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VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)

Food and Drug Administration

5630 Fishers Lane

Rockville, MD 20852

Re: Docket No. FDA-2012-N-1210; Food Labeling: Revision of the Nutrition and Supplement Facts Labels

The Council for Responsible Nutrition (CRN) respectfully submits these comments to the Food and Drug Administration (FDA) on the proposed rule titled, “Food Labeling: Revision of the Nutrition and Supplement Facts Labels.” CRN is the leading trade association for the dietary supplement and nutritional products industry, representing manufacturers of dietary ingredients and of national brand name and private label dietary supplements¹.

¹ The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 100 companies that manufacture dietary ingredients and/or dietary supplements, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN’s Code of Ethics. Learn more about us at www.crnusa.org.

Reference Daily Intakes for Vitamins and Minerals

CRN commends FDA for proposing to continue using the Recommended Dietary Allowance (RDA), when available, as the basis for determining the Reference Daily Intakes (RDIs) for nutrients. Basing the RDI on the Estimated Average Requirement (EAR), which was considered by FDA in developing the proposed rule, would effectively dilute the nutrient requirements for Americans since the EAR represents the daily intake level estimated to satisfy the needs of only half of the people in each life-stage and sex group. In contrast, an RDI based on an RDA would meet the daily requirements of nearly all (97.5%) healthy individuals in a given group.

Maintaining an RDA-based RDI is important given the significant nutrient shortfalls in the U.S. population, with many Americans not even achieving the EAR for several nutrients. As an example, a recent analysis of nutrient intake data shows that 54.5% of Americans fall short of the average requirement for magnesium when considering intake from food alone². With the addition of magnesium supplements, the percentage of Americans falling short of the EAR drops by nearly 10%.

CRN supports FDA's tentative conclusion that RDIs for vitamins and minerals should continue to be based on a population-coverage approach, that is, using the highest age/gender group RDA value (or highest AI, where an RDA has not been established). CRN agrees with FDA's rationale that the population-coverage approach would cover vulnerable or at-risk groups sufficiently. Using the population-weighted approach instead would result in a higher risk of

² Fulgoni VL 3rd, Keast DR, Bailey RL, et al. Foods, fortificants, and supplements: Where do Americans get their nutrients? J Nutr. 2011;141(10):1847-54.

nutrient inadequacy for some population groups because the RDIs would be derived by averaging the nutrient requirements for groups with lesser needs and those with greater needs.

CRN applauds FDA for addressing concerns for risk of excessive intakes of nutrients through the use of the current and proposed population-coverage and RDA-based approach for determining RDIs. Based on a thorough analysis of NHANES (2003-2006) data, FDA concluded that “total nutrient intakes (from both conventional foods and dietary supplements)...do not exceed the [Tolerable Upper Levels] for most vitamins and minerals.” CRN agrees with FDA’s evaluation.

Vitamin B₁₂

Vitamin B₁₂ is a water-soluble vitamin that is essential for the synthesis of nucleic acids and erythrocytes, as well as in the maintenance of myelin. Deficiency may result in a variety of symptoms; some symptoms may be severe while others may be irreversible. FDA proposes to reduce the RDI for vitamin B₁₂ from 6 mcg to 2.4 mcg, in line with the RDA established by the Institute of Medicine (IOM) in 2000. The agency noted in the proposed rule that lowering the RDI could decrease fortification levels of this vitamin. CRN is concerned that decreased vitamin B₁₂ fortification would lower the amount of crystalline vitamin B₁₂ in the food and dietary supplement supply, making it more difficult for those at risk for deficiency to achieve adequacy for this nutrient.

Chapter 4 of the 2010 Dietary Guidelines for Americans discusses several foods and nutrients that should be increased in the American diet. On average, older Americans consume adequate dietary vitamin B₁₂; however a substantial proportion of individuals 50 years and older have reduced capacity to absorb dietary vitamin B₁₂. Therefore, the Guidelines encourage

individuals 50 years and older to obtain adequate vitamin B₁₂ by consuming foods fortified with vitamin B₁₂, such as fortified cereals, or take dietary supplements³.

Similarly at risk for vitamin B₁₂ deficiency are millions of Americans that choose to eat a vegetarian or vegan diet. Eating these diets results in suboptimal intake of vitamin B₁₂ unless fortified foods or dietary supplements are also consumed. A recent review found that vitamin B₁₂ deficiency, as assessed by serum vitamin B₁₂, is prevalent in vegetarians of all age groups⁴. Prevalence was 45% among infants and ranged from 0 to 33% among children and adolescents; 17 to 39% among pregnant women, depending on trimester; and 0 to 87% among adults and elderly individuals. Vegans had a higher deficiency prevalence than vegetarians, and especially at high risk were vegans who did not ingest vitamin B₁₂ supplements.

CRN is concerned that the substantial decrease in the RDI for vitamin B₁₂ would result in lower amounts of crystalline vitamin B₁₂ in the food and dietary supplement supply, making it more difficult for those at risk for deficiency, including older adults, vegetarians and vegans, to achieve adequacy for this nutrient. CRN recommends that FDA retain the current RDI for vitamin B₁₂.

Choline

FDA proposes to establish RDIs for choline based on AI values set by the IOM in 1998. Additionally, FDA has tentatively concluded that voluntary declaration of choline on Nutrition Facts labeling will be permitted. For dietary supplements, FDA proposes to add choline to the

³ Dietary Guidelines for Americans, 2010. Chapter 4. Foods and Nutrients to Increase. Available at: <http://www.cnpp.usda.gov/publications/dietaryguidelines/2010/policydoc/chapter4.pdf>

⁴ Pawlak R, Lester SE, Babatunde T. The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B₁₂: a review of literature. *Eur J Clin Nutr.* 2014;68:541-548.

list of ordered nutrients in 21 CFR 101.36(b)(2)(i)(B), and will require that, when declared, choline will follow potassium on the label.

CRN supports the aforementioned proposed changes regarding the labeling of choline. Data from NHANES 2005-2008 presented in Table 1 of the proposed rule show that only 10% of Americans ages 4 years and older consume choline at levels above the weighted AI. Similarly, NHANES data from 2007-2008 indicate that mean intakes of choline are well below the current AI for the majority of age groups surveyed.⁵ Permitting voluntary labeling of choline on food and dietary supplement products may help more Americans to become aware of this nutrient and to make food and dietary supplement selections that contribute to achieving adequacy.

Essential Vitamins and Minerals of Public Health Significance

CRN was encouraged to see that FDA recognized vitamin D and potassium as nutrients of “public health significance” and proposed to require mandatory declaration of these important nutrients, if present, on Nutrition and Supplement Facts labels. CRN’s comments on specific vitamins and minerals of public health significance are below.

Vitamin D

No mention was made in the proposed rule regarding whether FDA considers the main two forms of vitamin D, ergocalciferol (D₂) and cholecalciferol (D₃), as bioequivalent. It would be helpful if FDA could either define them as bioequivalent or list a potency conversion factor if, in fact, the agency considers one form more bioactive than the other.

⁵ Figure 1b in Comment ID# FDA-2012-N-1210-0112.

Potassium

FDA's analysis of NHANES 2003-2006 data indicates that usual mean intakes of potassium from conventional foods only (2,644 mg/day) and conventional foods plus dietary supplements (2,651 mg/day) are below the current (3,500 mg) or proposed (4,700 mg) RDI. A potential reason for the lack of contribution by dietary supplements to potassium intake is that many manufacturers limit the amount of potassium in supplement products to 99 mg potassium per serving. This practice may be unnecessary and is based on FDA's conclusion in 1975 that any capsule or coated tablet of a potassium salt intended for oral ingestion (without prior dilution with an adequate volume of liquid to preclude gastrointestinal injury) should carry a prescribed warning statement regarding small-bowel lesions related to the use of oral drug products containing 100 mg or more potassium (21 CFR 201.306).

In the April 29, 1992 Federal Register (57 FR 18157), FDA withdrew approval of the New Drug Applications of oral drug products containing more than 100 mg of potassium chloride in solid oral dosage form because, among other things, they were not established to be safe because of reports of small-bowel lesions associated with the use of concentrated solid oral dosage forms of potassium salts. It is probable that this action is the source of the "100 mg" limit that is often believed to exist for dietary supplements. FDA did not make any statement at that time, however, regarding the use of potassium in dietary supplements.

CRN requests that FDA revisit its 1975 statement (and the evidence to support the statement) in light of the agency's recognition that potassium is a nutrient of public health significance. Increasing potassium levels in dietary supplement products could help Americans achieve adequacy for this nutrient. CRN suggests that FDA clarify in a guidance, rather than the final rule, that it has not established a regulatory limit for potassium in dietary supplements

whether as solid or liquid dosage forms. FDA previously provided clarity on folic acid in the Dietary Supplement Labeling Guide⁶, in which the agency explicitly stated that there is no limit on the content of folic acid contained in dietary supplements. CRN recommends that FDA offer similar guidance for potassium.

Vitamins A and C

FDA proposes to amend 21 CFR 101.9(c)(8)(ii) to no longer require the declaration of vitamins A and C on Nutrition and Supplement Facts labels (but to allow voluntary declaration of these nutrients), based on the agency's tentative conclusion that these vitamins are no longer nutrients of public health significance for the general U.S. population. CRN recognizes that overt deficiency of these nutrients is not common in the U.S. population, but inadequate intake of vitamins A and C continues to be of concern. Notably, the 2010 Dietary Guidelines Advisory Committee (DGAC) indicated that "the probability of adequate dietary intake of 10 nutrients is tenuous for men and women. These nutrients include vitamins A, C, D, E, and K, and choline, calcium, magnesium, potassium, and dietary fiber."⁷ For school-aged children, the DGAC report included NHANES 1999-2004 intake data showing that vitamins A, C, D, and E, and phosphorus and magnesium are shortfall nutrients, particularly for adolescents.

Analyses of more recent NHANES data (2003-2004 and 2005-2006) indicate that 45% of American males and females over 2 years of age (excluding pregnant/lactating women) do not achieve the EAR for vitamin A from food.⁸ With the addition of dietary supplements,

⁶ Food and Drug Administration. Guidance for Industry. A Dietary Supplement Labeling Guide. April 2005.

⁷ Dietary Guidelines Advisory Committee. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010, to the Secretary of Agriculture and the Secretary of Health and Human Services. U.S. Department of Agriculture, Agricultural Research Service. Washington, DC. 2010.

⁸ Fulgoni VL 3rd, Keast DR, Bailey RL, et al. Foods, fortificants, and supplements: Where do Americans get their nutrients? J Nutr. 2011; 141(10):1847-54.

approximately one-third of Americans still did not meet the EAR for vitamin A. Additionally, a portion of vitamin A activity that is consumed by Americans is from provitamin A carotenoids. Since the conversion rate of carotenoids to vitamin A is lower than previously thought, many reports of vitamin A intake may have been overestimated.⁹

With respect to vitamin C, 37% of the U.S. population consume this nutrient from food at levels below the EAR.¹⁰ When intake from dietary supplements is considered, 25.3% of Americans do not meet the EAR for vitamin C. It also should be noted that there is vitamin C inadequacy in the population as approximately 29% of Americans 20 years and older have serum ascorbic acid concentrations below 50 $\mu\text{mol/L}$, which is the level the IOM stated would be expected in those meeting the RDA for vitamin C¹¹.

Maintaining vitamins A and C as vitamins for which label declaration is mandatory helps consumers understand their daily intake of these important nutrients. CRN is concerned that FDA's proposal to no longer require the declaration of vitamins A and C on Nutrition and Supplement Facts labels may result in a missed opportunity to help Americans achieve recommended intake levels. CRN requests that FDA consider maintaining vitamins A and C as mandatory for declaration on Nutrition and Supplement Facts labeling.

⁹ Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press. 2000.

¹⁰ Fulgoni VL 3rd, Keast DR, Bailey RL, et al. Foods, fortificants, and supplements: Where do Americans get their nutrients? *J Nutr.* 2011;141(10):1847-54.

¹¹ Institute of Medicine. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press. 2000.

Folate and Folic Acid

Terminology: Folate versus Folic Acid

CRN has several questions and concerns about the proposed changes to the labeling of folate and folic acid. FDA proposes “to only allow the use of the term ‘folic acid’ for the labeling of dietary supplements.” The term “folate” would be reserved for use on conventional food labels. CRN appreciates this effort by the agency to clarify these terms and promote their accurate use by distinguishing between folic acid (pteroylglutamic acid) and naturally occurring folates in food (various polyglutamate forms). However, both folic acid and synthetic folates are currently used as dietary ingredients for inclusion in dietary supplement products. Since these folate ingredients do not meet the definition of folic acid, the proposed rule would prevent companies from communicating the folate content of their products to consumers, and its contribution to the % DV for this nutrient. The changes proposed by FDA would have a negative impact on many products currently in the market that provide supplemental forms of folate to consumers.

The 1998 IOM Dietary Reference Intake (DRI) report that serves as the scientific basis for the current FDA proposal on folate and folic acid considered only two sources of dietary folate: synthetic folic acid and natural food folates. Synthetic folates, such as (6S)-5-methyltetrahydrofolic acid, calcium salt (5MTHF-Ca) and (6S)-5-methyltetrahydrofolic acid, glucosamine salt (5MTHF-glucosamine), were not available at the time of the IOM report but are now used as ingredients in foods and dietary supplements. The omission of newer synthetic forms of folate may be an oversight, and FDA should correct this omission when it issues the final rule.

CRN urges FDA to use its discretion in not adopting this recommendation from the IOM report to only allow the use of the term “folic acid” for the labeling of dietary supplements. If, on the other hand, FDA intended to omit supplemental folates, or prevent their accurate labeling on Supplement Facts panels, then we must ask for further clarification, as this decision lacks a scientific basis and has tremendous negative consequences for industry and consumers.

CRN believes the following clarification in the rule would satisfy FDA’s objective: Pteroylglutamic acid must be labeled as “folic acid” and not as “folate” in Supplement Facts or Nutrition Facts panels when no polyglutamate forms are present in the food or supplement. Importantly, however, FDA must not prohibit the use of the term “folate” in Supplement Facts panels when, in fact, the dietary supplement product contains a source of folate other than pteroylglutamic acid.

Furthermore, as currently written, it is our understanding that the proposed rule would not prohibit identifying a form of folate, such as 5MTHF-Ca and 5MTHF-glucosamine, as the source ingredient providing the vitamin “folic acid.” This means that the proposed rule would require industry to identify synthetic folates in the Supplement Facts panel but as a source of “Folic Acid,” which is technically incorrect. We understand two options for labeling synthetic folates in dietary supplement products under FDA’s current proposal:

- 1) Identify the source of Folic Acid in the Supplement Facts panel as (6S)-5-methyltetrahydrofolic acid, calcium salt (5MTHF-Ca) or similar, e.g., “Folic Acid (as 5MTHF-Ca)”; or,
- 2) List Folic Acid and the quantification in the Supplement Facts panel and list synthetic forms of folate as an additional ingredient below the box.

Neither of these options provides accurate information to the consumer, as 5MTHF-Ca and 5MTHF-glucosamine are not sources of folic acid, but sources of folate. CRN does not agree with the proposed approach, and seeks further clarification in this area because we anticipate the proposed labeling of folic acid and folate would create significant industry and consumer confusion. CRN encourages FDA to consider permitting the proper identification of supplemental folate sources on dietary supplement labels, e.g., “Folate (5MTHF-Ca)” or similar.

In addition, we request that FDA clarify whether limitations on the use of the terms “folic acid” and “folate,” if they are to remain in the final rule, apply only to Supplement Facts and Nutrition Facts panels, or would they also apply elsewhere on the product label, such as the front panel. For example, would it be acceptable for a single ingredient product providing 5MTHF-Ca to be named “Folate” or “Methyltetrahydrofolate” or similar, regardless of the terminology applied to the Supplement Facts panel? Please confirm whether FDA’s proposal to limit the use of the term “folate” on dietary supplement labels applies only to the Supplement Facts panel and not to the rest of the label.

Dietary Folate Equivalents

FDA has proposed that folic acid and folate will be declared as mcg Dietary Folate Equivalents (mcg DFE) instead of mcg, to account for the difference in the bioavailability of folate and folic acid. According to FDA, 1 mcg DFE is equivalent to 1 mcg of food folate, which is equivalent to 0.6 mcg folic acid from fortified food or a supplement consumed with food. Conversely, 1 mcg of folic acid represents 1.7 mcg DFE. Therefore, the contribution of folic acid to fortified food and dietary supplement products is to be subject to a conversion factor of 1.7x. For a dietary supplement not labeled to be consumed with food, 1 mcg DFE is equivalent to

0.5 mcg folic acid.¹² Therefore, the contribution of folic acid to a dietary supplement product not to be consumed with food is to be subject to a conversion factor of 2.0x.

Example #1: A dietary supplement to be consumed with food that now declares 400 mcg folic acid would declare the same amount as 680 mcg DFE or 170% of the proposed RDI. A dietary supplement not to be consumed with food that now declares 400 mcg folic acid would declare the same amount as 800 mcg DFE or 200% of the proposed RDI.

Example #2: A fortified food with 200 mcg of naturally occurring food folate and fortified with 200 mcg folic acid would be labeled as 540 mcg DFE ($200 \text{ mcg} + 1.7(200 \text{ mcg}) = 540 \text{ mcg}$).

As a result of this proposed change, two possible scenarios would occur in practice:

- 1) Some manufacturers lower the amount of folic acid in dietary supplement products in order to maintain a 100% DV, meaning that those consumers expecting to maintain a steady intake of supplemental folic acid would be receiving only 60% or 50% of their previous intake, despite no change in the % DV contributed by their daily supplement; or,
- 2) Some manufacturers do not change product formulas and continue to provide the same input of folic acid into their dietary supplement products, thus the same products previously identified to provide 100% DV would provide a folate contribution in excess of the RDA.

Neither scenario would be in the best interest of the public health, as both could run the risk of undoing several decades of U.S. public health policy, as well as efforts by numerous

¹² p. 11971 of the proposed rule.

health and professional organizations that promote a minimum of 400 mcg of supplemental folic acid for women of childbearing age. Twenty years of effort have been made on the part of the CDC, the Public Health Service, and the March of Dimes to educate women of childbearing age about the importance of getting 400 mcg of folic acid daily in addition to whatever amount of naturally-occurring dietary folate they may consume, in order to reduce the risk of having a baby with a neural tube defects (NTDs) such as spina bifida. FDA adoption of the change in the unit of measure would mean that a lower level of folic acid would be represented in the Nutrition Facts labels of fortified foods as providing 100% of the DV for folate. Women would be unaware that 100% of the proposed DV does not provide the full 400 mcg of folic acid recommended for protection against NTDs. FDA has also proposed to change the DV for pregnancy and lactation to 600 mcg DFEs. Under the proposal, women of childbearing age that consume a prenatal multivitamin that provides 100% DV of folic acid (600 mcg DFEs, consumed without food) actually would be consuming 300 mcg of folic acid, despite the body of evidence and recommendations from numerous health organizations to consume 400 mcg of folic acid.

CRN requests that FDA retain the current DV of 400 mcg as folate or folic acid and not adopt dietary folate equivalents (mcg DFE).

Dietary Fiber

With respect to FDA's proposed definition for dietary fiber, isolated and synthetic non-digestible carbohydrates (with three or more monomeric units) would only meet the proposed definition if a) FDA grants their inclusion in the definition in response to a petition

demonstrating that such carbohydrates have a physiological effect(s) that is beneficial to human health; or b) they are the subject of an authorized health claim. The proposed requirement to demonstrate a physiological effect beneficial to human health through a petition process is a drastic shift from the analytical-based approach that has been historically used. If the proposed requirements become final, dietary fiber (specifically isolated or synthetic) would be the only nutrient listed in 21 CFR 101.9 that 1) requires evidence of a physiological effect; and 2) requires the submission of a petition demonstrating the physiological effect for review and approval by FDA or authorization of a health claim in order to meet the regulatory definition and be listed on product labeling. CRN requests that FDA reconsider whether a resource-intensive petition or health claim-based system for the labeling of dietary fiber is appropriate and necessary.

CRN recognizes that results of many epidemiologic and interventional studies have demonstrated the benefit of dietary fiber to human health. Authoritative bodies such as the IOM, International Life Science Institute (ILSI), and the Food and Agriculture Organization of the United Nations (FAO) have assessed and confirmed a growing number of physiologic benefits of fibers that are scientifically supported by both pre-clinical and human studies.

In the proposed rule, FDA does not specify what would be considered a “physiological benefit” that would qualify isolated and synthetic non-digestible carbohydrates as dietary fiber. CRN recommends that FDA recognize the list of beneficial physiological effects developed at the Ninth Vahouny Fiber Symposium in 2010¹³ (organized by the ILSI North America and ILSI

¹³ Howlett JF, Betteridge VA, Champ M, et al. The definition of dietary fiber - discussions at the Ninth Vahouny Fiber Symposium: building scientific agreement. *Food Nutr Res.* 2010;54:5750.

Europe committees on dietary carbohydrates). This core list includes the following physiological benefits:

1. Reduced total and/or LDL cholesterol levels
2. Attenuation of postprandial glycemia/insulinemia
3. Reduced blood pressure
4. Increased fecal bulk/laxation
5. Decreased transit time
6. Increased colonic fermentation/short chain fatty acid production
7. Positive modulation of colonic microflora
8. Weight loss/reduction in adiposity
9. Increased satiety

This non-exhaustive list would be updated should scientific advances demonstrate additional beneficial physiological effects for dietary fiber.

The proposed requirement for petitions to demonstrate that isolated and synthetic non-digestible carbohydrates qualify as dietary fiber would put a substantial burden on manufacturers and marketers of innovative fiber products, as well as on the agency, while concurrently delaying the marketing of an important nutrient increasingly recognized for its range of health benefits. Currently, there are numerous dietary fiber sources in the U.S. marketplace; and with the proposed 2-year compliance period, it would be extremely difficult for petitions to be prepared, submitted, and reviewed by FDA within the specified timeframe. CRN is concerned that the proposed requirement for petitions in a short timeframe would create inadvertent competitive advantage to companies that file first. It is also unclear whether every manufacturer of a specific fiber would be required to have its fiber approved or if a single approval covers all

manufacturers. Additionally, while FDA plans to issue guidance on the petition process, it is uncertain how this could be accomplished within the specified timeframe and how the agency will address existing products on the market for which petitions have been submitted within the compliance period but not yet evaluated by FDA.

As an alternative to the petition process and creation of a list of accepted fibers, CRN recommends that FDA utilize the list of beneficial physiological effects (from the Ninth Vahouny Fiber Symposium) as the decision point for what is or is not considered a dietary fiber. Manufacturers or marketers of dietary fiber products should keep information supporting one or more of the recognized beneficial physiological effects in-house and notify FDA of such effect(s) associated with the product, in a manner similar to the current process for substantiation of structure/function claims for dietary supplements. The notification should indicate that the notifying firm has substantiation that the statement [i.e., of the physiological benefit(s)] is truthful and not misleading.

Should FDA mandate a list of acceptable fibers in the final rule, CRN recommends that the agency utilize existing lists of dietary fibers recognized by regulatory and authoritative bodies, including the list of substances on p. 344-347 in the *IOM Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*¹⁴ (2005). Additionally, it is important to harmonize global regulations and recognize substances from the *List of Dietary Fibres Reviewed and Accepted by Health Canada's Food Directorate*¹⁵ (2013) and the main types of dietary fiber listed by the European Safety Authority (2010)¹⁶.

¹⁴ National Research Council. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. Washington, DC: The National Academies Press, 2005.

¹⁵ Bureau of Nutritional Sciences, Food Directorate, Health Products and Food Branch. *List of Dietary Fibres Reviewed and Accepted by Health Canada's Food Directorate*. Revised December 2013.

¹⁶ EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA); *Scientific Opinion on Dietary*

Additionally, if FDA chooses to require a petition process, CRN recommends that FDA extend the compliance date for dietary fiber a minimum of two years beyond the compliance date for the remainder of the final rule. This time is necessary for FDA to develop guidance on the petition process, for firms to complete the scientific studies required to demonstrate a physiological benefit and submit petitions or health claim applications, and for FDA to respond to industry submissions.

Further, the Analytical methods section of the proposed rule (Section II.D.5.a.iii) suggests that the dietary fiber content may be determined by adding the amount of non-digestible carbohydrates added during processing that do not meet the definition of dietary fiber from the value obtained using AOAC 2009.01, AOAC 2011.25 or an equivalent method of analysis as given in the *Official Methods of Analysis of the AOAC International 19th edition (AOAC 19th edition)*. CRN recommends that FDA modify this section in the final rule to allow firms to use future editions of the *Official Methods of Analysis of the AOAC International* as they become available.

Protein

CRN recommends that FDA provide clarity with respect to protein quantification in 21 CFR 101.9(c)(7). In addition to the appropriate method analysis as given in the *AOAC 19th edition*, the quantity of protein in a product should be calculated to include only proteins that meet the following definition: “A chain of amino acids connected by peptide bonds.” Further, non-protein nitrogen-containing (NPN) substances should not be counted toward total protein

Reference Values for carbohydrates and dietary fibre. EFSA Journal 2010; 8(3):1462 [77 pp.].

content on product labels. NPN substances should be accounted for and subtracted from the total nitrogen content when protein is measured by nitrogen content. Similarly, 21 CFR 101.36(b)(2) should be modified to include the aforementioned definition of protein in dietary supplements.

Calculation of Total Carbohydrate

Section II.D.1.a of the proposed rule defines total carbohydrate as a sum of starch, sugars, sugar alcohols, and dietary fiber. The method used to calculate total carbohydrates is the “carbohydrate by difference” method as described by Merrill and Watt in the USDA Handbook No. 74. The calculation can overestimate total carbohydrate value when a product has a significant amount of fortified vitamins and other ingredients which are neither carbohydrate as defined, nor protein, fat, water or ash. We recommend the “carbohydrate by difference” method should allow the subtraction of these fortified vitamins and ingredients which are not carbohydrate, protein, fat, water or ash. The total carbohydrate content can then be calculated by subtracting the sum of protein, total fat, moisture, ash, other fortified vitamins and non-carbohydrate ingredients. Furthermore, in section II.D.5.a, a new definition of dietary fiber is proposed, which now creates a new category of non-digestible carbohydrates that are excluded from the definition of dietary fiber. To reflect this change, the declaration of “total carbohydrate as including starch, sugars, sugar alcohols, and dietary fiber” should be modified to include non-digestible carbohydrates now excluded from the definition of dietary fiber. FDA should affirmatively state in the final rule that total carbohydrates include starch, sugars, sugar alcohols, dietary fiber, and other non-digestible fibers.

Polyunsaturated Fatty Acids

FDA indicated in the proposed rule that the declaration of individual polyunsaturated fatty acids (PUFAs) is not permitted on the Nutrition Facts label. CRN is concerned that not allowing the declaration of individual PUFAs, in particular the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may confuse consumers who are seeking products containing these fatty acids in an effort to follow public health guidelines. The 2010 Dietary Guidelines for Americans concluded there is moderate evidence that the intake of 250 mg EPA+DHA/day is associated with “reduced cardiac deaths among individuals with and without pre-existing cardiovascular disease.”¹⁷ Additionally, FDA has permitted the use of a qualified health claim regarding EPA and DHA and coronary heart disease risk. Consumers who look for food products containing EPA and DHA will not find information on EPA and DHA content on the Nutrition Facts label. While the EPA and DHA content may be expressed on other parts of the product label, it would be difficult for consumers to determine if meaningful amounts of these fatty acids are present in comparison to other fats in the product.

Moreover, the declaration of total PUFA only on Nutrition Facts labels may confuse consumers who are not aware of the differences among individual PUFAs with respect to their ability to reduce heart disease risk. FDA acknowledges in the proposed rule that the 2010 DGAC concluded that there is limited evidence for the role of alpha-linolenic acid (ALA) in reducing mortality among those with existing cardiovascular disease. Also, there is a lack of conclusive evidence that omega-6 fatty acids independently decrease blood cholesterol levels, which are a biomarker for coronary heart disease. If Nutrition Facts labels only indicate total PUFA content,

¹⁷ U.S. Department of Health and Human Services. Dietary guidelines for Americans 2010. U.S. Department of Agriculture, 7th edition. Washington, DC: U.S. Government Printing Office. 2010.

consumers seeking products containing omega-3 PUFAs for cardiovascular health benefits could unknowingly select products with a high PUFA content that has been inflated by ALA and/or omega-6 fatty acids, but with little or no EPA and DHA.

In addition to voluntary declaration of PUFAs, CRN requests that FDA permit the voluntary declaration of individual PUFAs, particularly EPA and DHA, on Nutrition Facts labels. This request extends to the labels of foods for children less than 2 years of age.

Units of Measure

In general, CRN agrees with the proposed change in units of measure for vitamins from International Units (IU) to mg; however, we note that consumers would be confused by these changes. CRN recommends an extensive educational campaign to explain the changes in conjunction with the final rule, as well as a phase-in period in which dual listings of IU and mg are permitted on labeling. Comments on units of measure for specific vitamins and other dietary ingredients are below.

Vitamin E

CRN agrees with FDA that adopting the recommendations of the IOM Labeling Committee pertaining to units of measure for vitamin E is scientifically supported. The IOM recommends that units of measure for vitamin E be consistent with the units used in the new DRI reports. Under the proposed rule, IU would be replaced by mg α -tocopherol for vitamin E.

Vitamin E activity is a complex issue that will require a significant amount of industry and consumer education to promote awareness. In the proposed rule FDA stated that *all rac- α -*

tocopherol acetate in fortified foods or dietary supplements has one-half the activity of *RRR*- α -tocopherol naturally found in foods or the *2R* stereoisomeric forms of α -tocopherol. For clarity, CRN suggests that the final rule provide this same information as a conversion factor. For example:

1 mg α -tocopherol (label claim) = 1 mg *RRR*- α -tocopherol

1 mg α -tocopherol (label claim) = 2 mg *all rac*- α -tocopherol

Furthermore, the availability of appropriate and affordable analytic test methods for distinguishing between different forms of vitamin E in a finished product should be carefully considered prior to finalizing the rule. The proposed rule indicates that when vitamin E is present in a food as a mixture of all *rac*- α -tocopherol acetate and *RRR*- α -tocopherol, manufacturers are required to make and keep written records to verify the amount of all *rac*- α -tocopherol acetate added to the food and *RRR*- α -tocopherol in the finished food. There is no official method of analysis of the AOAC International or other reliable or appropriate analytical procedure to distinguish between these different forms of vitamin E in many food and dietary supplement matrices. In the absence of reliable and appropriate methods, CRN agrees that it is necessary to use written records to verify the declarations of each of these nutrients in the labeling of the food associated with such records. However, appropriate and reliable methods may be developed in the future and CRN requests that FDA affirmatively state that if appropriate and reliable methods are available manufacturers must declare the amount of vitamin E by appropriate and reliable analytical testing.

Niacin

The proposed unit of measure for niacin as niacin equivalents (NE) (1 mg niacin = 60 mg tryptophan) will require knowledge of the preformed niacin content of the food/dietary supplement product, as well as the tryptophan content. Thus, for many protein-containing products for which there is presently no information on tryptophan required, manufacturers would be required to determine tryptophan content, either *via* analytic testing or existing databases. Another potential concern is that, for some foods, the overall protein and tryptophan contents are quite high. As such, the estimate of niacin content as NE will be elevated. Given that the conversion of tryptophan to niacin is highly variable among individuals and that the priority usage in the body for tryptophan is for its role in protein synthesis *versus* niacin production¹⁸, utilization of NE as the unit of measure could represent an over-estimate of niacin intake in the diet. For example, a whey protein powder containing 550 mg tryptophan per 39 g serving, with no niacin fortification, would bear a label content of ~ 9 mg NE, or 56% of the proposed RDI, which is 16 mg NE. It seems unlikely, in a typical U.S. diet which is largely sufficient in pre-formed niacin, that significant tryptophan to niacin conversion will occur. Yet this product, with no added pre-formed niacin, would appear to provide over half the daily requirement. CRN recommends that the existing unit of measure for niacin (i.e., mg) be retained.

Vitamin K

FDA proposes that the definition of vitamin K for nutrition and supplement labeling purposes, should be limited to vitamin K₁ (phylloquinone) and not include other forms of

¹⁸ Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: The National Academies Press, 1998.

vitamin K. FDA takes this position because (1) the AI for vitamin K is based on NHANES data that account for the intake of vitamin K₁, and do not account for the intake of menaquinone (vitamin K₂) or menadione (vitamin K₃); (2) the contributions of menaquinones to the maintenance of vitamin K status has not been established; and (3) menadione is a synthetic form of vitamin K that can be converted to a form of menaquinone in animal tissues. Therefore, the agency proposes that the RDI for vitamin K should be specific to vitamin K₁. However, CRN contends that the contribution of menaquinone (vitamin K₂) to the nutritional requirements for vitamin K, its role in human health, and its availability in commonly consumed foods supports an expansion of the definition of vitamin K to include vitamin K₂ as well. This expansion would be in line with other regulatory bodies, such as the European Food Safety Authority (EFSA), which recognizes vitamin K₂ as a source of vitamin K¹⁹, as well as Health Canada, which permits the statement “Helps to prevent vitamin K deficiency” for both vitamin K₁ and vitamin K₂ in multivitamin/mineral supplements²⁰. Foods commonly consumed globally such as dairy and meat products are important sources of vitamin K₂ and contribute to the total daily intake of vitamin K. For example, the USDA National Nutrient Database for Standard Reference (released in April 2014) lists a 3 oz. serving of pork as providing 12.7 mcg of vitamin K₂. Thus, a single serving of a commonly consumed food provides over 10% of the AI for vitamin K, as vitamin K₂. Ten percent is a meaningful contribution to recommended intake levels. Furthermore, studies have similarly shown that in some diets, notably those rich in dairy, intake of vitamin K₂ can comprise about 10% of the total vitamin K intake²¹.

¹⁹ Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission on the safety of ‘Vitamin K₂’. The EFSA Journal (2008) 822, 1-32.

²⁰ Multi-vitamin/mineral supplement monograph. Health Canada (2007).

²¹ Journal of Nutrition 2004. 134:3100-3105.

The bioavailability of vitamin K₂ also has been demonstrated in both *in vitro* and *in vivo* studies. Vitamin K₂ is rapidly absorbed intact from the gastrointestinal tract²², and is more bioavailable than vitamin K₁, which is strongly bound to vegetable fiber^{23,24}. Scientific evidence indicates that vitamin K₂ plays an important role in human health. It has been well established that dietary intake of vitamin K₁ meets the nutritional requirements necessary for coagulation through the activation of biochemical pathways in the liver. Vitamin K₂ has similar activity as vitamin K₁ in the blood coagulation system²⁵, and data also suggest an important role for vitamin K₂ in extra-hepatic processes. Vitamin K₂ intake has been shown to have a protective effect against CHD²⁶, help regulate bone metabolism and play a role in reducing the risk of osteoporotic fractures^{27,28}.

CRN requests that FDA reconsider its definition of vitamin K for nutrition and supplement labeling purposes to include menaquinone (vitamin K₂). FDA should also consider including phytonadione, which is an additional name for vitamin K₁, in its definition of vitamin K.

Other Dietary Ingredients

The proposed revision to 21 CFR 101.36 pertaining to information on dietary ingredients for which RDIs and DRVs have not been established suggests that, "amounts shall be expressed using metric measures in appropriate units." Metric measures may not be appropriate for some ingredients. CRN requests that FDA consider providing flexibility regarding units of measure for

²² EFSA J 2008. 822, 1-32.

²³ *Id.*

²⁴ J Nutr 2004. 134:3100-3105.

²⁵ EFSA J 2008. 822, 1-32.

²⁶ Nutrition, metabolism, and cardiovascular diseases 2009. 19:504-510.

²⁷ EFSA J 2008. 822, 1-32.

²⁸ Nutrients 2014. 6:1971-1980.

dietary ingredients that are more accurately labeled with units of measure specific to the ingredient, such as enzymes (activity units) and probiotics (colony forming units).

Labeling of Foods and Dietary Supplements for Children

FDA proposes to adopt the same age categories as those used in the IOM DRIs for infants and young children. The current category of infants and children less than 4 years would be replaced with infants 7 through 12 months and children 1 through 3 years of age (hereafter referred to as “young children”). FDA’s rationale for this change is that the proposed DVs are based on IOM’s age-specific DRIs. For both infants and young children, RDAs (and in the absence of RDAs, AIs) would be used to determine RDIs for vitamins and minerals. FDA also proposes to require declarations of percent DV for those nutrients for which the agency is establishing a DRV or RDI for infants 7 to 12 months, for children 1 through 3 years of age, and for pregnant and lactating women.

The proposed rule, however, does not account for children ages 4 through 18 years. One RDI value would be used for all persons ages 4 years and older, despite the fact that the IOM has established separate DRIs for children ages 4 through 8 years, 9 through 13 years, and 14 through 18 years. As an example, the RDA for vitamin A is 400 mcg/day for children 4-8 years, 600 mcg for children 9-13 years, and 700 mcg (females)/900 mcg (males) for individuals 14+ years.

CRN recommends that FDA also establish RDI values for children 4 through 13 years of age, recognizing that their nutritional needs are different from those of adults. Similar to the approach for infants and young children, the IOM age-specific RDAs (or AIs if RDAs have not

been established) would be used to determine the RDIs. For nutrients with RDA values for 4 through 8 years and 9 through 13 years that differ, the higher value should be used. For example, in the case of vitamin A, an RDA of 600 mcg would be proposed for children 4 through 13 years. This method is consistent with FDA's proposed approach for other population groups (i.e., using population-coverage RDAs and AIs). Since the RDA values for children 14 through 18 years of age are often close or equal to the adult values, CRN concludes that separate RDIs for this age category are not required. CRN also recommends that declarations of percent DV should be required for products targeted to children 4 through 13 years of age that contain nutrients for which this age-specific DRV or RDI is established. Setting RDIs for children would provide an opportunity for more companies to formulate children's products to age-specific RDAs (rather than adult values which may not be appropriate for children's nutritional needs) and communicate the information to consumers via product labeling.

Compliance for Nutrient Content

Although the proposed rule does not include changes to the compliance requirements for Class I nutrient (added nutrients in fortified or fabricated foods) content to be at least equal to the value for that nutrient declared on the label, CRN recommends that changes be implemented in the final rule. CRN proposes the following changes, which would promote harmonization with other jurisdictions as well as pharmacopoeial standards.

When a product has reached the end of its shelf-life, the ingredient levels claimed on the label must meet the minimum legal requirements as detailed in 21 CFR 101.9(g)(3)(i) and (ii) and (g)(4)(i) and (ii), which mandate that for added nutrients, i.e., dietary ingredients, the "nutrient

content ...is at least equal to the value for that nutrient declared on the label,” that is, that there is 100% of the label claim. There is discrepancy between these CFR-mandated end of shelf-life levels, and the requirements for vitamins, minerals, and other dietary ingredients in the United States Pharmacopeial Convention, US Pharmacopeia and Dietary Supplements Compendium, which have ingredient by ingredient acceptance criteria minimum values of 90%. In every case, the inherent variability in manufacturing and analytical testing, especially towards the end of shelf-life, is recognized such that the 90% minimum of each range is sufficient to provide the expected level.

Outside the U.S., many jurisdictions recognize the minimum value as 80-90% of label claim. For example, the Danish and Korean authorities allow a shelf-life minimum of 80% of label claim for added vitamins and minerals, and the United Kingdom allows -50% for water soluble vitamins and minerals, and - 30% for oil soluble vitamins. U.S.-designed products with inputs typically 10-50% higher than the label claim to meet 100% minimum requirement at end of shelf life can exceed upper specification limits for non-U.S. countries with maximum overage limits. This leads to inefficient manufacturing operations and costly development of multiple products to support U.S. and non-U.S. markets.

CRN recommends that FDA revise the minimum nutrient content requirement for Class I nutrients to 90% of the label claim at end of shelf life. This would increase the utility of U.S.-designed and manufactured formulations for export opportunities and for competing in the global markets. Reducing the minimum nutrient content requirement would also help to prevent excessive overages that may be added to ensure 100% of the label claim throughout shelf life.

Proposed Compliance Date

FDA proposes a compliance date that is 2 years after the effective date of the final rule. However, the proposal does not clearly indicate whether the compliance date applies to the application of new labels to product packages or to the date of shipment or sale of product. CRN requests that FDA affirmatively indicate in the final rule that the compliance date applies to the application of new labels.

Furthermore, the proposed rule includes sweeping changes that impact all food and dietary supplement marketers. Millions of products would need to be re-formulated and re-labeled. Significant resources would be needed to coordinate analytical, quality control, legal, and regulatory tasks to comply with the proposed new framework for labeling food and dietary supplements. Wholesale changes of this magnitude for the entire food and dietary supplement industries would result in sizeable demands on consulting, laboratory, printing, labeling, and packaging firms that support these industries. FDA should carefully consider adding additional time required to comply. Authoritative industry stakeholders such as the American Frozen Food Institute, the Grocery Manufacturers Association, the Food Marketing Institute, the American Bakers Association and the National Confectioners' Association with decades of experience adapting to food label regulation updates have affirmed that a compliance period of a minimum of 3-5 years from the effective date of the final rule would be more appropriate²⁹. CRN contends that food and dietary supplements are important to U.S. consumers and it is not advisable to unduly burden these industries with untenable compliance parameters. Therefore, CRN

²⁹ Oral comments at FDA Public Meeting: Proposed Rules Proposed Rules on the Nutrition and Supplement Facts Labels. June 26, 2014, Washington, DC.

recommends FDA perform a thorough impact analysis prior to setting compliance dates to determine the most appropriate timeline for industry to comply with the final rule.

Respectfully submitted,

Douglas MacKay, N.D.

A handwritten signature in black ink, appearing to read "D. MacKay", with a checkmark-like flourish at the end.

Senior Vice President, Scientific & Regulatory Affairs

Andrea Wong, Ph.D.

A handwritten signature in black ink, appearing to read "Andrea Wong", with a large, stylized flourish at the end.

Vice President, Scientific & Regulatory Affairs