



William Turney  
DSM Nutritional Products  
45 Waterview Boulevard  
Parsippany, NJ 07054

Re: GRAS Notice No. GRN 000915

Dear Mr. Turney:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000915. We received DSM Nutritional Products' (DSM) notice on December 9, 2019, and filed it on May 6, 2020. DSM submitted an amendment to the notice on July 31, 2020, that provided additional information to clarify the identity, specifications, stability, and intended use.

The subject of the notice is calcium L-methylfolate for use as a replacement for folic acid as a source of the vitamin folate in non-exempt and exempt infant formulas for term infants at a level equivalent on a molar basis to that of folic acid. The notice informs us of DSM's view that this use of calcium L-methylfolate is GRAS through scientific procedures.

DSM describes calcium L-methylfolate as a white to yellow or beige crystalline powder with the scientific name N-{4-[[[(6S)-2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl)methyl]amino]benzoyl}-L-glutamic acid, calcium salt. Calcium L-methylfolate is identified by the CAS No. 151533-22-1 and has a specified 1:1 ratio of L-5-methyltetrahydrofolate (L-5-MTHF) and Ca<sup>2+</sup>. DSM states that calcium L-methylfolate has the 6S, αS configuration, which corresponds to the naturally-occurring isomer of folate. Its molecular formula is C<sub>20</sub>H<sub>23</sub>CaN<sub>7</sub>O<sub>6</sub> with a molecular weight of 497.5 g/mol.

DSM describes the method of manufacture for calcium L-methylfolate as a 3-step synthesis conducted using current good manufacturing practices. Calcium L-methylfolate is synthesized from folic acid by catalytic hydrogenation or reduction with sodium borohydride (NaBH<sub>4</sub>), condensation of the resulting tetrahydrofolic acid benzenesulfonate intermediate with formaldehyde, reduction of the formed 5,10-methylene-tetrahydrofolic acid to L-5-methyltetrahydrofolic acid with NaBH<sub>4</sub>, and diastereoselective crystallization as the calcium salt of L-5-MTHF. The salt is then milled to yield the final calcium L-methylfolate product.

DSM states that the specifications for calcium L-methylfolate meet or exceed the U.S. Pharmacopeia (USP) specifications for calcium L-methylfolate. DSM provides specifications for calcium L-methylfolate that include: assay for calcium L-methylfolate (95.0% to 102%, w/w, dry basis); 4-aminobenzoylglutamic acid (≤ 0.5%); 4α-hydroxy-5-

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methyltetrahydrofolic acid ( $\leq 1.0\%$ ); Mefox ( $\leq 1.0\%$ ); tetrahydrofolic acid ( $\leq 0.5\%$ ); 7,8-dihydrofolic acid ( $\leq 0.5\%$ ); folic acid ( $\leq 0.5\%$ ); 5,10-methylenetetrahydrofolic acid ( $\leq 0.5\%$ ); 5-methyltetrahydropteroic acid ( $\leq 0.5\%$ ); dimethyltetrahydrofolic acid ( $\leq 0.15\%$ ); sum of all related compounds ( $\leq 2.5\%$ ); and (6R)-mefolate ( $\leq 1.0\%$ ). DSM also provides limits for calcium (7-8.5% on a dry basis); water content (6-17%); boron ( $\leq 10$  mg/kg); platinum ( $\leq 10$  mg/kg); arsenic ( $\leq 1.5$  mg/kg); cadmium ( $\leq 0.5$  mg/kg); lead ( $\leq 1.0$  mg/kg); mercury ( $\leq 1.5$  mg/kg), ethanol ( $\leq 0.5\%$ ); isopropanol ( $\leq 0.5\%$ ); chloride (0.5%); *Salmonella* spp. (negative in 125 g), *Enterobacteriaceae* (including *Cronobacter* spp.) (negative in 100 g); and microorganisms. DSM provides analytical results for 3 non-consecutive lots of calcium L-methylfolate demonstrating compliance with the stated specifications. DSM indicates that the manufacturer states that calcium L-methylfolate has a shelf life of 24 months when stored in the unopened original container at 2-8 °C. Additionally, DSM demonstrates the stability of calcium L-methylfolate added to powdered infant formula for 18-months at room temperature (5-25 °C), as well as in prepared infant formula.

DSM indicates that calcium L-methylfolate will be used as a partial or complete replacement for folic acid in non-exempt and exempt infant formulas at a level equivalent on a molar basis to current folic acid levels. DSM states that the level of folic acid in several commercially-available infant formulas ranges from 15 to 16  $\mu\text{g}/100$  kcal. The amount of calcium L-methylfolate needed to replace folic acid in these formulas would be 17 to 18  $\mu\text{g}/100$  kcal.

DSM states that the energy intake from infant formula for infants aged 0-6 months and 6-12 months is approximately 400 kcal/day. Considering the energy intake of infant formula and the typical levels of folic acid in commercially-available formula, DSM estimates that replacement of folic acid in typical infant formulas by calcium L-methylfolate to provide an equivalent amount of folate would result in an estimated daily exposure to calcium L-methylfolate of 72  $\mu\text{g}/\text{p}/\text{d}$  for infants aged 0-12 months. In addition, DSM provides exposure to calcium L-methylfolate on a body weight basis for each month of age from 0 through 11 months using mean infant formula intake values as described in Ref. 1. At the intended use level to replace folic acid in infant formula, the exposure to calcium L-methylfolate would range from 7.2 to 20.4  $\mu\text{g}/\text{kg}$  bw/d at the mean and from 11.9 to 30.1  $\mu\text{g}/\text{kg}$  bw/d at the 90th percentile for infants between the ages of 0 and 11 months.

DSM notes that replacement of folic acid with calcium L-methylfolate would not change the daily exposure to folate for infants aged 0-11 months. DSM also notes that the additional exposure to calcium for infants from the replacement of folic acid with calcium L-methylfolate is insignificant ( $< 0.0001\%$ ) compared to the normal daily exposure to calcium from dietary sources.

DSM states that calcium L-methylfolate readily and completely dissociates into  $\text{Ca}^{+2}$  and L-5-methyltetrahydrofolate ions in aqueous solution or following ingestion. DSM states that folate in human milk is present as L-5-MTHF, and that the proposed use levels meet the recommended minimum described in 21 CFR 107.100, as well as the Guidance

Upper Level (GUL) and Adequate Intake (AI) levels.<sup>1</sup> DSM discusses publicly available data and information from a comprehensive literature search conducted through October 2019 on the metabolic fate of L-5-MTHF, as well as those relevant to the safety evaluation of calcium L-methylfolate. DSM states that once absorbed, the fate of the L-5-MTHF is indistinguishable from that of all other absorbed and metabolized natural folate or the L-5-MTHF formed from synthetic folic acid. DSM discusses studies performed in rats and humans indicating that the bioavailability of calcium L-methylfolate, whether consumed as a supplement or as a folate source in milk or infant formula, is equivalent to or slightly higher than folic acid.

DSM discusses published toxicological studies with the article of commerce. DSM discusses a repeated-dose sub-chronic and a developmental oral toxicity studies in rats and states that no test article relevant adverse effects were observed up to the highest dose tested in both studies, which are 400 mg/kg bw/d and 1000 mg/kg bw/d, respectively. Based the highest 90<sup>th</sup> percentile exposure estimated, DSM concludes that the margin of exposure for calcium L-methylfolate is adequate to support the safety for the intended use. DSM also concludes from *in vitro* Ames and mammalian gene mutation tests, as well as *in vivo* mammalian erythrocyte micronucleus and unscheduled DNA synthesis tests, that calcium L-methylfolate is non-mutagenic and non-genotoxic.

DSM also discusses relevant safety information on calcium,<sup>2</sup> including Institute of Medicine's (now National Academy of Medicine) upper limit for calcium and concludes that the additional estimated exposure of 6 µg/d from the intended use is insignificant and not a safety concern.

To further support general recognition of safety, DSM discusses evaluations of calcium L-methylfolate by other regulatory agencies, including the European Food Safety Authority, Joint FAO/WHO Expert Committee on Food Additives, Food Standards Australia New Zealand, and Health Canada. DSM also includes the statement of a panel of individuals (DSM's GRAS panel). Based on its review, DSM's GRAS panel concluded that calcium L-methylfolate is safe under the conditions of its intended use.

Based on totality of data and information, DSM concludes that calcium L-methylfolate is GRAS for its intended use.

### **Potential Labeling Issues**

Under section 403(a) of the Federal Food, Drug, & Cosmetic (FD&C) Act, a food is

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<sup>1</sup> Under section 412 of the FD&C Act and 21 CFR 107.100, the minimum amount of folic acid in infant formula is specified to be 4.0 µg/100 kcal, but no maximum amount is specified. DSM states that the Codex Alimentarius has set the minimum amount of folic acid to be 10 µg/100 kcal and GUL to be 50 µg/100 kcal. DSM also states that the Institute of Medicine's (now National Academy of Medicine) AI folate levels for healthy breastfed infants aged 0-6 months and 7-12 months of age as expressed as folic acid are 39 and 48 µg/day, respectively.

<sup>2</sup> DSM states that upper limits for calcium established by the Institute of Medicine for infants 0-6 months and 7-12 months of age are 1000 and 1500 mg/d, respectively.

misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing calcium L-methylfolate bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (OFAS) did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

### **Intended Use in Infant Formulas**

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to DSM's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing calcium L-methylfolate to make the submission required by section 412. Infant formulas are the purview of ONFL.

### **Section 301(ll) of the FD&C Act**

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of DSM's notice concluding that calcium L-methylfolate is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing calcium L-methylfolate. Accordingly, our response should not be construed to be a statement that foods containing calcium L-methylfolate, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

### **Conclusions**

Based on the information that DSM provided, as well as other information available to FDA, we have no questions at this time regarding DSM's conclusion that calcium L-methylfolate is GRAS under its intended conditions of use. This letter is not an affirmation that calcium L-methylfolate is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000915 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.  
Carlson -S

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Susan Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

## Reference

1. Neal-Kluever, A., Aungst, J., Gu, Y., Hatwell, K., Muldoon-Jacobs, K., Liem, A., Ogungbesan, A., and Shackelford M. 2014. Infant toxicology: state of the science and considerations in evaluation of safety. *Food and Chemical Toxicology* 70: 68–83.