

CRN Comments on IOM FNB calcium and vitamin D DRIs

The Council for Responsible Nutrition (CRN) appreciates the opportunity to provide the Institute of Medicine (IOM) with general comments regarding the current efforts to revise the calcium and vitamin D Dietary Reference Intakes (DRIs), and regarding the selection of the expert committee to undertake the revision. CRN is a Washington, DC-based trade association representing the dietary supplement industry. Our members include some of the largest and most well known manufacturers of dietary ingredients and dietary supplements. For more information visit www.crnusa.org.

We commend the IOM and sponsoring organizations for undertaking this important project, which should result in updated guidance regarding recommended intakes of these two critical nutrients and amendment of the Upper Level of Tolerable Intake (UL) for vitamin D. We provide here some general comments and recommendations for the Food and Nutrition Board (FNB) committee that we hope will assist the committee in its review process.

Vitamin D

It is now widely recognized in both the US and Canada, that the last iteration of recommendations for vitamin D published back in 1997 (1), the first in a series of publications on nutrient DRIs, are woefully outdated (2-8). These recommendations (adequate intake, AI, ranging from 200 to 600 IU/day) appear to have been based on avoidance of rickets or osteomalacia, diseases of overt vitamin D deficiency. Since that time, a plethora of new data has been collected and published indicating a need for a prompt revision of these recommendations. New recommendations must go beyond avoidance of diseases of overt deficiency affecting only bone related outcomes, and must address avoidance of long-term inadequacy or insufficiency, a consequence of which may be increased risk for several chronic diseases.

Data published over the past ten years suggest that lower vitamin D status is associated with increased risk for falls in the elderly (9-15), cardiovascular disease (16-18), immune disorders (19-24), certain types of cancers (25-28) (29, 30) and diabetes (31-33). Many of these findings are based on serum 25-hydroxyvitamin D₃ (25-(OH)D) levels. It is now well established that serum 25-(OH)D levels are an excellent marker of vitamin D status (34). Although still a matter of debate, many experts suggest that the optimal range of serum 25-(OH)D is between 80 and 120 nmol/L (35-37). Data from NHANES reveals that on average,

Americans' serum 25(OH)D levels are far below this, especially in the obese, the elderly and those of ethnicities with darker skin (38). Furthermore, NHANES shows that Americans' serum 25(OH)D levels have declined over the past two decades (39).

Data suggest that the amount of vitamin D Americans need to achieve serum 25(OH)D levels between 80 and 120 nmol/L is somewhere at or above 1000 IU per day (35, 36, 40), well above the current recommendations. Furthermore, doses in this range have been shown to lower the risk of falls in the elderly, lower total cancer risk and even higher doses (> 6000 IU/day) are needed to increase vitamin D content of human breast milk (41).

Clearly, the FNB committee should have sufficient evidence at its disposal to increase the recommended intake of vitamin D and perhaps even replace the AI with an estimated average requirement (EAR) and an RDA.

Second to the revision of the recommended intake for vitamin D is the tolerable upper intake level (UL). The current UL (2000 IU/day) for adults has been repeatedly characterized as outdated and inappropriate (42, 43). The studies on which this value is based have serious flaws and limitations but were the only appropriate studies available to the FNB at the time. Since the 1997 publication, a number of well conducted randomized trials have been published involving vitamin D doses that far exceed the current UL, all with no adverse effects. The literature also includes a number of case reports of vitamin D toxicity. When and where assessed, these case reports all reveal vitamin D doses in excess of 100,000 IU/day equivalent and serum 25(OH)D levels above 600 nmol/L are needed to evoke toxicity. In a recent literature review and risk assessment, a new vitamin D UL of 10,000 IU was proposed (44). This risk assessment represents a much more accurate view of the current literature than what the FNB evaluated more than ten years ago.

Calcium

For calcium, it is most important that IOM replace the current set of AIs with EARs in order to provide a more precise recommendation. As with vitamin D, adequate data has been accrued for calcium to warrant this update. We urge the FNB committee to consider in its process other relevant endpoints, in addition to bone health, such as colon cancer risk. Furthermore, for both bone and cancer-related endpoints, it will be critical to assess calcium

requirements based on optimal vitamin D status, as the two nutrients are intimately linked in these endpoints.

Evidence-based reviews

Scientists charged with evaluating the literature for the purposes of establishing nutrition recommendations have in recent years implemented the practice of evidence-based reviews (EBR) (45, 46). Defined as an objective, systematic approach to evaluating the evidence base, EBR has been used with the last iteration of DRI reports, the 2005 USDA Dietary Guidelines, FDA's evaluation of health claims and is continuing with the 2010 Dietary Guidelines.

While in concept EBR appears to be a sound approach for the basis of forming unbiased recommendations, in its current form it may suffer from limitations that do not take into account the proper nutrition context. For example, EBR holds the randomized, controlled trial (RCT) as the "gold standard" of evidence. However, it fails to account for the fact that many RCTs to date have been designed as if they were assessing the effects of drug therapies (the origin of the RCT), rather than nutrients, where a true placebo group is neither ethical nor feasible. Many reviews and editorials have questioned the appropriateness of relying on the traditional placebo-controlled RCT to assess the effects of nutrients in humans (47-50). While all would agree that RCTs are needed to firmly establish causality between, for example, intake of a given nutrient and a relevant health-related outcome, in actuality, most RCTs are not adequately designed to properly assess such relationships. The reasons for this are many, including issues related to cost and feasibility. For RCTs to be the true "gold standard" and serve as the basis of nutrition policy, they must be redesigned to appropriately assess nutrition-related questions. Potential new approaches might include, but should not be limited to, measurement of global indices of health; a more holistic approach that combines assessment of multiple nutrients together with other behavioral modifications; measurement of single nucleotide polymorphisms (SNPS); and baseline and ongoing assessments of nutrient status. Revising the design of RCTs to make them more relevant to assessing the effects of nutrients will take considerable time. In the meantime, the question for nutrition policy makers is, can recommendations be made in the absence of convincing data from RCTs? The answer clearly is yes, as this is already common practice. Recommendations for fruit and vegetable intake, for example, are based almost solely on observational data (49). While epidemiological data cannot establish a causal link between fruits

and vegetables and chronic disease risk, the data are consistent enough such that the relationship can be deemed probable, if not definite.

A parallel exists with the literature on vitamin D and chronic disease risk. The overwhelming majority of data linking higher vitamin D status with lower risk for cardiovascular disease, cancers of the colon, prostate and breast, diabetes and all-cause mortality are observational in nature. The consistency of these data is quite strong, and most importantly the data are based on the accepted marker of vitamin D nutritional status, serum 25(OH)D levels. This is in contrast to other nutrient-disease relationships which may be based primarily on estimated intakes extrapolated from dietary surveys or measurement of serum metabolites, which are often not accepted indicators of nutrient status. The data on vitamin D are capable of affording a high level of certainty about vitamin D's role in chronic disease risk reduction.

The most recent EBR conducted on vitamin D have provided little in the way of recommendations that might assist the FNB committee and instead raise many more questions than answers (51, 52). By concluding that multiple gaps exist in the data (achieved by excluding a large portion of the evidence base), these reviews do not accurately reflect the strength of the evidence for vitamin D.

Another limitation of EBR is the deliberate exclusion of expert opinion, as an element for consideration. Established with the intent of eliminating bias, EBR suffers from an overly standardized approach that eliminates scientific judgment. In any review process where public health recommendations are at stake, no matter the topic, the data are always both complex and incomplete. This is where expert opinion is the most critical; to place findings in the proper context and render the most appropriate judgments where the data are grey. Excluding expert opinion has the unwanted effect of rendering meaningless decisions, i.e. no decision (53, 54). In the case of the DRIs (for any nutrient), the results of which serve as the basis for all nutrition policy in the US and Canada, "no decision" is not an option. In its attempt to eliminate a perceived bias on the part of experts in the field, the IOM would ultimately do more harm than good if it excluded or minimized the impact of such a valuable resource.

Regarding the FNB committee that has been compiled to review the literature and devise new recommendations, we are pleased to see the inclusion of experts such as Dr. John Aloia, Dr. Richard Gallo and Dr. Chris Gallagher. However, we are concerned about the absence of other noted experts who are well published in the areas of calcium and vitamin D and who are

considered the pioneers of the respective fields, such as Robert Heaney (Creighton University), Connie Weaver (Purdue University), Bruce Hollis (University of South Carolina), Reinhold Vieth (University of Toronto) and Ed Giovannucci (Harvard University). This is not in any way intended to be a slight against the choice of the other committee members, all of whom possess outstanding credentials and whose appointment to the committee may be well deserved. However, we are concerned that the exclusion of experts such as those mentioned above may cripple the process.

We urge the IOM and FNB committee to consider these comments, not only for vitamin D and calcium, but as they apply to the DRI process for all nutrients.

Sincerely,

Andrew Shao, PhD
Vice President, Scientific & Regulatory Affairs
Council for Responsible Nutrition
Washington, DC

REFERENCES

1. Food and Nutrition Board. Institute of Medicine. Dietary reference intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, D.C.: National Academy Press, 1997.
2. Weaver CM, Fleet JC. Vitamin D requirements: current and future. *Am J Clin Nutr* 2004;80:1735S-9S.
3. Vieth R. Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol* 2004;89-90:575-9.
4. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006;81:353-73.
5. Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr* 2004;80:1706S-9S.
6. Heaney RP, Weaver CM. Calcium and vitamin D. *Endocrinol Metab Clin North Am* 2003;32:181-94, vii-viii.
7. Alvarez-Leite JJ. Nutrient deficiencies secondary to bariatric surgery. *Curr Opin Clin Nutr Metab Care* 2004;7:569-75.
8. Whiting SJ, Calvo MS. Dietary recommendations to meet both endocrine and autocrine needs of Vitamin D. *J Steroid Biochem Mol Biol* 2005;97:7-12.
9. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res* 2003;18:343-51.
10. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. *Jama* 2004;291:1999-2006.
11. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *Qjm* 2007;100:185-92.
12. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med* 2008;168:103-8.

13. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 2007;55:234-9.
14. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med* 2006;166:424-30.
15. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis* 2005;20:187-92.
16. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008;168:1174-80.
17. Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. *Curr Opin Clin Nutr Metab Care* 2008;11:7-12.
18. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503-11.
19. Adams JS, Liu PT, Chun R, Modlin RL, Hewison M. Vitamin D in defense of the human immune response. *Ann N Y Acad Sci* 2007;1117:94-105.
20. Smolders J, Damoiseaux J, Menheere P, Hupperts R. Vitamin D as an immune modulator in multiple sclerosis, a review. *J Neuroimmunol* 2008;194:7-17.
21. Schaubert J, Gallo RL. The vitamin D pathway: a new target for control of the skin's immune response? *Exp Dermatol* 2008;17:633-9.
22. Baeke F, van Etten E, Gysemans C, Overbergh L, Mathieu C. Vitamin D signaling in immune-mediated disorders: Evolving insights and therapeutic opportunities. *Mol Aspects Med* 2008;29:376-87.
23. Bikle DD. Vitamin D and the immune system: role in protection against bacterial infection. *Curr Opin Nephrol Hypertens* 2008;17:348-52.
24. van Etten E, Stoffels K, Gysemans C, Mathieu C, Overbergh L. Regulation of vitamin D homeostasis: implications for the immune system. *Nutr Rev* 2008;66:S125-34.
25. Giovannucci E. The epidemiology of vitamin D and colorectal cancer: recent findings. *Curr Opin Gastroenterol* 2006;22:24-9.
26. Gross MD. Vitamin D and calcium in the prevention of prostate and colon cancer: new approaches for the identification of needs. *J Nutr* 2005;135:326-31.
27. Giovannucci E. Strengths and limitations of current epidemiologic studies: vitamin D as a modifier of colon and prostate cancer risk. *Nutr Rev* 2007;65:S77-9.
28. Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev* 2006;15:1427-37.
29. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-91.
30. Newmark HL, Heaney RP. Calcium, vitamin D, and risk reduction of colorectal cancer. *Nutr Cancer* 2006;56:1-2.
31. Luong K, Nguyen LT, Nguyen DN. The role of vitamin D in protecting type 1 diabetes mellitus. *Diabetes Metab Res Rev* 2005;21:338-46.
32. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007;92:2017-29.
33. Palomer X, Gonzalez-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes Obes Metab* 2008;10:185-97.
34. Hollis BW. Assessment of vitamin D status and definition of a normal circulating range of 25-hydroxyvitamin D. *Curr Opin Endocrinol Diabetes Obes* 2008;15:489-94.
35. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005.
36. Holick MF. Optimal vitamin D status for the prevention and treatment of osteoporosis. *Drugs Aging* 2007;24:1017-29.

37. Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Adv Exp Med Biol* 2008;624:55-71.
38. Yetley EA. Assessing the vitamin D status of the US population. *Am J Clin Nutr* 2008;88:558S-564S.
39. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. *Am J Clin Nutr* 2008;88:1519-27.
40. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr* 2008;87:1952-8.
41. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med* 2006;1:59-70.
42. Heaney RP. The Vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol* 2005.
43. Vieth R. Critique of the considerations for establishing tolerable upper intake levels for vitamin D. *J Nutr* 2005.
44. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85:6-18.
45. Balk EM, Horsley TA, Newberry SJ, et al. A collaborative effort to apply the evidence-based review process to the field of nutrition: challenges, benefits, and lessons learned. *Am J Clin Nutr* 2007;85:1448-56.
46. Lichtenstein AH, Yetley EA, Lau J. Application of systematic review methodology to the field of nutrition. *J Nutr* 2008;138:2297-306.
47. Heaney RP. Nutrition, chronic disease, and the problem of proof. *Am J Clin Nutr* 2006;84:471-2.
48. Heaney RP. Nutrients, endpoints, and the problem of proof. *J Nutr* 2008;138:1591-5.
49. King JC. An evidence-based approach for establishing dietary guidelines. *J Nutr* 2007;137:480-3.
50. Gann PH. Randomized trials of antioxidant supplementation for cancer prevention: first bias, now chance--next, cause. *Jama* 2009;301:102-3.
51. Brannon PM, Yetley EA, Bailey RL, Picciano MF. Overview of the conference "Vitamin D and Health in the 21st Century: an Update". *Am J Clin Nutr* 2008;88:483S-490S.
52. Effectiveness and Safety of Vitamin D in Relation to Bone Health. Prepared for: Agency for Healthcare Research and Quality U.S. Department of Health and Human Services, Rockville, MD. Contract No. 290-02-0021 Prepared by: University of Ottawa Evidence-based Practice Center, Ottawa, Canada, 2007.
53. Petticrew M. Why certain systematic reviews reach uncertain conclusions. *Bmj* 2003;326:756-8.
54. Mullen PD, Ramirez G. The promise and pitfalls of systematic reviews. *Annu Rev Public Health* 2006;27:81-102.