FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

8-06
13 December 2006

INITIAL ASSESSMENT REPORT

APPLICATION A566

L-5-METHYLTETRAHYDROFOLATE, CALCIUM AS A PERMITTED FORM OF FOLATE

DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 7 February 2007
SUBMISSIONS RECEIVED AFTER THIS DEADLINE WILL NOT BE CONSIDERED
(See 'Invitation for Public Submissions' for details)

For Information on matters relating to this Assessment Report or the assessment process generally, please refer to http://www.foodstandards.gov.au/standardsdevelopment/

Executive Summary

An Application has been received from Axiome Pty Ltd, on behalf of Merck Eprova AG, seeking permission to use L-5-methyl tetrahydrofolate, calcium salt (L-MTHF) as an alternative vitamin form of folate in foods wherever voluntary fortification with folate is currently permitted in the *Australia New Zealand Food Standards Code* (the Code).

Background

Folates that occur naturally in foods are susceptible to oxidation and losses can occur during food processing, manufacturing and storage. Fortification of foods with certain essential nutrients such as folate can compensate for these losses and assist in maintaining adequate daily intakes.

Folic acid is the most common synthetic form of folate and is currently the only permitted form of this nutrient listed in the Code. Folic acid must undergo chemical modification in the body to convert it to a functional form. In contrast, L-MTHF is the predominant form of folate found naturally in foods, and is the form directly utilised and stored in the human body. Permission to add L-MTHF would require an amendment to the respective Schedule in Standards 1.1.1 and 2.9.1 in the Code where permitted forms of vitamins and minerals are listed.

Purpose

The purpose of this Initial Assessment Report is to provide relevant information, supplied by the Applicant, to assist in identifying the affected parties and to outline the relevant issues necessary to evaluate the Application.

Since 1995, in Australia, and 1996 in New Zealand, folic acid has been permitted to be voluntarily added to the following foods: flour, savoury biscuits, breads, breakfast cereals, vegetable and meat extracts, pasta, fruit and vegetable juices and drinks, and beverages derived from legumes. Folic acid may also be added to legume analogues of dairy foods and meat but in smaller amounts. More recently voluntary folic acid fortification permissions have been extended to cereal based beverages e.g. rice and oat 'milks'. These permissions are provided in Standard 1.3.2 – Vitamins and Minerals of the Code. In addition, folate (as folic acid) must be added to infant formula and follow-on formula under Standard 2.9.1 – Infant Formula Products.

The Applicant has developed L-MTHF as a form of folate suitable for use in food and pharmaceutical products. The applicant claims that L-MTHF is nutritionally preferable because it is the form of folate that is (i) normally present in the body, (ii) naturally present in foods, and (iii) unlikely to mask the clinical symptoms of a vitamin B_{12} deficiency. The amounts of L-MTHF used would be equivalent on a molar basis to the currently permitted levels for folic acid.

Reasons for Assessment

After considering the requirements for Initial Assessment as prescribed in section 13 of the *Food Standards Australia New Zealand Act 1991* (FSANZ Act), FSANZ has decided to accept the Application for the following reasons:

- The Application seeks approval to use L-MTHF as a permitted form of folate for the fortification of certain foods as specified in the Code. Such an approval, if accepted, would warrant a variation to the Schedules to Standard 1.1.1 and Standard 2.9.1 in the Code.

- There is currently no permission in the Code for L-MTHF.

- The Application is not so similar to any previous application that it ought not be accepted.

- There are no other measures that would be more cost-effective than a variation to Standards 1.1.1 and 2.9.1 that could achieve the same end.

- At this stage no other relevant matters are apparent.

Consultation

Public submissions are now invited on this Initial Assessment Report. Comments are specifically requested on the scientific aspects of this Application, in particular, information relevant to a safety and nutritional evaluation of L-MTHF as a suitable form of folate for the fortification of foods including infant formula products.

Responses to this Initial Assessment Report will be used to develop the next stage of the Application and the preparation of a Draft Assessment Report.

CONTENTS

INVITATION FOR PUBLIC SUBMISSIONS

FSANZ invites public comment on this Initial Assessment Report based on regulation impact principles and the draft variation/s to the Code for the purpose of preparing an amendment to the Code for approval by the FSANZ Board.

Written submissions are invited from interested individuals and organisations to assist FSANZ in preparing the Draft Assessment of this Application. Submissions should, where possible, address the objectives of FSANZ as set out in section 10 of the FSANZ Act. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant studies, research findings, trials, surveys etc. Technical information should be in sufficient detail to allow independent scientific assessment.

The processes of FSANZ are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of FSANZ and made available for inspection. If you wish any information contained in a submission to remain confidential to FSANZ, you should clearly identify the sensitive information and provide justification for treating it as commercial-in-confidence. Section 39 of the FSANZ Act requires FSANZ to treat in-confidence, trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

Submissions must be made in writing and should clearly be marked with the word 'Submission' and quote the correct project number and name. Submissions may be sent to one of the following addresses:

Food Standards Australia New Zealand
PO Box 7186
Canberra BC ACT 2610
AUSTRALIA
Tel (02) 6271 2222
www.foodstandards.gov.au

Food Standards Australia New Zealand
PO Box 10559
The Terrace WELLINGTON 6036
NEW ZEALAND
Tel (04) 473 9942
www.foodstandards.govt.nz

Submissions need to be received by FSANZ by 6pm (Canberra time) 7 February 2007.

Submissions received after this date will not be considered, unless agreement for an extension has been given prior to this closing date. Agreement to an extension of time will only be given if extraordinary circumstances warrant an extension to the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.

While FSANZ accepts submissions in hard copy to our offices, it is more convenient and quicker to receive submissions electronically through the FSANZ website using the Standards Development tab and then through Documents for Public Comment. Questions relating to making submissions or the application process can be directed to the Standards Management Officer at the above address or by emailing slo@foodstandards.gov.au.

Assessment reports are available for viewing and downloading from the FSANZ website. Alternatively, requests for paper copies of reports or other general inquiries can be directed to FSANZ's Information Officer at either of the above addresses or by emailing info@foodstandards.gov.au.

INTRODUCTION

Axiome Pty Ltd, on behalf of the Applicant Merck Eprova AG, has submitted an application to Food Standards Australia New Zealand (FSANZ) seeking permission to use L-5-methyl tetrahydrofolate, calcium salt (L-MTHF) as an alternative vitamin form of folate in any foods where addition of folate or voluntary fortification is currently permitted in the Code. The Application was received on 6 July 2005 and was placed in Work Group 2 (non-paid), with an anticipated commencement date towards the end of 2006.

1. Background

Folate, a B-group vitamin, is a general name for a group of structurally related compounds, both naturally occurring and synthetic. Folates are widely distributed in nature and are essential components for the maintenance of cellular functions and health. The chemically reduced forms, such as L-5-methyl tetrahydrofolate, function as coenzymes in a range of biochemical reactions in the body. In addition to the general biological importance of folates, adequate blood levels are associated with a reduced incidence of neural tube defects (NTDs) in the developing foetus during early pregnancy.

Folates that occur naturally in foods are susceptible to oxidation and losses can occur during food processing, manufacturing and storage. Whilst procedures can be implemented during food processing operations to minimise these losses, fortification of foods with folate can compensate for the losses and assist in maintaining adequate daily intakes.

Folic acid is the most common synthetic form of folate used in the fortification of foods and in the majority of dietary supplements. Although folic acid is rarely found naturally in foods, it is currently the only permitted form of folate listed in the Code. It does not function directly as a coenzyme, but undergoes reduction following absorption from the intestine which converts it to a functional form. In contrast, L-5-methyl tetrahydrofolate is the predominant form of folate found naturally in foods, and is the essential endogenous form utilised and stored in the human body.

1.1 Historical Background

Regulations are in place to restrict the addition of vitamins to food and the claims that manufacturers may make concerning the presence of a vitamin in a food. Under Standard 1.3.2 – Vitamins and Minerals, a vitamin or mineral must not be added to a food unless there is a specific permission listed in the Table to clause 3 of the Standard, or elsewhere in the Code. The vitamin or mineral must also be in a permitted form specified in the Schedule to Standard 1.1.1 – Preliminary Provisions – Application, Interpretation and General Prohibitions. The purpose of these restrictions and the associated labelling requirements are to ensure that consumers are not mislead by manufacturers statements in relation to the vitamin content of foods.

Under the existing food regulations, permitted claims made on the presence of a vitamin and mineral in a food refer to the total of both naturally-occurring and added forms of the nutrient. In the case of dietary folate in food the amount declared on a label is the sum of naturally-occurring folate and added folic acid and is listed as ‘folate’ in the Nutrition Information Panel.

In addition, under Standard 1.1A.2 – Transitional Standard for Health Claims, a health claim highlighting the link between increased maternal dietary folate intake and reduction in NTD risk is permitted for some fortified and non-fortified foods that contain at least 40 μg folate per serving. The claim should state that increased maternal folate consumption in at least the month before and three months following conception may reduce the risk of NTDs. It must also include the recommendation that women consume a minimum of 400 μg of folate per day during this time.

1.2 Regulatory status overseas

In the US, L-MTHF is 'generally recognized as safe' (GRAS) for use as a source of folate in conventional and medical foods and dietary supplements. In the European Union, the European Food Safety Authority (EFSA) adopted a favourable opinion of its scientific panel which, on evaluation of the data submitted with this Application, concluded that L-MTHF as a source of folate in foods for specific nutritional uses, food supplements and normal foods, with a tolerable upper level of 1 mg/adult person/day, is not a safety concern (EFSA, 2004).

2. The Issue / Problem

2.1 Current Standards

Since 1995, in Australia, and 1996 in New Zealand, folic acid has been permitted to be voluntarily added to the following foods: flour, savoury biscuits, breads, breakfast cereals, vegetable and meat extracts, pasta, fruit and vegetable juices and drinks, and beverages derived from legumes. Folic acid may also be added to legume analogues of dairy foods and meat but in smaller amounts. More recently voluntary folic acid fortification permissions have been extended to cereal based beverages e.g. rice and oat 'milks'. These permissions are provided in Standard 1.3.2 – Vitamins and Minerals of the Code.

In addition, under subclause 24(1) of Standard 2.9.1 – Infant Formula Products, a minimum amount of folate must be added to infant formula products (infant formula and follow-on formula). The only permitted form of folate listed in the Schedule to Standard 2.9.1 is currently folic acid.

2.2 Alternative form of folate

The Applicant has developed L-MTHF as a form of folate suitable for use in food and pharmaceutical products. The Applicant claims that L-MTHF is nutritionally preferable because it is the form of folate that is (i) normally present in the body, (ii) naturally present in foods, and (iii) unlikely to mask the clinical symptoms of a vitamin B_{12} deficiency.

The use levels of L-MTHF would be equivalent on a molar basis to the levels currently permitted in Standards 1.3.2 and 2.9.1 for folic acid; 1.123 units of L-MTHF (anhydrous base) are equivalent to 1 unit of folic acid (that is, 112 μg L-MTHF is equivalent to 100 μg folic acid).

3. Objectives

The objective of this assessment is to determine whether it would be appropriate to amend Standards 1.1.1 and 2.9.1 of the Code to approve the use of L-MTHF as a form of folate added to foods where fortification with this vitamin is permitted. In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives, which are set out in section 10 of the FSANZ Act. These are:

- the protection of public health and safety;
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food; and
- any written policy guidelines formulated by the Ministerial Council.

4. Key Assessment Questions

Based on information provided by the Applicant on the chemical nature of L-MTHF and its biochemical and food technology properties, key questions in this assessment include:

- Is L-MTHF bioequivalent to folic acid?
- Is L-MTHF stable when added to processed food products?
- Are the upper tolerable limits on daily intake specified for folic acid appropriate for L-MTHF?
- Is L-MTHF safe for human consumption?
- Are there benefits in using L-MTHF instead of folic acid in fortified foods?

RISK ASSESSMENT

5. Risk Assessment Summary

5.1 Safety of L-MTHF

The Applicant has submitted a comprehensive package of information allowing an evaluation of the safety of L-MTHF. The data submitted include toxicity studies (acute, subchronic and teratogenicity studies), Ames test, TK locus test, *in vivo* DNA synthesis and repair test, *in vivo* micronucleus test, as well as a study on tolerance in humans. In addition to information supplied by the Applicant, FSANZ will also consider other information relevant to the safety assessment including from the scientific literature, general technical information, independent scientists, other regulatory agencies and international bodies, and the general community.

5.2 Nutritional properties

The nutritional implications arising from the use of L-MTHF in specified foods will be fully considered at Draft Assessment. The risk assessment will address key questions including whether L-MTHF in foods is bioequivalent to folic acid. The Applicant has submitted a package of information for use by FSANZ in assessing the nutritional properties of L-MTHF. The studies include randomised controlled trials in humans in which absorption was compared with folic acid, in-food stability data, and evidence to suggest that L-MTHF does not mask vitamin B_{12} deficiency.

Further, FSANZ will evaluate information from the Applicant suggesting that L-MTHF may be nutritionally advantageous for people with genetically reduced activity of 5,10-methylenetetrahydrofolate reductase, a folate metabolising enzyme.

5.3 Food technology

L-MTHF is produced synthetically from folic acid, and can be used in foods in dry crystalline or microencapsulated form. A draft specification for L-MTHF has been prepared in consultation with the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2005). The full manufacturing details have been provided as confidential commercial information (CCI).

RISK MANAGEMENT

6. Options

FSANZ is required to consider the impact of various regulatory (and non-regulatory) options on all sectors of the community, which includes consumers, food industries and governments in Australia and New Zealand.

There are no non-regulatory options for this Application. The two regulatory options available for this Application are:

6.1 Option 1 – Prohibit the use of L-MTHF as a permitted form of folate

Maintain the *status quo* by not amending Standard 1.1.1 and 2.9.1 of the Code to approve L-MTHF as a permitted form of folate for the nutrient fortification of certain foods.

6.2 Option 2 – Approve the use of L-MTHF as a permitted form of folate

Amend the Schedule to Standards 1.1.1 and 2.9.1 of the Code to list L-MTHF as a permitted form of folate for the nutrient fortification of certain foods listed in Standard 1.3.2 – Vitamins and Minerals and elsewhere in the Code.

7. Impact Analysis

7.1 Affected Parties

The affected parties may include the following:

- consumers, including women of child bearing age and the elderly, a group at risk of vitamin B_{12} deficiency;
- the manufacturing and retail sectors of the food industry; and
- Government generally.

7.2 Benefit Cost Analysis

In the course of developing food regulatory measures suitable for adoption in Australia and New Zealand, FSANZ is required to consider the impact of all options on all sectors of the community, including consumers, the food industry and governments in both countries. The regulatory impact assessment identifies and evaluates, though is not limited to, the costs and benefits of the regulation, and its health, economic and social impacts.

To develop the analysis of the costs and benefits of the regulatory options proposed, FSANZ seeks comment on the following:

- What are the potential costs or benefits of this application to you as a stakeholder? Do the benefits outweigh the costs?
- What are the costs or benefits for consumers in relation to public health and safety, consumer information and labelling, etc?
- What are the costs or benefits for business – compliance, reporting, costs, savings, increased market opportunities both domestically and overseas?
- What are the costs or benefits for government – administration, enforcement, public health and safety, etc?

COMMUNICATION

8. Communication and Consultation Strategy

This is a routine standards matter. As a result, FSANZ has applied a basic communication strategy to this Application that involves advertising the availability of assessment reports for public comment in the national press and placing the reports on the FSANZ website. In addition, FSANZ will issue a media release drawing journalists' attention to the matter.

The Applicant and individuals and organisations who make submissions on this Application will be notified at each stage of the Application. If approval is recommended, once the FSANZ Board has approved the Final Assessment Report, we will notify the Ministerial Council.

The Applicant and stakeholders, including the public, will be notified of the gazettal of changes to the Code in the national press and on the website. In addition, FSANZ provides an advisory service to the jurisdictions on changes to the Code.

9. Consultation

9.1 Public consultation

The purpose of the Initial Assessment Report is to seek input from the public on a range of specific issues considered to be of interest to various stakeholders, the likely regulatory impact at an early stage and any matter of interest in relation to this Application.

All stakeholders that make a submission on this Application will be included on a mailing list to receive further FSANZ documents relating to the Application. Other interested parties, as they come to the attention of FSANZ, will be added to the mailing list for public consultation.

At this stage, public comment is sought on the Initial Assessment Report to assist in assessing this Application. All stakeholders must observe the relevant due date for submissions.

Comments that would be useful could cover:

- Scientific aspects of this application, in particular, information relevant to the safety and nutritional evaluation of L-MTHF when used for folate fortification of certain foods;
- Parties that might be affected by the approval or rejection of this Application;
- Arguments supporting or opposed to the approval of L-MTHF as a permitted form of folate, in addition to the existing permission for folic acid; and
- Potential costs and benefits to consumers, industry and government.

9.2 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade. In this case, there are no relevant international standards and amending the Code to allow L-MTHF as an alternative form of folate is unlikely to have a significant effect on international trade. This issue will be fully considered at Draft Assessment and, if necessary, notification will be recommended to the agencies responsible in accordance with Australia's and New Zealand's obligations under the WTO Technical Barriers to Trade (TBT) or Sanitary and Phytosanitary Measures (SPS) Agreements. This will enable other WTO member countries to comment on proposed changes to standards where they may have a significant impact on them.

CONCLUSION

10. Conclusion

This Initial Assessment Report is based mainly on information provided by the Applicant and discusses relevant issues in relation to the evaluation of L-MTHF as a permitted form of folate for the nutrient fortification of certain foods listed in the Code.

After having regard to the requirements for Initial Assessment as prescribed in section 13 of the FSANZ Act, FSANZ has decided to accept the Application for the following reasons:

- The Application seeks approval to list L-MTHF as a permitted form of folate for the fortification of certain foods listed in the Code. Such an approval, if accepted, would warrant a variation to Standards 1.1.1 and 2.9.1 in the Code;

- There is currently no permission in the Code for L-MTHF;

- The Application is not so similar to any previous application that it ought not be accepted;

- There are no other measures that would be more cost-effective than a variation to Standards 1.1.1 and 2.9.1 that could achieve the same end; and

- At this stage no other relevant matters are apparent.

Responses to this Initial Assessment Report will be used to develop the next stage of the Application and the preparation of a Draft Assessment Report.