



James T. Heimbach, Ph.D.  
JHeimbach, LLC  
4530 Broad Branch Road, N.W.  
Washington, DC 20008

Re: GRAS Notice No. GRN 000209

Dear Dr. Heimbach:

The Food and Drug Administration (FDA) is responding to the notice, dated July 26, 2006, that you submitted on behalf of Taiyo International, Inc. (Taiyo) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on July 31, 2006, filed it on August 9, 2006, and designated it as GRAS Notice No. GRN 000209. Taiyo responded to questions from FDA in an amendment dated November 27, 2006.

The subject of the notice is L-theanine. The notice informs FDA of the view of Taiyo that L-theanine is GRAS, through scientific procedures, for use as an ingredient in fruit juices and drinks, non-herbal teas, sports beverages, specialty bottled waters, chocolate bars and chews, hard candies and breath mints, and chewing gum at a level up to 250 milligrams (mg) of L-theanine per serving.

As part of its notice, Taiyo includes the report of a panel of individuals (Taiyo's GRAS panel) who evaluated the data and information that are the basis for Taiyo's GRAS determination. Taiyo considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Taiyo's GRAS panel evaluated the following: review of the starting materials, specifications, and methods of manufacture of L-theanine; absorption, distribution, metabolism and excretion of L-theanine; genetic, acute, subacute, subchronic, and chronic toxicity of the product; and, safety of increasing the L-theanine intake of the U.S. population to the extent anticipated by the intended use of L-theanine. Taiyo's GRAS panel concluded that the intended use of L-theanine is GRAS according to scientific procedures.

Taiyo discusses the chemical identity of L-theanine. L-theanine is a non-protein forming amino acid that occurs naturally in tea (*Camellia sinensis*) and in a non-edible mushroom (*Xerocomus badius*). L-theanine is a water-soluble, white crystalline powder. L-theanine is also known as N-ethyl-L-glutamine and L-glutamic acid- $\gamma$ -monoethylamide, and is identified by the Chemical Abstracts Service (CAS) Registry Number 3081-61-6. L-theanine has the molecular formula  $C_7H_{14}N_2O_3$ , with a molecular weight of 174.2.

Taiyo describes the method of manufacture and provides food grade specifications for its L-theanine. Taiyo indicates that L-theanine is produced from food grade L-glutamine and

ethylamine using the enzyme glutaminase. Taiyo states that the glutaminase is derived from either *Pseudomonas nitroreducens* or *Bacillus amyloliquefaciens*, both of which are not known to be pathogenic or toxicogenic to humans and are currently utilized in the manufacture of enzymes for food use. These microorganisms are cultured, immobilized in a gel, and placed into columns. L-glutamine and ethylamine are then pumped through the columns. The resulting reacted mixture is cooled and purified through several steps to extract dry, crystalline L-theanine. Taiyo provides food grade specifications for L-theanine including limits on lead and other heavy metals, and microbiological specifications.

Taiyo provides an estimated daily intake (EDI) of L-theanine from its intended uses in GRN 000209. The notifier estimates that intake would be 628 milligrams per person per day (mg/p/d) at the mean and 1284 mg/p/d at the 90<sup>th</sup> percentile of intake. Taiyo also estimates the current intake of naturally-occurring L-theanine from consumption of tea. Based on the typical concentration of L-theanine in tea (1-2.5%), Taiyo estimates the intake of L-theanine from tea to be between 153 and 382 mg/p/d at the mean and between 330 and 825 mg/p/d at the 90<sup>th</sup> percentile. Taiyo concludes that the EDI of L-theanine under its intended conditions of use corresponds with the levels of L-theanine currently consumed by the heaviest tea drinkers in the United States.

Taiyo summarizes published and unpublished studies supporting the safe use of L-theanine in foods. Taiyo describes several published studies examining the absorption, distribution, metabolism and excretion of L-theanine. Taiyo further describes published and unpublished toxicity studies including: a published 90-day subchronic toxicity study in rodents, an unpublished 78-week chronic carcinogenicity study, an unpublished *in vitro* mutagenicity study, and two unpublished acute toxicity studies. Taiyo indicates that these studies found no consistent treatment-related effects. Taiyo concluded from the published 90-day study that L-theanine is safe at levels up to 4,000 milligrams L-theanine per kilogram of body weight, the highest dose tested.

Taiyo notes that evidence of kidney lesions was observed in three rodents in the 90-day subchronic study. Taiyo states that these findings are consistent with a genetic predisposition shared by the three rodents, rather than a direct toxic effect. Taiyo reports that a separate published pathology study was undertaken to confirm these findings. Taiyo summarizes this pathology study, and concludes that the pathology study provides evidence that these effects arose spontaneously as a result of a genetic susceptibility shared by the three rodents, and that these effects were not dose-dependent, or considered related to the treatment of L-theanine.

### **Standards of Identity**

In the notice, Taiyo states its intention to use L-theanine in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

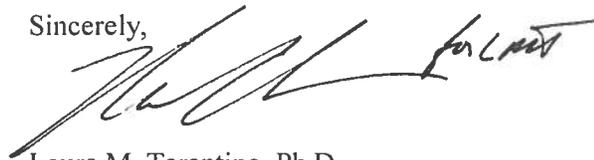
### **Conclusion**

Based on the information provided by Taiyo, as well as other information available to FDA, the agency has no questions at this time regarding Taiyo's conclusion that L-theanine is GRAS under

the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of L-theanine. As always, it is the continuing responsibility of Taiyo to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000209, as well as a copy of the information in this notice that conforms to the information in the proposed GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at <http://www.cfsan.fda.gov/~lrd/foodadd.html>).

Sincerely,

A handwritten signature in black ink, appearing to read "Laura M. Tarantino" with a stylized flourish at the end.

Laura M. Tarantino, Ph.D.  
Director  
Office of Food Additive Safety  
Center for Food Safety  
and Applied Nutrition