



#### WHY I CREATE RESEARCH REVIEWS

I am frequently asked about forms and dosages of nutritional supplement ingredients.

Research Reviews provide information to answer these questions.

Scientific references are cited and text from abstracts is included to provide research details and background.

I evaluate ingredients and dosages by the following criteria:

- 1) Is it natural to and easily used by the human body?
- 2) Has it had a long history of safe use in humans?
- 3) Is it supported by science or traditional herbal wisdom?
- 4) Is it nutritionally effective?
- 5) Is it cost-effective?
- 6) Is it concentrated enough that optimal doses can be supplied in a reasonable amount of tablets?

I have no vested interest in any form of ingredient and no financial involvement with any raw materials manufacturer. My recommendations are based on what I believe is best for my own health and for yours, too.

## Vitamin & Mineral Doses: Safety & Effectiveness

**Question:** Are high doses of vitamins and minerals toxic?

**Answer:** The newly discovered more nutritionally effective doses of vitamins and minerals are often significantly higher than US Government assigned Daily Values.

The safety of these higher doses is confirmed by conservative medical, scientific and government organizations.

See *Vitamin Safety Table* on page 6.

**Question:** Are small doses of vitamins and minerals, such as Daily Value levels of vitamins and “food-grown-type” nutrient amounts as effective as higher doses of USP-type nutrients?

**Answer:** Specific health benefits derived from higher doses of vitamins and minerals have not been duplicated using RDA levels or “food-grown-type” amounts of vitamins and minerals.

In many scientific studies, only higher doses have been shown to deliver these health benefits.

### INSIDE

- Complete Vitamin Safety Table
- Optimum Doses

I am asked whether higher doses of vitamins and minerals are more effective than Daily Value (DV or RDA) levels, and whether higher doses may be toxic. This Research Review examines these questions in the light of scientific research about vitamin and mineral dosages and their effectiveness at optimum doses that are known to be safe.

## Dosing and Effectiveness

All available published scientific studies show that if you eat the average American diet that provides approximately 600 mg of food calcium per day, low doses, such as 100 mg per day of supplemental calcium, no matter what type or form of calcium is considered, are not effective for important health applications, such as building bone.

For instance, one three-year placebo-controlled study of senior women showed that while a typical daily intake of calcium from food (683 mg average per day) allowed 3% bone loss in a dose-dependent manner, 1,000 mg of supplemental calcium carbonate added to the 683 mg of dietary calcium, totaling 1,683 mg of daily calcium, improved spinal bone density (3.7%) and hip bone density (3%).

*Storm D, et al. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: a randomized placebo-controlled trial. Clin Endocrinol Metab, 83(11):3817-25 1998) (Fact Vs Fiction #2, Calcium, p 8.)*

Low supplemental doses of any type of calcium (calcium carbonate, calcium citrate, calcium gluconate, or “food-grown-type” calcium) have not been shown to protect bone density. All independent published scientific studies conclusively agree that approximately 1,000 mg of supplemental elemental calcium per day, from any source, is required for bone health and bone maintenance in American adults who consume the average American diet, and more is required by seniors, 65 years or older. (1,300 mg to 1,700 mg of supplemental calcium, according to a study by Heaney, J Am Coll Nutr 2001 Apr;20(2 Suppl):192S-197S.)

While studies show that calcium carbonate, citrate and other types of calcium can improve bone density at doses of 1,000 mg per day added to dietary calcium, there are no published studies at any dose that examine “food-grown-type” calcium’s effect on bone density, although it is likely that “food-grown-type” calcium would produce similar benefits at a similar 1,000 mg amount.

## Studies Showing Higher Doses Are Required To Support Optimum Long-Term Health

There are over 20,000 studies in the National Library of Medicine showing health benefits of vitamins and minerals at much higher than Daily Value (RDA) levels. Below are a few examples.

### **Vitamin B6 – Higher Doses Reduce PMS Symptoms While Not Low Doses Did Not**

A study of 630 women showed that while 40 mg of Vitamin B6 produced no significant benefit, 100 mg to 150 mg reduced PMS symptoms in about 66% of the women, while 160 mg to 200 mg of Vitamin B6 reduced PMS symptoms in about 79% of the women.

*Brush MG, et al. Pyridoxine in the treatment of premenstrual syndrome: a retrospective survey in 630 patients. Brit J Clin Pract 1988;142(11):448-4562.) Consult your doctor about the use of higher dose Vitamin B6 for PMS.*

### **Vitamin B6 – Fewer Kidney Stones**

In a study of 121,701 females (Curhan, 1999) who took between 10 and 500 mg of Vitamin B6 per day, higher doses were shown to be associated with fewer kidney stones. For instance, a 21% decrease in stone formation was seen in healthy women who took 200 mg per day.

*Edwards P, et al. Effects of oral pyridoxine upon plasma and 24-hour urinary oxalate levels in normal subjects and stone formers with idiopathic hypercalciuria. Urol Res. 18:393-396, 1990.*

### **Vitamin E – Lower Doses Do Not Reduce Cholesterol Oxidation – Higher Doses Do**

The Daily Value for Vitamin E is currently 30 IU. A placebo-controlled study showed that Vitamin E dosing of 60 IU or 200 IU had no effect on reducing the oxidation of LDL cholesterol that precedes cholesterol plaque formation in arteries, but that doses of 400 IU, 800 IU and 1,200 IU had a significant effect on safely reducing the oxidization of LDL cholesterol in the blood stream.

*Jialal I, et al. The effect of alpha-tocopherol supplementation on LDL oxidation. A dose-response study. Arterioscler Thromb Vasc Biol 1995;15(2):190-198.*

### **Vitamin C – Higher Doses Maintain Bone Density Better Than Lower Doses**

The Daily Value for Vitamin C is currently 60 mg. Studies on Vitamin C show that doses of Vitamin C that have the potential to optimize various components of overall health, like bone density, begin at about 1,000 mg per day. One peer-reviewed study showed that senior women who took supplements that contained between 1,000 mg and 5,000 mg of Vitamin C per day had 5% greater bone density than women who took 500 mg or less per day over three years.

*Morton DJ, et al. Vitamin C supplement use and bone mineral density in postmenopausal women. J Bone Min Res 2001;16(1):135-140.*

### **Vitamin C – Higher Doses Reduce Duration of Colds - Lower Doses Have No Effect**

Another peer-reviewed study stated that Vitamin C doses of 250 mg to 500 mg per day produced no effect on reduction of cold symptoms, while doses from 1,000 mg to 6,000 mg per day decreased cold durations an average of 21%.

*Hemila H, et al. Vitamin C and the common cold: a retrospective analysis of Chalmers' review. J Am Coll Nutr 1995;14(2):116-123.*

### **Vitamin C – Increased Human Lifespans**

One of the first human studies that demonstrated increased human lifespans, showed that men who took 800 mg per day of Vitamin C lived six years longer than men who consumed the 60 mg per day that is the Daily Value.

*Enstron, et al. Vitamin C intake and mortality among a sample of the United States population. Epidemiology 1992 May;3(3):194-202.*

### **Multi-Vitamins – 10 Times RDA Improves Mood, Sleep, Reaction Times**

A double-blind, placebo-controlled study of 129 students over one year showed that those who took a multivitamin with 10 times the RDA of Vitamins B-1, B2, B3, B6, B12, Biotin, Vitamin C and Vitamin E, had better reaction times, better mood, more restful sleep, and described themselves as more agreeable and better composed.

*Benton D, et al. Vitamin supplementation for 1 year improves mood. Neuropsychobiology (Switzerland), 1995, 32(2) p98-105.*

### **High Dose Vitamin Therapies – May Help Protect Against 50 Genetic Diseases**

Noted nutrient researcher and one of the world's most respected cell biologists, Bruce Ames, PhD, of UC California at Berkeley, published a study that stated that high dose vitamin therapies may help treat many genetic defects. His conclusion stated, "*High dose vitamin therapies have been efficacious in ameliorating about 50 genetic diseases...*" These diseases included heart disease, cancer, Alzheimer's, migraines and alcohol tolerance.

*Ames BN, et al. High dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased Km): relevance to genetic disease and polymorphisms. Am J Clin Nutri, 2002;75:616-658.*

### **Calcium – Better Baby's Bones**

While a calcium dose of 1,000 mg or more is important for bone health for senior women, a double-blind peer-reviewed study of 256 prenatal women showed that if the women ate an average American diet that provided less than 600 mg of calcium per day, when they took 1,200 mg or more of calcium carbonate per day their baby's were born with bones that were 15 percent more dense than those women who took less calcium. This study showed no adverse effect on their baby's bones, even when mother's consumed 3,000 mg of supplemental calcium carbonate per day.

*Koo WW, et al. Maternal calcium supplementation and fetal bone mineralization. Obstet Gynecol 1999 Oct;94(4):577-582.*

## **The Differences Between Daily Value (RDA's), Safety (No or Lowest Observed Adverse Effects Level) And Minimum Toxic Dose**

I have received questions about Daily Value levels of vitamins and essential minerals. What levels are safe and what are toxic doses of vitamins and essential minerals. Below is an explanation of the various levels of dosages of vitamins and essential minerals.

**Level 1. Daily Value (DV) formerly called Recommended Daily Allowances (RDA).** This is usually the dosage that has been determined to be enough of a given nutrient to keep people from experiencing "classic" nutrient deficiency diseases, like rickets (Vitamin B1 deficiency), pellagra (Vitamin B3 deficiency) or scurvy (Vitamin C deficiency). There is a growing concern in the scientific community, based on the most current studies, including some sponsored by the US Government's Department of Agriculture, that the DV/RDA doses for some nutrients may not be high enough to support optimum health or long-term well-being.

**Level 2. The low-to-moderate dose ranges** (somewhat above the DV/RDA's) that are in most vitamin formulas

**Level 3. The optimal health and anti-aging dose ranges.** (These are moderately high potencies.)

**Level 4. No Observed Adverse Effect Level (NOAEL)** This dosage is safe enough that no observed adverse effect has been seen at this dose when taken over long periods of time. According to the Institute of Medicine, this dosage level "*requires no application of a safety factor to determine a safe intake, based on the most sensitive subgroup.*" The NOAEL is determined to be safe by in-depth conservative analysis of all available scientific databases from around the world for many years. This is generally where optimal health effects are seen.

**Level 5. Lowest Adverse Effect Level (LOAEL)** This is a dosage where toxicity has rarely occurred, and then only for some people with unusual sensitivities, who are considered to be in “sensitive subgroups.” This is rare. This dosage may be safe for most people, but “*may require the application of a safety factor to calculate a safe intake.*” “*Application of a safety factor*” means that groups that are sensitive, such as people who have unusual vitamin or mineral storage problems, may have side effects or a toxic response that most other people might not have at this dose. (Example: 1 in about 300 people have iron storage problems.<sup>1</sup>)

**Level 6. Minimum Toxic Dose (MTD)** Pharmacy Times, in their 1985 Vitamin Safety Index, listed MTD’s as the lowest estimated dose that might cause a toxic effect. As you will see in the Vitamin and Essential Mineral Safety Table, the MTD’s for all vitamins and minerals (except Vitamin A and niacin) are 4 to 20 times higher than the No Observed Adverse Effect Level (NOAEL). This is an extremely conservative estimate in the case of some nutrients, such as occurred with the calculation for Vitamin C. In the period of time after 1985, comprehensive analysis has shown that some of these estimated dosages are probably too low. I include the *Pharmacy Times* information in the interest of full disclosure of very conservative suggestions.

**There is no solid scientific reason for an LOAEL (or NOAEL) for Vitamin C.**

The National Academy of Sciences established a NOAEL for Vitamin C June, 2000, because they were directed to establish one. They could not find support for any toxic dose for Vitamin C, so they arbitrarily placed an NOAEL with no solid data to validate it.

The above statement regarding “*no solid data to validate it*” is supported by a study sponsored by the U.S. Government Institute of Medicine-sponsored Food and Nutrition Board.

*Johnston CS. Biomarkers for establishing a tolerable upper intake level for vitamin C. Nutr Rev 1999 Mar;57(3):71-77.*

Dietary reference intakes (DRIs) for vitamin C for healthy U.S. populations are currently being formulated by the Panel on Dietary Antioxidants and Related Compounds of the Food and Nutrition Board of the Institute of Medicine. A major task of the Panel is to analyze the evidence of adverse effects of high-dose vitamin C intakes to derive, if appropriate, a Tolerable Upper Intake Level (UL) for vitamin C. The present report details current and past research examining potential adverse effects of supplemental vitamin C. The available data indicate that very high intakes of vitamin C (2-4 g/day) are well tolerated biologically in healthy mammalian systems. *Currently, strong scientific evidence to define and defend a UL for vitamin C is not available.*

Dr. Johnston said that there is no “*strong scientific evidence*” to defend a position for a “*tolerable upper limit*” (UL) for Vitamin C --- because Vitamin C has not been shown to cause toxicity to cells in the body, even at very high doses. (Note: UL equals the Tolerable Upper Limit, which is generally in the same dosage range as the NOAEL.)

## The Vitamin and Essential Mineral Safety Table

The Vitamin and Essential Mineral Safety Table on the next page shows the DV, NOAEL, LOAEL and MTD dosage levels for each vitamin and essential mineral. The table was compiled using data from *The US Government Institute of Medicine’s Food and Nutrition Board*, the *Council For Responsible Nutrition’s* dosages (I provide whichever is most current), and *Pharmacy Times* Minimum Toxic Dose (MTD) information. The *Pharmacy Times* information is dated 1985. I could find no updated information on a current calculation of the MTD from *Pharmacy Times*, so the 1985 MTD’s are included here only as very conservative references.

**VITAMIN AND ESSENTIAL MINERAL SAFETY TABLE**  
**Vitamin and Essential Mineral Doses And Safety For Most Adults**

<b>NUTRIENT</b>		Daily Value US Gov't Minimum Level For Health	NOAEL <u>CRN or Inst/Med</u> No Observed Adverse Effect Level	LOAEL <u>CRN or Inst/Med</u> Lowest Observed Adverse Effect Level	MTD <u>Pharmacy Times</u> First Signs Of Toxicity
Vitamin A	IU	3,000	10,000	21,600	25,000 – 50,000
Vitamin C	MG	60	More than 1,000	None	2,000 – 5,000
Vitamin D	IU	400	2,400 (Inst of Med)	3,800 (Inst Med)	50,000
Vitamin E	IU	30	1,200	None	1,200
Vitamin K	MCG	80	30,000	None	None given
Thiamine (Vit. B1)	MG	1.5	200	None	300
Riboflavin (B2)	MG	1.7	200	None	1,000
Niacin (B3) SR = Slow Release	MG	20	500 250 SR	1,000 500 SR	1,000
Niacinamide (B3)	MG	20	1,500	3,000	None given
Pyridoxine (B6)	MG	2	200	500	2,000
Folic acid	MCG	400	1,000	None	400,000
Vitamin (B12)	MCG	6	3,000	None	None given
Biotin	MCG	300	2,500	None	50,000
Pantothenic acid (B5)	MG	10	1,000	None	10,000
Calcium	MG	1,200	Approx. 2,400	5,000 (Inst Med)	12,000
Phosphorus	MG	1,200	1,500	2,500	12,000
Iron	MG	18	65	100	100
Iodine	MCG	150	1,000	None	2000
Magnesium	MG	400	700	None	6,000
Zinc	MG	15	30	60 mg	500
Selenium	MCG	70	200	910	1,000
Copper	MG	2	9	None (~385)	100
Manganese	MG	2	10	None	None given
Chromium (III)	MCG	120	1,000	None	None given
Molybdenum	MCG	75	350	None	None given
Beta-carotene	IU	None	41,666	None	None given

**DV (Daily Value):** Previously was Recommended Daily Allowance. These dosages are the minimum amount necessary for good health as determined by the National Academy of Sciences, acting for the U.S. Government. New nutritional research is leading some researchers and clinicians to estimate that these doses may not be high enough to support optimal health in today's stressful world.

**NOAEL:** Meaning the "No Observed Adverse Effect Level." These dosages have been estimated by The Food and Nutrition Board of The Institute of Medicine (Inst of Med) or The Council for Responsible Nutrition (CRN), and are updated periodically. No observed adverse reactions (side effects) have been recorded at these levels.

**LOAEL:** Meaning the "Lowest Observed Adverse Effect Level." These dosages were determined by The Institute of Medicine or CRN to be safe for almost everyone, but "may require the application of a safety factor to calculate safe intake" for people with unusual vitamin or mineral sensitivities.

**MTD's:** Meaning the "Minimum Toxic Dose." These dosage levels were published in *Pharmacy Times Vitamin Safety Index*, May, 1985, as very conservative estimates of the minimum doses that may cause toxic effects (side effects).

As can be seen from the table, the levels of vitamins and minerals found in high potency multi-vitamins are not in the adverse effects or toxic ranges. They are far lower than doses that have the potential to be lethal. (The U.S. Government Centers for Poison Control's first 10-year report showed no deaths from vitamins, 60 deaths from accidental iron poisoning, 2556 deaths from OTC drugs like aspirin, and over 1,000,000 deaths from prescription drugs.)

**Notes for the table:**

- In the column for LOAEL that says "*none*" (*none established*), it means that the National Academy of Sciences (NAS) has not determined a conclusive *Lowest Observed Adverse Effect Level* dose that may be unsafe for some "*sensitive subgroups*," either because there is none or because they do not have enough reports of toxic effects to establish one. For many vitamins, there simply are no reports or too few reports of adverse effects at any level and, therefore, no LOAEL number can be identified.

- The current NOAEL for Vitamin D is 2,400 IU, according to the Institute of Medicine's Food and Nutrition Board. This is known to "*cause no known risk*." The Food and Nutrition Board has conservatively placed the current LOAEL for Vitamin D at 3,800 IU. There is discussion in the scientific community that this is too low and that some people "*may need 4,000 to 10,000 IU per day in the absence of adequate sunlight*." (Vieth R. Vitamin D supplementation, 25-hydroxyVitamin D concentrations, and safety. Am J Clin Nutr, 69(5):842- 56 1999 May.)

- B-Vitamins, except B3 and B6, have either no potential or very little potential for toxicity. Some do not have LOAEL's because of their low potential for toxicity. The National Academy of Sciences reports no evidence of toxicity for oral doses of B1, B2 and B12, and no reports of toxicity for folic acid at 15,000 mcg, and biotin at 10,000 mcg.

- MTD's for B-vitamins are very high, in general. Any discussion of toxicity should include the MTD's. Vitamin E's MTD of 1,200 IU is extremely conservative. One study found 1,200 IU of Vitamin E produced a better effect than lower doses at reducing LDL cholesterol oxidation, which precedes artery plaque formation, with no toxicity. (Fuller CJ, et al. Effects of increasing doses of alpha-tocopherol in providing protection of low-density lipoprotein from oxidation. Am J Cardiol 1998 Jan 15;81(2):231-233.)

- Dr. Reinholdt Vieth, has confirmed that there has been no recorded Vitamin D toxicity (with hypercalcemia) at doses less than 40,000 IU per day. (Vieth R. Vitamin D supplementation, 25-hydroxyVitamin D concentrations, and safety. Am J Clin Nutr, 69(5):842- 56 1999 May.)

Dr. Vieth has also published a study that indicated that 4,000 IU of Vitamin D is safe for the general public. This requires further investigation. (Vieth R, et al. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr (United States), Feb 2001, 73(2):288-294.)

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