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VOLUME 3 ISSUE 10

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## The Next Big 'E'

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## The Next Big 'E'

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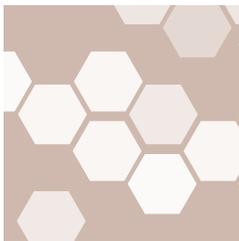


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While the vitamin E market has traditionally focused on tocopherols, an increasingly robust body of research is bolstering interest in tocotrienols, while consumer interest and formulation opportunities are poised to further expand the market.



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Taking the time to learn the other half of the vitamin E story can ultimately position your company to take a leadership position in a category ripe for growth. And knowing which tocotrienols have superior attributes and bioactivity in what amounts and combinations will permit you to create vitamin E formulations that can make a difference to consumers.

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# Poised for Greatness

**T**he development of this digital issue focused on tocotrienols (and the launch of our inaugural Post Conference Workshop on Tocotrienols at SupplySide West) is something that many of us have been working toward for a long time. As the body of science on tocotrienols has grown, it has become apparent that this form of vitamin E is ready to be the next big thing. Or as we have referred to it, The Next Big E.



So why do we think that? There are several factors that suggest tocotrienols should be high on your priority list for product development and commercialization. First, the global market for vitamin E surpassed the \$1 billion mark in 2012, with nearly one-third of that in the United States. This is in spite of the challenges vitamin E has faced in recent years following some studies questioning its safety. It is important to note the term “vitamin E” is generally used as a synonym for “alpha-tocopherol,” which is just one of eight forms of vitamin E that occur.

Second, the four tocotrienol forms have not been the common forms used in most products or most of the large-scale studies (including those raising safety questions). That said, there has been a big uptick in research around tocotrienols in recent years, with some very impressive results for a variety of health conditions. And while some of this evidence points toward drug/medical uses (impact following stroke, impact on certain cancers), there is clear benefit to ensuring adequate levels of these powerful nutrients for preservation of health.

Third, this growing body of science has begun to drive more attention from the media (Dr. Oz has already spoken highly of them), from the medical community (studies showing promise for many challenging conditions), and from regulators (there are increasing calls for the Food & Nutrition Board to expand its definition of vitamin E). This will result in greater awareness, acceptance and demand.

Finally, the potential for companies to differentiate their products by taking a lead in this area is upon us. As Alex Schauss writes, it is not easy to find products with tocotrienols in the retail sector. We look at this void as an opportunity.

As you read this digital issue and consider how tocotrienols might fit into your product development, formulation and go-to-market plans, please also consider joining us at our [Post-Conference Workshop on Tocotrienols](#) taking place at SupplySide West on Nov. 16 from 8:30 to 11:30 a.m. We have a great lineup of speakers to dive deeper into this topic.

Best regards,

Jon Benninger  
Vice President, Health & Nutrition Network  
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# Exploring the Robust Future for Tocotrienols

by Pete Croatto



**T**he market for vitamin E remains robust. According to Euromonitor International, worldwide sales of vitamin E (defined as the “fat-soluble vitamin used for the immune system and blood health”) rose from US\$964.6 million in 2008 to more than \$1 billion in 2012. Back in the United States, vitamin E sales were close to \$300 million in 2012.

In its “Nutritional Supplement/OTC/Rx Consumer Insight & Market Opportunity Report,” released in February 2012, the Natural Marketing Institute (NMI) ranked vitamin E seventh on its list of top used supplements: 14 percent of 2,355 U.S. adults polled claimed to take it.

And Americans can get their vitamin E in numerous ways—not just the traditional formats. According to Datamonitor’s Product Launch Analytics, the top 10 food and non-alcohol beverage categories in the United States featuring vitamin E as an ingredient from Jan. 1, 2012, to Aug. 15, 2013, were:



**1 Breakfast cereals**  
153 reports



**2 Juices**  
130 reports



**3 Functional drinks**  
(includes energy and sports drinks)  
91 reports



**4 Other savory snacks**  
78 reports



**5 Cookies**  
(sweet biscuits)  
70 reports



**6 Cereal bars**  
67 reports



**7 Milk**  
67 reports



**8 Fruit**  
67 reports



**9 Bread and rolls**  
51 reports



**10 Concentrates**  
(beverage concentrates)  
45 reports

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**SIMPLY. TOCOTRIENOL.**

that's it

What these data don't show is what kind of vitamin E consumers are purchasing: tocotrienols, tocopherols or a combination. And that might be a concern even if, "Alpha-tocopherol is found in most multivitamins and is supplemented in foods," according to Barrie Tan, Ph.D., founder of American River Nutrition.

However, vitamin E is more than just the alpha-tocopherol most commonly used in fortification. C.W. Fong, Ph.D., head of research and development (R&D) at Davos Life Science Pte. Ltd. based in Singapore, said despite research attempting to "unravel alpha-tocopherol's other effects," its main function in the body remains the same. He called it "a lipid-based, non-specific-chain-breaking antioxidant, mainly to protect polyunsaturated fatty acids from oxidative stress," based on current research.<sup>1</sup> He added tocotrienols have much to offer since "recent research indicates they confer additional benefits not provided by alpha-tocopherol." Studies, he added, show tocotrienols "have biological functions beyond acting as an antioxidant."

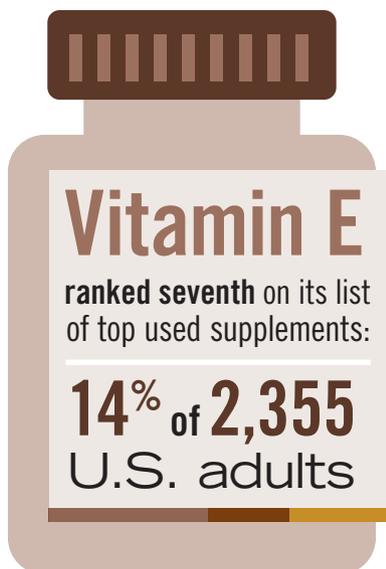
In other words, tocotrienols do not play the Jan Brady to tocopherols' Marcia Brady. "Tocotrienols have now stepped into the limelight of vitamin E research, and have proven to contain some exceptional benefits that are not shared by their 'older' tocopherol siblings," Tan said, adding that the availability of tocotrienol samples and standards has spurred research. "Today, the brightest spot for tocotrienol research is in cancer and CVD [cardiovascular disease]. Emergent fields of tocotrienol research

are promising, and include angiogenesis, bioavailability, bone health, gastric injury, inflammation, life extension, obesity, radiation protection, skin health, tocopherol interference and, recently, cognitive impairment."

Tocopherol interference? Tan cited several studies,<sup>2,3,4</sup> and said, "While alpha-tocopherol is found in most multivitamins and is supplemented in foods, a growing base of evidence suggests this popular vitamin E interferes with the uptake and function of tocotrienols," including interfering with tocotrienols' cardiovascular and cancer benefits.

Another consideration is the sourcing, as tocotrienols can be derived from rice, palm and annatto, among other sources. Further, the ratio of tocopherols and tocotrienols varies based on the source.

**Tocotrienols have now stepped into the limelight of vitamin E research, and have proven to contain some exceptional benefits that are not shared by their 'older' tocopherol siblings.**



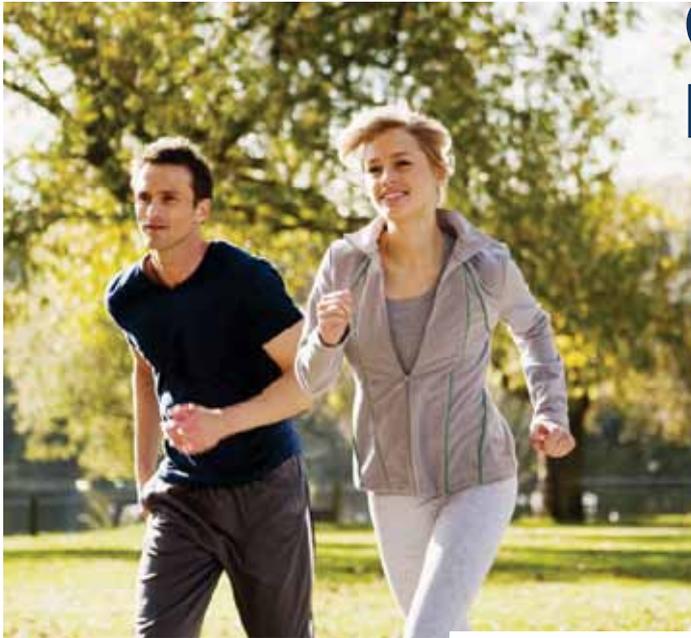
Source: Natural Marketing Institute (NMI)

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## Digging into a Young Body of Research

The supporting research is not being dragged from the dusty three-ring binders of yesteryear. According to Tan, more than half of the research on tocotrienols from the past 30 years has been published in the last five years.

“Most recently, tocotrienols have been indicated as beneficial interventions in inflammatory diseases,” Tan said. “In particular, delta-tocotrienol, in combination with antioxidant polyphenols, curb inflammation and manage dyslipidemia.”

The findings of this new trial were published in the *Journal of Clinical and Experimental Cardiology*.<sup>5</sup> Tan summarized: “The placebo-controlled study was conducted in two groups of elderly subjects, one with normal and the other with elevated lipid levels. The product formulation was composed of delta-tocotrienol from annatto, along with a B vitamin (niacin) and polyphenols. In both groups, supplementation led to a significant drop in C-reactive protein (CRP, a predictor for chronic inflammation) and  $\gamma$ -glutamyl-transferase (a predictor for non-fatal myocardial infarction and fatal coronary heart disease), while increasing total antioxidant status, a measure of the body’s capacity to counteract reactive oxygen species.”

There may also be benefits in bioavailability. Fong cited two studies<sup>6,7</sup> that found, compared to alpha-tocopherol, “tocotrienols are shown to have much higher cellular uptake of up to 70 times initial uptake in the first six hours and up to 20 times over time.”

In-house research at Davos Life Science, a leading manufacturer of palm tocotrienols, produced optimism. According to Fong, researchers “found much higher levels of tocotrienols than tocopherols in intracellular organelles.” That includes the nucleus and cytoplasm. Alpha-tocopherol, he observed, predominantly resides within the plasma membrane.

“The implication is that tocotrienols rather than tocopherols are more likely to be able to act on intracellular antioxidation, cell signaling pathways, regulation of gene expression, for example, in cellular inflammation, oxidative stress and metabolic processes,”<sup>8</sup> Fong said.

Not surprisingly, one doesn’t have to go far back to find promising research. A study from Sweden examining the relation of all plasma vitamin E forms and markers of vitamin E damage to mild cognitive impairment (MCI) and Alzheimer’s disease (AD) found low plasma tocopherols and tocotrienols levels are associated with increased odds of MCI and AD.<sup>9</sup> In another human study, a mix of supplementation including delta-tocotrienol reduced cardiovascular risk factors in humans over four weeks.<sup>10</sup>

There is also evolving research around tocotrienols and cancer prevention. A study in *Carcinogenesis*,<sup>11</sup> cited by Tan, concluded tocotrienols derived from the annatto plant helped prevent mammary tumor growth in mice. He stated: “The study found that

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supplementation with annatto tocotrienol delayed the development of mammary tumors. The research was performed in a HER-2/neu tumor model, an aggressive form of the disease found in 20 to 30 percent of metastatic breast cancers. The supplement was shown to delay mammary tumor development and reduced the number and size of tumors and lung metastases. The researchers believe that annatto tocotrienol's effect on the mammary tumor was due to its ability to create stress, cause death and growth arrest to the cancer cells."



## Alpha-tocotrienol

has been extensively studied for its ability to

**reduce brain  
DAMAGE**

**resulting from stroke.**



Another study,<sup>12</sup> published in *PLoS One*, investigating the effects of gamma-tocotrienol in human colon cancer SW620 cells, determined "gamma-tocotrienol induced a paraptosis-like cell death in SW620 cells characterized by a mass of cytoplasmic vacuoles formation, which may associate with the suppression of the Wnt signaling pathway."

The researchers also made the following observation, referencing a 2011 study<sup>13</sup>: "As one of the most important components of vitamin E, tocotrienols are the main bioactive components in palm oil, which not only has higher antioxidant potential, but also more other bioactivity than tocopherol, especially in the potent ability on killing cancer cells."

Ultimately, all four tocotrienol isomers have "unique and non-overlapping health benefits," Fong said, and should be considered for product development. He cited several human studies showing a mixture of tocotrienols could positively affect triglyceride and cholesterol levels, as well as markers of inflammation.<sup>14,15,16,17</sup>

What else?

"Alpha-tocotrienol has been extensively studied for its ability to reduce brain damage resulting from stroke," Fong added. "The gamma and delta isomers have clear anti-inflammatory and anti-cancer properties in various cell line and animal studies. A phase I study at Moffitt Cancer Center in Florida [recently] showed delta-tocotrienol supplied by Davos Life Science has good safety and efficacy against pancreatic cancer." He said the study should be published later this year.

It also appears that not all tocotrienols work the same in the body. "Most studies point to delta-tocotrienol and gamma-tocotrienol as most potent for the majority of applications (including cardiovascular and cellular health benefits)," Tan said. "An exception is alpha-tocotrienol, which has application[s] in trauma-induced stroke. Beta-tocotrienol is insignificant, and mostly absent as a significant natural source."

His conclusion: "The typical order of potency is delta-tocotrienol ≥ gamma-tocotrienol > alpha-tocotrienol >> beta-tocotrienol."

## Considerations for Manufacturers

Tocotrienols have plenty of promising research, but what can this form of vitamin E be used in?

Both Fong and Tan see tocotrienols in many cardiovascular health supplements. Fong also said he has seen skin care and broad-spectrum vitamin E supplements; Tan has seen cellular health products, with applications around heart health, blood sugar management, etc.

But there are certainly new areas to explore. “As more clinical studies based on tocotrienols are completed, it is envisioned that products targeted at brain, liver, gastrointestinal (GI) and cellular health will be incorporating tocotrienols either as their main or combination ingredient,” Fong said. “In addition, tocotrienols have distinct anti-inflammation properties over tocopherols, which opens up the market for conditions ranging from skin inflammation to rheumatoid arthritis.”

As far as applications, Tan said, “The main market is for dietary supplements, with growing market segments in functional foods and beverages, and cosmetics. Complementary adjuncts to tocotrienols include omega-3s, vitamin D, coenzyme Q10 (CoQ10) and inflammation-opposing combos with ingredients such as EGCG, curcumin, quercetin and resveratrol.”

Before that can happen, Fong said a few things must occur. “The key hurdle toward acceptance of the other forms of vitamin E—in particular by the U.S. Food & Nutrition Board (FNB)—just like the multiple forms of vitamins B, D and K, can be achieved jointly by a concerted effort by the scientists through more research and increased consumer awareness through education,” he said, noting tocopherols are currently the only form of vitamin E recognized by FNB. “The FNB, acknowledging uncertainties in their data on vitamin E, has called for research to identify other biomarkers for assessing vitamin E requirements.”

**The main market is for dietary supplements, with growing market segments in functional foods and beverages, and cosmetics.**

## Tocotrienols vs. Tocopherols: Who You Got?

Also potentially hindering market progress is that tocotrienols compare unfavorably to tocopherol in two areas—until you look closer.

“The cost of tocotrienols is about three to five times higher compared to natural alpha-tocopherol and mixed tocopherols,” Tan acknowledged. But, he said, it’s because of “the lower natural abundance of tocotrienols in plants plus the higher extraction cost needed to enrich it.”

When it comes to bioavailability, tocotrienols can also look shabby compared to tocopherols, Fong admitted. “In general, the oral bioavailability of tocotrienols is much



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lower versus alpha-tocopherol,” he said. “Most studies show a range of 5 to 30 percent bioavailability of alpha-tocopherol when absorbed through the GI tract. This is due to the low affinity by the alpha-tocopherol transport protein (aTTP) for the other isomers. The aTTP recovers alpha-tocopherol from the liver and recirculates to the plasma.”

The caveat is a point Fong made earlier: “Tocotrienols are absorbed by cells at a far higher rate than tocopherols, accumulate in the fatty tissues, and are able to penetrate the cell membranes into the sub-cellular levels.”

This concern can be alleviated without any R&D strain, Tan said. “Pre-solubilized forms of vitamin E for bioavailability enhancement contain added ingredients that are not natural and increase capsule size, which is even less desirable when used in formulations with other oils such as omega-3s or CoQ10,” he said. But he cited two recent studies<sup>19,20</sup> that may change the picture. “Bio-enhanced tocotrienol products claim two- to threefold increases in bioavailability in studies where supplements were taken on an empty stomach,” he said. “While this may be a useful application for those with malabsorption diseases, a study comparing tocotrienol absorption (non-enhanced) based on food status shows that when taken with a meal, natural tocotrienol absorbs two- to three-fold better than when taken on an empty stomach.”

In regards to dosage, Fong noted, “most clinical studies based on palm-derived tocotrienol rich fraction (TRF) and tocotrienol isomers indicate that at least 100 to 300 mg/d of palm vitamin E is needed to reduce triglyceride levels or cholesterol in hypercholesterolemic patients.”

Tan added, “As an antioxidant and for maintenance, 50 mg of tocotrienols per day are recommended, whereas 100 to 400 mg per day may be used for cardiovascular and cellular health benefits. In current cancer clinical studies, dosages ranging from 200 to 3,200 mg per day have been used without side effects.”

That said, Tan reiterated for vitamin E, claims can only be made for its antioxidant activity, not the bevy of benefits that have been researched.

For general supplementation, Fong recommended, “100 to 200 mg per day of tocotrienols, taken twice a day after meals. With palm source vitamin E, 100 mg per day of tocotrienols will also come with about 33 mg of alpha-tocopherol; the ratio of tocotrienols to tocopherol is 75 percent to 25 percent.”

### **Tocotrienol doses:**

- **50 mg/d** - antioxidant
- **100 to 400 mg/d** - heart and cellular health
- **200 to 3,200 mg/d** - used in cancer studies without side effects



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Ultimately, Fong said the goal isn't for there to be a clear-cut winner of this civil war. It comes down to people expanding their comfort zone regarding defining vitamin E.

“Scientific evidence increasingly shows the other natural forms of vitamin E besides alpha-tocopherol have benefits for human health and are not biologically irrelevant; and [this] will provide impetus for change and greater adoption of a mixed vitamin E supplementation,” he said. “However, more well-designed clinical studies are needed to prove the efficacy of these forms of vitamin E for specific health claims, and more effort is required by producers and the supplement industry to increase consumer awareness.”

Chris Schmidt, consumer health analyst for Euromonitor International, said vitamin E, in general, needs a bit of public relations help.

“Vitamin E has suffered from bad publicity in the United States lately, in part because of concerns over toxicity and overdosing, with it being linked to prostate cancer in a *JAMA* article<sup>21</sup> that got a lot of media attention a few years ago,” he said. “Additionally, compared to other popular single vitamins, consumers don't know it as well and don't associate it closely with a specific health outcome, like vitamin C and immunity. It's mostly touted as an antioxidant with anti-aging benefits, but it's not nearly as 'sexy' as superfruits that were the craze for the last few years or the new, Dr. Oz-ified supplements such as astaxanthin/zeaxanthin, etc.

“It also just doesn't get the volume of positive media coverage of vitamin D—immunity and bone health, and which most people think they can't get enough of naturally—or the B vitamins, which have benefitted enormously from the craze for 'natural energy,’” Schmidt concluded

But Fong did point to some good news: “Recently, the Dr. Oz Show highlighted the health benefits of tocotrienols found in red palm oil.”

Now if Dr. Oz could plant a bug in Oprah's ear, tocotrienols would be in business. □

*[Pete Croatto](#) is the manager of VIRGO's Supplement Perspectives. Previously the associate editor at Nutrition Industry Executive, he has written about and for the natural products industry since 2003. His writing has also appeared in The New York Times, Grantland, Philadelphia, Publishers Weekly and The Christian Science Monitor.*

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# Tocotrienols: The Forgotten Vital Bioactive Component of ‘Vitamin E’

by Alexander G. Schauss, Ph.D., FACN, CFS

**A**nyone educated reader knows what vitamin E is. Right? Well, maybe. Most folks would know the term “tocopherols” refers to vitamin E; however, many wouldn’t connect the term “tocotrienols” with vitamin E.

In actuality, vitamin E consists of eight isomers, four tocopherols and four tocotrienols. For various reasons, going back decades, the term “vitamin E” has become synonymous with tocopherols, particularly alpha-tocopherol. Fortunately, most supplements today contain natural alpha-tocopherol (d-alpha-tocopherol; RRR-alpha-tocopherol) rather than the synthetic form (dl-alpha-tocopherol; all-rac-alpha-tocopherol), which are actually seven stereoisomers, because the synthetic isomers do not appear in nature, while only one isomer in synthetic vitamin E is natural (or bio-identical to what would be found in nature).

Obviously, there are differences between natural and synthetic vitamin E, and many producers of natural alpha-tocopherol supplements would promote them as containing “natural vitamin E.” But what does this really mean, when tocotrienols are taken into account? The term “natural vitamin E” should imply that all eight isomers of vitamin E are present in the product.

But perhaps there is a benefit to isolating the tocotrienols, as new research is suggesting the full combination might actually dampen the bioactivity and benefits of some of the most active isomers.

## Understanding the Attributes and Properties of Tocotrienols

Tocopherols and tocotrienols are subgroups of the vitamin E family. Each of the four isomers within each subgroup is designated by the Greek symbols alpha,

## Vitamin E

consists of

### Eight Isomers



### Four Tocopherols



### Four Tocotrienols



beta, gamma and delta, of which alpha-tocopherol is the best known by far. By comparison, tocotrienols are virtually unknown.

The lack of knowledge at the retail level is telling. During my travels in the past year, I stopped in to numerous health food stores and asked the sales clerks for any tocotrienol products they might have. Often what I got was a blank stare. My follow-up request for a specific product, such as annatto seed delta-tocotrienols or palm oil-derived tocopherol/tocotrienol mixtures, was often met by a simple “no” or, after a quick inventory check, “no.”

However, some clerks wanted to know more. In one store in the Seattle area, we discussed that although tocopherols have been shown to have cholesterol-lowering ability, clinical studies had demonstrated that tocopherols had nowhere near the beneficial effects reported for a specific ratio of gamma- and delta-tocotrienols taken together.



**The differences between the two subgroups of vitamin E gets even much more interesting when one studies the literature.**

The differences between the two subgroups of vitamin E gets even much more interesting when one studies the literature.

Alpha-tocopherol has been shown to: interfere with tocotrienol’s ability to reduce cholesterol levels; interfere with inhibiting the formation of cancer cells; and block absorption of tocotrienols. This is not to say that tocopherols don’t offer cardiovascular benefits. What is important is to look a whether a supplement formulation considers the research.

Does the supplement reflect an understanding of how the isomers of vitamin E interact? Does it understand the impact of including tocopherols if the intent of the formulation is to prevent the adherence of circulating monocytes to the endothelium, or the “Velcro effect” that leads to plaque formation, which is the first step in atherogenesis? Would the formulation use a higher amount of gamma- or delta-tocotrienol to lower blood pressure, improve total antioxidant status, and reduce formation of plasma/blood lipid peroxides? While alpha-tocopherol has no effect on reducing the risk of atheroma formation associated with carotid atherosclerosis and/or stenosis, which tocotrienols would have a preventive benefit?



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If a formulation is directed toward metabolic syndrome, which includes hyperglycemia and diabetes, commonly associated with obesity, which tocotrienol is optimal? Which three of the four tocotrienols increases the ability of the immune system to fight the inflammatory response inherent in responding to pathogenic organisms? Does the formulation include those tocotrienols that have been shown to be a cholesterol reducer while increasing levels of coenzyme Q10 (CoQ10) by up to 20 percent?

If you are a product formulator, do you know the ratio of the various tocopherols and tocotrienols from different food sources? Which ones are most active or actually antagonistic to the intended benefit? What is the difference between palm, rice and annatto seed sources of tocopherols and tocotrienols? And why does it make a difference knowing which one to use in a supplement?

Why have government agencies around the world been studying tocotrienols? Were you aware of the research on specific tocotrienols as effective radioactive countermeasure agents?

Taking the time to learn the other half of the vitamin E story can ultimately position your company to take a leadership position in a category ripe for growth. And knowing which tocotrienols have superior attributes and bioactivity in what amounts and combinations will permit you to create vitamin E formulations that can make a difference to consumers. □

**Do you know  
the ratio of  
the various  
tocopherols and  
tocotrienols  
from different  
food sources?**

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