NUTRITION UNIT

Call for data relevant to the assessment of the conversion factor of calcium-L-methylfolate and (6*S*)-5-methyltetrahydrofolic acid, glucosamine salt into dietary folate equivalent

EFSA-Q-number:	**EFSA-Q-2020-00542**
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Deadline for submission of data:	**04/10/2021**

Background

Annex II to Directive 2002/46/EC[1] lists the chemical substances that may be used as **sources of vitamins and minerals in the manufacture of food supplements**.

On 12 March 2015, Commission Regulation (EU) No 2015/414 was adopted to allow the use of **(6*S*)-5-methyltetrahydrofolic acid, glucosamine salt (5MTHF-glucosamine)** as a source of folate in food supplements, following EFSA`s favourable opinion on (6*S*)-5-methyltetrahydrofolic acid, glucosamine salt as a source of folate added for nutritional purposes to food supplements and the bioavailability of folate from this source.[2]

The Annex to Regulation (EU) No 609/2013[3] establishes a Union list of **substances that may be added for nutritional purposes to one or more categories of food** covered by the scope of the Regulation. According to the Union list, **calcium-L-methylfolate (CaLMF)** may be used as a source of folate in food for special medical purposes and total diet replacement for weight control.

Following requests from the Commission, EFSA adopted Scientific Opinions on CaLMF as a source of folate (i) **in foods for particular nutritional uses, food supplements and foods intended for**

[1] OJ L 183, 12.7.2002, p. 51.
[2] EFSA Journal 2013;11(10):3358.
[3] OJ L 181, 29.6.2013, p. 35.

the general population on 28 October 2004,[4] and (ii) **added for nutritional purposes to infant and follow-on formula, baby food and processed cereal-based food** on 27 November 2019.[5]

In the latter Scientific Opinion, EFSA concluded that CaLMF is a source from which folate is bioavailable and that CaLMF is safe under the proposed uses and use levels for infants and young children. It was further noted that the bioavailability of CaLMF is expected to be comparable to that of folic acid in infants and young children.

Delegated Regulations[6][7][8] adopted under the scope of Regulation (EU) No 609/2013 as well as Commission Directive 2006/125/EC[9] lay down **specific requirements for the folate content of specific categories of food**. In some cases,[6,7,8] such compositional requirements are expressed in **Dietary Folate Equivalent (DFE) for which a legal definition is provided** for by the mentioned pieces of legislation.[10] Such legal definition, however, does not provide for a conversion factor that would allow to convert the amount of CaLMF into DFE. Concerns have been raised by some Member States that the absence of such a conversion factor might cause difficulties for the national competent authorities in enforcing compliance with the mentioned requirements on folate.

In addition, both Regulation (EU) No 1169/2011[11] and Directive 2002/46/EC foresee that the information on vitamins and minerals in a product shall be expressed as a percentage of the daily reference intakes. Annex XIII of Regulation (EU) No 1169/2011 lists these daily reference intakes, including that for folic acid, without providing for a conversion factor that would allow to convert the amount of CaLMF into DFE.

Overall objective

The **purpose of this call** is to provide the opportunity for stakeholders and other interested parties to submit studies relevant for the evaluation of the scientific evidence on the **conversion factor of**

[4] EFSA Journal 2004;2(11);135.
[5] EFSA Journal 2020;18(1):5947.
[6] Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding, OJ L 25, 2.2.2016, p. 1.
[7] Commission Delegated Regulation (EU) 2016/128 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for food for special medical purposes, OJ L 25, 2.2.2016, p. 30.
[8] Commission Delegated Regulation (EU) 2017/1798 of 2 June 2017 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for total diet replacement for weight control, OJ L 259, 7.10.2017, p. 2.
[9] OJ L 339, 6.12.2006, p. 16
[10] Dietary folate equivalent: 1 µg DFE = 1 µg food folate = 0,6 µg folic acid.
[11] OJ L 304, 22.11.2011, p. 18.

calcium-L-methylfolate and (6*S*)-5-methyltetrahydrofolic acid, glucosamine salt into dietary folate equivalent (DFE).

Opportunity is therefore open to stakeholders to submit **unpublished data** for the purpose of this call.

In particular, EFSA seeks to collect unpublished information on **comparative bioavailability** of the two compounds of interest **against a similar amount of folic acid or food folate** (ideally equimolar dose) and to fill-in the identified data gaps (See following section).

The **racemic mixture** of methyltetrahydrofolate, i.e. (6*RS*)-5MTHF, is **outside the remit** of this call for data.

Use of the submitted data by EFSA

The unpublished information submitted in the context of this call for data, if considered relevant by EFSA for this scientific assessment, may be used, in combination with other data already collected through a systematic search, for data analysis that would be included in the final scientific output that will be published on the EFSA website. Depending on the type of study, this combination may be done:

- at aggregated level, i.e. aggregated data of unpublished study report combined with aggregated data from published studies,
- or at individual level, i.e. individual data of unpublished study report combined with individual data from published studies,
- or narratively, i.e. short summary of the submitted unpublished study report discussed narratively in conjunction with other short summaries of published studies.

Information sought

EFSA kindly invites all interested parties (regulatory bodies/national competent authorities, business operators, academia and other research institutions) to submit the following three main types of information: (i) unpublished study reports, (ii) individual data **or** (iii) additional missing information on labelling or foods for special medical purposes (FSMPs).

A. Unpublished study reports

- **A.1. Possible unpublished reports of comparative bioavailability** studies of synthetic (6*S*)-5-methyltetrahydrofolate (5MTHF) in humans, or *in vitro*-gastro-intestinal models (bioaccessibility or absorption studies), using as a **comparator food folate or folic acid.**

  Studies using **only a placebo as a comparator will not be considered relevant** for this assessment.

  As mentioned above, studies on the **racemic mixture** of methyltetrahydrofolate, i.e. (6*RS*)-5MTHF, **will not be considered relevant** for this assessment either.

  Only studies using similar doses of the test items (ideally equimolar doses) will be accepted.

- **A.2. Possible unpublished study reports of comparative bioavailability** studies (in humans, animals or *in vitro*-gastro-intestinal models) on 5MTHF, using **different cations** (calcium, glucosamine, sodium, barium, etc.).

  Regarding the animal studies, relevant animal models would be mammals except ruminants (e.g. rats, mice, pigs, dogs, cats, guinea pigs, hamsters, primates, rabbits) as well as birds (e.g. hens).

Important note common to A.1 and A.2 (and B if submitted).

In particular, the **full description of the analytical method applied is needed** or at least a reference to a publication describing the method applied and providing relevant information on the performance of the analytical method.

A **summary of the study report** should be provided indicating at least the following information:

- **Settings**: chronic human studies (healthy or disease individuals), acute human studies (healthy or disease individuals), *in vitro*-gastro-intestinal studies (static or dynamic type of model), animal studies naming the species investigated (for A.2.).
- **Dose, frequency** (e.g. once or twice daily) and **cation** associated with 5MTHF and type of **comparator** (food folate or folic acid).
- For human studies, **conditions of consumption** (empty stomach or with a meal)
- **Duration** of the study and **biomarkers/parameters** investigated

Regarding the study settings:

- In case a **medicine or a/several nutrient(s)** is/are administered to the subjects investigated (co-intervention), they should be administered **in all study arms**, for the study to be considered relevant for this assessment.

- Relevant **biomarkers** for this assessment may be: serum/plasma total folate concentration, red blood cell total folate, and possibly plasma total homocysteine with vitamin B12 status if available.

Stability data of CaLMF or 5 MTHF glucosamine in foods/food matrices are **not** within the scope of this call for data.

Information provided **only in abstract form will not be considered relevant.**

Study reports should be in English or, otherwise, with a summary translated in English.

B. Individual data

- **Individual data of unpublished studies in humans of comparative bioavailability studies of CaLMF or 5MTHF glucosamine compared with folic acid, in chronic studies**.

These may be provided with the unpublished study reports mentioned above (point A). In that case, the **important note above** common to point A1 and A2 is applicable to point B.

Relevant **biomarkers** for this assessment will be: serum/plasma total folate concentration and red blood cell total folate.

These individual data should be provided **in MS Excel®, according to the submission template attached to this call and that shows the minimal information needed**.

If additional parameters are entered in the file in the form of **codes**, a **detailed list of the meaning** of these codes needs to be provided. Please also provide a short **description** of the information to be found in each additional **column**.

If the parameters entered contain **decimals**, please use a (**.**) to enter them.

C. Additional missing information

- C.1. What are the current **labelling practices** and **rationale for possible conversion factor** used for CaLMF or 5MTHF glucosamine, depending on the type of foods?

- C.2. For which **conditions/diseases** are the **foods for special medical purposes** (FSMPs) currently containing CaLMF manufactured?

Deadlines for submission of data

Interested parties should provide **by the deadline of 04/10/2021** the information described above

Information not submitted within the final deadline will only exceptionally be considered and EFSA can decide to finalise its opinion solely on the basis of the information provided within the final deadline (04/10/2021). Please communicate in writing by email to: nda_callfordata@efsa.europa.eu

In order to facilitate the collaboration of all interested parties to provide the data needed, we are seeking your **consent to disclose your personal data** (name, affiliation, e-mail address and telephone number) to the other parties that have expressed an interest to provide the requested information. If you do not wish to make your contact details available, clearly indicate it in your first communication.

Confidentiality

In order to comply with its requirements for transparency as outlined in Article 38 of Regulation (EC) No 178/2002, EFSA has to disclose in its published scientific opinions data received/available which are considered essential for the scientific assessment, as well as background information supporting the scientific reasoning. However, according to Article 39(1) of Regulation (EC) No 178/2002, EFSA may not divulge to third parties confidential information received for which confidential treatment has been requested, justified, and agreed, except for information which must be made public if circumstances so require, in order to protect public health, or whenever its conclusions highlight

foreseeable adverse health effects. Furthermore, EFSA is subject to Regulation (EC) No 1049/2001 regarding public access to European Parliament, Council and Commission documents[12].

Therefore, business operators or interested parties submitting relevant datasets in response to this call are requested to proactively and clearly identify, as part of their submission, all parts or bits of information/data they consider as deserving confidential treatment. For each item for which a request for confidential treatment is submitted, the concerned individual has to provide verifiable justification supporting each request by indicating the reasons and circumstances proving why the disclosure of these elements would cause them financial harm.

A decision is taken by EFSA on each confidentiality request submitted by concerned individuals. Confidential status may be granted to information the disclosure of which might significantly harm the competitive position of business operators or other interested parties.

Interested business operators or other interested parties will be informed by EFSA about which information or data will be granted confidential treatment, and on the legal remedies available thereto should a decision rejecting their confidentiality requests be taken.

Submission of information

Interested parties should submit the information to EFSA in electronic form (**searchable** files, including PDFs) to nda_callfordata@efsa.europa.eu including the supporting documents listed below.

The information should be submitted together with the supporting documents listed below:

Mandatory

- **Cover letter** stating:
    - The reference to the specific call for data (EFSA-Q-2020-00542)
    - The contact details[13] (name of contact person, name of company/organisation, e-mail address and telephone number) of the person responsible for the data submission and, if applicable, the list of interested business operators and/or interested parties represented and their contact details;

[12] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ L 145, 31.5.2001, p. 43–48.

[13] The interested parties shall notify EFSA of any change in the contact details by sending an e-mail to nda_callfordata@efsa.europa.eu

- Statement of the legal representative of the submitter that they hold all the necessary rights to **grant permission to EFSA to use and, where appropriate, to disclose**, the submitted information, data, document, paper or study for the purposes defined in this call. In case the submitter does not enjoy the necessary rights for these data or studies, they should share the contact details of the respective owner(s) of data and/or of the relevant intellectual property right, so that EFSA may seek their approval directly;

Optional

Confidentiality request:

- separate folders containing confidentiality requests concerning the submitted information or data. Information or data for which a confidentiality request is submitted should be kept to a minimum and shall be supported by verifiable evidence composed of precise and factual information proving that the disclosure of the information would result in concrete harm to the commercial or economic interest of the concerned individual, or would undermine the protection of the privacy and the integrity of the concerned individual.

- the explicit and written decision of the data owner to donate the information or data to EFSA. By donating to EFSA the submitted information or data, the concerned operator or interested party waives any right on the relevant information or data.

Contact details for submission of information/data

It is recommended that submissions are sent electronically to the following e-mail address: nda_callfordata@efsa.europa.eu

Please use the same e-mail address for enquiries and further clarifications.