Latest Science in Vitamin & Mineral Research

Principles In Formulating The Optimal Multi

Call it the *supplement paradox*.

A huge body of careful, prospective scientific research into the relationship between peoples' lifestyles and their long-term health has confirmed, again and again, that eating a diet rich in fruits and vegetables will lead you to a longer life, and lower your risk of chronic disease.

The most obvious thing about such diets is that they're rich in essential vitamins and minerals. And yet time and time again, controlled clinical trials of nutritional supplementation with vitamin and minerals – including key antioxidant nutrients like **"vitamin E," vitamin C, and beta-carotene – has failed to protect people from killer diseases.**

Whether it's "vitamin E" against heart disease,[1] or beta-carotene against cancer,[2-4] or antioxidant "cocktails" against atherosclerosis[5] or death from any cause,[6,7] again and again the results have come back negative. Either there's no effect at all … or the results are too ambiguous to pin your hopes on … or there's been a suggestion that the people taking their assigned pills were *worse off* than people taking the placebo stand-ins.

It's a pretty sad record.

How can this be? Before the results of these trials came in, many health-conscious people had their faith in their multivitamins boosted by the simple fact that these trials had even managed to *get off the ground* in the face of extreme skepticism from much of the medical establishment. Now those skeptics feel justified in their condescension – and the forces that oppose health freedom have been given ammunition in their anti-supplement attacks.

The reaction from most supplement companies has been disappointing. Many companies are in the business for no other reason than to make a quick buck, and have chosen to simply *ignore* these trials, hoping that the unsettling results will not reach the ears of their customers and cut off access to a reliable cash cow. Other companies are sincere in their belief in the value of supplementation – but they base this belief on blind faith, playing *hear no evil, see no evil* when large-scale, carefully-controlled, rigorous clinical studies fail to confirm a pre-established credo. Such companies have failed to respond to the latest discoveries in the rapidly-accelerating field of nutritional science, continuing instead to design their products based on accepted health-food-store dogmas.

Nutritional supplementation with "vitamin E," vitamin C, and beta-carotene – has failed to protect people from killer diseases

Health-conscious people can't afford to be blinded by wishful thinking, or to rely on formulas based on outmoded theories and fuzzy-headed, pseudoscientific notions. The fact is that **the conventional wisdom underlying 'basic' nutritional supplementation has been disproved**. If we are to gain the benefits that we expect from our supplement programs, we have to be ready to listen to what science is *actually saying today* instead of what it *suggested* twenty years ago. We will have to clear the ground, looking at the science with our old blinders removed, questioning our assumptions, turning over the graves of the 'authorities' of yesteryear, and laying the foundation for a genuinely new approach to nutritional supplementation.

But where to begin? With what we already *know*. We *know* that healthy *diets* support longer, healthier life. And we *know* that supplements based on old-school thinking do not. Once we accept these two facts, the way forward becomes clear: compare the contents of a health-promoting diet to typical multivitamin/multinutrient products, and see what's so fundamentally *different* between the two. And once you start *looking*, the contrast is so sharp that it strikes you like a barrel of ice water. Multivitamin supplements which *should* have been designed to be, in effect, super-concentrated versions of an optimal diet are revealed instead to be gross *caricatures* of those diets, *distorting* and *unbalancing* the real picture of preventive nutrition.

Let's see where previous products have gone wrong … and how we can get it *right* for the future.

First, Do No Harm

The most extreme disconnect between health-giving foods and badly-designed pills, is cases where a multivitamin not only doesn't *protect* the health of its users, but actively *harms* them. We are accustomed to thinking of nutritional supplements as fundamentally safe; and certainly, no multivitamin has ever caused the kind of killer toxicity we see from some xenobiotic drugs (except in cases of overdose resulting from sloppy manufacturing, or from accidental or intentional swallowing of too many pills). But there's now strong evidence that ***nearly all* multivitamin products contain one or more nutrient overdoses or imbalances extreme enough to cause real, long-term damage to the health of those swallowing them.**

One well-documented, crippling result of long-term, chronic supplement overdose is the association between **excessive preformed vitamin A** (**retinol/retinyl esters**) and the **loss of bone health.** It's long been known, from animal studies, that getting too much vitamin A is bad for the skeletal system. In recent years, these findings have been confirmed in humans. Several large, well-designed population studies (and a few smaller and less rigorous ones) have now reported that **men and women with the highest intake**[8,9] **or serum levels**[10,11] **of retinol are at the greatest risk of suffering a fracture**; taking in the most retinol also associates with **having the lowest bone mineral density (BMD).**[8,12-14] (It's important to understand that this refers to *preformed* vitamin A: **beta-carotene and other 'provitamin A' carotenoids have *not* been associated with loss of bone health**).

Frighteningly, the amount of preformed vitamin A which these studies have found to put consumers at risk of broken bones is right in the ballpark found in many – and perhaps *most* – multivitamins: "just" 1.5 milligrams (5000 IU) in one study,[8] and a similar 6 600 IU in another[9] is enough to roughly *double* your risk of a fracture. It's extremely unlikely that you'd get dosages like these from food – you'd have to spend all day gorging on liver, eggs, and fortified milk – but it's all too easy to exceed the safety limit if you're taking the kind of multivitamin designed around an unthinking 'more is better' paradigm. And indeed, nearly *no one* in these studies would have reached the extreme levels of intake associated with increased fracture risk if it were not for the badly thought-out supplements they were letting into their systems.

But this *doesn't* mean that you should avoid all intake of retinol, or depend *entirely* on carotenoids to get your vitamin A. The rate of conversion of "provitamin A" carotenoids into retinol varies nearly *ninefold* from person to person,[15] and can be altered by age, genes, body weight, and alpha-tocopherol intake. Remember that retinol is an absolutely essential nutrient – and in fact, one of its most important functions in the body is in normal skeletal metabolism! Indeed, some of the same studies that reported the impairment of bone health caused by years of retinol overdose have found that people with the *lowest* vitamin A levels[11] or intake[12] *also* suffer an elevated fracture risk[11] and lower BMD.[12] It appears that the *ideal* retinol intake – from diet and supplements combined – is in the ballpark of 2000 IU.

But remember that, because of government-mandated fortification, **a single serving of low-fat milk or yogurt contains between about 500 and 750 IU of vitamin A, and a standard 85g (3 oz) slice of liver contains an astounding 22 000 IU!**

Men and women with the highest intake of retinol are at the greatest risk of suffering a fracture

So it's very easy to overshoot your safe vitamin A intake if your supplement contains more than 1000 IU of retinol. The goal of supplementation should be to put you into that happy medium where bone health is optimized; *supporting* the balance of the diet instead of overbalancing it with levels you'd never get from well-chosen foods.

Another source of long-term health theft resulting from sloppily-designed supplements is **overbalanced zinc-to-copper ratios.** The body's metabolism of these two minerals is inextricably intertwined because of their similar atomic structure: they resemble each other so closely that they can compete with one another for absorption and transport, and interfere with one another's binding to enzymes, if one is present in excess. Getting *too much* of either nutrient creates a functional deficiency of the other. So keeping the two minerals in proper balance is important if you're going to reap the health benefits of either – or even to avoid doing yourself damage.

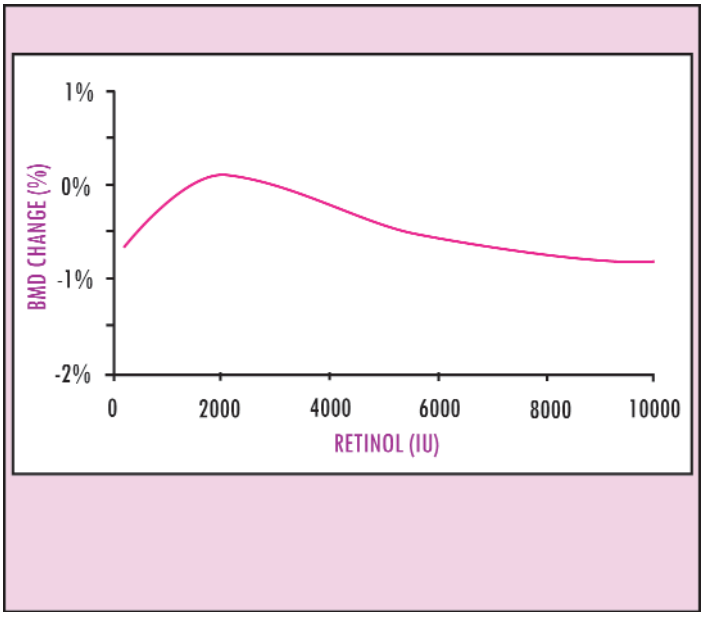


fig 1. Retinol intake and bone mineral density in the elderly. Modified from reference [54].

Both animal and human evidence suggests that, for optimal utilization of both minerals, the balance between zinc and copper should be about ten-to-one.[16] But most supplement formulators seem to have been dazzled by the exciting research which documents the importance of getting adequate zinc in your diet – so much so, that they've ignored the crucial place of copper in the equation. As a result, it's common for multivitamins to include very high doses of zinc, but little or no copper, so that **many – perhaps *most* – multivitamin and multimineral formulas contain potentially harmful zinc-to-copper imbalances.** Such imbalances are more than just a theoretical concern. In a series of human studies, using a ratio between zinc and copper of 23.5-to-one (and sometimes lower) – **common zinc-to-copper ratios, found in many multivitamins – resulted in wide-ranging metabolic disturbances,** including reduced levels of the copper-based antioxidants enzymes **cytosolic superoxide dismutase** and **ceruloplasmin,** high total *and* LDL ("bad") cholesterol, reductions in the body's levels of **enkephalins** (natural pain-killing molecules), and abnormal cardiac function (including rhythm disturbances and even *heart attacks*)![16-18]

And these are just the metabolic derangements observed over the course of a few weeks or months. Over *years* of functional copper deficiency created by excessive zinc intake, it seems inescapable that other problems known to result from 'simple' copper deficiency – such as **impaired bone metabolism, poor glucose control, and increased levels of *Advanced Glycation Endproducts (AGE)* –** would also manifest themselves.

The most bitterly ironic twist in the black comedy of zinc-mad pill design has only recently appeared. Many men take zinc supplements to support the health of their prostates, because of some evidence suggests that low zinc levels are associated with prostate cancer and other prostate disorders.[19] But a large new study,[20] which tracked the health habits of nearly 50 000 American male health professionals for 14 years, found that ***extreme* zinc over-supplementation was associated with a more than *doubled* risk of developing advanced prostate cancer,** especially if continued for more than 10 years.

All of this has lead to alarm amongst researchers who have devoted their academic careers to documenting the importance of copper in human health. Dr. Leslie M. Klevay, for instance, has warned of the "hazards of zinc supplements."[17] But the problem is not zinc supplements, but the *excessive zinc dosages,* and/or *unbalanced* zinc-to-copper *ratios*, found in far too many multivitamins. A properly-designed core nutritional program will work to ensure optimal intake of *both* nutrients – individually, *and* in balance.

Yet another example of "megadose mania," for which the evidence is disturbing if not yet conclusive, is the probable **neurological damage caused by excessive manganese supplementation.** It's well-established that workers in industries where *inhaling* manganese is common (such as manganese miners and welders) are at greater risk for neurological syndromes resembling **Parkinson's disease,** and animal studies clearly show that excessive manganese intake leads to neurological damage.[21] Furthermore, in a study that compared the level of manganese present in the drinking water in different communities with the rates of neurological symptoms amongst their residents,[22] it was found that neurological symptoms were more common amongst the elderly in high-manganese areas. (Another study, however, did not report an association[23]).

But the best evidence that manganese over-supplementation really is an issue worthy of our concern is a study which compared the manganese intake from diet and supplements of people with Parkinson's disease with those of people without the disease.[24] The study found that **people with high dietary intake of manganese are about 70% more likely to fall prey to this neurological disorder** – and that the risk was further increased among people who *also* consumed manganese-containing supplements, or who also had a very high intake of **iron.**

It's not clear *exactly* how much manganese is too much, in large part because of the different bioavailabilities and distribution in the body of manganese coming from fumes, water, food, and supplements. And it's hard to detect the early symptoms of manganese excess, because they are so nonspecific: loss of appetite, impaired reproduction, anemia, and retarded growth in children.

A review of the evidence by the National Academy of Sciences' Institute of Medicine found that the lowest level of *total* manganese intake at which suggestions of harm could be documented was at manganese intake from diet of 15 milligrams; they cautiously suggest that the safe upper limit of manganese consumption from *all* sources is 11 mg.[25] When you consider that unusually manganese-rich diets can contain between 6.3[25] and 8[26] milligrams of the mineral, the idea of *adding* an additional five, ten, or even more milligrams of manganese in the form of a badly-thought-out multivitamin becomes an increasingly bad notion – yet such dosages are common.

Again, this doesn't mean that you should treat manganese like a nutritional pariah, or a toxin like lead or cadmium. Manganese *is* an essential nutrient, needed for healthy skin, bone, and cartilage, for maintaining glucose tolerance, and for the formation of the mitochondrial form of the antioxidant enzyme **superoxide dismutase (SOD)**. But the bottom line is that there's no good evidence that getting *more* than a few milligrams of manganese makes you any healthier, and there *is* some pretty suggestive research indicating that a very high intake could ultimately do you harm. It seems clear that supplements should contain enough manganese to ensure that you aren't deficient, but not much more: a couple of milligrams is safe, and will meet your nutritional needs.

Nutritional Bait-And-Switch

But the problems with multivitamins extend into subtler territories than frank overdose. Another is using the *wrong molecule*. When studies show that people whose diets are chock-full of some key nutrient are protected against a ravaging disease, you'd think that it'd be a no-brainer to create supplements which contain that same nutrient. Far too often, however, supplement companies have cheated health-conscious consumers by **substituting counterfeit versions of these molecules for the real thing – versions with fundamentally different effects on the body**.

One example that we've previously documented in detail is **lipoic acid**: unless they say otherwise, supplement companies replace **R(+)-lipoic acid** – the form of this nutrient produced by the body for its own use – with an adulterated, 50-50 "racemic mixture" of **R(+)-lipoic acid** and the purely artificial S(-)-form of the molecule. Studies show that **the artificial S(-)-lipoic acid is not just *less potent* than the natural R(+)-form, but in some cases actually *interferes with,* or has the *opposite effect* of, R(+)-lipoic acid**. (For a review of some of the research on **R(+)-lipoic acid**, see "Your Two-Faced Lipoic Acid" in *Advances* 2(1), or visit *http://www.R-Lipoic.com*).

This same problem is common to many keystone nutritional supplements. One excellent example is **beta-carotene**. The studies designed to test the ability of beta-carotene to prevent cancer and heart disease were based on the very strong evidence that people whose diets contain more beta-carotene had a lower risk of lung (and other) cancers.[27] But when companies began making beta-carotene *supplements,* the *form* of 'beta-carotene' that they produced – and that was used in nearly all of the trials – was *not* the same 'beta-carotene' that occurs in food.
Beta-carotene *from food* contains two structural forms (**isomers**) of the molecule: all-*trans* and 9,*cis*-beta-carotene (see **Figure 1**). But the beta-carotene used in nearly all *supplements* has been *entirely* composed of the all-*trans*-form of the molecule.

The difference is important to all of us, not just organic chemists. Studies have clearly shown that the effects of natural and synthetic beta-carotene are fundamentally different. Synthetic beta-carotene has much lower antioxidant activity;[28-30] more alarmingly, studies performed in human white blood cells have revealed that **the synthetic beta-carotene used in most supplements causes genetic damage to the cells!**[31] *Natural* beta-carotene, by contrast, does not have this effect.[31] So perhaps it's no surprise that the studies designed to test the ability of beta-carotene supplements have actually found that the pills not only fail to *protect* users against cancer[2-4] but may actually *increase* the cancer risk:[2,4] all of these studies used the synthetic, all-*trans* form of the molecule.

Another example of molecular mismatch is "vitamin E." Numerous studies in the health habits of large populations have found that the "vitamin E" in food provides protection against **cardiovascular disease (CVD)**[32-34] and **Alzheimer's disease.**[35-37] Yet these *same* studies have reported that users of "vitamin E" *supplements* have not been given protection.[32-37] In fact, a "meta-analysis" study which pooled the results of 19 high-quality controlled trials found that **high-dose alpha-tocopherol supplements actually *increase* mortality** in patients with existing cardiovascular disease![1] Scientists now have a very good explanation for this: again, the "vitamin E" in *food* is very different from the "vitamin E" contained in nearly all supplements.

We're not just talking about the difference between so-called "natural" "vitamin E" (*d*-alpha-tocopherol, or more properly *RRR*-alpha-tocopherol) and "synthetic" "vitamin E," (*dl*- or all-*rac*-alpha-tocopherol). The only real difference between d- and dl-alpha tocopherol is in its *strength*: it takes *more dl*-alpha-tocopherol to get the same effect you get from d-alpha.[38]

No, the *real* distinction between the "vitamin E" you get from a healthy diet, and the "vitamin E" you'll find in most pills, is not one of *degree,* but of *kind*. While the "vitamin E" in food does *contain* d-alpha-tocopherol, this molecule actually makes up only a minor *fraction* of the vitamin E in healthy diets. "Vitamin E" is not this *one* molecule, but a *complex,* composed of *eight* distinct molecules – four *tocopherols,* and four *tocotrienols*. And in fact, the single largest amount of "vitamin E" in healthy diets appears as *gamma*-tocopherol, not its alpha cousin.[39-43]

***extreme* zinc over-supplementation was associated with a more than *doubled* risk of developing advanced prostate cancer**

Again, this isn't just trivia for biochemistry geeks. The different members (or "vitamers") of the E complex have different functions in the body, just as different B vitamins do. Recently, the unique properties of gamma-tocopherol, have become a particular focus of researchers' attention,[44,45] but the unique benefits of the "other" E vitamins are clearly also important. Some of these unique health properties were discussed in "There's No Such Thing as Vitamin E," in *The Holistic Lifestyle 1(4)*, and we hope to go into more detail in a future issue of *Advances*.

To jump to the punch line, however: these newly-discovered properties of gamma-tocopherol, tocotrienols, and other natural E vitamins explain why the "vitamin E" in food protects against chronic disease where supplements keep failing.[32-37] And indeed, by looking at levels of E vitamers in the body, the importance of the distinction becomes clear: **high levels of gamma- – and *not* alpha- – tocopherol is associated with reduced risk of CVD**[46-49] and heart attack,[50] and that the same is true of **prostate cancer**.[51,52] Likewise, evidence exists for a selective gamma-tocopherol depletion in the brains of people with Alzheimer's disease.[53,54]

And the real problem with unbalanced alpha-tocopherol supplements is not just that they're *missing* these other E vitamers, and therefore fail to provide their unique benefits. Astoundingly, **alpha-tocopherol, at doses typical of most supplements, actually *interferes with* the body's ability to hold onto and use of the other E complex members**!

Because of its specific importance to *reproduction,* and because a natural diet contains comparatively little of this *specific* E vitamin, evolution equipped the body to hang onto its supplies of alpha-tocopherol – even at the *expense* of other E vitamins. As a result, **when you flood yourself with unbalanced alpha-tocopherol supplements, you actually *deplete* your body of other E-complex members** (see **Figure 3**).[55-59]

It doesn't take a lot of unbalanced alpha-tocopherol to drive down your gamma-tocopherol supply: five months of swallowing just 150 IU of isolated alpha-tocopherol per day robs your body of *63%* of its plasma gamma-tocopherol levels, leaving you with *lower* levels than you would have had if you were taking *no supplement at all*.[55] And the effect can be long-lasting: after one year of high-dose (1200 IU) alpha-tocopherol supplementation, tissue gamma-tocopherol levels take *two* years of "cold turkey" to recover to the level they were at before supplementation began.[58]

And don't think that the "natural mixed tocopherols" added in as an afterthought to some "vitamin E" supplements will make up for this imbalance. These products throw in no more than 20% as much of the tocopherols *other than* alpha-tocopherol, almost as an afterthought – and they contain *no* tocotrienols. But it's been shown that it takes a *lot* more of the "other" E vitamins to make up for the alpha-tocopherol overdoses found in these pills. For example, if you take 371 milligrams of alpha-tocopherol into your body every day, you'll *still* suffer a 30% loss of gamma-tocopherol in plasma even if you try to balance it out with more than *400 milligrams* of gamma-tocopherol and other E complex members.[59]

In fact, careful examination of studies involving the cholesterol-balancing effects of tocotrienols reveals that **the body needs at least *twice* as much of the "other" E vitamins to prevent alpha-tocopherol from canceling out their benefits**.[60-62] It should come as no surprise that this ratio is similar to what's found in a balanced diet of whole foods.[39-43]

Yet another example of the kind of nutritional bait-and-switch at work in common multivitamin formulations is the ongoing use of inferior forms of **selenium**. Extensive research demonstrates that **Se-Methylselenocysteine (SeMC) is the most effective cancer-fighting form of selenium available**.[63-65] (We reviewed the revolution in selenium cancer research of the last decade in the Spring 2003 issue of *Advances*). Not surprisingly, foods with known cancer-fighting powers – such as high-selenium broccoli, garlic, and onions – contain much of their selenium in this form, whereas selenomethionine and other common selenium forms predominate in foods like beef and wheat – foods which are not particularly noted as being protective against cancer. Yet most companies continue to put selenomethionine, selenate, selenite, or selenium yeast into their pills.

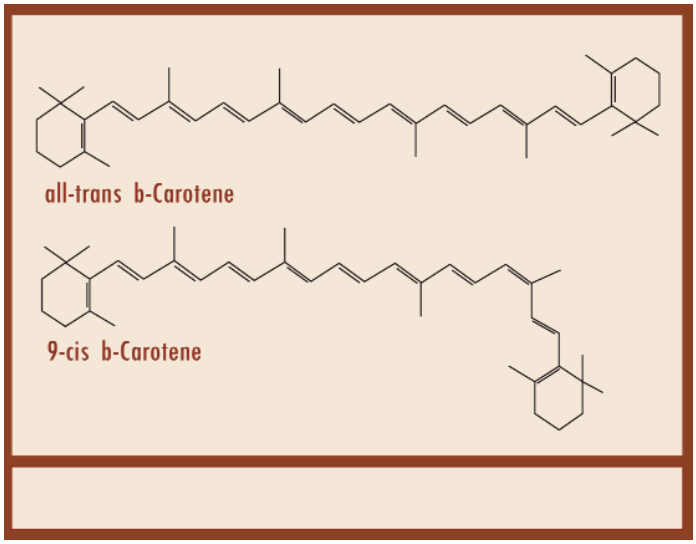


Figure 2: All-*trans* and 9,*cis*-beta-carotene.

Take, again, the difference between **menatetrenone** (MK-4, the form of vitamin K_2 biosynthesized by mammals) and **phylloquinone** (vitamin K_1 – the form used in nearly all supplements). We know that **menatetrenone delivers superior skeletal,**[66] **brain,**[67] **and cardiovascular**[68,69] **health benefits.** Yet supplements continue to use vitamin K_1 – or sometimes **bacterial menaquinones** (such as **menaquinone-7** (MK-7) – the main bacterial form of K_2), which are not the same molecule (see figure 4).

There's also the greater bioavailability and stronger clinical evidence for **calcium citrate-malate** compared with other vegetarian calcium sources (regular **calcium citrate** is *not* equivalent![70]). And we could go into other examples. But the point, by now, should be obvious. **When evidence suggests that high intakes of a nutrient found in healthy foods supports vibrant health, make sure that your supplement contains *the same molecule,* and not an impostor or second-best.**

Emerging Essentials

Official government nutrition panels recognize only 13 essential vitamins and 15 essential minerals. But in recent years, it's become increasingly clear that a few other substances are just as indispensable for your health. It was only recently that **chromium** was recognized by the Institute of Medicine to be necessary for your health. But **the evidence is compelling that boron, silicon, lithium, and vanadium are as necessary to your health as the "official" essential minerals,** such as calcium, magnesium, or zinc, and that **a little-known redox factor called *pyrroloquinoline quinone* (PQQ) is being considered as a vitamin just as essential to your health as vitamin C or pantothenic acid** (vitamin B_5).

Boron appears to be an essential to normal brain function,[71] a key factor in preserving the health of the skeleton and joints,[72] and has been linked to reduced risk of prostate cancer;[73] recent studies in the homeostatic control of boron concentration in the body[74] and in breast milk[75] show that the body is actively regulating levels, demonstrating its essentiality in the body, and a failure of this control is observed in mothers who subsequently undergo premature labor.[75]

Silicon has been shown to be essential to normal bone formation in animal studies,[76,77] and epidemiological studies,[78] and preliminary clinical trials[79] suggest that it builds stronger bones in humans, too, apparently through a cofactor role in collagen synthesis. And **vanadium** appears to have a key role in thyroid function, as well as having a "pharmacological" effect on glucose metabolism at extremely high doses.[80]

Supplement companies have substituted counterfeit versions with fundamentally different effects on the body.

Perhaps the most remarkable rise of a newly-identified mineral in recent years has been **lithium.**[81] Although most people think of this mineral as a "drug" to used treat bipolar disorder, lithium is a trace mineral found in "hard" water and food: typical diets contain between 0.650 and 3.1 milligrams of **lithium** per day, coming mostly from grains and vegetables.

Animal studies have shown that lithium is an essential mineral in mammals. Lithium-deficient laboratory rodents have impaired reproductive function and abnormal lipid metabolism. When USDA scientists sat down to reformulate the standard rodent chow used in laboratory experiments in 1997, one of the key changes to the diet was to fortify its **lithium** content beyond the amount that occurs naturally in the elements of the diet.[81]

Similarly, studies in goats show that lithium-deficient animals suffer depressed immune systems, chronic inflammation, splenic atrophy, excessive iron buildup in their tissues, and calcium deposits in their blood vessels; moreover, the activity of the enzymes involved in their mitochondrial energy production is depressed, and they develop "benign" tumors of the breast, salivary glands, and adrenal glands, as well as ovarian cysts.[81]

But the most fascinating research on lithium's role in health has come from studies comparing the health of people living in areas with higher and lower amounts of **lithium** in the rain or tap water, and individuals with higher and lower levels of the mineral in their hair, scalp, and urine. These studies have found that **people living in areas with low lithium have higher rates of neurosis, schizophrenia, psychosis, psychiatric ward admissions, homicide, suicide, forcible sexual assault, burglary, and runaways.**[81]

High-dose alpha-tocopherol supplements actually *increase* mortality

Based on the amount of **lithium** found in typical diets, and the amounts known to support brain health when consumed in the diet and drinking water, **nutrition researchers are now suggesting an 'RDA' of lithium in the range of 0.400 to 1 milligram per day.**[81] Lithium supplements are now becoming more readily available in the United States; unfortunately, the Canadian authorities continue to insist that even nutritional doses of organic lithium is a "drug," and threaten fines and imprisonment to anyone making it available except by prescription.

Plant Protectors

The most consistent finding in all of the science of epidemiology is that diets rich in fruits and vegetables are associated with reduced risk of cancer, heart disease, and age-related disability. Fruits and veggies are the best source of many vitamins and minerals, of course, but there's a lot more in a healthy diet than just these essential nutrients. For more than half a century, scientists have known that when experimental animals are fed highly-refined diets which contain all the protein, essential fats, vitamins, and minerals known to be essential to their normal growth and development, they are *still* more vulnerable to cancer than animals containing similar levels of all essential nutrients, but composed primarily of unrefined or semi-refined food sources.[82-87] The explanation for this phenomenon lies mostly in **phytochemicals.**

When you flood yourself with unbalanced alpha-tocopherol supplements, you actually *deplete* your body of other E-complex members

Strictly speaking, *any* biologically-active substance produced in plants can be called a "phytochemical." But the term is most often used to refer to those protective, disease-preventing bioactive compounds which – while not "essential" in the same sense as vitamin C or magnesium – none the less play a major role in the benefits of a good diet. In recent years, researchers have made rapid strides in teasing out the biological effects of these biomolecules – and every now and then, a phytochemical has been identified as being crucial to the health-promoting effects of individual foods, or groups of food, which have been singled out as especially potent medicines in Nature's pharmacy. Each of these discoveries reveals a critical element of good nutrition that has been *missing* from narrowly-defined "multivitamin" formulas.

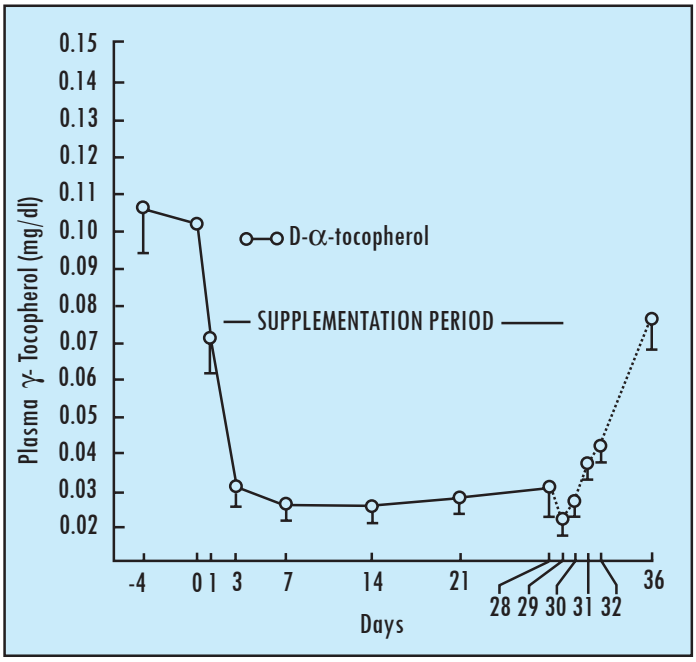


Figure 3: Unbalanced alpha-tocopherol supplements deplete your body of gamma-tocopherol. Redrawn from (55).

But there are literally *thousands* of biologically active substances in plants: over 5 000 have been identified, many of them only recently.[88] But while some of them are important contributors to the health of people consuming them, others are needed by the plant, but are of no value to us when we eat them – and *some* of these compounds (even if found in healthy foods) are known to be toxic.

The research on phytochemicals demands a new approach to nutritional supplementation. Those bioactive plant molecules which will help you reach a longer, healthier life need to be identified and placed on the "A" list for the core nutritional supplement of tomorrow. But other such compounds are helpful to only a few people with unique health concerns, and therefore should not be in a multinutrient formulation designed to be taken by *every* health-conscious person. Still others are of no nutritional value, and ultimately only of interest to agronomists. And a few are even *harmful*. So how do you know which is which? After decades of research, such an "A" list of phytochemicals has emerged. The process was long and painstaking, but its conclusions are proportionally solid. It began by narrowing down the broad category of "fruits and vegetables," and carefully looking at *which* plant foods have the most consistent associations with good health. The conclusion: while there are no doubt health benefits from *all* fruits and vegetables, and while any given plant food or phytochemical may catch a headline here and there, **the most powerful, consistent evidence points to cruciferous vegetables** (such as broccoli, cabbage, and mustard greens); ***Allium* vegetables** (such as garlic and onions); **green, leafy vegetables; citrus fruits, tomatoes, carrots,** and ***raw* vegetables** generally, as being especially powerful in promoting good health.[89-96]

Researchers next turned their attention to the question of why these *particular* plant foods should be more effective in keeping you healthy than others. In the case of carrots, the most likely player is its range of **mixed carotenoids**, including **lutein** and **alpha-carotene**. But they found that the other fruits and vegetables contain specific phytochemicals which are either unique to these foods, or are found in much higher amounts in these plant foods than in others. And by exploring these phytochemicals' effects on the body in experimental animals and cellular studies, **science has vetted a phytochemical dream team**.

The key plant bioactives are the **isothiocyanates** (most importantly **sulforaphane**) and **indoles** (especially **indole-3-carbinol (I3C)**), which appear as **glucosinolates** in cruciferous vegetables; the *Allium* vegetables' **allyl sulfides** (the most potent of which is **diallyl disulfide (DADS)**); the **limonene** and related monoterpenes found in citrus (and especially citrus *peel*); the **lycopene** that comes overwhelmingly from tomatoes and tomato products; ***trans*-resveratrol**, found in red wine; green tea's key polyphenol **EgCG**; and **chlorophyll**, which gives the hue to green, leafy vegetables. (The importance of *raw* vegetables probably comes from the fact that the enzymes which liberate sulforaphane and I3C from their storage forms are inactivated by longer, higher-temperature cooking, leading to reduced bioavailability of these cancer-fighting nutrients[97,98]). While it's currently not possible to put all of these phytochemicals into a single multivitamin formulation because of various interactions that make some of the specific combinations technically impossible or undesirable, it's clear that a supplement program designed to closely mimic an optimal diet must include as many of these phyto-powerhouses as possible.

A review of the scientific literature shows how consistently the consensus has crystallized around the central importance of these phytochemical elite.[90-96] One can certainly point to still *other* substances found in plants which *might* have health benefits, but none of them have this powerful weight of epidemiological, experimental, mechanistic, and in some cases clinical[99-101] evidence to back them.

So, for instance, test-tube studies on the effects of **ellagic acid** on DNA adduct formation are intriguing, but no studies in the health habits of large human populations show that people consuming lots of ellagic-acid-rich strawberries or raspberries are less likely to develop cancer than people eating *other* fruits and vegetables. The available results are intriguing – but not strong enough to justify designating it a critical phytonutrient which should be a part of every health-conscious person's supplement program. (In fact, the same objection applies to many other polyphenols. For one of the key reasons underlying many such disconnects, see **For Biochemistry Geeks Only!**).

There are also many phytochemicals which have benefits to people with serious health problems – but that aren't necessarily helpful to basically-healthy people looking to further enhance and protect their health. In many cases, these phytochemicals come from herbs and other botanicals which are not a part of the regular, habitual diets of anyone in the world: they should – and traditionally *have been* – regarded as *medicines* for people with *specific* health needs, not healthy *foods* that contribute to the well-being of health-conscious people.

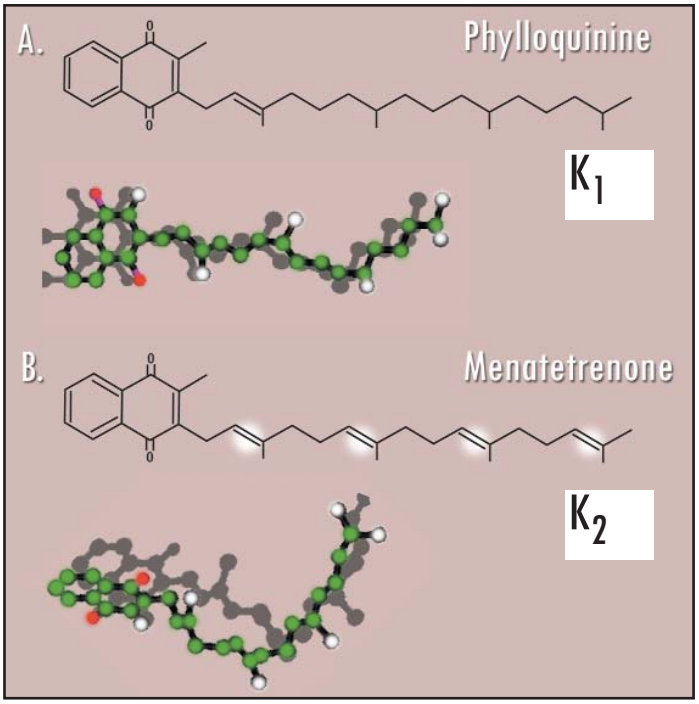


Figure 4 : Structural representation of Vit K_1 and Vitamin K_2.

Silymarin from milk thistle, for instance, is of great benefit to people with some kinds of liver disease, mostly because it fights the oxidative stress, membrane damage, and inflammation of the liver that's associated with **cirrhosis** (scarring) of the organ,[124,125] and also perhaps by increasing the amount of protein-biosynthesis "instructions" coming out of the tissue's DNA code.[125] All of this gives the cirrhotic liver the opportunity to heal itself – but there's no evidence that *healthy* people, with undamaged livers, will get "super-healthy" livers by taking this herb.

Since, in fact, we know virtually nothing about the effects of these kinds of herbs on otherwise-healthy people; it's hard to see the idea of taking these powerful extracts regularly as anything but an unnecessary gamble with your health. They do *not* belong in a core multinutrient formulation, designed to be taken by everybody, every day, for the rest of your life.

Your Body's "Detergent"

While these phytochemicals exert a wide range of important effects on cellular metabolism, most of them share the common feature that they modulate the balance of the

Flavonoids of which there are several thousands are abundant polyphenols in the human diet and are divided into six main classes: (Flavanols) (e.g. Catechins), Flavonols (e.g. Quercetin), Flavones (e.g. Luteolin), Flavanones (Naringin), Isoflavones (e.g. Genistein) and Anthocyanidins (e.g. cyanidin)

body's detoxification enzymes. Your body neutralizes toxic chemicals and many internal waste products using a two-step biochemical breakdown process. In **phase I detoxification**, '**procarcinogen**' compounds are first made more chemically reactive using a group of enzymes known as the **cytochrome P450s** or **mixed-function oxidases**. Think of phase I detoxification enzymes as "*agents provocateurs*," who infiltrate an enemy group to incite the more dangerous elements in an organization to show their cards. It's then the job of the **phase II detoxification** system to play the role of more conventional law enforcement, "arresting" those fired-up (more reactive) "cellular terrorists" and "handcuffing" them with molecules (**conjugates**) that make them easier to safely excrete through the urine or the bile.

The danger spot is in the step *between,* in which the "activated" procarcinogens are potentially even *more* dangerous, until they are "handcuffed" by the phase II system. This is where many phytochemicals lend a hand. Broadly, many of the best-documented phytochemicals increase the activity of the phase II system, while reducing down the activity of phase I. This slows the overproduction of *activated* procarcinogens, and ensures that there is enough phase II activity to ensure that activated procarcinogens are all bound up and sent packing.[126]

But of course, for phase II detoxification to take place, your phase II enzymes need an adequate supply of the "handcuffs" (conjugates) that render the procarcinogens tame. So it's important to ensure that your diet and supplement program contains plenty of key conjugation factors such as **acetic acid**, **glycine**, **taurine**, **trimethylglycine**, and **sulfur** sources such as **N-Acetylcysteine (NAC).**

Random Dosages

Almost every week, a new study comes out linking a diet rich in some key nutrient with a longer, healthier life. And when the popular press reports the story, they put it something like this: "the people whose diets contained the most of this nutrient were only two-thirds as likely to get breast cancer" – or heart attack, or Alzheimer's disease, or any of the myriad assaults of "normal" aging. The problem with these stories is that they rarely tell you *how much* of the nutrient in question the people eating those diets were consuming. Too often, in fact, the *medical abstracts* of the original scientific papers don't give you this information either. If you want to find out, you have to take a jaunt down to a medical library and dig up the full-text article.

But few people have the time to take this trouble, especially granted the wide range of individual ingredients in their core nutrient formulas, *plus* their "add-on" supplements. So, most of us depend on the formulators of these products, not just to include the *right* ingredients in their products, but to include a research-backed dose.

Too often, this just doesn't happen. In fact, comparing major research papers to the ingredients lists on typical supplement bottles, you'll be forced to wonder if the designers of such products used a dice roll to determine their dosages.

Let's take a couple of examples. There is powerful support for the ability of the carotenoid **lycopene** to reduce the risk of cancer – prostate cancer in particular,[92,99,100] but also cancers at many other sites in the body.[92] But *how much* lycopene is associated with cancer protection? Studies in large populations show that **high-lycopene diets, rich in tomato paste and other good sources of the carotenoid, provide from 13**[127] **or 14,**[128] **through 18,**[129,130] **to as high as 24**[131] **milligrams of lycopene a day**. (Earlier studies, which reported lower intakes (such as 6.5[132] or 9[133] mg/day) were using an outdated carotenoid database which neglected many lycopene-containing foods and which relied on an obsolete analysis method that low-balled the foods' carotenoid content[134,135]).

So a supplement designed to support the protective effects of high-lycopene diets should also contain these same established, protective amounts. Instead, nearly *no* multinutrient products contain more than 3 milligrams of this crucial carotenoid – and some contain as little as a *tenth* of this paltry amount! To put this into its full, damning perspective: because tomatoes and tomato products are consumed even by people eating very poor diets (in the form of ketchup on their MacGreaseburgers and a little tomato sauce on the occasional slice of 'za), even the *bottom 20%* of diets provide lycopene in doses such as 2.3[131] to 3.4[129] or even as much as 4.4[130] or 4.5[128] milligrams of lycopene on an average day!

Where do these senselessly low doses come from? Some formulators just formulate their products in ignorance, without bothering to dig into the original research; others know full well that the measly dose they're including won't do anyone any good, but cynically throw a token quantity of lycopene into their products for no other reason than to catch your eye as you scan their labels. Neither is providing you with anything like the amount of lycopene that the research says is needed to shield your body from the ravages of cancer.

Now let's look at the other – and more disturbing – extreme. While enthusiasm for beta-carotene has dampened thanks to the spectacular failures of several large trials, at one time most 'premium' multivitamins contained 25 to 50 milligrams (41 625 to 83 250 IU) of synthetic beta-carotene in a daily dose; indeed, many antioxidant combination products *still* contain such overdoses. (If you're double-checking a supplement label for its carotenoid content, you'll want to look for the *absolute milligram potency*, because many supplements list IU potencies using old, outdated conversion factors;[25] indeed, the proper way to make this conversion remains controversial today.[136] Milligram potencies are the clearest and best way to get this information on a label).

Science has vetted a phytochemical dream team: sulforaphane, indole-3-carbinol (I3C), limonene, lycopene, trans-resveratrol, EgCG, and chlorophyll

We've already seen that the use of *synthetic* beta-carotene was a disaster in the waiting; however, the use of these massive amounts of the stuff can only have made things worse. Because the strong evidence from epidemiological and experimental studies that beta-carotene protects you from cancer[27] never supported such huge doses – and since then, animal research has shown that **the overkill quantities of beta-carotene used in too many supplements actually *increase* cancer risk** when you're exposed to cigarette smoke.

Incredible – some would say *unconscionable* – but true. When we turn again to research using the latest carotenoid database to document the amount of beta-carotene being consumed by people whose diets are rich in this carotenoid – diets strongly and consistently associated with lower cancer risk[27] – we see that even the *richest* diets contain from as little as 6.8,[128] through 8.95[129] or 9.8,[131] and not more than 11.4[127] milligrams of beta-carotene per day. In other words, the amounts of beta-carotene which, in the diet, is associated with reduced risk of cancer is only about a third to one half of the amount used in far too many supplements – and also in the unsuccessful clinical trials of beta-carotene to prevent cancer.[2-4]

And recent studies suggest that this beta-carotene overdosing isn't *just* a matter of wasted money. At these extreme doses, scientists have observed that the body's carcinogen-detoxifying systems become unbalanced[137,138] and genes related to the cancer process become activated.[139] One study in ferrets (whose metabolism of beta-carotene is much more like that of humans than is other rodents') compared animals exposed to cigarette smoke alone to animals exposed to the smoke plus beta-carotene supplements at one of two doses: one designed to reflect the levels of beta-carotene present in a diet emphasizing this nutrient, and the other reflecting the kinds of mega doses typical of many antioxidant and multivitamin products.

The results: the "rich-diet" beta-carotene supplement dose resulted in lower levels of **squamous metaplasia** (precancerous lesions) of the lung – but giving the same animals the equivalent of a 30 milligram (49 950 IU) synthetic beta-carotene supplement led to the activation of several pro-cancer genes, and to the animals suffering *more* precancerous lung lesions than did those exposed to cigarette smoke alone![139]

Along with the use of *synthetic* (all-*trans*-) rather than *natural* (9-*cis*-containing) forms of the molecule, these findings provide one of the likely reasons for the suggestion of higher cancer risk in smokers given the equivalent, unjustifiable doses of beta-carotene in the disastrously failed clinical trials.[2-4,134] And the proof in the pudding has come from the massive **SU.VI.MAX** trial. This randomized, double-blind, placebo-controlled study tested effects of an antioxidant supplement containing doses that reflect the amounts found in good diets – including 6 mg of beta carotene and 120 mg of vitamin C, along with vitamin E, selenium, and zinc – in 13 017 healthy, middle-aged French men and women. After following the two groups for 7.5 years, it was found that **supplements of beta-carotene and other antioxidants, at doses typical of good diets, reduced cancer incidence by 31%, and death *from all causes* by 37%**– although there was no reduction observed in the women, apparently linked to fact that the women had higher levels of antioxidant nutrients to begin with.[140]

Without hammering the point to death, let's look at one more example. It's important to take *all* of the B vitamins, not only because they're essential nutrients but because they work as a complex, with their metabolism dependent on one another and an excess of one sometimes creates a deficiency of another.[141,142] But has it ever occurred to you how *weird* it is that so many multivitamins and B-complex vitamins contain *exactly* as much thiamin as niacin as riboflavin, and so on – the same 50 mg or 100 mg for each and every B vitamin except folic acid, all the way down the list? Does it physiologically make *sense* that the body would optimally use *exactly* the same amount of half a dozen *different* B vitamins, each with its own unique, irreplaceable functions in the body?

Comparing major research papers to the ingredients lists on typical supplement bottles, you'll wonder if the designers used a dice roll to determine their dosages.

Well, of course, it doesn't. The numbers used are arbitrary, with no physiological justification. Someone, years ago,

For Biochemistry Geeks ONLY!

Those Fickle Flavonoids

With so many phytochemicals showing favorable-looking results in test tube and animal studies, it's a bit surprising to see how few have been linked to better health in large population studies or clinical trials. In many cases, it's likely that this has to do with the way the body – and in particular, the *human* body – metabolizes these substances.

Polyphenols (including **flavonoids** and **phenolic acids**), in particular, **undergo a whole series of complex biotransformations which make it difficult to predict their effects *in the body* based on their effects *in the test tube***. Both the probiotic bacteria in your intestinal tract, and your body's own detoxification systems, really "go to town" on polyphenols, so that the original molecule will go through several cycles of having old conjugates cleaved and new ones added before it is finally excreted, creating diverse and largely unpredictable array of metabolites along the way (see **Figure 5**).[102-104]

With most nutrients, you can expect that the effects in humans will be similar to the effects in experimental animals. But in the case of flavonoids, this often doesn't pan out. Humans metabolize many flavonoids differently – and often much more heavily – than rodents do,[102] so that extrapolation from rodent studies becomes an extremely uncertain, speculative exercise.

Some of the metabolites of a given flavonoid will not be absorbed at all; others will be absorbed, but their biological activity will be much different from that seen in test-tube studies using the original, un-metabolized compound. It's these metabolites – and not the parent molecule – that will determine the real effect of flavonoids in the body: good, bad, or indifferent.[102]

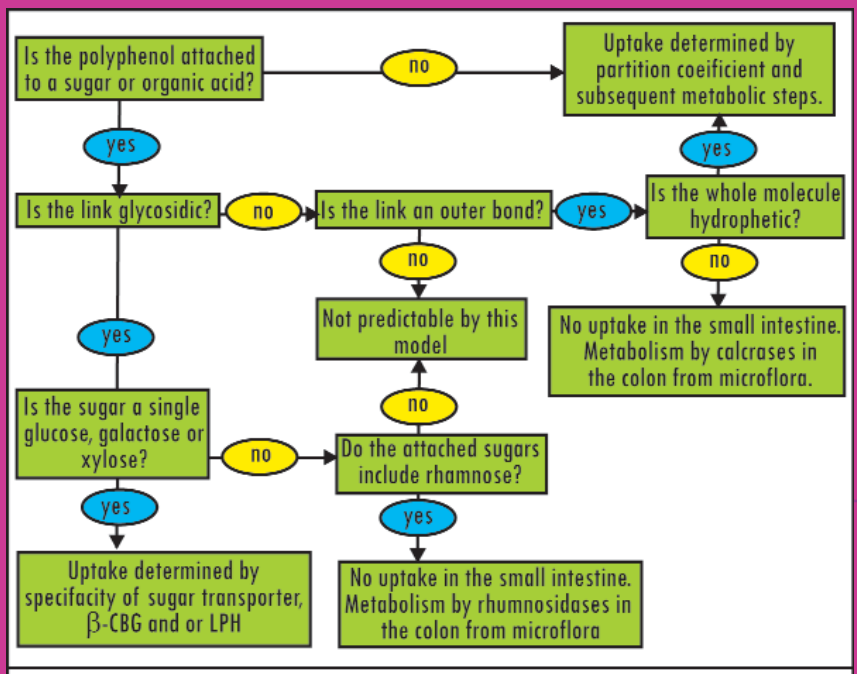


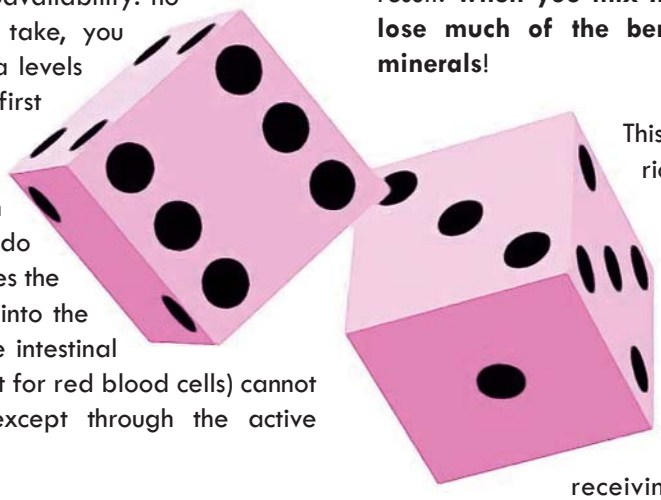
Figure 5: Factors Affecting Flavonoid Absorption. Redrawn from (102).

Let's take a few examples. The absorption and metabolism of **epigallocatechin gallate (EgCG)** in green tea is well-characterized,[105-112] the effects of its metabolites have been explored,[113] and there is extensive epidemiological evidence showing that people consuming high amounts (most consistently, ten servings of Japanese *sencha* green tea live longer,[114] develop less cancer,[114-118] and possibly suffer fewer heart attacks.[118, 119] Therefore, we can be confident that there really is value in bringing EgCG into your diet and supplement program. By contrast, we're only just *beginning* to get a handle on what the body does with apigenin,[120] luteolin,[121] or the flavonoids in strawberries,[122] and there is only very weak evidence to suggest a *specific* health benefit in people whose diets contain high amounts of foods rich in these *particular* polyphenols, as opposed to other plant foods.

This may also explain why research on the effects of flavonoids *as a class* in humans has been so conflicting. As one recent review of the field put it, "**Some studies support a protective effect of flavonoid consumption in cardiovascular disease and cancer, other studies demonstrate no effect, and a few studies suggest potential harm.**"[123] The bottom line: with such varying bioavailabilities and biological activities, you can't really generalize from one polyphenol to another – and you can't rely on work in the test tube, or even experimental animals. *Human* clinical and epidemiological data for *specific* foods and food flavonoids must be our touchstone.

plucked these numbers *out of thin air* – and somehow, they *stuck*. The irrationality of these numbers can clearly be seen in the case of **thiamin**.

The conventional form of thiamin cannot pass directly across cell membranes: it requires a special shuttle system to pump it across the intestinal wall and (later) into the cell. There are enough "seats" on the shuttles to ensure that you'll absorb the small doses typically found in food … but *most* of a 50 milligram dose gets left waiting at the harbor as the ship pulls away. And while a small amount of additional absorption occurs via diffusion into the fluid that bathes the cells, this adds little to total bioavailability: no matter how much thiamin you take, you don't materially increase plasma levels beyond what you get from the first 12 milligrams of the dose.[143-147]



Even greater problems occur in getting thiamin *into the cells* to do its job. While some thiamin crosses the intestinal wall through diffusion into the fluid surrounding the cells of the intestinal tract, the cells themselves (except for red blood cells) cannot absorb conventional thiamin except through the active transport system.[147,148]

The strictness of the limits of this system can be seen when you bypass the limited intestinal absorption of thiamin by *injecting* it directly into the blood. When 5 milligrams are injected, most of the dose is taken up by the cells, and the kidneys will excrete only 25% of the original dose. But increasing the dose does not increase the cellular absorption. The more thiamin you inject, the more ends up simply passing out through the urine, and at 100 milligrams or more, *100%* of the additional thiamin is excreted in the urine.[149]

The overkill quantities of beta-carotene used in too many supplements actually *increase* cancer risk

There's certainly no *harm* to taking this extra thiamin – but no *point* to it, either. This is one case where the old skeptic's taunt is true: **you really *are* flushing most of that extra thiamin down the toilet**! And the same is true of a lot of the other B vitamins you're taking. Doses should be based on science – not nice, round numbers.

When the Mix Won't Match

There are plenty of health-promoting substances out there that you may want to seriously consider taking in supplemental form, but that you wouldn't want to have included in your multivitamin for one reason or another. Many people, for instance, take supplemental **IP6 (inositol hexaphosphate** or "phytate"), a nutrient found in many plant foods which plenty of evidence suggests is a powerful nutrient protector against the horrors of cancer.[150] And it would certainly be convenient to get this important supplement along with your other core nutrients in one formula. We've even seen **IP6** included in some multivitamin and immune-boosting formulas. The problem with doing this lies in a key chemical property of **IP6:** its ability to react with many minerals – including calcium and zinc – to form tightly-bound, insoluble, *un-absorbable* complexes. The result: **when you mix IP6 with calcium in your gut, you lose much of the benefit of *both* the IP6 *and* these minerals**!

This problem is even seen in some **IP6**-rich grain foods. On the one hand, **bone disorders – including osteomalacia, rickets, and osteoporosis** – are commonplace in populations where unleavened breads and similar foods provide the bulk of the energy in the diet;[151-153] and on the other hand, studies show that animals receiving a diet high in wheat bran experience *two thirds less cancer protection* than animals given the *same* amount of IP6 in their *drinking water*,[154] where it doesn't come in contact with the nutrients in their food.

The key green tea polyphenol **EgCG (epigallocatechin gallate**) is a similar case. **Green tea polyphenols inhibit the absorption of many minerals.** The most famous case is iron: green tea extracts clearly reduce its bioavailability,[155] and it's clear that people who drink a lot of tea and who have marginal iron status are at higher risk of anemia.[156-159] Tea polyphenols may also inhibit absorption of calcium[160,161] and zinc,[161,162] although the effects appear to be minor and perhaps transient.

Of course, you may not *want* to absorb all of the iron in your diet, particularly if you're a man or a postmenopausal woman or eat a high-meat diet. Excess iron levels are associated with oxidative DNA damage[163] and may increase risk of several age-related diseases, including neurological disease,[24,164] diabetes,[165-167] and possibly heart disease.[168] But while most people don't need an iron *supplement,* people who are conscious about their diet – particularly if they don't eat much red meat – have little to gain from *actively inhibiting* their iron absorption. Overall, it just makes sense to **take your green tea supplements away from meals** – and thus separately from your main nutritional supplement.

Get Back to "Basics"

Oftentimes, people become so excited about the potential of exotic botanicals or emerging orthomolecular compounds to impact their health, that they pay less attention to the basic, essential nutrients. Maybe it's a case of "familiarity breeding contempt:" we're so familiar with zinc, copper, or vitamin C that we neglect to pay them any attention. But you can't expect to enjoy *optimized* health from advanced supplementation if your body is lacking the basic nutrient cofactors required for its essential biochemical processes. And on the flip side, as we've seen, it's all too easy to mistakenly imbalance yourself on these same nutrients or to fail to reap their full benefits, if you aren't paying enough attention to just *what* and *how much* you're taking.

Instead of just taking your supplements based on "one size fits all" nutritional formula, it's worthwhile to take careful stock of where you're at, nutritionally, from your diet alone. If your diet is particularly healthy, you may not need a full daily dose of a multivitamin formula; and if you have a diet that is especially strong on a specific nutrient, you may not need to add on extra nutrition on top of your multi as others might. Do you drink a lot of milk? Then you probably don't need a full 1000 milligrams of calcium from supplements alone. Are you absolutely addicted to oysters? Your zinc is likely covered. And so on.

A 30 milligram (49 950 IU) synthetic beta-carotene supplement led to *more* precancerous lung lesions than those exposed to cigarette smoke alone!

For those wishing to personalize their supplement program to the greatest possible degree, there are many software packages available that will actually tell you how much of the essential nutrients you're taking in each day. One of the best is http://www.nutritiondata.com , which is free, available online, and gives great, user-friendly graphical output. The time required to plug in the foods you eat every day for a couple of weeks will be worth it if it tells you where key deficiencies or imbalances may lie – and where you can rest on your nutritional laurels.

Supplements of beta-carotene and other antioxidants, at doses typical of good diets, reduced death from all causes by 37%

So the first rule of supplementation is: *begin at the beginning*. With this base, you can consider moving up to a more advanced multinutrient formula, incorporating key phytochemicals from the "superstar" team identified above, and then adding in additional, more advanced supplements such as powerful phytochemicals or cutting-edge orthomolecules like **benfotiamine** or extended release **R(+)-Lipoic Acid** based on your own priorities and health concerns. Once you have a well-laid foundation, you can build up a solid nutritional fortress.

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