

Thomas B. Shea, Ph.D.  
Head of Scientific Advisory Board  
Sevo Nutraceuticals, Inc.  
800 Main Street  
Holden, Massachusetts 01520

RE: Petition for a Qualified Health Claim for a Nutraceutical Formulation and Management of Behavior and Cognitive Difficulties that Can Accompany Dementia (Docket No. FDA-2016-Q-1523)

Dear Dr. Shea:

This letter responds to the qualified health claim petition submitted on behalf of Sevo Nutraceuticals, Inc., which was received by the Food and Drug Administration (FDA or the agency) on April 27, 2016. The petition was submitted in accordance with FDA's guidance on the procedures for the submission of qualified health claim petitions.<sup>1</sup> The petition requested that the agency exercise enforcement discretion for a qualified health claim characterizing the relationship between the consumption of a nutraceutical formulation and the "management of behavioral and cognitive difficulties that can accompany dementia."<sup>2</sup>

The petition proposed the following model claims to be used on the labels or in the labeling of foods and dietary supplements containing the specific vitamin and "nutraceutical formulation" found in the Perceptiv® dietary supplement:

- Protects against cognitive decline which can accompany normal aging. May help manage cognitive and mood difficulties that accompany dementia.
- Independent clinical trials conducted by a leading U.S. university have shown the unique Perceptiv® formula helps protect against the normal cognitive decline of aging while building the body's natural defenses against cell damage. These trials have also shown that Perceptiv® improves working memory and everyday cognitive abilities. These studies have also demonstrated that Perceptiv® can help manage cognitive and mood difficulties that accompany dementia.

---

<sup>1</sup> See FDA, "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," (July 10, 2003), <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm053832.htm>. Although not the case for this petition, many health claim petitions are also submitted pursuant to section 403(r)(4) and 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4), 343(r)(5)(D)).

<sup>2</sup> Petition, page 1.

FDA filed the petition on June 10, 2016 and posted the petition on the Regulations.gov website for a 60-day comment period, consistent with FDA's guidance on the procedures for the submission of qualified health claim petitions.<sup>3</sup> There were no comments submitted to the docket for this petition.

FDA and the petitioner held a telephone conversation on September 7, 2016. During this conversation, FDA explained that a health claim characterizes the relationship between a substance and a reduction in risk of a disease or health-related condition among individuals who do not already have the disease. FDA also noted that some of the studies in the petition, cited as evidence to support the proposed claims, involved subjects who had been diagnosed with a disease (e.g., Alzheimer's disease) prior to taking the Perceptiv® formulation. In your letter dated September 12, 2016, you indicated that, in two of the studies discussed in your petition, the subjects had not been previously diagnosed with a disease; Chan et al. (2010) used healthy subjects in their study, and Remington et al. (2015) studied individuals diagnosed with mild cognitive impairment who were at risk for dementia, but who had not yet received a diagnosis of Alzheimer's disease.

After reviewing the relevant materials, FDA is denying your petition for two reasons: 1) the proposed model qualified health claims fail to characterize the relationship between a substance and a reduction in the risk of a disease or health-related condition, and therefore fail to meet the definition of a health claim; and 2) even if the agency assumes the claim language characterizes the relationship between a substance and a reduction in the risk of a disease or health-related condition, FDA has determined that there is no credible evidence to support a qualified health claim based on Perceptiv® and a reduction in the risk of dementia. This letter sets forth the basis for FDA's determination and the reasons why the agency is denying the qualified health claim petition.

### **I. Denial of the Petition because the Proposed Language for the Qualified Health Claims Fails to Meet the Definition of a Health Claim**

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims are limited to claims characterizing the relationship between a substance and a reduction in risk of contracting a particular disease or health-related condition among individuals who do not already have the disease.<sup>4</sup> Further, health claims cannot include claims about the diagnosis, cure, mitigation, or treatment of any disease or health-related condition.<sup>5</sup>

---

<sup>3</sup> See *supra*, note 1.

<sup>4</sup> See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir. 2004) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

<sup>5</sup> See FDA, "A Food Labeling Guide: Guidance for Industry" (January 2013) at 80; 21 CFR 101.9(k)(1); 101.93(f).

The proposed model claims submitted by the petitioner<sup>6</sup> do not clearly identify a relationship between a substance and a reduction of risk of contracting a particular disease or health-related condition. Instead, the proposed model claims go beyond claiming disease risk reduction and claim that the product can mitigate, treat, or prevent a disease or health-related condition. Accordingly, the petitioner's model claims, as proposed, do not meet the definition of a health claim and as such cannot be a qualified health claim. Such disease claims on the product's label or labeling may render the product a new drug under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the Act). New drugs may not legally be introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in sections 301(d) and 505(a) of the Act. FDA approves a new drug on the basis of scientific data and information demonstrating that the drug is safe and effective. Therefore, FDA is denying this petition to exercise enforcement discretion for the use of the qualified health claims, based on the model qualified health claim language, in its entirety, as proposed and submitted by the petitioner.

## **II. Assuming the Model Qualified Health Claims Meet the Definition of a Health Claim, Denial of the Petition Based on Lack of Credible Evidence**

Even though the language of the proposed model qualified health claims, as submitted by the petitioner, does not meet the definition of a health claim, FDA proceeded to evaluate the petition by assuming that the petition proposed a qualified health claim characterizing a relationship between the petitioner's dietary supplement and the reduction in risk of a particular disease or health-related condition. The petition does not clearly identify a particular disease or health-related condition<sup>7</sup> to be the subject of the qualified health claim. The model claims seek to characterize the relationship between the petitioner's dietary supplement and "cognitive decline which can accompany normal aging," "normal cognitive decline of aging," and "cognitive and mood difficulties that accompany dementia." However, these conditions do not fit within the definition of "disease or health-related condition" as articulated in 21 CFR 101.14(a)(5). Cognitive decline associated with normal aging is not considered to be a disease or health-related condition because it is part of the normal aging process.<sup>8</sup> The use of "cognitive and mood difficulties that accompany dementia" describes the symptoms of a disease or health-related condition (i.e., dementia) in a population that already has the disease or health-related condition.<sup>9</sup>

---

<sup>6</sup> FDA reviewed the proposed model qualified health claims as a whole. We note that while dietary supplements may not have disease claims on their product labels or labeling, dietary supplements may have structure/function claims on their product labels and labeling, provided that certain requirements are met. See sections 201(1)(g)(1) and 403(r)(6) of the Act; 21 CFR 101.93(f)-(g).

<sup>7</sup> As discussed in section II.B.ii, a disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)).

<sup>8</sup> Harada et al., 2013.

<sup>9</sup> We note that FDA considers a claim about the reduction of symptoms of a disease to be a disease claim, which is outside the scope of the definition of "health claim."

The petition contains extensive discussion of Alzheimer's disease and dementia. Additionally, the petitioner submitted to FDA a letter, dated September 12, 2016, which discusses whether the petitioner's dietary supplement can "delay the onset" or "delay a diagnosis of" Alzheimer's disease. Specifically, the letter states, "We appreciate your review of our petition and its supportive data with regards to whether the Perceptiv formulation can delay the onset of Alzheimer's disease."

Alzheimer's disease is a progressive neurodegenerative condition and is the most common form of dementia.<sup>10</sup> Dementia is characterized by a decline in cognitive function in at least two domains (e.g., loss of memory, attention, language, or visuospatial or executive functioning) that is severe enough to impair social and/or occupational functioning.<sup>11</sup>

For the reasons discussed above and the relationship characterized and discussed by the petitioner in other parts of the petition, FDA reviewed the petition for a qualified health claim characterizing the relationship between the petitioner's dietary supplement and reducing the risk of dementia. However, even assuming the petition proposed a qualified health claim that characterized the relationship between the petitioner's dietary supplement and a reduction in risk of dementia, FDA determined there is no credible evidence to support such a qualified health claim. Therefore, FDA is also denying your petition based on the agency's review of the scientific evidence. The following sections discuss FDA's review of the scientific evidence and set forth FDA's basis for determining that there is no credible scientific evidence for the proposed claim.

### **III. Overview of the Review Process for the Scientific Evaluation of Health Claims**

As previously stated, a health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Since health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition, during a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.<sup>12</sup> FDA then considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the

---

<sup>10</sup> The American Psychiatric Association website. <https://www.psychiatry.org/patients-families/alzheimers/what-is-alzheimers-disease> (retrieved on August 27, 2018).

<sup>11</sup> Lin et al., 2013.

<sup>12</sup> See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009 ("guidance on scientific evaluation of health claims") [<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm>].

substance and the disease or health-related condition.<sup>13</sup> The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.<sup>14</sup>

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,<sup>15</sup> review articles,<sup>16</sup> and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, usually do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications<sup>17</sup> to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.<sup>18</sup> If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine (IOM), 2005). Therefore, animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

---

<sup>13</sup> We note that throughout the rest of this letter, “disease” will be used synonymously with “disease or health-related condition,” as defined in 21 CFR 101.14(a)(5), except when it is used in the name of a specific disease (e.g., Alzheimer’s disease).

<sup>14</sup> In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (e.g., disease). Intervention studies provide the strongest evidence for an effect. See *supra*, note 12 [Section III.B, “Intervention Studies”].

<sup>15</sup> A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

<sup>16</sup> Review articles summarize the findings of individual studies.

<sup>17</sup> Other examples include book chapters, abstracts, letters to the editor, and committee reports.

<sup>18</sup> Although FDA does not generally use meta-analyses in its health claim evaluations for the reasons discussed in the text, the agency will include a meta-analysis in its scientific evaluation if the meta-analysis was conducted with pooled data from all the publicly available studies from which scientific conclusions can be drawn (based on the criteria in FDA’s guidance on scientific evaluation of health claims) and the statistical analyses were properly conducted. See *supra*, note 12 [Section III.B, “Research Synthesis Studies”].

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker, 1991; National Research Council, 2011). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.<sup>19</sup> The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,<sup>20</sup> and the overall consistency<sup>21</sup> of the total

---

<sup>19</sup> See *supra*, note 12 [Section III.F].

<sup>20</sup> Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).

<sup>21</sup> Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill, 1965); See also, Agency for Healthcare Research and Quality, “Systems to rate

body of evidence.<sup>22</sup> Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance-disease relationship, and if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship and to prevent the claim from being misleading in other ways.

#### **IV. The Agency's Consideration of a Qualified Health Claim**

##### **A. Substance**

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, mineral, herbs, or other similar nutritional substances (21 CFR 101.14(a)(2)).

The petition identified a “nutraceutical formulation” having the brand name Perceptiv® (hereinafter referred to as the petitioner’s dietary supplement) as the substance that is the subject of the proposed claim. Although the form of the product was not specified in section II.A of the petition (“Description of the supplement”), the product serving size was identified as being “Two (2) caplets” in section VI. (“Labeling requirements”). The petitioner’s dietary supplement contains six ingredients, including three vitamins, found in many foods, and three nutritional substances. Because the serving size (or daily dose) is two caplets, each caplet (i.e., one-half serving) contains the following levels of vitamins: folic acid (200 mcg, 50% DV), vitamin B-12 (3 mcg 125% DV) and vitamin E (15 IU or 14 mg, 90 % DV). Each caplet also contains three nutritional substances (referred to in the petition as “nutraceuticals”) at the following levels: N-acetyl cysteine (300 mg), acetyl-L-carnitine (250 mg) and S-adenosyl methionine (200 mg). Daily values have not been established for these three nutritional substances. According to the petition, the concentrations of these nutritional substances in each caplet of the petitioner’s dietary supplement are similar to levels typically found in other commercially available dietary supplement products that contain these substances as single ingredients. Thus, the “substance” identified in this petition is a combination of six individual substances, each of which is present in a specific amount per two caplets.

Therefore, the agency concludes that the six individual substances in the petitioner’s dietary supplement are either components of food (i.e., folic acid, vitamin B-12, and vitamin E) or a dietary supplement that includes vitamins or other nutritional substances (i.e., N-acetyl cysteine, acetyl-L-carnitine, and S-adenosyl methionine), and therefore, the “nutraceutical formulation” meets the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)).

---

the scientific evidence” (March 2002) [<http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf>], defining “consistency” as “the extent to which similar findings are reported using similar and different study designs.”

<sup>22</sup> See *supra*, note 12 [Section III.F].

## **B. Disease or Health-Related Condition**

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). As previously discussed in section II, FDA proceeded to evaluate the qualified health claim petition for a reduction in risk of dementia based on the petition's extensive discussion and the petitioner's identification of dementia. Dementia is characterized by a decline in cognitive function in at least two domains (e.g., loss of memory, attention, language, or visuospatial or executive functioning) that is severe enough to impair social and/or occupational functioning, and the most common form of dementia, Alzheimer's disease, is a progressive neurodegenerative condition.<sup>23</sup> Therefore, the agency concludes that dementia is a disease or health-related condition because there is damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning, thereby satisfying the requirement in 21 CFR 101.14(a)(5).

## **C. Safety Review**

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

It is not necessary for FDA to make a determination about the safety of the petitioner's dietary supplement in this letter because we are denying the proposed claim for lack of credible evidence, as discussed in sections II of this letter.

## **V. Review of the Scientific Evidence**

The evidence for the relationship between the petitioner's dietary supplement and risk of dementia is evaluated below.

To date, no surrogate endpoints have been recognized for evaluating the risk of dementia.<sup>24</sup> Moreover, the petition included no data demonstrating that any of the outcomes assessed in the supporting studies are surrogate endpoints for the risk of dementia. Therefore, at this time, the relationship between the intake of the petitioner's dietary supplement and risk of dementia can only be evaluated by measuring the cognitive decline used to diagnose dementia.<sup>25</sup>

---

<sup>23</sup> See *supra*, notes 10 and 11.

<sup>24</sup> Currently, there are no outcome measures (endpoints) that are accepted by the Agency as surrogate endpoints for use in clinical intervention trials in dementia (including dementia of the Alzheimer's type) or in any other clinical condition in which there is impairment of one or more cognitive functions (Mani RB, 2016).

<sup>25</sup> See *supra*, note 12 [Section III.F].

The petition cited 124 publications as evidence to substantiate the risk reduction relationship between the petitioner's dietary supplement and dementia for the proposed claim (see Docket # FDA-2016-Q-1523-0002), including 21 human intervention studies,<sup>26</sup> 18 observational studies,<sup>27</sup> 22 animal studies,<sup>28</sup> 15 *in vitro* studies,<sup>29</sup> nine studies on biomarkers and diagnosis of Alzheimer's disease,<sup>30</sup> one study on the pharmacokinetics of *S*-adenosyl methionine (Giulidori et al., 1984), one article on the use of a computer-assisted protocol to identify the chemical structure (pharmacophore) of compounds that could bind molecules involved in the pathway (e.g., amyloid cascade) of the development of Alzheimer's disease (Dominguez et al., 2015), 22 review articles,<sup>31</sup> five meta-analyses,<sup>32</sup> three debate/opinion articles on Alzheimer's disease,<sup>33</sup> one hypothesis article (Selhub and Miller 1992), one report on Alzheimer's disease (Alzheimer's 2015), one manual on the Dementia Rating Scale-2 (Jurica 2001), one abstract (Di Domenico et al., 2015), one book chapter (Joseph et al., 2015), one study on costs associated with Alzheimer's disease (Stefanacci 2011), and one article written in a foreign language (Croisile et al., 2012). In addition, we identified through a literature search one intervention study that evaluated the relationship between consumption of the petitioner's dietary supplement and risk of dementia (Remington et al., 2016).

The ingredients specified in the petitioner's dietary supplement include *S*-adenosyl methionine (400 mg), acetyl-L-carnitine (500 mg), N-acetyl cysteine (600 mg), and three vitamins (folic acid (400 µg), vitamin B<sub>12</sub> (6 µg), and vitamin E (as alpha-tocopherol; 30 IU)). However, the majority

---

<sup>26</sup> Ma et al., 2016; Bianchetti et al., 2003; Adair et al., 2001; Thal et al., 2000; Thal et al., 1996; van Dyck et al., 2009; Rommer et al., 2016; Yang et al., 2015; Kok et al., 2015; de Sousa and Amaral, 2012; Chan et al., 2008a; Remington et al., 2015a; Remington et al., 2009; Chan et al., 2010; Remington et al., 2015b; Hoffmann et al., 2016; Bottiglieri et al., 1990; Carney et al., 1989; Rudolph et al., 2011; Lloret et al., 2009.

<sup>27</sup> Levine et al., 2015; Okello et al., 2009; Petersen et al., 2016; Shatenstein et al., 2007; Surtees et al., 1991; Lehallier et al., 2015; Feng et al., 2009; McCaddon and Davies, 2005; Tangney et al., 2009; Garcia-Alberca et al., 2012; Raggi et al., 2015; Sanders et al., 2008; Hyland et al., 1988; Muller et al., 2001; Llamas-Velasco et al., 2015; Morris et al., 2002; Morris et al., 2005; Ortega et al., 2002.

<sup>28</sup> Schatz et al., 1981; Barnes et al., 1990; Markowska and Olton, 1990; Hung et al., 2001; Fuso et al., 2008; Troen et al., 2008; Mihalick et al., 2003; Shea and Rogers, 2002; Tchanchou et al., 2005; Chan and Shea, 2006; Zhang et al., 2008; Farr et al., 2003; Fu et al., 2006; Chan and Shea, 2007a, 2007b, 2008b, 2009a, 2009b; De la Cruz et al., 2000; De La Cruz et al., 2002; Villalobos et al., 2000; Nishida et al., 2006.

<sup>29</sup> Li et al., 2015; Liu et al., 2016; Unnithan et al., 2014; Paintlia et al., 2008; Fuso et al., 2011a, 2011b; Kennedy et al., 2004; Dhitavat et al., 2002; Ho et al., 2003; Tjiattas et al., 2004; Fuso et al., 2005; Kifle et al., 2009; Dhitavat et al., 2005; Chan et al., 2008c; Serra et al., 2008.

<sup>30</sup> Wang et al., 2016; Janssen et al., 2016; De Meyer et al., 2010; Papp et al., 2016; Grimmer et al., 2013; Hatashita and Yamasaki, 2013; Grimmer et al., 2016; Nesteruk et al., 2015; Petersen et al., 2010.

<sup>31</sup> Rolandi et al., 2016, Scarpa et al., 2003; Schulz and Martire, 2004; Shah and Reichman, 2006; Wollen 2010; Mischoulon and Fava, 2002, Arenaza-Urquijo et al., 2015; Couto and Millis, 2015; Gardener et al., 2016; Berman and Brodaty, 2004; Noyes et al., 2010; Cooper et al., 2007; Langa and Levine, 2014; Rochtus et al., 2015; Cobb and Cole, 2015; Esposito et al., 2002; Mattson and Shea, 2003; Virmani et al., 2013; Monti et al., 2015; Bottiglieri 2002; Ulatowski and Manor, 2015; Farina et al., 2012.

<sup>32</sup> Montgomery et al., 2003; Strohle et al., 2015; Groot et al., 2016; Mourao et al., 2016; Cao et al., 2016.

<sup>33</sup> Shea and Chan, 2008; Waite 2015; Emery 2011.

of the studies cited in the petition pertained to the individual ingredients, rather than the exact formulation of the petitioner's dietary supplement as described above in section II.B.i. of this letter. The studies on individual ingredients included 19 studies on *S*-adenosyl methionine, eight studies on vitamin E, seven studies on acetyl-L-carnitine, and three studies on vitamin B<sub>12</sub>.

Other studies evaluated the combination of two or three of the ingredients: six studies on folate/folic acid and vitamin B<sub>12</sub>, three studies on folate and vitamin E, one study on various B vitamins and *S*-adenosyl methionine, and one study on *S*-adenosyl methionine, acetyl-L-carnitine, and N-acetyl cysteine. None of the 18 observational studies submitted by the petitioner evaluated the association between the petitioner's dietary supplement (as per formulation) and the risk of dementia. Consequently, FDA could not draw scientific conclusions from these studies about the relationship between the petitioner's dietary supplement and the reduced risk of dementia.

Six human intervention studies investigated the effect of all six ingredients in the petitioner's dietary supplement (as per formulation) and cognitive function. These human intervention studies were included in our evaluation for a qualified health claim on the relationship between the intake of the petitioner's dietary supplement and reduced risk of dementia.

#### **A. Assessment of Background Materials**

"Background materials" here refers to review articles, meta-analyses, book reviews, letters to the editor, federal reports, and website print-outs. Although useful for background information, these materials do not contain sufficient information on the individual studies that they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in these materials prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the background materials supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

#### **B. Assessment of Animal and *In Vitro* Studies**

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. They can also be used to generate hypotheses, investigate biological plausibility of hypotheses, or to explore a mechanism of action. However, these types of studies cannot adequately support a relationship between the substance and disease in humans. There were no animal or *in vitro* studies that evaluated the relationship between the petitioner's dietary supplement and dementia that were available to the agency.

### C. Assessment of Intervention Studies

There was a total of six intervention studies that evaluated the relationship between the petitioner's dietary supplement and risk of dementia (Chan et al., 2008a, 2010; Remington et al., 2009, 2015a, 2015b, 2016). FDA determined that scientific conclusions about the relationship between the petitioner's dietary supplement and dementia risk could not be drawn from these six studies for the reasons discussed below.

Four studies included individuals previously diagnosed with early to late stages of Alzheimer's disease (Chan et al., 2008a; Remington et al., 2009, 2015a, 2016). Thus, these studies evaluated the effect of the petitioner's dietary supplement on treating, rather than reducing the risk of dementia. Health claims characterize the relationship between the substance and a reduction in risk of a disease.<sup>34</sup> In these studies, however, participants already had the disease (i.e., dementia of the Alzheimer's type) that is subject of the claim. In evaluating qualified health claim petitions, FDA considers evidence from studies in individuals already diagnosed with the disease only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people.<sup>35</sup> Because there is no evidence to this effect, we could not draw any scientific conclusions from these studies. Furthermore, two of these studies (Chan et al., 2008a; Remington et al., 2016) did not include a control group. Without a control group, it was not possible to determine whether changes in cognitive function were due to the intake of the petitioner's dietary supplement or to unrelated or uncontrolled extraneous factors (Spilker 1991). Hence, scientific conclusions could not be drawn from the four studies described above about the relationship between the petitioner's dietary supplement and the risk of dementia.

Remington et al. (2015b) studied individuals who were previously diagnosed with mild cognitive impairment (MCI), which is characterized as a cognitive decline not severe enough to affect the usual activities of daily living. Individuals with MCI are not considered having dementia *per se*; they are at a greater risk of developing dementia compared with the general population, although the estimated progression of MCI to dementia varies greatly (from < 5% to 12-20%) depending on the population (Langa and Levine, 2014). In the United States, the prevalence of MCI in adults ages 71 years and older has been estimated to be approximately 22% with an annual progression rate to dementia of 12% (Plassman et al., 2008). The study did not indicate whether there were significant differences between the treatment and control groups (i.e., no p-values were reported). A statistical analysis is critical to determine whether there was a reduction in the

---

<sup>34</sup> See *supra*, note 4.

<sup>35</sup> See *supra*, note 12 [Section III. D].

risk of dementia among individuals taking the dietary supplement compared to individuals who did not take the supplement. If the appropriate statistical tests are not performed on the substance-disease relationship, it cannot be determined whether there is a statistically significant difference between the two groups or whether any differences are the result of chance alone.<sup>36</sup> As a result, scientific conclusions could not be drawn from this study about the relationship between the petitioner's dietary supplement and risk of dementia.

Chan et al. (2010) evaluated the effect of the petitioner's dietary supplement on cognitive performance in subjects from various senior centers and institutions. Participants were at least 18 years of age with no known or suspected dementia or clinical memory difficulties. Subjects performed one or more of the following cognitive tests: the California Verbal Learning Test II (CVLT-II),<sup>37</sup> the Trail-Making test (parts A and B),<sup>38</sup> and the Digit-Memory Test,<sup>39</sup> with different study designs and duration. For our evaluation of the scientific evidence of the various studies and for clarity purpose we have identified each study design with their respective cognitive tests as "trials" as it is described below.

### **Trial 1**

All subjects<sup>40</sup> were assigned to receive the petitioner's dietary supplement (two tablets of the petitioner's dietary supplement per day) in an open-label design for six months and their cognitive performance was assessed by the Trail-Making test (parts A and B) at baseline, and at three and six months.

---

<sup>36</sup> See *supra*, note 12 [Section III. D].

<sup>37</sup> The California Verbal Learning Test-II (CVLT-II) is the latest (2000) version of a widely used verbal learning and memory test. The current version contains recalling and recognition of two lists of words over immediate and delayed trials. List A includes 16 words and requires the examinee to recall the list over five trials. List B (interference), which is also 16 words, is administered after List A for one trial. Short-delay free recall and cued recall are administered after List B. A 20-minute delay follows the short-delay recalls, followed by nonverbal testing. Long-delay recall, long-delay-cued recall, and yes/no-recognition trials of List A follow the 20-minute delay ([Encyclopedia of Clinical Neuropsychology](#) pp 475-476).

<sup>38</sup> The Trail Making Test is a measure of attention, processing speed, and mental flexibility. On part A, examinees are required to connect 25 encircled numbers that have been randomly placed on a page in proper order. On part B, examinees are required to connect the encircled numbers and letters in alternating order. Examinees are instructed to connect the circles as fast as they can within 5 minutes for each task ([Encyclopedia of Clinical Neuropsychology](#) pp 2537-2538).

<sup>39</sup> In the Digit-Memory test, participants were asked to repeat a series of numbers, beginning with two numbers and increasing up to eight numbers; this was continued until they made an error or a series of 8 numbers was correctly repeated. They were then asked to repeat new series of numbers, again starting with a series of two numbers and increasing up to a series of 8 numbers (distinct from each other and from the first set), but were asked to repeat them in reverse order. The total number of correct responses was normalized according to age and percentiles (Chang et al., 2010).

<sup>40</sup> The total number of subjects that participated in trial 1 is not clear from the publication. For this reason, this trial was eliminated from FDA's scientific evaluation.

## **Trial 2**

In this 4-week trial, 43 subjects were randomly assigned to either a treatment (two tablets of the petitioner's dietary supplement per day) or a placebo group for two weeks, after which all subjects received the dietary supplement in an open-label design for another two weeks. The test instruments used included the Trail-Making test (parts A and B) and the Digit-Memory test to measure cognitive performance at baseline, and at two and four weeks.

## **Trial 3**

Trial 3 used an initial randomized, double-blind, placebo-controlled, parallel-arm study design with subjects randomly assigned to either a treatment group (two tablets of the petitioner's dietary supplement per day) or a placebo group. Test instruments used to measure cognitive performance included the CVLT-II Test and the Trail-Making Test (parts A and B). For the CVLT-II Test, 59 subjects received the petitioner's dietary supplement and 56 received the placebo, while for the Trail-Making Test, 51 subjects received the petitioner's dietary supplement and 42 received the placebo. Although the trial was conducted over a 12-month period, the control group was only followed for the first three months of the trial, after which, all subjects were instructed to take the petitioner's dietary supplement in an open-label design. The trial assessed study subjects' cognitive performance at baseline and every three months thereafter. However, due to problems encountered with the application of the CVLT-II Test, the trial discontinued use of the CVLT-II Test after three months.

## **FDA's Scientific Evaluation**

In an open-label design,<sup>41</sup> we cannot determine whether differences in endpoint measurements are due to the consumption of the dietary supplement or to unrelated and uncontrolled extraneous factors, and the lack of a control group creates a potential for bias.<sup>42</sup> Consequently, scientific conclusions could not be drawn from trial 1 and the open-label extension periods for trials 2 and 3. FDA only considered for our evaluation the first two weeks in trial 2 and first three months in trial 3, in which a control group was present,<sup>43</sup> for the relationship between the petitioner's dietary supplement and risk of dementia.

Moreover, all three trials lacked a comprehensive cognitive assessment of the study subjects at entry into the study. Only a vague description of the cognitive status of subjects at baseline was provided as the inclusion criteria: "*individuals with no known or suspected dementia or clinical memory difficulties were included in the study.*" If interpreted literally, the statement does not exclude the possibility that some subjects may have had impairment of one or more cognitive functions other than memory (e.g., learning, language, visuospatial perception, and higher

---

<sup>41</sup> In open-label studies, both the investigator and subjects know what substance is being tested and know that subjects are receiving the test substance. Open label trials are uncontrolled, as they involve only a treatment group. Without a concurrent control group that receives a placebo and is evaluated according to the same measures as the treatment group, it is not possible to determine whether effects on outcome measures are due to the test substance or to other extraneous factors. See *supra*, note 12 [Section III. D].

<sup>42</sup> See *supra*, note 12 [Section III. D].

<sup>43</sup> See *supra*, note 12 [Section III. D].

executive functions, such as, planning, organizing, and sequencing) at entry. Notably, the study authors recognized in their publication that “*the lack of a more rigorous pre-screening of participants for latent mental compromise*” was a limitation of their study.

The study authors did not include any information on demographic or other baseline characteristics of the study population. If baseline values are statistically significantly different between the treatment and control groups, then it is difficult to interpret a study’s findings regarding the intervention.<sup>44</sup> For example, the nutritional status of the subjects is an important baseline characteristic of the study population which was not reported in this study. Individuals deficient in vitamin B<sub>12</sub> may be cognitively impaired (Tangney et al., 2009), and their cognitive function may improve with supplementation of vitamin B<sub>12</sub> alone,<sup>45</sup> which is one of the components of the petitioner’s dietary supplement. Additionally, there was no indication of any intake assessment of other medication(s) and/or dietary supplement(s) that could possibly confound the results. In summary, because no information was provided on the baseline characteristics of the study subjects that could be used to evaluate whether the treatment and control groups were comparable, we cannot assume that the treatment and control groups were comparable at entry, which makes it difficult to interpret the study’s findings regarding the intervention. Therefore, no scientific conclusions can be drawn from all three trials described in Chang et al. 2010 on the improvement of executive function and memory for the treatment group compared to the control group.

In addition to the flaws mentioned above, there were other flaws in the study design for trials 2 and 3 that further hindered the interpretation of the results. These additional flaws are described below.

## **Trial 2**

For trial 2, only results from the portion of the trial with a control group (i.e., the first two weeks of the trial) were considered in FDA’s review. During the first two weeks of trial 2, Chan et al. (2010) reported that the subjects in the treatment group showed a statistically significant ( $p < 0.05$ ) improvement in their cognitive performance as measured by the Trail-Making Test and the Digit-Memory Test and that there was no change in cognitive performance among those receiving the placebo. However, during the data analysis, the authors did not properly conduct a statistical analysis of the results of the cognitive performance tests (i.e., the Trail-Making Test and the Digit-Memory Test). The results from the treatment group were not statistically compared with those from the control group; instead, the authors evaluated change from baseline to two weeks of supplementation separately for the treatment group and control group. Without

---

<sup>44</sup> See *supra*, note 12 [Section III. D].

<sup>45</sup> See FDA. “Coping with Memory Loss” (June 2016).

[<https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107783.htm>]

a comparison to the control group, it cannot be determined whether changes in the endpoint were due to the intake of the dietary supplement or to unrelated and uncontrolled extraneous factors.<sup>46</sup> Therefore, scientific conclusions cannot be drawn from trial 2 to evaluate the relationship between the petitioner's dietary supplement and reduced risk of dementia.

### **Trial 3**

As mentioned in the first paragraph of our evaluation of the proposed qualified health claims, FDA only considered the data generated during the first three months of trial 3 and did not consider the results from the open label phase (months 3-12) of the trial.

In this trial, the authors did not properly conduct a statistical analysis of the results of the executive function test (i.e., the Trail-Making Test). The results from the treatment group were not statistically compared with those from the control group; instead, the authors evaluated change from baseline to three months of supplementation separately for the treatment group and the control group. Without a comparison to the control group, it cannot be determined whether changes in the endpoint were due to the intake of the dietary supplement or to unrelated and uncontrolled extraneous factors.<sup>47</sup> Therefore, scientific conclusions cannot be drawn from the Trail-Making Test to evaluate the substance-disease relationship.

Consequently, the results from the memory test (i.e., CVLT-II Test) would be the only results from which scientific conclusions potentially could be drawn about the relationship between the petitioner's dietary supplement and risk of dementia. However, dementia is characterized by a decline in at least two cognitive domains that is severe enough to effect social and occupational functioning (Lin et al., 2013). Although trial 3, assessed two domains (executive function with the Trail-Making Test and memory with the CVLT-II Test), the results of the executive function test were eliminated due to the reasons described above, so the results for only one domain, memory, remained. Consequently, there was insufficient data to support any dementia-related findings. Therefore, scientific conclusions cannot be drawn from trial 3 to evaluate the relationship between the petitioner's dietary supplement and reduced risk of dementia.

In addition, the data on memory as assessed by the CVLT-II Test had some flaws. For the CVLT-II recall data, the authors created a composite score by combining all three free-recalls<sup>48</sup> (immediate-, short-, and long-), giving equal weight to each component. Chan et al. (2010) reported a statistically significant improvement in the CVLT-II Test composite score among those receiving the dietary supplement compared to the placebo group after three months of

---

<sup>46</sup> See *supra*, note 12 [Section III. D].

<sup>47</sup> See *supra*, note 12 [Section III. D].

<sup>48</sup> Free-recall involves the presentation of information, such as a list of words, to the examinee, followed by a period of either immediate or delayed recall, during which the examinee is asked to produce as much of the presented information as possible (Encyclopedia of Autism Spectrum Disorders, pp 1325-1326).

supplementation. However, we concluded that it was inappropriate to combine the results of the immediate-recall component with the short- and long-recall components of the CVLT-II Test. The immediate-recall component assesses attention and working memory, and the short- and long-recall components assess episodic memory. Since attention and working memory functions have different underlying mechanisms than those that underlie episodic memory, scientific conclusions cannot be drawn from a composite score of the immediate-, short-, and long-recall components of the CVLT-II Test.

The trial also had other design flaws, as described in the publication. Chan et al. (2010) stated that *“the CVLT-II test was discontinued during the open-label extension, since participants self-reported that they had committed portions of the word list to memory.”* Reports in the scientific literature suggest that it is not uncommon for participants to develop better test-taking strategies with repeated exposure to an identical list of words (i.e., the “practice effect”), thus invalidating the results of serial neuropsychological assessments (Benedict and Zgaljardic, 1998). We

contemplated whether the results from the CVLT-II Test during the first three months would still be valid, considering that the test was discontinued after three months due to the problems encountered with the practice effect. The practice effect has been observed as early as nine days until 74 days between the test-retest (Benedict and Zgaljardic, 1998; Woods et al., 2006). Therefore, it is possible that some study subjects had memorized the word list from the CVLT-II Test during the initial three months of the trial. This would, indeed, defeat the purpose of the test, and thus compromise the interpretation of the results. Additionally, the use of alternate forms for the CVLT-II Test is recommended during the test-retest to minimize the confounding effects of practice and repetition (Woods et al., 2006), which Chan et al. (2010) acknowledged in their publication by stating that *“the difficulty encountered with the CVLT-II could potentially be avoided by alternation of the test instruments.”* However, the trial did not use alternate forms for the CVLT-II Test to minimize confounding by practice effect. Furthermore, during the analyses of the results, the authors excluded parts of the CVLT-II Test, such as the cued-recall,<sup>49</sup> and only the components of the free recall (i.e., immediate-, short-, and long-recall) were reported. The authors excluded the cued-recall results because study subjects indicated that they had committed portions of the word list to memory based on the cued groupings of words. Yet, cued recall is usually a standard part of the CVLT-II Test and typically reported. The publication failed to include sufficient information for FDA to evaluate whether the authors’ reporting on the free-recalls, but not on cued-recalls, was appropriate in this instance (e.g., whether it was specified in the statistical analysis plan or whether it was a post-hoc analysis), such that scientific conclusions could not be drawn.

For the above reasons, scientific conclusions could not be drawn for the relationship between the petitioner’s dietary supplement and reduced risk of dementia.

---

<sup>49</sup> Cued recall is the retrieval of memory with the help of cues. Such cues are often semantic. Cued recall differs from free recall in that a cue or word is presented that is related to the information being remembered. The related cue or word aides in the process of memory retrieval (Encyclopedia of Clinical Neuropsychology, pp 751-752).

#### **D. Assessment of Observational Studies**

There were no observational studies that evaluated the association between the petitioner's dietary supplement and risk of dementia.

#### **VI. Strength of the Scientific Evidence**

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated, and the overall consistency of the total body of evidence.<sup>50</sup> Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance-disease relationship, and if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

As discussed in Section II.B., there were no intervention or observational studies from which scientific conclusions could be drawn about the relationship between the intake of the petitioner's dietary supplement and risk of dementia. Based on its review of the totality of publicly available scientific evidence,<sup>51</sup> FDA concludes that there is no credible evidence for a relationship between intake of the petitioner's dietary supplement and reduced risk of dementia.

#### **VII. Agency's Consideration of Disclaimers or Qualifying Language**

FDA considered but rejected use of a disclaimer or qualifying language to accompany the proposed claim for consumption of the petitioner's dietary supplement and a reduction in the risk of dementia. The agency concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in these instances, where there is no credible evidence to support the claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claims as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the message conveyed by the unsubstantiated claims. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (stating that pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*,

---

<sup>50</sup> See *supra*, note 12 [Section III. F].

<sup>51</sup> We note that the petitioner made several assertions regarding the level of evidence presented by the petition. Based on a scientific review of all the relevant evidence, including consideration of the comparative evidence addressed by the petitioner's assertions, FDA concludes that there is no credible evidence to support a qualified health claim.

290 F.3d 578, 598 (3d Cir. 2002) (“We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer.”); *Pearson v. Shalala*, 164 F.3d 650, 659 (D.C. Cir. 1999) (indicating that where the weight of evidence was against the claim, FDA could rationally conclude that the disclaimer “The FDA has determined that no evidence supports this claim” would not cure the misleadingness of a claim). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir. 1975) (per curiam) (upholding FTC order to excise “Dollar a Day” trade name as deceptive because “by its nature [it] has a decisive connotation for which any qualifying language would result in contradiction in terms.”), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing “self-contradictory labels”). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (finding that a disclaimer stating that “no claim is made that the product cures anything, either by the writer or the manufacturer” was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I. 1994) (“The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing.”), *judgment amended on other grounds*, 862 F. Supp. 717 (D.R.I. 1994).

Further, under the *Central Hudson* analytical framework, misleading commercial speech is not protected under the First Amendment.<sup>52</sup> Here, because the petitioner’s proposed claims are not supported by credible evidence, it is inherently misleading and thus not protected under the First Amendment. *See Alliance for Natural Health v. Sebelius*, 786 F. Supp. 2d 1, 17 (D.D.C. 2011) (“Claims which are not supported by credible evidence are misleading commercial speech and may be prohibited under the threshold step of the *Central Hudson* test.”).<sup>53</sup>

---

<sup>52</sup> Under the *Central Hudson* framework, the threshold question is whether the speech is false or inherently or actually misleading or concerns unlawful activity – such speech may be prohibited. *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 563-66 (1980). If the speech is truthful and not inherently or actually misleading, the government must establish that the regulation directly advances a substantial governmental interest and the regulation is no more extensive than necessary to serve that interest. *Id.*

<sup>53</sup> Even if the remaining prongs of the *Central Hudson* test applied, the Government clearly has a substantial interest in ensuring that consumers are not misled by false or misleading health claims that are not supported by credible evidence, and that requiring specific health claims on labels to be adequately substantiated by scientific or medical evidence directly advances the asserted governmental interest, and is no more extensive than necessary to serve that interest. *See POM Wonderful, LCC v. FTC*, 777 F.3d 478, 502 (D.C. Cir. 2015), *cert. denied*, 136 S. Ct. 1839 (2016) (“[T]he injunctive order’s requirement of *some* [randomized and controlled human clinical trial] substantiation for disease claims directly advances, and is not more extensive than necessary to serve, the interest in preventing misleading commercial speech.”).

### **VIII. Conclusions**

Based on FDA's consideration of the language of the proposed model claims, scientific evidence and other information submitted with your petition, and other pertinent scientific evidence and information, FDA concludes that 1) the proposed model claims as submitted by the petitioner fail to characterize a relationship between a substance and a reduction in the risk of a disease or health-related condition and, therefore, fail to meet the definition of a health claim; and 2) even if the agency assumes the petition proposed qualified health claim language that characterized a relationship between consumption of the petitioner's dietary supplement and a reduction in risk of dementia, there is no credible evidence to support such a qualified health claim. Thus, FDA is denying your petition for a qualified health claim.

Please note that scientific information is subject to change, as are consumer consumption patterns. In the event that new information is submitted to the agency, such as new scientific evidence or alternative claim language, FDA intends to evaluate the new information to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement.

Sincerely,

/s/

Douglas Balentine, Ph.D.  
Director  
Office of Nutrition and Food Labeling  
Center for Food Safety and Applied Nutrition

## References

- About Brain Injury. A Glossary of Terms (2003). <http://www.waiting.com/glossarye.html>.
- Adair, J. C., J. E. Knoefel & N. Morgan (2001). Controlled trial of N-acetylcysteine for patients with probable Alzheimer's disease. *Neurology*, 57, 1515-7.
- Alzheimer's Association (2015). Alzheimer's disease facts and figures. *Alzheimers Dement*, 11, 332-84.
- Arenaza-Urquijo, E. M., M. Wirth & G. Chetelat (2015). Cognitive reserve and lifestyle: moving towards preclinical Alzheimer's disease. *Front Aging Neurosci*, 7, 134.
- Barnes, C. A., A. L. Markowska, D. K. Ingram, H. Kametani, E. L. Spangler, V. J. Lemken & D. S. Olton (1990). Acetyl-L-carnitine. 2: Effects on learning and memory performance of aged rats in simple and complex mazes. *Neurobiol Aging*, 11, 499-506.
- Benedict, R. H. & D. J. Zgaljardic (1998). Practice effects during repeated administrations of memory tests with and without alternate forms. *J Clin Exp Neuropsychol*, 20, 339-52.
- Berman, K. & H. Brodaty (2004). Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs*, 18, 807-25.
- Bianchetti, A., R. Rozzini & M. Trabucchi (2003). Effects of acetyl-L-carnitine in Alzheimer's disease patients unresponsive to acetylcholinesterase inhibitors. *Curr Med Res Opin*, 19, 350-3.
- Bottiglieri, T. (2002). S-Adenosyl-L-methionine (SAME): From the bench to the bedside – molecular basis of a pleiotropic molecule. *Am J Clin Nutr*, 76, 1151S-7S.
- Bottiglieri, T., P. Godfrey, T. Flynn, M. W. Carney, B. K. Toone & E. H. Reynolds (1990). Cerebrospinal fluid S-adenosylmethionine in depression and dementia: Effects of treatment with parenteral and oral S-adenosylmethionine. *J Neurol Neurosurg Psychiatry*, 53, 1096-8.
- Cao, L., L. Tan, H. F. Wang, T. Jiang, X. C. Zhu, H. Lu, M. S. Tan & J. T. Yu (2016). Dietary patterns and risk of dementia: A systematic review and meta-analysis of cohort studies. *Mol Neurobiol*, 53, 6144-54.
- Carney, M. W., T. K. Chary, T. Bottiglieri & E. H. Reynolds (1989). The switch mechanism and the bipolar/unipolar dichotomy. *Br J Psychiatry*, 154, 48-51.
- Chan, A., J. Paskavitz, R. Remington, S. Rasmussen & T. B. Shea (2008a). Efficacy of a vitamin/nutriceutical formulation for early-stage Alzheimer's disease: A 1-year, open-label pilot study with an 16-month caregiver extension. *Am J Alzheimers Dis Other Dement*, 23, 571-85.

Chan, A., R. Remington, E. Kotyla, A. Lepore, J. Zemianek & T. B. Shea (2010). A vitamin/nutriceutical formulation improves memory and cognitive performance in community-dwelling adults without dementia. *J Nutr Health Aging*, 14, 224-30.

Chan, A., E. Rogers & T. B. Shea (2009a). Dietary deficiency in folate and vitamin E under conditions of oxidative stress increases phospho-tau levels: Potentiation by ApoE4 and alleviation by S-adenosylmethionine. *J Alzheimers Dis*, 17, 483-7.

Chan, A. & T. B. Shea (2006). Dietary and genetically-induced oxidative stress alter tau phosphorylation: Influence of folate and apolipoprotein E deficiency. *J Alzheimers Dis*, 9, 399-405.

Chan, A. & T. B. Shea (2007a). Effects of dietary supplementation with N-acetyl cysteine, acetyl-L-carnitine and S-adenosyl methionine on cognitive performance and aggression in normal mice and mice expressing human ApoE4. *Neuromolecular Med*, 9, 264-9.

Chan, A. & T. B. Shea (2007b). Folate deprivation increases presenilin expression, gamma-secretase activity, and A $\beta$  levels in murine brain: Potentiation by ApoE deficiency and alleviation by dietary S-adenosyl methionine. *J Neurochem*, 102, 753-60.

Chan, A., F. Tchanchou, V. Graves, R. Rozen & T. B. Shea (2008b). Dietary and genetic compromise in folate availability reduces acetylcholine, cognitive performance and increases aggression: Critical role of S-adenosyl methionine. *J Nutr Health Aging*, 12, 252-61.

Chan, A., F. Tchanchou, E. J. Rogers & T. B. Shea (2009b). Dietary deficiency increases presenilin expression, gamma-secretase activity, and A $\beta$  levels: Potentiation by ApoE genotype and alleviation by S-adenosyl methionine. *J Neurochem*, 110, 831-6.

Chan, A. Y., A. Alsaraby & T. B. Shea (2008c). Folate deprivation increases tau phosphorylation by homocysteine-induced calcium influx and by inhibition of phosphatase activity: Alleviation by S-adenosyl methionine. *Brain Res*, 1199, 133-7.

Cobb, C. A. & M. P. Cole (2015). Oxidative and nitrate stress in neurodegeneration. *Neurobiol Dis*, 84, 4-21.

Cooper, C., T. B. Balamurali & G. Livingston (2007). A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. *Int Psychogeriatr*, 19, 175-95.

Couto, P. J. & R. M. Millis (2015). PET imaging of epigenetic influences on Alzheimer's disease. *Int J Alzheimers Dis*, Article ID:575078.

Croisile, B., S. Auriacombe, F. Etcharry-Bouyx, M. Vercelletto, National Institute on Aging (U.S.) & Alzheimer Association (2012). [The new 2011 recommendations of the National Institute on Aging and the Alzheimer's Association on diagnostic guidelines for Alzheimer's

disease: Preclinical stages, mild cognitive impairment, and dementia]. *Rev Neurol (Paris)*, 168, 471-82.

De la Cruz, J. P., J. Pavia, J. A. Gonzalez-Correa, P. Ortiz & F. S. de la Cuesta (2000). Effects of chronic administration of S-adenosyl-L-methionine on brain oxidative stress in rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 361, 47-52.

De La Cruz, J. P., M. A. Villalobos, M. A. Cuerda, A. Guerrero, J. A. Gonzalez-Correa & F. S. De La Cuesta (2002). Effects of S-adenosyl-L-methionine on lipid peroxidation and glutathione levels in rat brain slices exposed to reoxygenation after oxygen-glucose deprivation. *Neuroscience Letters*, 318, 103-7.

De Meyer, G., F. Shapiro, H. Vanderstichele, E. Vanmechelen, S. Engelborghs, P. P. De Deyn, E. Coart, O. Hansson, L. Minthon, H. Zetterberg, K. Blennow, L. Shaw, J. Q. Trojanowski & Alzheimer's Disease Neuroimaging Initiative (2010). Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. *Archives of Neurology*, 67, 949-56.

De Sousa, O. L. V. & T. F. Amaral (2012). Three-week nutritional supplementation effect on long-term nutritional status of patients with mild Alzheimer disease. *Alzheimer Disease & Associated Disorders*, 26, 119-23.

Dhitavat, S., D. Ortiz, E. Rogers, E. Rivera & T. B. Shea (2005). Folate, vitamin E, and acetyl-L-carnitine provide synergistic protection against oxidative stress resulting from exposure of human neuroblastoma cells to amyloid-beta. *Brain Res*, 1061, 114-17.

Dhitavat, S., D. Ortiz, T. B. Shea & E. R. Rivera (2002). Acetyl-L-carnitine protects against amyloid-beta neurotoxicity: Roles of oxidative buffering and ATP levels. *Neurochemical Research*, 27, 501-5.

Di Domenico, F.E, G. Pupo, E. Giraldo, M. Badia, P. Monllor, A. Lloret, M. Schininà, A. Giorgi, C. Cini, A. Tramutola, D. Butterfield, J. Viña & M. Perluigi (2016). Oxidative signature of cerebrospinal fluid from mild cognitive impairment and Alzheimer disease patients. *Free Radic Biol Med*, 91, 1-9.

Dorland's Illustrated Medical Dictionary (2002). Philadelphia and London: W.B. Saunders Company.

Dominguez, J. L., F. Fernandez-Nieto, M. Castro, M. Catto, M. R. Paleo, S. Porto, F. J. Sardina, J. M. Brea, A. Carotti, M. C. Villaverde & F. Sussman (2015). Computer-aided structure-based design of multitarget leads for Alzheimer's disease. *J Chem Inf Model*, 55, 135-48.

Emery, V. O. B. (2011). Alzheimer disease: Are we intervening too late? *J Neural Transmission*, 118, 1361-78.

Esposito, E., D. Rotilio, V. Di Matteo, C. Di Giulio, M. Cacchio & S. Algeri (2002). A review of specific dietary antioxidants and the effects on biochemical mechanisms related to neurodegenerative processes. *Neurobiology of Aging*, 23, 719-35.

Farina, N., M. G. E. N. Isaac, A. R. Clark, J. Rusted & N. Tabet (2012). Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database of Systematic Reviews*.

Farr, S. A., H. F. Poon, D. Dogrukol-Ak, J. Drake, W. A. Banks, E. Eyerman, D. A. Butterfield & J. E. Morley (2003). The antioxidants alpha-lipoic acid and N-acetylcysteine reverse memory impairment and brain oxidative stress in aged SAMP8 mice. *J Neurochemistry*, 84, 1173-83.

Feng, L., J. Li, K. B. Yap, E. H. Kua & T. P. Ng (2009). Vitamin B-12, apolipoprotein E genotype, and cognitive performance in community-living older adults: Evidence of a gene-micronutrient interaction. *Am J Clin Nutr*, 89, 1263-8.

Fu, A. L., Z. H. Dong & M. J. Sun (2006). Protective effect of N-acetyl-L-cysteine on amyloid beta-peptide-induced learning and memory deficits in mice. *Brain Res*, 1109, 201-6.

Fuso, A., V. Nicolìa, R. A. Cavallaro, L. Ricceri, F. D'Anselmi, P. Coluccia, G. Calamandrei & S. Scarpa (2008). B-vitamin deprivation induces hyperhomocysteinemia and brain S-adenosylhomocysteine, depletes brain S-adenosylmethionine, and enhances PS1 and BACE expression and amyloid-beta deposition in mice. *Mol Cell Neurosci*, 37, 731-46.

Fuso, A., V. Nicolìa, R. A. Cavallaro & S. Scarpa (2011a). DNA methylase and demethylase activities are modulated by one-carbon metabolism in Alzheimer's disease models. *J Nutritional Biochemistry*, 22, 242-51.

Fuso, A., V. Nicolìa, A. Pasqualato, M. T. Fiorenza, R. A. Cavallaro & S. Scarpa (2011b). Changes in Presenilin 1 gene methylation pattern in diet-induced B vitamin deficiency. *Neurobiology of Aging*, 32, 187-99.

Fuso, A., L. Seminara, R. A. Cavallaro, F. D'Anselmi & S. Scarpa (2005). S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production. *Molecular and Cellular Neuroscience*, 28, 195-204.

Garcia-Alberca, J. M., B. Cruz, J. P. Lara, V. Garrido, A. Lara & E. Gris (2012). Anxiety and depression are associated with coping strategies in caregivers of Alzheimer's disease patients: results from the MALAGA-AD study. *International Psychogeriatrics*, 24, 1325-34.

Gardener, S. L., S. R. Rainey-Smith & R. N. Martins (2016). Diet and inflammation in Alzheimer's disease and related chronic diseases: A review. *J Alzheimers Dis*, 50, 301-34.

Giulidori, P., M. Cortellaro, G. Moreo & G. Stramentinoli (1984). Pharmacokinetics of S-adenosyl-L-methionine in healthy volunteers. *European J Clinical Pharmacology*, 27, 119-21.

Grimmer, T., C. Wutz, P. Alexopoulos, A. Drzezga, S. Forster, H. Forstl, O. Goldhardt, M. Ortner, C. Sorg & A. Kurz (2016). Visual versus fully automated analyses of F-18-FDG and amyloid PET for prediction of dementia due to Alzheimer disease in mild cognitive impairment. *J Nuclear Medicine*, 57, 204-7.

Grimmer, T., C. Wutz, A. Drzezga, S. Forster, H. Forstl, M. Ortner, R. Perneczky & A. Kurz (2013). The usefulness of amyloid imaging in predicting the clinical outcome after two years in subjects with mild cognitive impairment. *Current Alzheimer Research*, 10, 82-5.

Groot, C., A. M. Hooghiemstra, P. G. H. M. Raijmakers, B. N. M. van Berckel, P. Scheltens, E. J. A. Scherder, W. M. van der Flier & R. Ossenkoppele (2016). The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Research Reviews*, 25, 13-23.

Harada C.N., M.C. Natelson Love & K. Triebel (2013). Normal Cognitive Aging. *Clin Geriatr Med*, 29, 737-52.

Hatashita, S. & H. Yamasaki (2013). Diagnosed mild cognitive impairment due to Alzheimer's disease with PET biomarkers of beta amyloid and neuronal dysfunction. *Plos One*, 8, e66877.

Hill, A.B. (1965). The environment and disease: Association or causation? *Proc R Soc Med*, 58, 295-300.

Ho, P. I., D. Ashline, S. Dhitavat, D. Ortiz, S. C. Collins, T. B. Shea & E. Rogers (2003). Folate deprivation induces neurodegeneration: Roles of oxidative stress and increased homocysteine. *Neurobiology of Disease*, 14, 32-42.

Hoffmann, K., N. A. Sobol, K. S. Frederiksen, N. Beyer, A. Vogel, K. Vestergaard, H. Braendgaard, H. Gottrup, A. Lolk, L. Wermuth, S. Jacobsen, L. P. Laugesen, R. G. Gergelyffy, P. Høgh, E. Bjerregaard, B. B. Andersen, V. Siersma, P. Johannsen, C. W. Cotman, G. Waldemar & S. G. Hasselbalch (2016). Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: A randomized controlled trial. *J Alzheimers Dis*, 50, 443-53.

Hung, M. C., K. Shibasaki, R. Yoshida, M. Sato & K. Imaizumi (2001). Learning behaviour and cerebral protein kinase C, antioxidant status, lipid composition in senescence-accelerated mouse: influence of a phosphatidylcholine-vitamin B-12 diet. *British J Nutrition*, 86, 163-71.

Hyland, K., I. Smith, T. Bottiglieri, J. Perry, U. Wendel, P. T. Clayton & J. V. Leonard (1988). Demyelination and decreased S-adenosylmethionine in 5,10-methylenetetrahydrofolate reductase deficiency. *Neurology*, 38, 459-62.

Janssen, B., D. J. Vugts, U. Funke, G. T. Molenaar, P. S. Kruijer, B. N. van Berckel, A. A. Lammertsma & A. D. Windhorst (2016). Imaging of neuroinflammation in Alzheimer's disease, multiple sclerosis and stroke: Recent developments in positron emission tomography. *Biochim Biophys Acta*, 1862, 425-41.

Joseph, J.A., G. Casadeus, M.A. Smith, G. Perry & B. Shukitt-Hale (2015). Nutrients and food constituents in cognitive decline and neurodegenerative disease. In *Nutrition and the Prevention and Treatment of Disease*, eds. A. Coulston, C. Boushey & M. Ferruzzi, 373-90. Elsevier.

Jurica, P.J., C.L. Leitten & S. Mattis (2001). DRS-2 Dementia Rating Scale-2 Professional Manual.

Kennedy, B. P., T. Bottiglieri, E. Arning, M. G. Ziegler, L. A. Hansen & E. Masliah (2004) Elevated S-adenosylhomocysteine in Alzheimer brain: Influence on methyltransferases and cognitive function. *J Neural Transm (Vienna)*, 111, 547-67.

Kifle, L., D. Ortiz & T. B. Shea (2009). Deprivation of folate and B12 increases neurodegeneration beyond that accompanying deprivation of either vitamin alone. *J Alzheimers Dis*, 16, 533-40.

Kok, D. E., R. A. Dhonukshe-Rutten, C. Lute, S. G. Heil, A. G. Uitterlinden, N. van der Velde, J. B. van Meurs, N. M. van Schoor, G. J. Hooiveld, L. C. de Groot, E. Kampman & W. T. Steegenga (2015). The effects of long-term daily folic acid and vitamin B12 supplementation on genome-wide DNA methylation in elderly subjects. *Clin Epigenetics*, 7, 121.

Langa, K. M. & D. A. Levine (2014). The diagnosis and management of mild cognitive impairment: A clinical review. *JAMA*, 312, 2551-61.

Lehallier, B., L. Essioux, J. Gayan, R. Alexandridis, T. Nikolcheva, T. Wyss-Coray, M. Britschgi & Alzheimer's Disease Neuroimaging Initiative (2015). Combined plasma and cerebrospinal fluid signature for the prediction of midterm progression from mild cognitive impairment to Alzheimer disease. *JAMA Neurol*, 1-10.

Levine, M. E., A. T. Lu, D. A. Bennett & S. Horvath (2015). Epigenetic age of the pre-frontal cortex is associated with neuritic plaques, amyloid load, and Alzheimer's disease related cognitive functioning. *Aging (Albany NY)*, 7, 1198-211.

Li, W., M. Jiang, S. Zhao, H. Liu, X. Zhang, J. X. Wilson & G. Huang (2015). Folic acid inhibits amyloid beta-peptide production through modulating DNA methyltransferase activity in N2a-APP cells. *Int J Mol Sci*, 16, 25002-13.

Lin, J., E. O'Connor, R. Rossom, L. Perdue, B. Burda, M. Thompson & E. Eckstrom. Screening for cognitive impairment in older adults: An evidence update for the U.S. Preventive Services Task Force. Evidence Report No. 107. AHRQ Publication No. 14-05198-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013.

Liu, H., W. Li, S. Zhao, X. Zhang, M. Zhang, Y. Xiao, J. X. Wilson & G. Huang (2016). Folic acid attenuates the effects of amyloid beta oligomers on DNA methylation in neuronal cells. *Eur J Nutr*, 55, 1849-62.

Llamas-Velasco, S., I. Contador, A. Villarejo-Galende, D. Lora-Pablos & F. Bermejo-Pareja (2015). Physical activity as protective factor against dementia: A prospective population-based study (NEDICES). *J Int Neuropsychol Soc*, 21, 861-7.

Lloret, A., M. C. Badia, N. J. Mora, F. V. Pallardo, M. D. Alonso & J. Vina (2009). Vitamin E paradox in Alzheimer's disease: it does not prevent loss of cognition and may even be detrimental. *J Alzheimers Dis*, 17, 143-9.

Ma, F., T. Wu, J. Zhao, F. Han, A. Marseglia, H. Liu & G. Huang (2016). Effects of 6-month folic acid supplementation on cognitive function and blood biomarkers in mild cognitive impairment: A randomized controlled trial in China. *J Gerontol A Biol Sci Med Sci*. 71, 1376-83

Mani, R. B. (2002). Memorandum Summarizing the Review and Evaluation of Clinical Data on Phosphatidylserine and Cognitive Impairment and Dementia. U. S. Food and Drug Administration.

Mani, R. B. (2016). Memorandum Summarizing the Review and Evaluation of Clinical Data on Petitioner's Dietary Supplement and Cognitive Decline and Dementia. U.S. Food and Drug Administration.

Markowska, A. L. & D. S. Olton (1990). Dietary acetyl-L-carnitine improves spatial-behavior of old rats. *International J Clinical Pharmacology Research*, 10, 65-8.

Mattson, M. P. & T. B. Shea (2003). Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. *Trends in Neurosciences*, 26, 137-46.

McCaddon, A. & G. Davies (2005). Co-administration of N-acetylcysteine, vitamin B-12 and folate in cognitively impaired hyperhomocysteinaemic patients. *International J Geriatric Psychiatry*, 20, 998-1000.

Mihalick, S. M., D. Ortiz, R. Kumar, E. Rogers & T. B. Shea (2003). Folate and vitamin E deficiency impair cognitive performance in mice subjected to oxidative stress. *Neuromolecular Medicine*, 4, 197-201.

Mischoulon, D. & M. Fava (2002). Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am J Clin Nutr*, 76, 1158s-61s.

Moby's Medical, Nursing, and Allied Health Dictionary (1994). Mosby, St. Louis MO.

Montgomery, S. A., L. J. Thal & R. Amrein (2003). Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol*, 18, 61-71.

Monti, J. M., C. J. Moulton & N. J. Cohen (2015). The role of nutrition on cognition and brain health in ageing: a targeted approach. *Nutrition Research Reviews*, 28, 167-80.

Moreno, M. D. (2003). Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: A multicenter, double-blind, randomized, placebo-controlled trial. *Clinical Therapeutics*, 25, 178-93.

Morris, M. C., D. A. Evans, J. L. Bienias, C. C. Tangney & R. S. Wilson (2002). Vitamin E and cognitive decline in older persons. *Archives of Neurology*, 59, 1125-32.

Morris, M. C., D. A. Evans, C. C. Tangney, J. L. Bienias, R. S. Wilson, N. T. Aggarwal & P. A. Scherr (2005). Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. *Amer J Clin Nutr*, 81, 508-14.

Mourao, R. J., G. Mansur, L. F. Malloy-Diniz, E. Castro Costa & B. S. Diniz (2016). Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: Systematic review and meta-analysis. *Int J Geriatr Psychiatry*, 31, 905-11.

Muller, T., D. Voitalla, B. Hauptmann, B. Fowler & W. Kuhn (2001). Decrease of methionine and S-adenosylmethionine and increase of homocysteine in treated patients with Parkinson's disease. *Neurosci Lett*, 308, 54-6.

National Research Council (2011). Reference Manual on Scientific Evidence: Third Edition. The National Academies Press, Washington, DC, 220.

Nesteruk, M., T. Nesteruk, M. Styczynska, A. Barczak, M. Mandecka, J. Walecki & M. Barcikowska-Kotowicz (2015). Predicting the conversion of mild cognitive impairment to Alzheimer's disease based on the volumetric measurements of the selected brain structures in magnetic resonance imaging. *Neurol Neurochir Pol*, 49, 349-53.

Nishida, Y., T. Yokota, T. Takahashi, T. Uchihara, K. Jishage & H. Mizusawa (2006). Deletion of vitamin E enhances phenotype of Alzheimer disease model mouse. *Biochem Biophys Res Commun*, 350, 530-6.

Noyes, B. B., R. D. Hill, B. L. Hicken, M. Luptak, R. Rupper, N. K. Dailey & B. D. Bair (2010). The role of grief in dementia caregiving. *Am J Alzheimers Dis Other Demen*, 25, 9-17.

Okello, A., J. Koivunen, P. Edison, H. A. Archer, F. E. Turkheimer, K. Nagren, R. Bullock, Z. Walker, A. Kennedy, N. C. Fox, M. N. Rossor, J. O. Rinne & D. J. Brooks (2009). Conversion of amyloid positive and negative MCI to AD over 3 years An (11)C-PIB PET study. *Neurology*, 73, 754-60.

Ortega, R. M., A. M. Requejo, A. M. Lopez-Sobaler, P. Andres, B. Navia, J. M. Perea & F. Robles (2002). Cognitive function in elderly people is influenced by vitamin E status. *J Nutrition*, 132, 2065-68.

- Paintlia, M. K., A. S. Paintlia, M. A. Contreras, I. Singh & A. K. Singh (2008). Lipopolysaccharide-induced peroxisomal dysfunction exacerbates cerebral white matter injury: Attenuation by N-acetyl cysteine. *Experimental Neurology*, 210, 560-76.
- Papp, K. V., E. C. Mormino, R. E. Amariglio, C. Munro, A. Dagley, A. P. Schultz, K. A. Johnson, R. A. Sperling & D. M. Rentz (2016). Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology*, 30, 624-30.
- Petersen, R. C., P. S. Aisen, L. A. Beckett, M. C. Donohue, A. C. Gamst, D. J. Harvey, C. R. Jack, Jr., W. J. Jagust, L. M. Shaw, A. W. Toga, J. Q. Trojanowski & M. W. Weiner (2010). Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. *Neurology*, 74, 201-9.
- Petersen, R. C., H. J. Wiste, S. D. Weigand, W. A. Rocca, R. O. Roberts, M. M. Mielke, V. J. Lowe, D. S. Knopman, V. S. Pankratz, M. M. Machulda, Y. E. Geda & C. R. Jack, Jr. (2016). Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. *JAMA Neurol*, 73, 85-92.
- Plassman, B. L., K. M. Langa, G. G. Fisher, S. G. Heeringa, D. R. Weir, M. B. Ofstedal, J. R. Burke, M. D. Hurd, G. G. Potter, W. L. Rodgers, D. C. Steffens, J. J. McArde, R. J. Willis & R. B. Wallace (2008). Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med*, 148, 427-34.
- Raggi, A., D. Tasca, S. Panerai, W. Neri & R. Ferri (2015). The burden of distress and related coping processes in family caregivers of patients with Alzheimer's disease living in the community. *J Neurol Sci*, 358, 77-81.
- Remington, R., C. Bechtel, D. Larsen, A. Samar, L. Doshanjh, P. Fishman, Y. Luo, K. Smyers, R. Page, C. Morrell & T. B. Shea (2015a). A phase II randomized clinical trial of a nutritional formulation for cognition and mood in Alzheimer's disease. *J Alzheimers Dis*, 45, 395-405.
- Remington, R., C. Bechtel, D. Larsen, A. Samar, R. Page, C. Morrell & T. B. Shea (2016). Maintenance of cognitive performance and mood for individuals with Alzheimer's disease following consumption of a nutraceutical formulation: A one-year, open-label study. *J Alzheimers Dis*, 51, 991-5.
- Remington, R., A. Chan, J. Paskavitz & T. B. Shea (2009). Efficacy of a vitamin/nutraceutical formulation for moderate-stage to later-stage Alzheimer's disease: A placebo-controlled pilot study. *Am J Alzheimers Dis Other Demen*, 24, 27-33.
- Remington, R., J. J. Lortie, H. Hoffmann, R. Page, C. Morrell & T. B. Shea (2015b). A nutritional formulation for cognitive performance in mild cognitive impairment: A placebo-controlled trial with an open-label extension. *J Alzheimers Dis*, 48, 591-95.

Rochtus, A., K. Jansen, C. Van Geet & K. Freson (2015). Nutri-epigenomic studies related to neural tube defects: Does folate affect neural tube closure via changes in DNA methylation? *Mini Rev Med Chem*, 15, 1095-102.

Rolandi, E., G. B. Frisoni & E. Cavedo (2016) Efficacy of lifestyle interventions on clinical and neuroimaging outcomes in elderly. *Ageing Res Rev*, 25, 1-12.

Rommer, P. S., D. Fuchs, F. Leblhuber, R. Schroth, M. Greilberger, E. Tafeit & J. Greilberger (2016). Lowered levels of carbonyl proteins after vitamin B supplementation in patients with mild cognitive impairment and Alzheimer's disease. *Neurodegener Dis*, 16, 284-9.

Rudolph, M.L., M. Rabinoff & B.L. Kagan (2011). A prospective, open-label, 12 week trial of S-adenosylmethionine in the symptomatic treatment of Alzheimer's disease. *Neuroscience & Medicine*, 2, 222-25.

Sanders, S., C. H. Ott, S. T. Kelber & P. Noonan (2008). The experience of high levels of grief in caregivers of persons with Alzheimer's disease and related dementia. *Death Stud*, 32, 495-523.

Scarpa, S., A. Fusco, F. D'Anselmi & R. A. Cavallaro (2003). Presenilin 1 gene silencing by S-adenosylmethionine: A treatment for Alzheimer disease? *FEBS Lett*, 541, 145-8.

Schatz, R. A., T. E. Wilens & O. Z. Sellinger (1981). Decreased in vivo protein and phospholipid methylation after in vivo elevation of brain S-adenosyl-homocysteine. *Biochem Biophys Res Commun*, 98, 1097-107.

Schulz, R. & L. M. Martire (2004). Family caregiving of persons with dementia: Prevalence, health effects, and support strategies. *Am J Geriatr Psychiatry*, 12, 240-9.

Selhub, J. & J. W. Miller (1992). The pathogenesis of homocysteinemia: Interruption of the coordinate regulation by S-adenosylmethionine of the remethylation and transsulfuration of homocysteine. *Am J Clin Nutr*, 55, 131-8.

Serra, M., A. Chan, M. Dubey, V. Gilman & T. B. Shea (2008). Folate and S-adenosylmethionine modulate synaptic activity in cultured cortical neurons: acute differential impact on normal and apolipoprotein-deficient mice. *Physical Biology*, 5, 044002.

Shah, S. & W. E. Reichman (2006). Treatment of Alzheimer's disease across the spectrum of severity. *Clin Interv Aging*, 1, 131-42.

Shatenstein, B., M. J. Kergoat & I. Reid (2007). Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with early-stage Alzheimer dementia compared to cognitively intact matched controls. *J Am Diet Assoc*, 107, 2091-9.

- Shea, T. B. & A. Chan (2008). S-adenosyl methionine: A natural therapeutic agent effective against multiple hallmarks and risk factors associated with Alzheimer's Disease. *J Alzheimers Dis*, 13, 67-70.
- Shea, T. B. & E. Rogers (2002). Folate quenches oxidative damage in brains of apolipoprotein E-deficient mice: augmentation by vitamin E. *Molecular Brain Research*, 108, 1-6.
- Spilker, B. (1991). *Guide to Clinical Trials*. New York, New York: Raven Press.
- Stefanacci, R. G. (2011). The costs of Alzheimer's disease and the value of effective therapies. *Am J Manag Care*, 17 Suppl 13, S356-62.
- Strohle, A., D. K. Schmidt, F. Schultz, N. Fricke, T. Staden, R. Hellweg, J. Priller, M. A. Rapp & N. Rieckmann (2015). Drug and exercise treatment of Alzheimer disease and mild cognitive impairment: A systematic review and meta-analysis of effects on cognition in randomized controlled trials. *Am J Geriatr Psychiatry*, 23, 1234-49.
- Surtees, R., J. Leonard & S. Austin (1991). Association of demyelination with deficiency of cerebrospinal-fluid S-adenosylmethionine in inborn errors of methyl-transfer pathway. *Lancet*, 338, 1550-4.
- Tangney, C. C., Y. Tang, D. A. Evans & M. C. Morris (2009). Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline. *Neurology*, 72, 361-7.
- Tchantchou, F., M. Graves, E. Rogers, D. Ortiz & T. B. Shea (2005). N-acetyl cysteine alleviates oxidative damage to central nervous system of ApoE-deficient mice following folate and vitamin E-deficiency. *J Alzheimers Dis*, 7, 135-8.
- Thal, L. J., M. Calvani, A. Amato & A. Carta (2000). A 1-year controlled trial of acetyl-L-carnitine in early-onset AD. *Neurology*, 55, 805-10.
- Thal, L. J., A. Carta, W. R. Clarke, S. H. Ferris, R. P. Friedland, R. C. Petersen, J. W. Pettegrew, E. Pfeiffer, M. A. Raskind, M. Sano, M. H. Tuszynski & R. F. Woolson (1996). A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. *Neurology*, 47, 705-11.
- Tjiattas, L., D. O. Ortiz, S. Dhivant, K. Mitton, E. Rogers & T. B. Shea (2004). Folate deficiency and homocysteine induce toxicity in cultured dorsal root ganglion neurons via cytosolic calcium accumulation. *Aging Cell*, 3, 71-6.
- Troen, A. M., M. Shea-Budgell, B. Shukitt-Hale, D. E. Smith, J. Selhub & I. H. Rosenberg (2008). B-vitamin deficiency causes hyperhomocysteinemia and vascular cognitive impairment in mice. *Proc Natl Acad Sci U S A*, 105, 12474-9.

Ulatowski, L. M. & D. Manor (2015). Vitamin E and neurodegeneration. *Neurobiol Dis*, 84, 78-83.

Unnithan, A. S., Y. Jiang, J. L. Rumble, S. H. Pulugulla, J. M. Posimo, A. M. Gleixner & R. K. Leak (2014). N-acetyl cysteine prevents synergistic, severe toxicity from two hits of oxidative stress. *Neurosci Lett*, 560, 71-6.

van Dyck, C. H., J. M. Lyness, R. M. Rohrbaugh & A. P. Siegal (2009). Cognitive and psychiatric effects of vitamin B12 replacement in dementia with low serum B12 levels: A nursing home study. *Int Psychogeriatr*, 21, 138-47.

Villalobos, M. A., J. P. De la Cruz, M. A. Cuerda, P. Ortiz, J. M. Smith-Agreda & F. S. De la Cuesta (2000). Effect of S-adenosyl-L-methionine on rat brain oxidative stress damage in a combined model of permanent focal ischemia and global ischemia-reperfusion. *Brain Res*, 883, 31-40.

Virmani, A., L. Pinto, Z. Binienda & S. Ali (2013). Food, nutrigenomics, and neurodegeneration--neuroprotection by what you eat! *Mol Neurobiol*, 48, 353-62.

Waite, L. M. (2015). Treatment for Alzheimer's disease: Has anything changed? *Aust Prescr*, 38, 60-3.

Wang, S., Y. Zhang, G. Liu, P. Phillips & T. F. Yuan (2016). Detection of Alzheimer's disease by three-dimensional displacement field estimation in structural magnetic resonance imaging. *J Alzheimers Dis*, 50, 233-48.

Wilson, E.B. (1990). *An Introduction to Scientific Research*, (Toronto, Canada: General Publishing Company), 46-8.

Wollen, K. A. (2010). Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. *Altern Med Rev*, 15, 223-44.

Woods, S. P., D. C. Delis, J. C. Scott, J. H. Kramer & J. A. Holdnack (2006). The California Verbal Learning Test - second edition: Test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. *Archives of Clinical Neuropsychology*, 21, 413-20.

Yang, S. Y., C. L. Shan, H. Qing, W. Wang, Y. Zhu, M. M. Yin, S. Machado, T. F. Yuan & T. Wu (2015). The Effects of aerobic exercise on cognitive function of Alzheimer's disease patients. *CNS Neurol Disord Drug Targets*, 14, 1292-7.

Zhang, X., S. Chen, L. Li, Q. Wang & W. Le (2008). Folic acid protects motor neurons against the increased homocysteine, inflammation and apoptosis in SOD1 G93A transgenic mice. *Neuropharmacology*, 54, 1112-9.