



December 09, 2013

U.S. Preventive Services Task Force

Attn: Dr. Robert Cosby

540 Gaither Road

Rockville, MD 20854

Re: Opportunity for Comment - U.S. Preventive Services Task Force Draft Recommendation Statement on Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer.

The Council for Responsible Nutrition (CRN) appreciates the opportunity to comment on the U.S. Preventive Services Task Force (USPSTF) Draft Recommendation Statement on Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer. CRN, based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN's member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug store and discount chains. They include some of the largest and most well-known ingredient suppliers, product manufacturers and marketers, direct sellers and specialty retailers of dietary supplements and dietary ingredients as well as specialty products sold by healthcare professionals.

CRN has organized its comments according to the questions posed by the USPSTF in the USPSTF Public Comment Form.

The USPSTF is committed to understanding the needs and perspectives of the public it serves. Please share any experiences that you think could further inform the USPSTF on this draft Recommendation Statement.

CRN respectfully reminds the task force that the choice of words in the final recommendation has vast implications. Given that the USPSTF's recommendations are highly influential, it is important that the task force's final recommendation is clearly communicated to stakeholders to ensure the accuracy of the report's meaning when transferred to the public by secondary sources.

The draft recommendation clearly identifies that there are few rigorous randomized controlled trials (RCTs) of multivitamin combinations in groups generalizable to the U.S. population. Furthermore, the task force has noted that there are significant challenges to studying nutrient supplementation using methods similar to those used in studying pharmaceutical interventions, and that new and innovative research methodologies for examining the effects of nutrients that account for the unique complexities of nutritional research but maintain rigorous designs should be explored. Therefore, the task force concludes that the limited nature of the existing evidence makes it difficult to draw meaningful conclusions on the balance of benefits and harms without a coordinated research effort and focus.

CRN emphasizes that a determination of "no firm conclusion based on existing evidence" is very different from a conclusion that "the available evidence demonstrates a lack of benefit." In this case, the absence of an adequate number of robust RCTs of multivitamin supplements that prove multivitamins prevent cardiovascular disease and cancer, based on standards used to establish the efficacy of drugs, should lead to a call for more research and a new research paradigm, not a conclusion of no benefit.

CRN has already observed misinterpretation of the draft recommendation statement on vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer by secondary sources. An example is found in a *Newsweek* article¹ with a title that reads: "Take Your Vitamins, Or Don't: Study Shows It May Not Matter;" and the first paragraph reads: "Talk about a bitter pill: Vitamins might not do anything to prevent cancer or cardiovascular disease. According to a new report from the U.S. Preventive Services Task Force, there's not enough evidence to suggest that single or paired-nutrient supplements curtail the

¹ Bekiempis V. (2013, November 12). Take Your Vitamins, Or Don't: Study Shows It May Not Matter. *Newsweek.com*. Retrieved December 2, 2013, from <http://www.newsweek.com/take-your-vitamins-or-dont-study-shows-it-may-not-matter-3151>.

development of those maladies.” The author interpreted from the draft recommendation that scientific studies show a lack of benefit associated with taking vitamins with respect to preventing cancer and cardiovascular disease, rather than a lack of adequate evidence. Similarly, an article in *Time* titled, “Want to Stay Healthy? Don’t Rely on Vitamins”² may mislead consumers into thinking that there is no benefit to filling nutrient gaps with supplementation.

How could the USPSTF make this draft Recommendation Statement clearer?

The USPSTF should underscore that the inability to draw firm conclusions based on the limited nature of the existing evidence is not equivalent to a conclusion that existing evidence demonstrates a lack of benefit. The USPSTF should also emphasize the limited scope of the report by including text clarifying that this report did not address other benefits of multivitamin/mineral (MVM) supplementation, such as providing folic acid to women of childbearing age or vitamin B₁₂ to those at risk for insufficient intake, including adults 50 years of age and older and those who consume a strictly vegan diet. CRN recommends that the USPSTF include language in the report that clarifies that these recommendations apply to “healthy adult populations without known or suspected nutritional deficiencies.”³ However, for those with known or suspected intakes of nutrients that are considered inadequate, daily supplementation with a MVM fills nutrient gaps when nutrient requirements are not met from the diet alone.

In the Rationale section, under “Benefits of Vitamin Supplementation,” the task force writes, “USPSTF found inadequate evidence on the benefits of supplementation with vitamins to reduce the risk of cardiovascular disease or cancer.” CRN suggests the task force reword this statement to reflect that this evidence is limited to those individuals without known or suspected

² Sifferlin A. (2013, November 11). Want to Stay Healthy? Don’t Rely on Vitamins. *Time.com*. Retrieved December 2, 2013, from <http://healthland.time.com/2013/11/11/want-to-stay-healthy-dont-rely-on-vitamins/>.

³ Fortmann SP, et al. 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 [Epub ahead of print].

inadequate intake of nutrients. It would also be accurate to clarify that there is emerging evidence of benefit from large intervention studies^{4,5,6} and that additional research is needed.

Based on the evidence presented in this draft Recommendation Statement, do you believe that the USPSTF came to the right conclusions? Please provide additional evidence or viewpoints that you think should have been considered.

The USPSTF has identified a critical gap in the evidence characterized by the lack of studies of multivitamin combinations in groups generalizable to the U.S. population. It is noteworthy that the small number of rigorous clinical trials on the benefits of nutrient supplementation in chronic disease risk reduction is related to several limitations of the current nutrition research approach. First and foremost, the USPSTF identified as a major obstacle the significant challenges to studying nutrient supplementation using methods similar to those employed in studying pharmaceutical interventions. The USPSTF recommends that new and innovative research methodologies for examining the effects of nutrients that account for the unique complexities of nutritional research but maintain rigorous designs are needed. CRN commends the task force for noting that research methods for assessing pharmaceutical interventions may not be appropriate for evaluating nutrient supplementation and that new methodologies are needed.

In the absence of new methodologies, policy makers continue to rely on drug-based research models (RCTs) as the gold standard, without considering the totality of evidence. In addition, nutrients are not drugs and cannot be patented like new chemical compounds. Therefore, unlike drugs, there is no financial incentive for an individual firm to invest millions of dollars to establish MVM efficacy through a coordinated and focused research agenda, as

⁴ Gaziano J, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308:1871–1880.

⁵ Hercberg S, et al. The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. 2004;164:2335–2342.

⁶ Christen WG, et al. A Multivitamin Supplement and Cataract and Age-Related Macular Degeneration in a Randomized Trial of Male Physicians. *Ophthalmology* 2013 [Epub ahead of print].

recommended by the USPSTF⁷. For these reasons, the majority of nutrition research is funded by the National Institutes of Health (NIH), which does not have the commercial interests that would support a coordinated and focused research effort similar to a firm that is seeking FDA drug approval. CRN commends the USPSTF for recognizing the need for additional focused research on the MVM and hopes this report encourages the NIH and other federal agencies to provide continued funding for nutrition research.

In the Rationale section, under “Importance,” it is stated that “[m]ost supplements are used with the intent of preventing illness or slowing the progress of existing disease.” The reference cited for this observation is Bailey et al. (2011)⁸. CRN respectfully disagrees that the manuscript by Bailey et al. (2011) or other existing scientific literature supports a conclusion that most supplements are used with the intent of preventing illness or slowing the progress of disease. The review by Bailey et al. (2011) does not support such a conclusion because the authors did not identify *why* individuals choose to use supplements, but instead reported on how many Americans use different types of dietary supplements. However, numerous articles have been published on patterns of dietary supplement use as shown in large surveys^{9,10}. These articles often include findings regarding certain characteristics of dietary supplement users. These surveys indicate that somewhere between half and three-quarters of American adults use dietary supplements – mostly vitamins and minerals. The evidence shows that dietary supplement users are more likely than nonusers to adopt a number of positive health-related habits. These include better dietary patterns, exercising regularly, maintaining a healthy body weight, and avoidance of tobacco products.

⁷ USPSTF Draft Recommendation Statement on Vitamin, Mineral, and Multivitamin Supplements for the Primary Prevention of Cardiovascular Disease and Cancer 2013. Available at: <http://www.uspreventiveservicestaskforce.org/draftrec2.htm>

⁸ Bailey RL, et al. Dietary supplement use in the United States, 2003-2006. *J Nutr* 2011;141:261-266.

⁹ Radimer K, et al. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol* 2004;160:339-349.

¹⁰ Foote JA, et al. Factors associated with dietary supplement use among healthy adults of five ethnicities: the Multiethnic Cohort Study. *Am J Epidemiol* 2003;157:888-897.

A report on NHANES 2007-2010 for the first time provides national survey data on consumers' reasons for using dietary supplements¹¹. And CRN has conducted two series of surveys, one series on consumer use of supplements (submitted for publication) and one series on health professionals' use of supplements, and these surveys also include an analysis of the reasons given for supplement use. Evidence from these published reviews suggest that supplement users take dietary supplements as an important component of overall efforts to adopt a healthy lifestyle, not to treat or prevent disease^{12,13,14}. These surveys indicate that improving or maintaining overall health, supporting bone health, and filling nutrient gaps rank at or near the top as reasons for using supplements.

Surveys that have examined the relationship between supplement use and medical conditions do not support the idea that most supplements are used with the intent of preventing or treating a disease. Analysis of the 2001 and 2003 California Health Interview Surveys identified 1576 cancer survivors and 4951 subjects with no history of cancer¹⁵. When supplement usage was examined, the authors found that "a diagnosis of cancer, by itself, does not have an independent effect on supplement use." In the Vitamins and Lifestyle (VITAL) survey, overall supplement use in more than 45,000 respondents was 75%¹⁶. People with disease or health complaints were no more likely to be supplement users than people without disease.

¹¹ Bailey RL, et al. Why US Adults Use Dietary Supplements. *JAMA Intern Med* 2013;173:355-361.

¹² Dickinson A, et al. Dietitians use and recommend dietary supplements: report of a survey. *Nutr J* 2012;11:14.

¹³ Dickinson A, et al. Use of dietary supplements by cardiologists, dermatologists and orthopedists: report of a survey. *Nutr J* 2011;10:20.

¹⁴ Dickinson A, et al. Physicians and nurses use and recommend dietary supplements: report of a survey. *Nutr J* 2009;8:29.

¹⁵ Miller MF et al. Dietary supplement use in individuals living with cancer and other chronic conditions: a population-based study. *J Am Diet Assoc* 2008;108:483-494.

¹⁶ Satia-Abouta J et al. Dietary supplement use and medical conditions: the VITAL study. *Am J Prev Med* 2003;24:43-51.

CRN recommends that the USPSTF modify the current text found in the Rationale section, under “Importance,” that states that “[m]ost supplements are used with the intent of preventing illness or slowing the progress of existing disease” to a truthful statement that reflects the current scientific literature. A more appropriate statement may be that “*most supplements are used as an important component of overall efforts to adopt a healthy lifestyle, improving or maintaining overall health, supporting bone health, and filling nutrient gaps.*”

What information, if any, did you expect to find in this draft Recommendation Statement that was not included?

Beta-carotene

In the Rationale section, under “Harms of Vitamin Supplementation,” it is stated that there is “adequate evidence that supplementation with beta-carotene increases the risk of lung cancer in persons who are at increased risk of lung cancer.” This statement should be modified to indicate that risk is increased at high doses of beta-carotene (≥ 20 mg/day)^{17,18}. Nutrients are complex and many factors influence the benefits and risks of supplementation. However, for most nutrients both inadequate intake and supplementation at very high levels may pose a risk (classic “U” shaped curve) and benefit is achieved from regular consumption at or near recommended intake levels. It is important to identify that the evidence of harm pertains only to high doses of beta-carotene in at risk individuals. In fact, there is preliminary evidence that low-dose beta-carotene is protective¹⁹. CRN believes that information about the *dose* of beta-carotene that has been demonstrated to pose a risk in individuals at increased risk of lung cancer is important information to communicate to health care practitioners and consumers.

Similarly, in the Rationale section, under “USPSTF Assessment” it is stated that “[t]he USPSTF concludes with moderate certainty that the harms of supplementation with beta-

¹⁷ The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers. *New Engl J Med* 1994;330:1029-1035.

¹⁸ Omenn GS, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New Engl J Med* 1996;334:1150-1155.

¹⁹ Liu, et al. Low dose beta-carotene supplementation of ferrets attenuates smoke-induced lung phosphorylation of JNK, p38 MAPK and p53 proteins. *J Nutr* 2004; 134:2705-2710.

carotene, either alone or in combination, outweigh the benefits.” This statement also lacks context and is misleading without information related to the doses at which harm has been reported. A more accurate statement would indicate that supplementation with beta-carotene is associated with harms at high doses and in individuals who are at increased risk of lung cancer (i.e., smokers and asbestos workers). Also, while the focus of the USPSTF recommendations is on cancer and cardiovascular disease, it should be emphasized that beta-carotene is an important nutrient at the appropriate dosages (such as the amounts contained in typical multivitamins) and that there are other documented benefits of beta-carotene supplementation, such as serving as an important source of vitamin A.

Vitamin E

In the Discussion section, under “Effectiveness of Preventive Medication,” there are inconsistent findings reported with respect to vitamin E supplementation and cardiovascular disease endpoints and cancer incidence. However, on page 2 in the Rationale section, under “Benefits of Vitamin Supplementation,” the USPSTF states that there is “adequate evidence that supplementation with beta-carotene or vitamin E in healthy populations without nutritional deficiencies does not reduce the risk of cardiovascular disease or cancer.” Also, in the Discussion section, under “Estimate of Magnitude of Net Benefit,” the USPSTF states that a “large and consistent body of evidence has demonstrated that vitamin E supplementation has no effect on cardiovascular disease, cancer, or all-cause mortality. The USPSTF concludes with moderate certainty that the net benefit of vitamin E supplementation is zero.” Given the inconsistency of the evidence, why did the task force conclude that there is no benefit of vitamin E supplementation and recommend against vitamin E supplementation for these purposes? A more accurate interpretation of the evidence is that the data are conflicting. CRN suggests that an explanation of how the inconsistent evidence was used to reach moderate certainty of no benefit for vitamin E supplementation is missing from the USPSTF recommendation statement. In addition, health care practitioners and consumers should be aware that many national surveys

demonstrate that Americans do not consume the recommended intakes levels of vitamin E^{20,21} and that supplementation can help address this nutrient gap.

What resources or tools could the USPSTF provide that would make this Recommendation Statement more useful to you in its final form?

CRN has no comments for this section.

Do you have other comments on this draft Recommendation Statement?

In the Rationale section, under “Harms of Vitamin Supplementation”, it is stated that “[t]he USPSTF found inadequate evidence on the harms of supplementation with multivitamins and most single vitamins, minerals, or functional pairs.” However, this statement is based on the systematic review conducted by Fortmann et al. (2013)²² in which the authors stated there was “no consistent pattern of harms from nutritional dosages of multivitamins” and “little consistent evidence of harm across studies” on single and paired vitamins and minerals (with the exception of beta-carotene). The wording of the USPSTF recommendations should reflect the evidence that demonstrates a lack of harms reported in the reviewed studies. CRN recommends the statement in the Rationale section be modified to, “[t]he USPSTF found consistent evidence on the lack of harm of supplementation with multivitamins and most single vitamins, minerals, or functional pairs.”

In the “Additional Approaches to Prevention” section the USPSTF suggests that, “[d]espite the absence of benefit of vitamin supplementation, adequate nutrition by eating a diet rich in fruits, vegetables, whole grains, fat-free and low-fat dairy products, and seafood may play

²⁰ Gao X, et al. The maximal amount of dietary α -tocopherol intake in U.S. adults (NHANES 2001-2002). *J Nutr* 2006;136:1021-1026.

²¹ Interagency Board for Nutrition Monitoring and Related Research. Third Report on Nutrition Monitoring in the United States. Washington, DC: U.S. Government Printing Office, 1995.

²² Fortmann SP, et al. 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 [Epub ahead of print].

a role in the prevention of cancer or cardiovascular disease.” CRN agrees that a healthy diet is a prudent choice, however we are confused about what evidence the USPSTF used to draw this conclusion. There is a significant lack of robust RCTs demonstrating a causal relationship between the consumption of fruits, vegetables, whole grains, fat-free and low-fat dairy products, and seafood and reduced risk for cancer and cardiovascular disease. Given the USPSTF’s strict standards of scientific evidence used to develop its recommendations, it is difficult to determine how the USPSTF came to a conclusion that these specific foods reduce the risk of cancer or heart disease. If the USPSTF is willing to explore other forms of scientific evidence other than RCTs to recommend healthy foods, then there should be more flexibility in the types of evidence used to evaluate vitamin, mineral, and multivitamin supplements.

Respectfully Submitted,
Council for Responsible Nutrition

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

Douglas MacKay, ND
V.P. Scientific and Regulatory Affairs
Council for Responsible Nutrition