Council for Responsible Nutrition
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VIA ELECTRONIC SUBMISSION

Anne L. Thurn, Ph.D.
Office of Dietary Supplements
National Institutes of Health
6100 Executive Boulevard
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Re: Office of Dietary Supplements 2015-2020 Strategic Plan Request for Comments. FR Doc No: 2015-02370.

Dear Dr. Thurn:

The Council for Responsible Nutrition (CRN)[1], 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 supplements, respectfully submits these comments to the Office of Dietary Supplements (ODS) to provide input for the development of the ODS Strategic Plan 2015-2020.

CRN applauds ODS for executing many action items in accordance with its Strategic Plan for 2010-2014 to achieve goals of fostering research on the role of dietary supplements in

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and 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 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, 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 and food 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.

health promotion and disease risk reduction and expanding the general scientific knowledge base on dietary supplements by funding new research and training. Extramural research grants on dietary supplement ingredients, such as vitamins, minerals, and botanicals, have resulted in major contributions to the body of scientific evidence related to dietary supplements. Furthermore, CRN supports renewed funding of the five Botanical Research Centers and the continuation of workshops and conferences where ODS brings together experts--including its own scientists--and engages stakeholders, including the dietary supplement industry, on important issues with regard to dietary supplements. For these reasons, CRN is disappointed that the Dietary Supplement Research Practicum was canceled for 2015. The Practicum is a valuable educational program that helps academic researchers and healthcare practitioners gain an understanding of dietary supplement research and regulation. Two thirds of American adults use dietary supplements; however, many healthcare professionals do not receive adequate training in the areas of nutrition and dietary supplements to provide guidance to their patients on the role of dietary supplements in achieving wellness. CRN strongly supports the re-initiation of the Practicum in 2016 and beyond and encourages ODS to consider collaboration with stakeholders to continue funding this important event.

CRN supports ODS Strategic Plan for 2010-2014, Strategy 1-1 to stimulate and support evidence-based reviews of dietary supplements. However, we are concerned that the AHRQ systematic review model is over-reliant on a research paradigm developed for assessing efficacy of drugs in diseased populations and does not account for several important differences between drugs and dietary supplements. Unlike drugs, dietary supplements tend to have a modest effect size and, therefore, supplement studies require a very large sample size and long duration (decades) in order to detect an effect. This results in resource-prohibitive study designs and limited availability of large randomized controlled trial data for any one dietary ingredient or supplement in the peer-reviewed literature. Therefore, systematic reviews often have a predictable outcome: There are not enough studies, and the studies available are done on slightly different products; therefore, no firm conclusions can be drawn. Furthermore, subjects in dietary supplement trials often receive the standard of care for their medical conditions, including pharmacological management. In order to evaluate efficacy in these studies, the effect of the nutrient must be observable on top of the effect of drug management. So, the effect of a dietary supplement can be difficult to quantify because the benefits are modest and take decades to

manifest. Nevertheless, even modest benefits observed across a population can be significant, as evidenced in the CRN report[2] on health care cost savings resulting from the targeted use of dietary supplements. CRN recommends that AHRQ take more into consideration the inherent limitations of research methods developed to assess the efficacy of drugs, and consider the totality of the evidence for dietary ingredients or supplements, including observational data, when conducting comprehensive reviews of the available evidence.

CRN supports Strategy 1-2 to stimulate the development and use of research designs for investigating the safety, efficacy, and effectiveness of vitamins, minerals, and other bioactives as dietary supplements, which takes into account factors unique to dietary supplement research. For example, in nutrient studies, it should be recognized that there is no true placebo group; background diet influences results; there are multiple effects of a single nutrient; and co-nutrient status can influence outcomes[3]. A modified research paradigm is needed that can evaluate the benefits of adequate nutrition on chronic disease outcomes. Such a framework can be applied to essential nutrients to determine optimal intake ranges that support physiological function beyond avoiding deficiency. Furthermore, this framework could be applied to non-essential nutrients and other bioactive food components derived from plant foods such as polyphenols, carotenoids, anthocyanins, and flavonoids.

Currently, there is no accepted scientific framework that can be used to help inform recommendations on the potential health benefits of vitamins, mineral, and other bioactive food components on chronic disease outcomes. ODS can play a key role in informing federal partners, through interagency collaborations and agreements, on the necessity of new frameworks for conducting and interpreting dietary supplement research. CRN notes that the U.S. Preventive Services Task Force (USPSTF) is aware of the differences between research on nutrients and drugs. We were pleased to see that in the systematic evidence-based review used to inform the USPSTF report on the use of vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer, the authors noted that, "This is a review of trials, a study design used primarily to evaluate drug therapy. This design might not be ideally

[2] Shanahan CJ, de Lorimier R.J. From Science to Finance-A Tool for Deriving Economic Implications from the Results of Dietary Supplement Clinical Studies. J Diet Suppl. 2014 Aug 28. [Epub ahead of print].

[3] Shao A, MacKay, D. A Commentary on the Nutrient-Chronic Disease Relationship and the New Paradigm of Evidence-Based Nutrition. Nat Med J. 2010;12:2.

suited to evaluating nutrients"[4]. CRN applauds the USPSTF for including this language its systematic review for proper consideration and context, and encourages ODS to continue to educate other government-affiliated groups on the limitations of applying drug-like research models to dietary supplement research. CRN identifies two key opportunities in the 2015–2020 period: update of the Dietary Reference Intakes (DRIs) to include chronic disease endpoints and the Dietary Guidelines for Americans.

ODS has an important role in supporting the work of the Dietary Guidelines Advisory Committee (DGAC). In the 2015 DGAC Advisory Report[5], the committee listed a series of future research needs regarding dietary supplements. ODS is the logical organization to help address research gaps identified by the 2015 DGAC including, investigation of the validity, reliability, and reproducibility of new biomarkers of nutrient intake and biomarkers of nutritional status; evaluation of effects of fortification strategies and supplement use on consumer behavior related to the intake of foods and supplements containing key nutrients of concern, including calcium, vitamin D, potassium, iron, and fiber; understanding the rationale for and consequences of the use of supplements above the UL for vitamins and minerals; and identification of biochemical markers that would indicate the effects of high-dose supplement use. Strategies 1-3, 1-4 and 1-5 already relate to the evaluation of dietary supplement use by Americans and the validity and utility of biomarkers for exposure and assessing the effects of dietary supplements on surrogate and clinical endpoints. CRN commends ODS for its significant contributions to the scientific literature in these areas and encourages ODS to continue to align programs under these strategies to address the future research needs identified by the 2015 DGAC in order to inform the evaluation of the role of dietary supplements in future Dietary Guidelines for Americans.

CRN supports ODS initiatives that focus on the development of tools for dietary supplement research and quality control. CRN specifically commends ODS for collaborating with AOAC to establish voluntary consensus standards for high-priority ingredients. The

[4] Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;159(12):824-34.

[5] Scientific Report of the 2015 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Health and Human Services and the Secretary of Agriculture. Available at: http://www.health.gov/dietaryguidelines/2015-scientific-report/PDFs/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf

initiative is expected to result in 25 standard method performance requirements for high priority dietary supplement ingredients. CRN is pleased to see that this project includes engagement with the dietary supplement industry and has involved our members in the process to help ensure that selected high-priority ingredients are relevant and that standards are up-to-date. Similarly, CRN sees value in the Dietary Supplement Label Database (DSLD) and is encouraged by the collaboration with industry, as evidenced by Vitamin Shoppe's commitment to submit all labels to the DSLD by the end of 2015.

CRN encourages ODS to continue to seek ways to engage the dietary supplement industry. Our industry is unique because supplement products are an extension of the food supply; therefore, there is extremely limited intellectual property and patent protection for dietary ingredients. The lack of exclusivity on ingredients limits the financial incentive for individual companies to bear the burden of significant research investments. ODS's efforts to provide research tools, training, and direct support for extramural research, as well as to ensure the purity and quality of products used in research studies, are needed and appreciated by industry. CRN applauds ODS for accomplishing many initiatives with virtually no increase in budget over the last decade. However, we believe ODS can further its efforts by initiating government-private sector collaborations to expand research and training programs.

Thank you for considering our comments.

Sincerely,

Douglas MacKay, N.D.
Senior Vice President, Scientific and Regulatory Affairs