-methylfolate as a novel food ingredient under the Novel Food Regulation (EC) No. 258/97. The Committee is asked whether it agrees with the initial opinion 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 16 August 2007, the European Commission forwarded the Irish Competent Authority's (CA's) initial assessment report on an application made on behalf of Merck Eprova AG under Article 4(1) of Regulation (EC) 258/97, for the authorisation of calcium L-methylfolate as a novel food ingredient. Under the time scales set out in the regulation, the UK and other Member States have until 15 October 2007 to provide comments and/or reasoned objections to this initial opinion.
2. The central part of the dossier provided by the applicant is attached as **Annex 1** (restricted). The Irish CA has drawn on a recent opinion from the European Food Safety Authority (EFSA). The Initial Assessment Report is attached as **Annex 2** (restricted) and the EFSA opinion is at **Annex 3**.

Background

3. The application from Bioresco, on behalf of Merck Eprova AG, is for the placing on the market of the calcium salt of L-5-methyltetrahydrofolic acid (5-MTHF) as a novel food ingredient (NI), for use as an alternative to folic acid. 5-MTHF is the predominant natural form of folate in many foods and it is also the form in which folate is stored in the human body and enters the circulation.
4. The NI has previously been considered at EU level and has been formally authorised for use as a source of folate in foods for particular nutritional uses ("PARNUTS" foods) and in food supplements. However, these authorisations cannot be put into effect by manufacturers as the ingredient remains subject to novel foods legislation, even if it is listed as a permitted ingredient in the other legislation.
5. Prior to these authorisations, the NI was reviewed by EFSA, which concluded in 2004 that "the use of L-5-MHTF-Ca as a source of folate in foods for particular nutritional uses, food supplements and foods intended for the general population,

with a tolerable upper level of 1 mg/adult person/day is not of concern from a safety point of view. This evaluation is based on the assumption that the previously established tolerable upper intake levels for folic acid of 1 mg/adult person/day would also be applied to the combined intake of folic acid and L-5-MHTF-Ca (expressed as folic acid)".

6. The NI was also evaluated by JECFA¹ in 2005, when JECFA had no concern about the safety of its proposed use as an alternative to folic acid in food supplements, foods for special dietary uses and other foods.
7. In addition to these "authorised" uses mentioned in paragraph 4, the applicant proposes that the NI would be added to other foods that might be fortified with folate and also to infant formulae and follow-on formulae. The composition of infant formulae is controlled by EU legislation and the applicant would have to seek a suitable amendment to allow the use of the NI. The fortification of other foods is subject to national legislation, although there is now a framework that can be used to draw up EU-wide rules at a future date.
8. In accordance with the European Commission Regulation 258/97, the NI falls under the category described under Article 1(2)(d) " foods and food ingredients with a new or intentionally modified primary molecular structure". This corresponds to class 1.2 under Commission Recommendation 97/618/EC, which sets out the guidelines for novel food applications. The requirements for a submission for 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

9. The information in the dossier is structured according to this scheme with the omission of items III and XII, which are not applicable to the NI. The information is summarised below.

¹ Joint FAO/WHO Expert Committee on Food Additives: The purity criteria for calcium methylfolate can be found at <http://www.fao.org/ag/agn/jecfa-additives/details.html?id=904>

I Specification of the NF

Annex 1 p 17-31

10. The NI is a white or light yellowish crystalline powder containing not less than 95% of calcium L-5-methyltetrahydrofolate. Detailed purity criteria were drawn up and published by JECFA in 2005 and the applicant has provided analytical reports on 5 representative batches demonstrating compliance with the JECFA specifications. EFSA has noted that the purity of two batches used in the safety was reported to be 97.1 and 99.9% but was content with the minimum figure of 95%. The relevant impurities are discussed in Section II below.
11. The naturally-occurring forms of folate, unlike synthetic folic acid, are potentially prone to oxidation and the applicant has provided data on the stability of the NI in various foods and model systems. The applicant concludes that these results, coupled with evidence of the stability of L-5-MTHF in foods, indicate that the NI is as suited as folic acid for the purposes of enrichment of foods.

II Effect of the production process applied to the NF

Annex 1 p 32-33

12. The NI is synthesised from folic acid by a series of chemical processes resulting in reduction, methylation and stereoselective crystallisation. Apart from folic acid, seven other folate derivatives have been identified at low levels in the final product. Each of these has been subjected to acute toxicity and Ames tests (see Annex 1, sections 9.1 and 9.4).

IX Anticipated intake/extent of use of the NF

Annex 1 p 35-44

13. The applicant has not provided intake estimates for the NI, but states that it is intended to be used as a partial or complete substitute for folic acid in food supplements, PARNUTS foods and other processed foods. The applicant considers that the NI has several advantages over folic acid, including improved bioavailability and bioefficacy.
14. The NI is also intended to be used for the provision of folate in infant formulae, follow-on formulae and other processed foods destined for consumption by infants and young children. (Note: this will require a future amendment to the EU legislation that governs the composition of infant formulae and weaning foods).

X Information from previous human exposure to the NF or its source

Annex 1 p 45-47, 48

15. The applicant highlights that L-5-MTHF occurs in regular foods and also in human milk. The applicant does not indicate whether the ingredient is in current use in any other countries but states that it may lawfully be used in the USA, having fulfilled the US requirements for food ingredients and dietary supplements.

XI Nutritional information on the NI

Annex 1 p 49-57

16. The applicant notes that dietary folates are converted to L-5-MTHF in the cells of the intestine and that this is to only form in which folate is usually found in the circulation. A number of clinical studies have shown that the NI is well absorbed and its bioavailability is comparable with that of folic acid. The NI may be more readily absorbed than folic acid when provided in fortified foodstuffs, some of which contain folate-binding proteins.
17. Studies in healthy volunteers have shown that equimolar doses of the NI and folic acid result in similar increases in circulating folate levels.
18. The applicant notes that 5-15% of the population have a genetically reduced activity of the enzyme responsible for converting folic acid to the active form (L-5-MTHF) and it would be more logical to administer folate in the form of the NI, rather than as folic acid, to such individuals (see page 57 of Annex 1). However, no studies are available to confirm whether the NI is a superior form of supplementation in these individuals; studies comparing folic acid with racemic D,L-5-MTHF or naturally occurring folates are inconclusive and not directly relevant to the NI.

XIII Toxicological information on the NI

Annex 1 p 59-67

19. A range of oral toxicity studies have been carried out on the NI, covering acute toxicity, subchronic toxicity (13 weeks), reproductive toxicity and mutagenicity. There is some supporting evidence from clinical studies showing that high doses of the NI and its racemic (D,L-) counterpart are well tolerated in human subjects, although these studies were not specifically designed to evaluate the safety of the compound.
20. The EFSA Panel on Food Additives has confirmed that these studies give no cause for concern.

General conclusion

21. The initial assessment report (Annex 2) concludes that the use of the NI in food intended for the general population does not raise any safety concerns. The report refers to the recent evaluation by EFSA, which concludes that there are no safety concerns over the use of the NI in parnuts foods, food supplements and foods intended for the general population. EFSA's evaluation is based on the assumption that the NI would be a replacement for folic acid and that the previously established tolerable upper intake level for folic acid (1mg/adult person/day) would be applied to the combined intake of folic acid and the NI (expressed as folate).
22. The initial assessment report notes that there is some additional information on the NI that was not available at the time of the EFSA assessment and states that

these do not raise any safety concerns that would require further evaluation by EFSA.

23. Neither EFSA nor the Irish CA has evaluated the proposed use of the NI in infant formulae and follow-on formulae although the initial assessment report notes that the use of the NI will have to comply with the relevant legislation (Directive 2006/141/EC). As noted above (paragraph 7) the use of the NI in these products will require an amendment to this Directive and the Secretariat understands that the Commission is obliged to seek specific advice from EFSA before proposing such an amendment.

Committee action required

24. The Committee is asked whether it agrees that the use of the NI in infant formulae and follow-on formulae requires further assessment by EFSA, which should be undertaken by EFSA prior to any authorisation for this use.

25. With that proviso, the Committee is asked whether it agrees with the initial assessment by the Irish CA, that the use of calcium L-methylfolate produced by Merck Eprova AG should be granted authorisation as a novel food ingredient, and whether it wishes to make any additional comments on this application.

26. The Committee's views will form the basis of the UK's formal response to the European Commission.

**Secretariat
September 2007**

Annexes:

Attached:

Annex 1 (**restricted**): L-Methylfolate, calcium. Dossier prepared and submitted on behalf of Merck Eprova AG (19 June 2007).

Annex 2 (**restricted**): Initial assessment report from the Food Safety Authority of Ireland (13 August 2007)

Annex 3: EFSA opinion on calcium L-methylfolate. *The EFSA Journal* (2004) 135, pages 1-20.

This document is available from www.efsa.europa.eu

Available on request:

- Copies of references listed in the application dossier (Annex 1)

ANNEX 1 to ACNFP/64/6

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Dossier prepared and submitted on behalf of Merck Eprova AG

(19 June 2007)

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**Initial assessment report from the
Food Safety Authority of Ireland**

(13 August 2007)

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EFSA opinion on calcium L-methylfolate

The EFSA Journal (2004) 135, pages 1-20.
This document is available from www.efsa.europa.eu