

# Supplementing Dietary Nutrients

A Guide for Healthcare Professionals

Foundational Dietary Principles • Nutrients as Genomic & Epigenetic signals • Macronutrient Balance  
Protein Supplementation • Fatty Acid Supplements • Vitamin Sources & Forms • Mineral Sources & Forms  
Natural vs. Synthetic Vitamins • Whole Food vs. Isolates • Choosing a Probiotic  
Botanical & Phytonutrient Basics • Fundamentals of Dietary Supplement Regulations  
Deciphering Supplement Labels • And Much More....

THE STANDARD

ROAD MAP SERIES

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POINT INSTITUTE

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# Supplementing Micronutrients

The majority of products used for nutrient supplementation are primarily designed to deliver micronutrients. In fact, more than 40% of dietary supplement sales are products described as vitamin or mineral supplements, or a combination of both. The reasons individuals use such supplements, or clinicians recommend them, are wide ranging: from filling in nutrient gaps in individuals with mostly healthy diets, as insurance for those whose diets are far from healthy, or as therapeutic agents designed to trigger specific metabolic functions. Likewise, the products and doses available in this category are wide ranging: from single nutrient supplements dosed at 1,000% of the DV, to comprehensive multi-nutrient products with more than 50 ingredients.

While we will not review the detailed function of each nutrient, nor the clinical data available for each, this section will cover some of the most frequent issues clinicians face in selecting and recommending micronutrient supplements for their patients. Once we cover these pertinent issues, we will list each of the major vitamin, mineral and nutrient ingredients, covering relevant details unique to each.

## Micronutrient Supplementation in “Healthy” Subjects: An Overview

Before we discuss the nuances of supplement ingredients, forms and doses, we want to address one of the basic questions, and criticisms, of nutrient supplementation in “healthy” populations: Do so-called “healthy” subjects really need micronutrient supplementation? After all, every few months or so news reports recount a “failed” nutrient study followed by a medical journal editorial repeating the mantra that vitamin and mineral supplements are a “waste of money.” Are these criticisms fair?

In evaluating this issue, recall the discussion in the first section of this handbook, where a distinction was made between determining the amount of a nutrient a person consumes, usually through dietary estimations; compared to ascertaining an individual’s “adequate” or “optimal” requirement for that nutrient based on the person’s particular health need: weight, health status, genetic predisposition, or a host of other factors that may create an increased need for one or more nutrients. Most research is simply based on epidemiological estimates of population intakes, which then gives rise to estimated adequate requirements (EAR) and daily reference intakes (DRI). However, even using these

limited estimates, the number of Americans not meeting the intake guidelines of important nutrients is alarming.

Further complicating matters is that while many nutrients are found in low levels in foods, many methods of food preparation diminish those naturally occurring nutrients. Recognizing this, many processed foods have nutrients added back (enriched)—in some cases, higher than natural amounts added (fortified) before distribution. The NHANES (National Health and Nutrition Estimation Survey) data attempts to calculate nutrient intake from food, whether naturally occurring, fortified or enriched, as well as from dietary supplementation, when estimating the level of nutrient intake in the U.S. population. According to this data, the number of Americans over the age of two not consuming guideline levels of vitamin D, calcium, vitamin A, vitamin C, vitamin E, thiamin, folate and magnesium from natural sources is more than 40%—that’s well over 100 million Americans.<sup>1</sup> Even after including fortification and supplementation, this is still the case for vitamin D, vitamin E and magnesium (see nutrient monographs for details on each nutrient). Considering that these data assume that the guideline EAR levels are “adequate” for only 50% of individuals, these numbers are even more problematic.

In view of the overwhelming safety of micronutrient

1. Fulgoni VL 3rd, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: Where do Americans get their nutrients? *J Nutr.* 2011 Oct;141(10):1847-54.

supplementation (exceptions discussed for some below) and the inadequate intake of basic guideline-levels of certain nutrients among a large population of Americans, routine supplementation of most patients is clinically justified. Since most micronutrients are critical to the basic activities that allow cells to function and build the metabolic reserve needed to delay or prevent chronic diseases in the first place, micronutrient supplementation can be a vital foundation for a variety of therapeutic interventions in today's clinical practice, if for no other reason than to increase the likelihood a patient is consuming the minimum guideline amounts of most nutrients. It should be noted, however, that broad, non-specific nutrient supplementation alone in individuals without known deficiencies in a particular nutrient is unlikely to result in measurable disease-related clinical outcomes.

This does not mean there are not studies that show clinical benefits for specific vitamins or minerals, but there are varying opinions as to which studies should be used to determine micronutrient efficacy. In some cases, like the Physician's Health Study-2, the same one-a-day multivitamin that showed a small, but statistical reduction in the risk for cancer and cataracts<sup>2,3</sup> showed no benefit for other outcomes like cognitive performance.<sup>4</sup> In either case, there were many other variables that might account for these outcomes, not the least of which is the fact that the multivitamin supplement used in this study was not specifically designed for any of these outcomes and none of the subjects were known to have vitamin or mineral deficiencies.

Generally speaking, the types of studies and end-points used to evaluate the efficacy of pharmaceutical agents, for FDA approval, with regard to disease management are inappropriate and unsuitable to test the relative benefit of "optimal" nutrient supplementation. Drug trials can be managed to ensure subjects in the control group have never consumed the pharmaceutical agent being tested, something untrue and even unethical in nutrient studies. The clinical goal of multivitamin-mineral supplementation, therefore, is

not to reduce the risk of a particular outcome but to diminish the likelihood the patient will have limited metabolic capacity due to inadequate availability of a necessary nutrient.

Overall, nearly half of the U.S. population consumes vitamin and mineral supplements on a regular or semi-regular basis. Even the Physicians Health Study showed long-term use of supplements amongst this cohort (male physicians) was 36%, and healthcare professionals interested in, or knowledgeable about, dietary supplements were much more likely to use and recommend dietary supplements.<sup>5</sup>

### Multivitamins: A wide range in available doses

Comparing one multivitamin-mineral product with another is often a daunting and confusing task, even for those well-versed in nutrient supplementation. For the most part, the greatest difference in these products is the number of total ingredients, the dose of each ingredient and, in many cases, the form of those ingredients. Most one-a-day multivitamins are designed to provide 100% of the DV of as many ingredients that will fit in one tablet or capsule. This turns out to be feasible for nearly all vitamins, but is impossible when attempting to supplement key minerals like calcium and magnesium. When these products do add minerals, they are almost always in cheap forms that are inferior for absorption (oxides, carbonates, etc.)

On the other hand, a number of products designed for physician use are available; these products typically include higher doses of most vitamins, higher doses and quality of minerals, as well as additional nutrients with no official DVs. Compared to the one-a-day approach, these additional ingredients are delivered in higher numbers of capsules—three, six, eight or sometimes more. Clinicians should realize that while some patients may benefit from adhering to the full dose, six-plus capsules per day, of certain multivitamin-mineral supplements, many patients would be adequately served by using half the dose, which, in many cases, still provides most nutrients above the DV/ DRI.

2. Gaziano JM, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012 Nov 14;308(18):1871-80.

3. Christen WG, et al. A Multivitamin Supplement and Cataract and Age-Related Macular Degeneration in a Randomized Trial of Male Physicians. *Ophthalmology*. 2013 Nov 20.[Epub ahead of print].

4. Grodstein F, et al. Long-Term Multivitamin Supplementation and Cognitive Function in Men: A Randomized Trial *Ann Intern Med*. 2013;159(12):806-814-814.

5. Gardiner P, Woods C, Kemper KJ. Dietary supplement use among health care professionals enrolled in an online curriculum on herbs and dietary supplements. *BMC Complement Altern Med*. 2006 Jun 12;6:21.

### Generally, nutrient supplements should be taken with meals

Usually we recommend taking micronutrient supplements with meals whenever possible. We do so for three basic reasons. First, when eating a meal, the body naturally begins producing the necessary agents—acid, intrinsic factor, enzymes, bile, etc.—to digest and absorb macro and micronutrients. These agents are designed to deal with both fat-soluble and water-soluble nutrients within the matrix of a complex food environment. Second, many people report GI complaints when consuming high-dosed multivitamins apart from a meal, something usually solved by taking them with a meal. Third, since adherence to a multivitamin regimen is often related to forgetfulness and fear of GI side effects, adherence is often better when patients are initially told to use their nutrient supplements with meals.

Since the main purpose of micronutrient supplementation is long-term nutrient sufficiency, the answer here may not be applicable for very specific nutrient use in every patient, but should be helpful for the vast number of patients using multivitamin-mineral products. While it is true that certain foods or nutrient combinations can actually reduce the full benefit of some supplemental nutrients, usually by inhibiting absorption, long-term benefits of improved adherence with a simple recommendation may still have better long-term benefits than creating a schedule that attempts to optimize the absorption of each nutrient. [This advice may not apply to specific non-nutrient dietary supplements such as herbal extracts, concentrated phytonutrients or enzymes].

### Supplemental nutrient needs for men and women

The guideline recommendations for daily intake of certain nutrients are slightly different for men and women (see DRI tables in the Appendix). These recommendations are not generally based on scientific analysis of gender-based nutrient needs; they are based on estimated intakes and, in some cases, historical body weight differences between men and women (see specifics for prenatal needs below). Since there is no other evidence that men and non-pregnant women have substantially different *basic* nutrient needs, there is no scientific justification for products designed specifically for men or women. Some professional companies provide their multivitamin-mineral formulas with or without iron, allowing clinicians to use iron-free supplements for most men and post-menopausal

women, while providing multivitamin-mineral supplements with iron for menstruating, pregnant and nursing women, vegetarians or those known to have low iron levels.

Still, there are many commercially available nutrient supplements marketed specifically for men or women. Many companies choose to add additional ingredients to their nutrient supplement formulas intended for gender-targeted marketing. Ingredients for prostate health are popular in products marketed to men, while ingredients designed to boost bone health or promote hormone balance are popular in products marketed to women. These ingredients, however, are rarely provided in doses needed to match therapeutic potential and, in some cases, include botanical agents that may increase the likelihood of allergic responses. While generally harmless, problems arise when patients believe these low-dosed additional ingredients neutralize their risk for gender-specific diseases, something not supported by clinical research.

### Nutrient needs for pregnant and lactating women

While the guideline recommendations for nutrient intake is only slightly different in pregnant and lactating women, clinical urgency and patient awareness of micronutrient supplementation in these subjects is much greater. The NHANES data from 1999 – 2006 suggests about 75% of pregnant women in the U.S. report taking nutrient supplements, mostly multivitamins with extra folic acid and iron.<sup>6</sup> One note of concern among these data is that supplement use increases with each trimester, from a low of about 55% in the first trimester to a high of nearly 90% in the third trimester. This pattern of supplement use resulted in the lowest folate status (RBC levels) in the first trimester of pregnancy, when the need for folate is most critical for the prevention of neural tube defects. As you might imagine, clinical research on pregnant subjects is limited in developed countries and most of the information available is based on observational data.<sup>7</sup>

6. Branum AM, Bailey R, Singer BJ. Dietary supplement use and folate status during pregnancy in the United States. *J Nutr.* 2013 Apr;143(4):486-92.

7. Sfakianaki AK. Prenatal vitamins- A review of the literature on benefits and risks of various nutrient supplements. *Formulary.* January 1, 2013.

In light of specific nutrient needs for pregnant women, many clinicians and institutions recommend nutrient supplementation for pregnant woman, usually in the form of a prenatal multivitamin.<sup>8</sup> Some products are designed to provide only limited prenatal needs, such as increased iron, folic acid, and B-vitamins; others attempt to provide a full multivitamin-mineral approach. In some cases, products will provide additional ingredients, such as DHA and choline for healthy brain development, or even herbs like ginger to help with nausea.

Clinicians should have a readily available recommendation for a prenatal vitamin/mineral supplement because the desire to find a product is usually an urgent concern for the patient. An iron-containing multivitamin-mineral product from a professional brand is likely to be adequate, though products designed specifically as prenatal supplements may have additional benefits for patients.

The nutrient needs of lactating women are similar to those of pregnant women, though the guidelines make a few distinctions. Vitamin A recommendations are nearly double for lactating women, as vitamin A stores are low in newborns, and the recommendation for vitamin C is nearly 50% higher at 120 mg.<sup>9</sup> Other small differences in nutrient needs reflect the higher calorie intake generally required for lactating/breastfeeding women.

### Nutrient needs for children and adolescents

Once again, the guideline nutrient recommendations for children and adolescents (in the U.S.) are determined by estimates of intake and age. In some cases, rapid growth in adolescents accounts for a higher recommendation than in adulthood. For instance, the RDA for calcium is highest (1,300 mg) for adolescent boys and girls (nine–18 years old), lowest (1,000 mg) at maturity, and then increases (to 1,200 mg) after age 50 in women and 70 in men.

The specific nutrient recommendations for infants are much less certain, and are listed as adequate intakes (AIs), rather than RDAs. Infant nutrient needs and supplementation are also tied to other factors, such as whether the child is consuming formula or breast milk, and if breast milk, the nutritional status of the

mother. In general, nutrient supplementation is not recommended for healthy infants, with the exception of vitamin D. According to the American Academy of Pediatrics, exclusively breastfed infants or babies drinking less than one liter of baby formula should receive 400 IU of vitamin D each day. Liquid products (typically in dropper bottles) are designed specifically for delivering this dose to children. Other micronutrients, probiotics or fatty acid supplements (e.g. DHA) are often recommended for infants and children, and can be found packaged and dosed specifically for these subjects.

Even though foods marketed to children are often fortified, NHANES data shows American children between the ages of 2–18 are consuming less than the EAR for vitamin D (73%), vitamin E (66%), magnesium (48%), vitamin A (25%) and vitamin C (28%).<sup>1</sup>

### Multivitamin-mineral use in U.S. Children (2003-2006)

Percent use of multivitamin-mineral supplements in children by age.

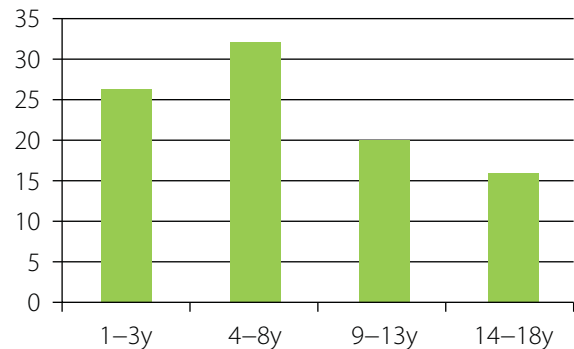


Figure 12: Multivitamin use in children and adolescents (2003-2006).

Use of multivitamin-mineral supplements in U.S. children and adolescents ranges from 16–32%.<sup>10</sup> As figure 12 shows, nutrient supplementation is highest in those four to eight years old, and lowest in the late teenage years. Since nutrient intake from foods is also lower in adolescents (nine–18 years old), these individuals are known to have a higher prevalence of inadequate nutrient intake. While supplementation

8. Some, like the American College of Obstetrics and Gynecology, recommend supplementation for only iron and folic acid-believing the diet will suffice for the rest. See their FAQ: [www.acog.org/~media/For%20Patients/faq001.pdf](http://www.acog.org/~media/For%20Patients/faq001.pdf).

9. Haskell MJ, Brown KH. Maternal vitamin A nutriture and the vitamin A content of human milk. *J Mammary Gland Biol Neoplasia*. 1999 Jul;4(3):243-57.

10. Bailey RL, Gahche JJ et al. Dietary supplement use in the United States, 2003-2006. *J Nutr*. 2011 Feb;141(2):261-6.



does not alleviate all inadequate nutrient intakes in children older than eight years, especially for calcium and vitamin D, dietary supplements added micronutrients to diets that would have otherwise been inadequate for magnesium, phosphorus, and vitamins A, C and E.<sup>11</sup> We believe these data are sufficient to recommend routine multivitamin-mineral supplementation in children over two years old, and especially in children ages nine to 18.

Popular children's multivitamins usually lack adequate levels of quality minerals and often have excessive zinc and copper; the most common nutrients consumed above the tolerable upper limit in children using supplement. Look for products that use natural sweeteners such as polyol sugars, sucrose, etc., and avoid artificial sweeteners, colors and flavorings.

### Special needs for vegetarians and vegans

While there is much to commend in an appropriate vegetarian or vegan diet, there are also a few nutrient deficiencies more common in individuals who choose this lifestyle, recognizing that not all diets that exclude animal product are of equal nutrient content. The most commonly cited nutrient deficiencies are vitamin B<sub>12</sub>, vitamin D, long-chain omega-3 fatty acids, calcium, iron, and zinc, carnitine and protein.<sup>12,13</sup>

Vitamin B<sub>12</sub> deficiency is probably the most studied of these deficiencies, where researchers have shown vegetarians to have elevated levels of plasma homocysteine (tied to low B<sub>12</sub>) and related arterial dysfunction which can be mitigated by supplementing vitamin B<sub>12</sub>.<sup>14,15</sup> These common deficiencies, along with the wide range of diets deemed "vegetarian," should compel clinicians to ask specific dietary questions (see questionnaires in the appendix) to determine nutrient supplementation needs in these individuals. Most multivitamin-mineral products are appropriate for vegetarian subjects, though some vegans may object

to fish-derived omega-3 fatty acids or vitamin D<sub>3</sub> (see Vitamin D monograph).

## Food and Supplement Forms of Nutrients: How do they Differ?

Here we'll discuss a few issues that can be contentious within the world of marketing vitamins and minerals: the relative differences and benefits between various forms of vitamins, minerals or other nutrients (for a complete discussion of marine-derived omega-3 fatty acids, see the complete discussion on page 175). As it turns out, almost every vitamin or mineral we will list below can be delivered in different chemical forms. In some cases this might mean different isomers of the same molecule (d vs. d-l tocopherol), a modified form of a molecule (pyridoxal-5-phosphate vs. pyridoxine HCl) or different mineral forms (calcium carbonate vs. calcium citrate). In some cases, attempts to define nutrients based upon their supposed origins: "whole-food," "natural concentrate," "active-form" or "synthetic" create an additional level of differentiation.

Unfortunately, the terms "natural," "whole-food," "synthetic" and "active-forms" have different meanings to different people, and for the most part, are often used to mislead consumers about nutritional supplements. Here, we will provide clear definitions of each of these concepts, revealing the real potential differences between some nutrient forms, while showing most marketing information about these differences is unsubstantiated and, in some cases, false.

### Synthetic vs. natural vitamins

Few terms are more loaded with implied meaning in the supplement world as the terms "natural" and "synthetic." The former is nearly always viewed as being better than the latter. Many supplement users would be surprised to learn that nearly all vitamins and minerals used for making dietary supplement products—and for food fortification—are not strictly "natural." This means the nutrient ingredient, as it is used in the capsule or tablet, has been changed in some way from the form found in nature, or is a bioequivalent (or chemically identical) molecule derived by organic synthesis. An example of this is ascorbic acid, the most common source of vitamin C in dietary supplements.

Vitamin C compounds, natural ascorbates, are found in a variety of fruits and vegetables and are fairly

11. Bailey RL, Fulgoni VL 3rd, Keast DR, Lentino CV, Dwyer JT. Do dietary supplements improve micronutrient sufficiency in children and adolescents? *J Pediatr.* 2012 Nov;161(5):837-42.

12. Craig WJ, Mangels AR. Position of the American Dietetic Association: vegetarian diets. *J Am Diet Assoc.* 2009 Jul;109(7):1266-82.

13. Craig WJ. Nutrition concerns and health effects of vegetarian diets. *Nutr Clin Pract.* 2010 Dec;25(6):613-20.

14. Kwok T, Choek P et al. Vitamin B-12 supplementation improves arterial function in vegetarians with subnormal vitamin B-12 status. *J Nutr Health Aging.* 2012;16(6):569-73.

15. Oversby D, Chappell DC, Dunnett A, Tsiami AA. Plasma total homocysteine status of vegetarians compared with omnivores: a systematic review and meta-analysis. *Br J Nutr.* 2013 Mar 14;109(5):785-94.

stable when the food source maintains its integrity. Ascorbic acid, on the other hand, is made from corn-derived sugars via a multistep process. While natural ascorbate compounds found in foods are often believed to be associated with other compounds, most notably bioflavonoids, there is no evidence that ascorbates/vitamin C from food and ascorbic acid are different chemically or biologically (see vitamin C monograph for details and references). Like the bioidentical “human” hormones derived “synthetically” from wild yam or soy compounds, there are many organically synthesized vitamins that function in a bioidentical or “bioequivalent” manner compared to their “natural” counterpart (some call these nature-identical). This is not to say that 60 mg of ascorbic acid will have all the biological effects of 60 mg of vitamin C from an orange, but any difference there may be (studies looking for such differences have not found any) would likely be due to the other, non-vitamin C ingredients in the orange. In the case of these “bioequivalent” vitamins or previtamins (see below), there is no known clinical difference between these compounds and their natural counterparts, except that the organically synthesized versions allow for higher doses at reasonable prices.

On the other hand, not all “synthetic” vitamins are bioidentical equivalents of their “natural” counterpart and are, in many cases, inferior biological alternatives. The best example of this is “synthetic” vitamin E, a blend of eight closely related isomers, only one of which is identical to natural d-alpha-tocopherol. The chemical differences are subtle but result in measurable differences in nutrient benefits (see vitamin E monograph). Similar diminished benefits might also be true of folic acid, synthetic beta-carotene, the retinyl form of vitamin A, vitamin D<sub>2</sub> and vitamin K<sub>1</sub>, each discussed in their respective monograph.

Describing a vitamin within a dietary supplement product either as “natural” or “synthetic” needs to be considered on a case-by-case basis. While marketers of so-called “whole-food” or “natural” multivitamins will routinely vilify all “synthetic” vitamins as harmful, the evidence to support these claims is lacking. We are aware that industrial chemicals are often used in the processing of these vitamins, though these substances are not present in the finished vitamin ingredient added to foods or supplements (there are monograph standards that set limits for these). Moreover, nearly every research study on almost every vitamin, whether chemistry, basic science, cell culture, animal or human clinical trials, has been performed using these “synthetic” vitamins. For better or worse, the evidence-based knowledge of the dose, bioavailability, pharmacokinetics, deficiencies, toxicities, metabolites and supplementation has all been documented

in reference to these nutrients, in these forms. While many of us may not consider most of these substances to be strictly “natural,” there is no evidence to suggest our body’s biochemistry would see these compounds, those that are truly “bioequivalent,” as anything but.

### Food or Supplements: Which is better?

Some who read this section may be confused about whether we are advocating the use of supplements in place of food nutrients, and how this fits in with the Lifestyle Synergy model we discussed in earlier sections of this handbook. Let us be clear: our bodies are designed with the necessary processes (digestion, absorption, enzymes, etc.) to extract from foods the essential nutrients our bodies need to function properly. For many individuals, the amount of food-derived nutrients obtained is below their functional nutrient needs due to poor dietary habits, poor food quality, insufficient digestion, nutrigenetics or a higher need for particular nutrients than a healthy diet can provide. In these cases, we advocate what we call augmented lifestyle therapy, where we rely on known signals, in this case nutrient signals, that can be isolated and provided in higher doses within the context of the original signal—another reason to take supplements with food.

Scores of research studies over a half-century or more have shown augmentation through the supplementation of isolated nutrients, or combinations of isolated nutrients through fortification and dietary supplements, has been remarkably helpful to human health in developed countries, even if only to compensate for decreased nutrient density from our agricultural practices and industrialized food supply, and has been instrumental for helping to alleviate nutritional deficiencies and save the lives of millions throughout the underdeveloped world. Clinicians are responsible for choosing the best therapeutic options for their patients using all available evidence. This means helping them choose and implement the optimal dietary pattern for their current and future health needs, and to help them determine the most appropriate supplemental ingredients, if needed, to target specific nutrient deficiencies or as a basis of a therapeutic intervention.

### Provitamins and activated forms

We now need to take this one step further to understand how our body converts vitamins into vital nutrients. For the most part, vitamins consumed in foods and supplements are compounds the body turns into their final bioactive vitamin compound. Therefore, most vitamins are really what we might call provitamins or, as they are often referred to, vitamin precursors, vitamers or provitamins. Most people know that beta-carotene, and a few other carotenoids, are converted into vitamin A and often referred to as provitamin A. Most others are less well known, like the vitamin riboflavin (or B2), a precursor to two critical metabolic coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD); or niacin being converted to the coenzyme nicotinamide adenine dinucleotide (NAD and NADH). These and many more will be discussed in the monograph for each vitamin.

Establishing that many vitamins are converted from a provitamin form before use at the cellular level, researchers and manufacturers of vitamins have experimented with modified forms of several vitamins in an attempt to deliver vitamins in a readily usable or “activated” form. The most popular of these are niacinamide, methylated folate, phosphorylated riboflavin and B<sub>6</sub>, and, for minerals, amino acid chelates. These ingredients are an attempt to mimic natural forms (mineral chelates) or an activated intermediate of the vitamin. In most cases, while some would deem these compounds “natural,” they are almost universally synthesized from other so-called “synthetic” vitamins. For instance, pyridoxal-5-phosphate is derived from pyridoxine HCl, a common provitamin.

Are these so-called activated forms better than other food or supplement forms of vitamins? It depends on which one. A case can be made that a small, but consistent, benefit can be derived from the use of methylated folate, instead of folic acid, in subjects with genetic polymorphisms that reduce folate methylation, though this benefit is often exaggerated well beyond the published literature. However, phosphorylated B<sub>6</sub> and riboflavin must necessarily be dephosphorylated in the gut before entering circulation, making these products equivalent, except for added cost, to their non-phosphorylated versions. In the case of mineral chelates, intended to mimic the plant-based delivery of minerals, they often improve bioavailability over more commonly used mineral salts.

With few exceptions, “activated” vitamins as

supplement ingredients add much confusion with little clinical benefit. More importantly, all vitamins function in the body by a constant conversion between various active and inactive forms. In many cases, active vitamins are converted to their inactive forms by specific enzymes in order to be transported from one part of the body to another. Inactivating the vitamin prevents it from reacting prior to reaching the target tissue. Even in the case of methylated folate, the amount of stored body folate that needs to be continually remethylated could never be overcome by oral methylfolate supplementation alone. We will make the case for or against the various activated forms within each vitamin monograph based on available biochemical, pharmacokinetic, animal and human study data.

### “Whole-food” supplements: What are they?

Let us take this one step further as we discuss what are often referred to as “whole-food” nutrient supplements. This unofficial term can mean a few different things, depending on how the product is designed. It can describe a product (capsule, tablet or powder) made of dried powders of various foods, mostly fruits and vegetables. For instance, many products generally referred to as “green drinks” are made from a variety of grasses, dried fruit and vegetable powders, and added-phytonutrient/herbal powders. These types of products are often organic or mostly organic and promote themselves as ways of helping consumers receive the types of phytonutrients they may be missing from an abundant and diverse diet. Unless they are fortified, however, these products rarely provide minimal RDA levels of vitamins and minerals. So while these products may be excellent sources of key phytonutrients, something that may prove to be a clinical benefit to individuals with little diversity or under-consumption of fruits and vegetables, they may not be a substitute for the increased vitamin and mineral supplementation some patients need.

The largest group of products sold under the rubric of “whole-food” supplements are quite different and, in many cases, highly problematic. These are products that claim to deliver adequate levels of supplemental vitamins and mineral in capsules or tablet, which they claim are derived from whole-food sources. There are two basic problems with these products. One: They are almost never derived from what most people would consider a “whole food.” Two: Those with any substantial level of vitamin or mineral claims have been

“spiked” with the “synthetic” and concentrated forms of vitamins they market their products against.

While there is some debate about whether truly whole-food supplements offer *clinical* benefits, there are three types of widely available products inappropriately, and fraudulently in some cases, marketed as “whole-food” supplements. They are: products whose ingredients are plainly not natural or whole-food derived; products that contain vitamins and minerals from unmodified natural sources that are not strictly foods or “whole” parts of those “foods”; and products whose “food” ingredients are intentionally spiked with synthetic vitamins and minerals prior to preparing the ingredients. We will explain each below.

**1. Products sold as “whole-food,” which clearly are not:**

As we have seen in the sections above, and will detail for each vitamin in the next sections, spotting a vitamin or provitamin source is fairly easy. However, some manufacturers and marketers simply do not know the difference or, believing the public won’t know the difference, sell “synthetic” ingredients as if they were whole-food or naturally derived. In many cases, they use alternative names or slightly unique forms to disguise this fact. For instance, look at the Supplement Facts box for a product widely marketed as a “whole-foods” multivitamin in figure 13. While this formula may very well be a good multivitamin product, it is in no way delivering these vitamins and minerals as whole foods. In fact, of all the vitamins and minerals listed, only a few (beta-carotene, vitamin E, and iodine) are likely to be unmodified and “natural-sourced”; all the others have been modified in some way or are organically synthesized bio-equivalent compounds. Notice that while additional food ingredients have been added to the multivitamin, none of these ingredients are listed in the parenthesis for the vitamin claims. In other words, these food ingredients are not intended to be the source for any of the vitamin or mineral claims.

Another confusing issue for consumers and unknowledgeable

manufacturers and marketers is the idea that using so-called activated forms or combined forms, in order to avoid the most obvious synthetic compound names, makes the product appear more natural. In this product, the use of mineral or vitamin ascorbates is used to obscure the fact that these compounds are merely salts (or mixtures) derived from commercial ascorbic acid—with calcium, magnesium, palmitic acid, or niacin. Also, while we are generally in favor of using mineral chelates (see mineral section), these compounds are chemically reacted to mimic the mineral-amino acid complexes found in plants; but would not be considered strictly natural- and are far from whole food.

There are a host of products with similar designs (adding fruit and vegetable powders to a standard multivitamin blend) masquerading as natural or “whole-food.” Because the term “whole-food” is not defined from a regulatory stand-point, the marketers of these products have done a great disservice to the nutrient supplement world and added much confusion to patients and clinicians, intentionally or not. Thankfully, these products should be easy to spot due to the mandatory disclosure of ingredient sources within the supplement facts box- something that was not true prior to 1997. If each vitamin and mineral in the supplement facts

Supplement Facts <sup>V1</sup>		
Serving Size: 8 Tablets      Servings Per Container: 30		
Amount Per Serving		%DV
Vitamin A (from natural beta carotene)	5,000 IU	100%
Vitamin C (as Calcium, Magnesium, Niacinamide, Ascorbate and Ascorbyl Palmitate)	500 mg	833%
Vitamin D-3 (as cholecalciferol)	5,000 IU	1,250%
Vitamin E (natural, as d-alpha tocopherol plus mixed tocopherols)	400 IU	1,333%
Thiamine (as Thiamine Pyrophosphate)	3 mg	200%
Riboflavin (as Riboflavin-5-Phosphate)	3.4 mg	200%
Niacin/Niacinamide (as Niacinamide Ascorbate)	40 mg	200%
Vitamin B-6 (as Pyridoxal-5-Phosphate)	4 mg	200%
Folate (as L-methylfolate, Metafolin™)	400 mcg	100%
Vitamin B-12 (as methylcobalamin)	100 mcg	1,667%
Biotin	900 mcg	300%
Pantothenic Acid (as d-Calcium Pantothenate)	30 mg	300%
Calcium (as Calcium Ascorbate, Citrate/Malate Complex)	250 mg	25%
Iodine (from Kelp)	200 mcg	133%
Magnesium (as Magnesium Ascorbate/Amino Acid Chelate Complex)	500 mg	125%
Zinc (as Zinc Amino Acid Chelate)	15 mg	100%
Selenium (as Amino Acid Chelate Complex)	200 mcg	266%
Copper (as Copper Amino Acid Chelate)	50 mcg	3%
Manganese (as Manganese Amino Acid Chelate)	2 mg	100%
Chromium (as Amino Acid Chelate)	200 mcg	167%
Molybdenum (as Amino Acid Chelate)	100 mcg	133%
Potassium (as Potassium Krebs† and Amino Acid Chelate Complex)	99 mg	2%
Lutein (natural)	6 mg	-
Lycopene (natural)	6 mg	-
Zeaxanthin	1 mg	-
Other Minerals, Nutrients and Trace Elements		
Inositol	100 mg	-
Trace Elements (from Sea Vegetation) approx	100 mcg	-
Strontium (from 0.5 mg strontium carbonate)	297 mcg	-
Silica	100 mg	-
Choline (from 150 mg Choline Citrate/Bitartrate)	60 mg	-
Amount Per Serving		%DV
PABA (para-aminobenzoic acid)	50 mg	*
Boron (as Amino Acid Chelate Complex)	1.5 mg	*
Vanadium	50 mcg	*
Amino Acids and Enzymes		
L-Cysteine/N-Acetyl Cysteine	150 mg	*
Betaine (from 150 mg Betaine HCl)	114 mg	*
Bromelain (2,000 GDU/g)	50 mg	*
Glutamic Acid (from 25 mg Glutamic Acid)	20 mg	*
L-Methionine	12.5 mg	*
Biflavonoids and Proanthocyanidins		
Rose Hips	100 mg	*
Lemon Biflavonoids	100 mg	*
Red Wine Proanthocyanidins/Pine Bark Extract	50 mg	*
Hesperidin	35 mg	*
Rutin	25 mg	*
Vegetables Fruits and Herbs		
Proprietary Blend	700 mg	*
Kale (leaf), Spinach (leaf), Carrot (root), Radish (root), Celery (leaf and stalk), Apricot (fruit), Blackberry (fruit), Cranberry (fruit), Grape (fruit), and Pineapple (fruit)		
Blueberry (fruit)	100 mg	*
Garlic (d bulb, Pure-Gar® odorless)	100 mg	*
Broccoli (entire plant)	100 mg	*
Cauliflower (entire plant)	100 mg	*
Spirulina	100 mg	*
Chlorella (broken cell wall)	100 mg	*
Green Papaya Extract (fruit)	100 mg	*
Green Tea Extract (leaf)	50 mg	*
Sprouted Barley Juice (entire plant)	50 mg	*
Wheat Grass Juice (entire plant)	50 mg	*
Beet Extract (root)	50 mg	*
Apple Pectin (fruit)	50 mg	*

\* Daily Value not Established

Figure 13 : Sample of Product Label Incorrectly marketed as “Whole Foods”

box does not list its source (in parenthesis) adjacent to the claim, they are almost certainly misleading the consumer by using standard multivitamin sources of nutrients, falsely marketing them as natural or whole-food.

## **2. Products made with mostly non-food yeast extracts or wheat germ:**

Concentrating and stabilizing vitamins and minerals from whole foods, predominantly fruits and vegetables, is expensive and difficult, which is why many products that attempt to use only unmodified vitamins use mostly yeast extracts, often labeled as *Saccharomyces cerevisiae* or just *S. cerevisiae*, or wheat germ, which is less popular with today's gluten-free focus. These products will sometimes have a few other ingredients to supply vitamins not high enough in the yeast extract. These products, if they haven't been spiked with undeclared vitamins, will be limited in the dose of each vitamin, but especially low in mineral content.

While these types of products are designed to avoid ingredients they claim are “unnatural,” the notion that a concentration of fermented yeast grown in a factory represents a natural food source is a bit of a stretch, and since these products deliver a limited amount of nutrients, their clinical utility is also limited. If these products are labeled correctly, clinicians and patients can decide if they are helpful in their quest for sufficient nutrient intake.

## **3. Products made with ingredients spiked with undeclared synthetic vitamins:**

Marketers of “whole-food” nutrients quickly realized vitamins and minerals are difficult to concentrate and deliver from truly whole-food sources. So, when using non-yeast foods such as fruits and vegetables, it is difficult to deliver even measurable amounts well below the USRDA of key vitamins and minerals. Consequently a number of deceptive methods have been used to sell products higher in vitamins and (some) minerals, while claiming the ingredients to be food-derived or natural. This is accomplished by various techniques, usually described in marketing literature and websites as a patented or unique process, referred to as some form of “culturing” or “fermentation.” Essentially what these marketers, or their raw material suppliers, are doing is adding large amounts of synthetic vitamins to the process (fermentation vessel of yeast or foods) at some point prior to “extraction” and then claiming the

measured vitamin content is from the natural source. These products typically avoid making source claims within the Supplement Facts box, but vaguely describe patented or proprietary processed sources in a notation below or outside the box.

While these products may deliver the vitamin content they claim, these deceptive and fraudulent practices lead to confusion about nutrient supplementation and falsely imply that high doses of natural-sourced vitamins and minerals can be delivered in capsules for a reasonable price. By doing so, they falsely exaggerate the differences between whole-food sourced vitamins and those they deem harmful (synthetic isolates), while at the same time using these same ingredients to “fortify” their product by deceptively hiding behind their proprietary process.

### **USP/NF Ingredients: What are they?**

Oftentimes you will see the designation USP or NF next to an ingredient or excipient within a food or dietary supplement. This means that the ingredient conforms to the standards set forth in monographs published by the United States Pharmacopeia/National Formulary (US Pharmacopeial Convention). These raw material monographs describe all the specific physical and chemical properties (including maximum levels of contaminants) of the ingredient, along with the specific testing methods required to ensure the ingredient conforms to the monograph. There are USP/NF monographs for at least one form of almost every vitamin and mineral. In some cases, USP has created no monograph for specific quality micronutrient sources (like mineral amino acid chelates).

The USP also has a dietary supplement verification program that can be used to certify some finished products as well. However, only certain limited-ingredient formulas have monograph standards available for such a certification.

### **The clinical utility of single nutrients:**

#### **Is it appropriate?**

The question often arises as to whether the use of single-nutrient therapies is clinically appropriate. This question stems from two key observations. First, since vitamin and mineral nutrients are typically consumed in various combinations within their normal food matrix, supplementing isolated nutrients appears to be inherently

unnatural. The second is the perception that many clinical trials with negative findings are performed with single nutrients (similar to drug trials), and criticism of the design of these trials often points to the use of nutrients in isolation. While these observations may be valid, it's equally true that many foods provide only limited vitamins and minerals in dose and diversity, and our bodies are designed to appropriately store key nutrients for days, weeks or even months as a resilient mechanism to handle fluctuations in food availability and seasonality. The notion that our bodies depend on an ideal ratio of macronutrients, micronutrients and other compounds at each meal conflicts with what we know about the design and adaptability of nutrient usage in humans. Moreover, the vast majority of *positive* clinical trials are also done with isolated nutrients (e.g. studies on vitamin D, folic acid, DHA, CoQ<sub>10</sub>, vitamin K, etc.). This is due to the fact that most intervention trials choose to use a limited number of variables in order to limit the range of interpretations, even if this is bad dietary advice.

Clinicians should have a diverse formulary of nutrient supplements available to meet the clinical needs of their patients. On the one hand, clinicians should utilize products that combine a variety of nutrients, such as high-dose multivitamins or multi-nutrient products designed for specific purposes, and also a handful of key single-nutrient products. It is common to see products that combine all the B-vitamins with their B-complex nutrients, or calcium-containing supplements with additional vitamin D. In some cases, isolated nutrients at high or therapeutic doses can result in an imbalance of other nutrients, such as when high doses of zinc depletes copper, or high-dose folic acid masks a vitamin B<sub>12</sub> deficiency. Most well-informed professional supplement companies are aware of these issues and formulate to compensate for these well-known interactions. Of course, not every interaction can be anticipated in each patient; it is important to always be aware that high-dose therapy with any single nutrient, even if clinically warranted, has a higher likelihood of side effects, most of which are documented.

### Nutrient Assessment using Laboratory Tests

It is common to use laboratory analysis for patient nutrient assessment, though the utility of laboratory results for making clinical and dietary recommendations is not universally agreed upon. Most frank nutritional deficiencies are easy to spot by a trained nutritional expert, but many still prefer laboratory analysis to confirm findings or discover subtle deficiencies and imbalances difficult to detect during physical examination or diet diary analysis.

Nutrient analysis can be performed using whole blood, serum, RBCs, lymphocytes, blood spot, tissue biopsy, urine, hair, stool or saliva, depending on the nutrient or metabolite being tested. In some cases, analysis of more than one type of sample, or analyte, is needed in order to capture the true status of that nutrient. In addition, nutrients can be measured directly, without challenge, much like a fasting blood glucose is done; after challenge or functional test, much like an oral glucose tolerance test; or by assessing related metabolites to understand the functional activity of the metabolite over time, much like glycated hemoglobin helps us understand blood glucose levels over weeks and months.

Several laboratories that serve the functional and integrative healthcare community have developed nutritional assessment test panels, which combine different testing methods using a variety of collected samples in a single report of nutritional status. Some laboratories even combine stool analysis, which can provide status of probiotic species and estimations of fiber intake and digestive efficiencies. In addition, many labs now provide a number of genetic tests that can point to the potential for specific nutrigenetic-driven supplementation protocols.

Since each laboratory provides different tests and reports, often using completely different technologies and philosophies of nutrient testing, it is important for the clinician to understand the test methods, the laboratory test results and the ways these results affect dietary or supplement recommendations. Clinicians should be familiar with several labs and laboratory methods, and consult closely with them to interpret their findings as it applies to specific patients.

### The Use of Magnesium Stearate in Dietary Supplements

For the past several decades, a small but vocal group of individuals, including some well-known clinicians, have raised concerns about the use of magnesium stearate (MagS) and stearic acid. The claims made about the potential harms of MagS use are baseless and unscientific; nonetheless, numerous individuals have believed these claims and some dietary supplement companies actually promote their products based on their refusal to use such ingredients. Let's examine what this is all about.

As mentioned before, MagS and stearic acid are used as lubricants when manufacturing capsules and tablets. For reference, usage of these ingredients is between 1 – 5% for stearic acid and 0.5 – 2% for MagS. Stearic acid is a saturated fatty acid (18:0) found in plants and animals. MagS is the salt formed between one molecule of magnesium and two molecules of stearic acid. Nearly all the stearic acid and MagS used in dietary supplements is plant-source stearic acid (usually palm oil or coconut oil). Once consumed, MagS is separated in the acid environment of the stomach into stearic acid and free (ionic) magnesium. Stearic acid is absorbed along with other fats in the diet and used directly or converted into oleic acid (18:1w9).

Controversy swirls around the unscientific and misapplication of only a few published papers unrelated to the use of stearic acid or MagS in the context of supplements. In 1990 a publication in the journal *Immunology* titled “Molecular basis for the immunosuppressive actions of stearic acid in T-cells” concluded isolated mouse T-cells exposed to stearic acid (as a fatty acid complex with bovine serum albumin and diatomaceous earth) would die due to altered cell membrane function.<sup>[1]</sup> What most individuals do not realize is this stearic acid phenomenon only occurs in the T-cells of these BALB/c mice, because their T-cells do not properly express the enzyme needed to convert stearic acid to oleic acid (stearoyl-CoA desaturase).<sup>[2]</sup> These authors later discovered other mice strains have ample expression of this enzyme in T-cells and this response may actually be a strain-specific phenomenon.<sup>[3]</sup> Perhaps more important, since human T-cells have this enzyme and are rarely bathed in stearic acid-albumin-diatomaceous earth, the relationship between this study and consuming stearates in the diet (e.g. 2,500 mg in 25 gm of chocolate or nearly 4,000 mg in a steak) or through supplements (perhaps a few hundred mg for high supplement users) is unknown. While much has been said about this single study from 1990 (on the Internet and from podiums), this model should never have been considered remotely related to MagS or stearic acid use in supplements.

The other “issues” with MagS use in supplements are more difficult to refute because they simply have no basis in fact. One often repeated is that MagS causes biofilm formation in the gastrointestinal tract, which, according to these detractors, is a sign of something unhealthy. Without delving into the nuances of biofilm (the extracellular matrix produced by mixed colonies of bacteria), it is important to remember biofilm is a normal part of both friendly commensal organisms and potentially harmful organisms. Beyond the basics of biofilm biology, there has never been a referenced study to explain where this MagS-biofilm story originated. Many who have looked into this biofilm issue have even cited a paper that appears to show stearic acid *inhibits* biofilm formation.<sup>[4]</sup> While this is one way to interpret this study, the result (using a mixture of stearic, palmitic and oleic acids) was isolated to only a few strains of bacteria and not in a biologically relevant (biofilm producing) context. There is no evidence or plausible biology that would lead us to connect MagS in supplements (or drugs) to a change in biofilm formation.

Finally, the issue of whether MagS or stearic acid can inhibit the absorption of the encapsulated or tableted nutrients is often raised. While excessive use of stearic acid or MagS in tablets can increase the disintegration time of tablets, reputable companies should be testing each batch to standard specifications to ensure their formula does not exceed these limits. It is worth pointing out that almost everything we know about supplementing nutrients in tablets and capsules (dosing levels, pharmacokinetics, pharmacodynamics, etc.) have been done with products made with appropriate levels of MagS and/or stearic acid. Nearly every positive (and negative) study performed using an encapsulated or tableted vitamin, mineral, herb or nutraceutical has been performed with products containing these and other excipients.

Supplementing nutrients using the convenience of capsules and tablets has invited a wealth of regulatory and quality guidelines, most of which are focused on the accuracy and consistency of each single dose. Machines currently available to efficiently manufacture capsules and tablets from powdered materials are designed to function properly when lubricants are added directly to the powder (they are not self-lubricating). In an attempt to confuse consumers with baseless claims of harm, manufacturers claiming to exclude MagS and stearic acid as a means to market their products as “better” or “safer” need to provide documented and peer-reviewed evidence for their claims. Until such evidence exists, the use of these excipients should be considered harmless and, in many cases, necessary to produce products of both high quality and sensible economy.

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# A Balanced and Evidence-Based Approach

The popularity of dietary supplementation continues to grow and is the basis of the health-promoting strategies of thousands of healthcare professionals and millions of Americans. Yet clinicians and patients are routinely faced with an onslaught of confusing, contradictory, over-hyped and often misleading information about nutrition, especially dietary supplementation. Unfortunately, many nutrition guideline recommendations and references are decades old and out-of-sync with the latest nutritional research; lacking the practical and clinically-relevant relationship linking the evidence-based science of nutrition with the actual ingredients and products available in today's supplemental nutrient products. *Supplementing Dietary Nutrients—A Guide for Healthcare Professionals* aims to bridge this gap.

Designed to help answer the real-world questions about supplementing dietary nutrients within the clinical practice, this guide contains both fundamental principles of nutrient use as well as detailed monographs on over 30 micronutrients. All of this, with an insider's look into the supplement industry; revealing the ingredient sources, manufacturing processes and marketing controversies.

**This guide is intended to be an indispensable resource for anyone making nutrient-based or dietary supplement recommendations within a healthcare setting:**

- Clinicians
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- Nutritionists
- Dietitians
- Nurses/Nurse Practitioners
- Medical Technicians
- Nutritional Researchers and Educators
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