

New scientific resource: CRN-I is providing brief summaries of journal articles relevant to international regulatory science for nutrients and food (dietary) supplements, including risk assessments and claims substantiation. These summaries—in English, Arabic, Chinese, French and Spanish—are linked to the original journal publications (in English).

SAFETY:

[Reexamination of a meta-analysis of the effect of antioxidant supplementation on mortality and health in randomized trials](#)

Biesalski HK, Grune T, Tinz J, Zöllner I, Blumberg JB.

Nutrients 2010; 2: 929-949

A recent meta-analysis of selected randomized clinical trials (RCTs) found that antioxidant (beta-carotene, vitamin A and/or vitamin E) interventions increased all-cause mortality, which was not a primary outcome in any of the 66 RCTs included in the meta-analysis. This reexamination evaluated the same data based on the primary outcome of the RCTs and identified whether the results provided a positive (*i.e.*, benefit), null (no effect), or negative (*i.e.*, harm) outcome. Of the RCTs, 24 had a positive outcome, 39 had a null outcome and 3 had a negative outcome; this suggests usefulness in application of benefit/risk ratio to assessment of potential risks of antioxidant supplementation.

[Benefit-risk assessment of vitamin D supplementation.](#)

Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC.

Osteoporos Int. 2010 Jul; 21(7):1121-32.

Current intake recommendations of 200 to 600 IU vitamin D per day are insufficient for important disease outcomes reduced by vitamin D. An analysis based on double-blind, randomized controlled trials (RCTs) suggests greater fall, fracture, cardiovascular disease and colorectal cancer prevention with serum 25(OH)D means between 75 and 110 nmol/L (30-44 ng/mL). Adverse risk of increased serum calcium levels was associated with high vitamin D intake of 100,000 IU per day, or achieved 25(OH)D up to 643 nmol/L. The serum 25(OH)D levels associated with benefits can be best and safely obtained with oral doses in the range of 1,800 to 4,000 IU vitamin D per day.

[Evidence-based criteria in the nutritional context.](#)

Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM, Zeisel SH.

Nutr Rev. 2010 Aug; 68(8):478-84

Randomized clinical trials are the gold standard for determining drug efficacy, but have limitations in the context of nutrition science and policy due to inherent complexities of nutrient actions and interactions. Advancing evidence-based nutrition will depend upon research approaches that not only include RCTs but go beyond them to include the totality of the available evidence. It may be that the level of certainty needed for policy making decisions, such as defining nutrient

requirements or dietary recommendations to prevent disease, must be different from that needed to make recommendations to treat disease.

[Expanded approach to tolerable upper intake guidelines for nutrients and bioactive substances.](#)

Hathcock JN, Shao A.

J Nutr. 2008 Oct; 138(10):1992S-1995S.

The Observed Safe Level (OSL) method, equivalent to the official Highest Observed Intake (HOI) method, can be utilized to provide risk assessment values for nutrients and bioactive substances for which no known adverse effects related to high intakes, and thus a policy value equivalent to the tolerable upper intake level (UL), can be established. The OSL method involves arranging in decreasing order the daily intake in human clinical trial data, followed by evaluation of each trial for quantity and quality of data. The intake level with no observed adverse effects from a trial of sufficient quality to justify no further correction for uncertainty is selected as the OSL.

[Risk assessment for vitamin D.](#)

Hathcock JN, Shao A, Vieth R, Heaney R.

Am J Clin Nutr. 2007 Jan; 85(1):6-18.

Data that emerged after the 1997 publication of the safe Tolerable Upper Intake Level (UL) for vitamin D (50 micrograms, or 2,000 IU per day) by the Food and Nutrition Board (FNB) suggest benefits of vitamin D beyond bone health and support a significantly higher UL. A recent risk assessment based on well designed and conducted human clinical trial data on vitamin D proposes 250 mcg/d (10,000 IU) as the revised UL for vitamin D3. This amount is not a threshold for adverse effects, but is an amount that is safe by a comfortable margin. The kidney stones observed in a large clinical trial of high calcium intakes with 400 IU of vitamin D seem related to calcium and not to vitamin D.

[Risk assessment for glucosamine and chondroitin sulfate.](#)

Hathcock JN, Shao A.

Regul Toxicol Pharmacol. 2007 Feb; 47(1):78-83. Epub 2006 Aug 30.

Glucosamine and chondroitin sulfate are two popular dietary ingredients with a large body of human and animal evidence suggesting their oral intake for reducing joint pain and improving mobility in persons with osteoarthritis. Human clinical trial data, evaluated using the Observed Safe Level (OSL) risk assessment method, indicate that chronic intakes of glucosamine up to 2,000 mg/d are safe, as are intakes of chondroitin sulfate up to 1,200 mg/d. Most clinical trial data on glucosamine relate to a 1,500 mg/d administration that was completely without adverse effects. This suggests that the complete absence of adverse effects in the single trial at 2,000 mg/d was a legitimate and reliable result.

[Risk assessment for carnitine.](#)

Hathcock JN, Shao A.

Regul Toxicol Pharmacol. 2006 Oct; 46(1):23-8. Epub 2006 Aug 9.

Carnitine is a conditionally essential amino acid-like compound involved in the transport of long-chain fatty acids into the mitochondria during the beta-oxidation process. Carnitine has become an increasingly popular ingredient in dietary supplements in the weight loss and sports nutrition categories. Regarding safety, the Observed Safe Level (OSL) or Highest Observed Intake (HOI) risk assessment indicates that chronic supplementation of L-carnitine is safe up to 2,000 mg/d, the highest observed safe level in human clinical trial data.

[Risk assessment for coenzyme Q10 \(Ubiquinone\).](#)

Hathcock JN, Shao A.

Regul Toxicol Pharmacol. 2006 Aug; 45(3):282-8. Epub 2006 Jun 30.

Coenzyme Q10 (CoQ10) naturally occurs in organisms and tissues, and is available as both a drug and a dietary supplement in the U.S. Reports of nausea and other adverse gastrointestinal effects of CoQ10 cannot be causally related to the active ingredient because there is no dose-response relationship; that is, nausea occurs as frequently in subjects given 60 mg/d as in those given 1,200 mg/d. Evaluation of safety based on the Observed Safe Level (OSL) risk assessment method concludes CoQ10 at intakes up to 1,200 mg/d is safe in humans.

[Vitamins E and C are safe across a broad range of intakes.](#)

Hathcock JN, Azzi A, Blumberg J, Bray T, Dickinson A, Frei B, Jialal I, Johnston CS, Kelly FJ, Kraemer K, Packer L, Parthasarathy S, Sies H, Traber MG.

Am J Clin Nutr. 2005 Apr; 81(4):736-45.

Vitamins E and C are antioxidant nutrients that protect against free radical damage among other functions. As safety guidance, tolerable upper intake levels (ULs) have been established by the Food and Nutrition Board at 1,000 mg for vitamin E and 2,000 mg for vitamin C in adults. Many clinical trials with these vitamins have involved subjects with various diseases, and no consistent pattern of adverse effects has occurred at any intake. The clinical trial evidence support the safety of supplements of vitamin E providing $\leq 1,600$ IU/d and vitamin C providing amounts $\leq 2,000$ mg/d for most adults. Published meta-analyses that reported increased all-cause mortality with high intakes of vitamin E used questionable inclusion criteria, invalid extrapolation methods, or both.

[Does high intake of vitamin A pose a risk for osteoporotic fracture?](#)

Hathcock JN.

JAMA. 2002 Mar 20; 287(11):1396-7.

To the Editor: Dr Feskanich and colleagues found that high intake of dietary retinol (i.e., vitamin A) was related to risk of hip fracture in postmenopausal women. They interpret these data as supportive but not conclusive of a causal relationship. The issue for vitamin A and bone health is not whether mechanisms exist, however, but instead whether the effect occurs at the usual levels of retinol intake experienced by most persons. The evidence relating to a possible relationship between moderately high vitamin A intake and possible adverse effects on bone health remains inconclusive.

[Dietary supplements: how they are used and regulated.](#)

Hathcock J.

J Nutr. 2001 Mar; 131(3s):1114S-7S.

Dietary supplements are widely used and are regulated by the U.S. Food and Drug Administration as a category of food under the Dietary Supplement Health and Education Act (DSHEA). This law, passed in 1994, expanded and clarified the definition of dietary supplements, specified additional requirements for safety and provided for four types of claims of nutritional support. These include prevention of classic nutritional deficiencies, structure or function (S/F) effects, mechanisms for S/F effects and general well-being. Claims suggesting that a product will treat, cure, mitigate or diagnose a disease are reserved for drugs and not allowed for dietary supplements.

[Calcium supplementation and incident kidney stone risk: a systematic review.](#)

Heaney RP.

J Am Coll Nutr. 2008 Oct; 27(5):519-27.

Kidney stone risk in postmenopausal women has increased substantially in the past 40 years, but absolute population incidence estimates vary widely. A review of calcium studies and adverse event report data indicate no increase in risk of kidney stone with high calcium intake; on the contrary, there is substantial evidence suggesting an inverse relationship between calcium intake and stone risk.

[Vitamin D: criteria for safety and efficacy.](#)

Heaney RP.

Nutr Rev. 2008 Oct; 66(10 Suppl 2):S178-81.

The functional indicator of vitamin D status, for both safety and efficacy, is serum 25-hydroxyvitamin D concentration. A 25-hydroxyvitamin D serum level of at least 80 nmol/L, but no more than 500 nmol/L (level at which toxicity occurs), is required for positive health outcomes. To achieve optimal status, supplemental amounts between 1000 to 2000 IU/day cholecalciferol is typically needed.

[Are low tolerable upper intake levels for vitamin A undermining effective food fortification efforts?](#)

Kraemer K, Waelti M, de Pee S, Moench-Pfanner R, Hathcock JN, Bloem MW, Semba RD. *Nutr Rev.* 2008 Sep; 66(9):517-25. [Erratum in: *Nutr Rev.* 2008 Oct; 66(10):610.]

Vitamin A deficiency (VAD) is a major health problem in less developed countries. In contrast to affluent countries where more foods in the diet contain retinol, vitamin A supplementation in populations with prevalent VAD does not warrant concerns of increased risk of bone fracture associated with high vitamin A intakes. Recently developed risk management tools can be implemented to safely reduce vitamin A deficiency and associated diseases through supplementation and fortification in specific target groups in low-resource countries.

[Risk management of vitamins and minerals: a risk categorisation model for the setting of maximum levels in food supplements and fortified foods](#)

Richardson DP.

Food Science and Technology Bulletin: Functional Foods. 2007 Nov; 4 (6) 51–66

A risk management model can be utilized in setting maximum levels of vitamins and minerals in fortified foods and food supplements. The proposed model takes into account international risk assessments of tolerable upper intake levels (ULs) of vitamins and minerals and elaborates on risk characterization using a 'population safety index' and qualitative and quantitative data analysis to allocate nutrients into three categories of risk.

[Risk assessment for the amino acids taurine, L-glutamine and L-arginine.](#)

Shao A, Hathcock JN.

Regul Toxicol Pharmacol. 2008 Apr; 50(3):376-99.

The absence of a systematic pattern of adverse effects in humans in response to orally administered taurine (Tau), L-glutamine (Gln) and L-arginine (Arg) precluded the application of the usual risk assessment method for identification of a tolerable upper intake level (UL). Instead, the newer method described as the Observed Safe Level (OSL) or Highest Observed Intake (HOI) was utilized to identify observed safe levels, supported by available human clinical trials, of 3 g/d for L-aurine, 14 g/d for L-glutamine and 20 g/d for L-arginine.

[Risk assessment for the carotenoids lutein and lycopene.](#)

Shao A, Hathcock JN.

Regul Toxicol Pharmacol. 2006 Aug; 45(3):289-98. Epub 2006 Jun 30.

Emerging research involving oral administration of lutein and lycopene, carotenoids found in the diet and dietary supplements, suggest benefits for eye, prostate, skin and cardiovascular health. Risk assessment based on the Observed Safe Level (OSL) or Highest Observed Intake (HOI) method indicates observed safe levels for long term supplementation in humans of 20 mg/d for lutein and 75 mg/d for lycopene.

These values from clinical trials are more conservative (lower) than risk assessments based on animal data.

[Risk assessment for creatine monohydrate.](#)

Shao A, Hathcock JN.

Regul Toxicol Pharmacol. 2006 Aug; 45(3):242-51. Epub 2006 Jun 30.

Creatine monohydrate (creatine) is commonly used in dietary supplements in the sports nutrition category. Its ergogenic effect, particularly during exercise or activities requiring high intensity short bursts of energy, has been observed in human and animal studies. The data do not show causally related adverse effects and therefore do not provide a basis for a safe upper level of intake (UL), but risk assessment utilizing the Observed Safe Level (OSL), also known as the Highest Observed Intake (HOI), method indicates the evidence of safety is excellent for long term supplementation of creatine at intakes up to 5 g/d.

CLAIMS—Health and Function:

[The process for the assessment of scientific support for claims on food.](#)

Aggett PJ.

Eur J Nutr. 2009 Dec; 48 Suppl 1:S23-6.

The process for the systemic evaluation of the evidence to support a claim for foods is described. This entails application of specific criteria, including data and intervention characteristics (defined target population, valid and quality surrogate endpoints, etc...), and use of the totality of published and unpublished evidence and expert judgment to weigh the strength of evidence against that of the claim.

[Optimizing clinical trial design for assessing the efficacy of functional foods.](#)

AbuMweis SS, Jew S, Jones PJ.

Nutr Rev. 2010 Aug; 68(8):485-99.

Randomized clinical trial data can establish causal relationships between functional food components and health and disease/disease risk and provide the substantiation for health claims. Selection of appropriate control arm, duration, statistical tests and validated surrogate endpoints are among essential design considerations of quality clinical trials examining the efficacy of functional foods.

[How the US Food and Drug Administration evaluates the scientific evidence for health claims.](#)

Ellwood KC, Trumbo PR, Kavanaugh CJ.
Nutr Rev. 2010 Feb; 68(2):114-21.

This article describes the process by which the U.S. Food and Drug Administration (FDA) reviews the scientific evidence for health claims and qualified health claims for both conventional foods and dietary supplements; this is also the topic of the FDA guidance document titled “Evidence-Based Review System for the Scientific Evaluation of Health Claims” issued in January 2009.

[Food label use and its relation to dietary intake among US adults.](#)

Ollberding NJ, Wolf RL, Contento I.
J Am Diet Assoc. 2010 Aug; 110(8):1233-7.

This study describes patterns of food label use in a nationally representative sample of US adults. Use of food labels is associated with healthier nutrient consumption, particularly relating to total energy and fat. Despite food label use being associated with improved dietary factors, label use alone is not expected to be sufficient in modifying behavior ultimately leading to improved health outcomes.

[Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research.](#)

Rijkers GT, Bengmark S, Enck P, Haller D, Herz U, Kalliomaki M, Kudo S, Lenoir-Wijnkoop I, Mercenier A, Myllyluoma E, Rabot S, Rafter J, Szajewska H, Watzl B, Wells J, Wolvers D, Antoine JM.
J Nutr. 2010 Mar; 140(3):671S-6S.

This article provides guidelines and recommendations for the assessment of probiotics in relation to health effects, based on an ILSI international expert group’s evaluation of the published evidence for the functionality of probiotics in the areas of human metabolism, chronic intestinal inflammatory and functional disorders, infections, and allergy.