



April 27, 2016

USPSTF Coordinator
c/o USPSTF
540 Gaither Road
Rockville, MD 20850

Re: Opportunity for Comment - U.S. Preventive Services Task Force Draft Research Plan for Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Adults

The Council for Responsible Nutrition (CRN) appreciates the opportunity to comment on the U.S. Preventive Services Task Force (USPSTF) Draft Research Plan for Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Adults. CRN, 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. CRN 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 has organized its comments according to the questions posed by the USPSTF in the USPSTF Public Comment Form.

Do you have any comments about the analytical framework?

The proposed analytical framework (as well as all other aspects of the draft research plan) is focused on supplementation with vitamin D, calcium, or vitamin D and calcium in combination. Vitamin D status is included in the framework as an intermediate outcome rather

than a component of Key Questions 1 and 2. However, CRN considers vitamin D status (indicated by serum concentrations of 25-hydroxyvitamin D [25(OH)D]) to be a critical component of any research that is conducted to investigate the relationship between vitamin D and health outcomes, and recommends that vitamin D status be the focus of the proposed research plan. Therefore, the overarching research question regarding vitamin D should ask “whether vitamin D status influences fracture and fracture-related morbidity and mortality health outcomes,” instead of “whether supplementation with vitamin D [alone]...or vitamin D combined with calcium leads to improved fracture and fracture-related morbidity and mortality health outcomes” (as currently written).

Supplementation with a particular dose of vitamin D will not have the same impact across individuals in a population group. It may provide benefits to some individuals but may not have an effect in others, depending on the individual’s vitamin D status at baseline, along with other factors (such as absorption, metabolism, and polymorphisms in key vitamin D dependent genes). As an example, using the Institute of Medicine’s classifications of vitamin D status¹, an individual who is vitamin D-deficient [25(OH)D levels <30 nmol/L] could benefit from supplementation with 1,000 IU vitamin D, whereas the same dose of vitamin D may not confer additional benefits in an individual who is already considered sufficient [25(OH)D levels ≥50 nmol/L]. Assessing fracture risk and other health outcomes (including potential harms) based on vitamin D dose in isolation does not provide meaningful information. Instead, vitamin D status, which may be altered by vitamin D supplementation, is a determinant of health outcomes. Therefore, CRN recommends that the proposed analytical framework be modified to reflect vitamin D status as a central component of the research plan.

CRN recognizes that currently there are no measures of calcium status; therefore, a separate analytical framework for calcium supplementation alone may provide clarity.

Do you have any comments about Key Question 1?

CRN has concerns about Key Question 1 because it focuses on the role of vitamin D and/or calcium supplementation in fractures and fracture-related morbidity and mortality, instead of vitamin D status. As discussed in CRN’s comments regarding the proposed analytical

¹ Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

framework, vitamin D status should be an essential component of the research plan, and this should be reflected in the key questions. Therefore, CRN recommends the following wording for Key Question 1: Does vitamin D status affect the risk of fractures or fracture-related morbidity and mortality? Do the benefits of modifying vitamin D status by vitamin D supplementation alone or vitamin D combined with calcium supplementation vary by:

- a. Dose or dosing interval?
- b. Fracture type?
- c. Subpopulation (including, but not limited to: age, sex, or race/ethnicity)?

CRN does not have comments about Key Question 1 for calcium supplementation alone.

Do you have any comments about Key Question 2?

CRN has concerns about Key Question 2, which asks, “What are the harms associated with vitamin D or calcium alone or vitamin D combined with calcium? Do the harms of supplementation vary by:

- a. Dose or dosing interval?
- b. Subpopulation (including, but not limited to: age, sex, or race/ethnicity)?”

The phrasing of the question as currently written assumes that there are harms associated with vitamin D and/or calcium supplementation; however, harms have not been established. Further, as stated previously, vitamin D status should be a central consideration in researching health outcomes, including harms. Therefore, CRN recommends that the first sentence be reworded as follows: Are there harms associated with modification of vitamin D status by supplementation with vitamin D alone or vitamin D combined with calcium?

For the second sentence, CRN recommends the following wording: Do any harms of modifying vitamin D status by supplementation with vitamin D vary by:

- a. Dose or dosing interval?
- b. Subpopulation (including, but not limited to: age, sex, or race/ethnicity)?

CRN does not have comments about Key Question 2 for calcium supplementation alone.

Do you have any comments about the contextual questions?

CRN recommends that the contextual questions be removed because vitamin D status should be included in the key questions and thus be systematically reviewed. However, the

effects of different preparations of vitamin D (e.g., vitamin D₂ versus vitamin D₃) or different calcium formulations on the rate of vitamin D and calcium absorption could be investigated under contextual questions.

Do you have any comments about the research approach?

CRN recommends that the research approach for vitamin D include the assessment of vitamin D status. In the “Outcomes” section, studies should be included for both KQ1 and KQ2 if vitamin D status [indicated by serum 25(OH)D levels] was measured at baseline and end of intervention. Accordingly, studies should be excluded for both KQ1 and KQ2 if vitamin D status was not measured at baseline and end of intervention. Further, the research approach should include other factors that may impact the bone-related response to vitamin D supplementation, including resistance exercise, lean body mass, and excess body fat. Also, the research approach should include studies with vitamin D deficient subjects. Without data on vitamin deficient subjects, it would not be possible to parse out the potential relationship between vitamin D status and risk of fracture and fracture-related morbidity and mortality.

CRN also recommends that the analytical method used to measure 25(OH)D be considered when evaluating each study included in the Evidence Review. Analytical methods for 25(OH)D vary in accuracy and precision, leading to diverse results. Therefore, efforts should be made to calibrate the different methods of analysis when assessing vitamin D status across studies. At minimum, analytical methods should be included as a confounding variable in the Evidence Review.

With respect to calcium supplementation, CRN does not have comments about the research approach.

Respectfully Submitted,
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Vice President, Scientific & Regulatory Affairs