FORUM

Safety of Vitamins and Minerals: Controversies and Perspective

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Available information suggests that currently over 47% of males and 59% of females use dietary supplements for health benefits, and the number of users is rapidly increasing. However, numerous studies published over more than a decade have linked some supplements (including vitamins E, C, D, A, and B, as well as selenium) to no health benefits or even to adverse health effects. Recent studies with negative results, which drew media attention, include the following: a 2008 study on the ability of vitamin E and selenium to lower the risk of prostate cancer was halted amidst fear of potential harm; vitamin C may do more harm than good as it may protect cancer cells; intake of vitamins E and C by 15,000 male physicians for 10 years had no health benefits. In contrast, there are compelling cause and effect data linking the use of folic acid with consistent and significant reductions in fetal adverse pregnancy outcomes, demonstrating no beneficial effects of calcium and vitamin D supplements in improving bone strength and reducing fractures. These equivocal and conflicting findings on the effects of supplements on health outcomes have left consumers confused about their benefits and wary of the possible adverse effects of vitamin and mineral supplementation. The objectives of this session are to characterize the current state of the science as it relates to the impact of vitamin and mineral supplementation on human health, review the statutory and regulatory perspective of vitamin use from a safety perspective, assess the credibility of meta-analysis in the safety assessment of vitamins, and elicit the mechanisms of these interactions—pro-oxidant versus antioxidant effects and beneficial versus adverse effects.

Key Words: antioxidants; safety; vitamins; minerals; supplements; toxicity.

Introduction and Overview (M. G. Soni)

This paper summarizes a roundtable discussion held at the 2010 Annual Meeting of the Society of Toxicology (SOT) organized by the SOT Food Safety Specialty Section and endorsed by the Carcinogenesis Specialty Section, Regulatory and Safety Evaluation Specialty Section, and the Risk Assessment Specialty Section.

An association between diets containing fruits and vegetables and health has been noted since Hippocrates (460–377 BC)—and in fact long before (Bjelakovic and Gluud, 2007). It has been known for a long time that a diet that includes fruits and vegetables contains vitamins, minerals, and other bioactive nutrients. In recent years, we have isolated, purified, and by various manufacturing techniques made these vitamins, minerals, and other bioactive compounds available in the form of dietary supplements. This has resulted in a high rate of supplement use. Approximately 47% of males and 59% of females in the United States regularly take dietary supplements, and the supplements industry generates around $53 billion in sales annually. Given such high supplement consumption, we are starting to see reports indicating that there might be some dangers associated with such levels of use. Two examples of these reports include the following: a meta-analysis of 67 randomized controlled trials that showed that vitamin E, vitamin A, and beta-carotene supplements may be associated with an increased incidence of mortality (Bjelakovic et al., 2008) and the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Trial (ATBC Cancer Prevention Study Group, 1994) found higher incidence (18%) of lung cancer and all-cause mortality (8%) among the men who received beta-carotene than among those who did not. In 2008, a large randomized controlled trial (SELECT) was halted after reporting that vitamin E and selenium resulted in an increase in incidence of prostate cancer (Lippman et al., 2009). The Physician Health Study (Gaziano et al., 2009) illustrated that vitamin C showed neither health benefits nor safety issues, and (Combs, 2008) reported that increased vitamin C intake had adverse effects, e.g., kidney stones and iron-related disorders. In contrast to studies that indicate possible adverse effects...
to the FDA 75 days prior to introducing the supplement into interstate commerce. The NDI must contain information that demonstrates that the supplement is chemically pure and safe. Generally, the notification must include information that is the basis on which manufacturers/distributors have concluded that a dietary supplement containing a NDI will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling. Any claims made by a company for such supplements must be substantiated by adequate evidence showing that they are not false or misleading. It is the company that is responsible for the safety, quality, and labeling of their products. Starting in 2007, the FDA began phasing in current good manufacturing practices for producing dietary supplements. (http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm110858.htm).

Although the FDA cannot assure the premarket safety of dietary supplements, it does conduct postmarket surveillance or monitoring through the CFSAN Adverse Event Reporting System, the FDA Med Watch Program, and collaboration with the Centers for Disease Control and Prevention (CDC) and poison control centers, as well as through the use of advanced data mining software.

Second, the FDA also regulates vitamin and mineral supplements as direct food additives (e.g., vitamin D supplementation of orange juice) through the food additive petition (FAP) route. The manufacturer must submit complete chemistry and safety information for their product, which undergo a thorough assessment by FDA review scientists. If a product is not generally recognized as safe (GRAS), then an FAP may be required, e.g., vitamin D is usually considered GRAS at established levels when it is added to cereals, milk and milk products, infant formulas, and margarine; however, it is not considered GRAS when it is added to orange juice.

The 2000 National Health and Nutrition Examination Survey (NHANES, 2000) found that a third of the population took some form of vitamin or mineral supplement in the previous month. A study of children and adolescents, conducted from 1994 to 2000, also showed that a third took a dietary supplement in the previous month. It should be noted that both studies probably underestimate their use because of under-reporting by the participants.

There is substantial evidence (Berdanier and Zempleni, 2009) demonstrating that the use of vitamin and mineral supplements can be beneficial, such as vitamin D and calcium can increase bone density in postmenopausal women, multivitamin supplements may be beneficial for human immunodeficiency virus and acquired immune deficiency syndrome patients, and taking multivitamins may reduce birth defects beyond that found for the use of folic acid by women of childbearing age. Many people take a supplement, and many consume food that is enriched with vitamins and minerals. As noted previously, supplements are not essential for those consuming a healthy diet, and there is the possibility of over

Are Vitamins and Minerals Used for Prevention or Treatment? Statutory and Regulatory Perspective (T. S. Thurmond)

Vitamins and minerals are nutrients required by the body for normal growth and maintenance. Examples of these include the vitamin B complex, A, D, K, E, magnesium, and calcium. Vitamin and mineral supplements can complement a regular diet but are not meant to be food substitutes because they cannot replicate all the nutrients in whole foods. Unfortunately, not all segments of the public are fully aware of the difference between foods and supplements. First, the regulation of dietary supplements within the Food and Drug Administration (FDA) is accomplished in two ways. The vitamins and minerals used as dietary supplements are regulated under the Dietary Supplement Health and Education Act (DSHEA) passed in 1994 (DSHEA, 1994). The FDA Center for Food Safety and Applied Nutrition (CFSAN) for Food Science is responsible for implementing DSHEA through its Office of Nutrition, Labeling, and Dietary Supplements. DSHEA places dietary supplements under a special category under foods, not drugs, and requires that they are labeled as dietary supplements. The disclaimer required by FDA is that claims have not been evaluated or endorsed by FDA. Dietary ingredients and new dietary ingredients (NDI) are considered components of dietary supplements as defined by DSHEA. In order to be a dietary supplement ingredient, a substance must have one or a combination of the following: vitamin or mineral, herb, botanical, biological, amino acid, a dietary substance used to supplement the diet by increasing the total dietary intake, e.g., enzymes or tissues, a concentrate, metabolite, constituent, or extract. To be considered as an NDI, it must meet the previous definition and not have been sold in the United States prior to 15 October 1994. In addition, an NDI notice must be submitted to the FDA 75 days prior to introducing the supplement into interstate commerce. The NDI must contain information that demonstrates that the supplement is chemically pure and safe. Generally, the notification must include information that is the basis on which manufacturers/distributors have concluded that a dietary supplement containing a NDI will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling. Any claims made by a company for such supplements must be substantiated by adequate evidence showing that they are not false or misleading. It is the company that is responsible for the safety, quality, and labeling of their products. Starting in 2007, the FDA began phasing in current good manufacturing practices for producing dietary supplements. (http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm110858.htm).

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supplementation. There is little evidence that supplements are useful for the treatment of common cancers, cardiovascular disease (CVD), or total mortality in postmenopausal women. There is, however, evidence that vitamin supplementation may enhance cancer cell survival in those undergoing cancer treatment (Kristal and Lippman, 2009) and that supplementation with very high doses of beta-carotene and vitamin A may increase the risk of CVD in female smokers (Omenn et al., 1996).

The FDA does not ensure premarket safety of all multivitamin supplements, although there is a common public misconception that it does evaluate their safety prior to being marketed. In the paraphrased words of Paracelsus, dose makes the poison, which is true for all substances including vitamins and minerals. For example, there are dose-related acute toxicity issues with vitamin A at 25,000 international units (IU) per kilogram of body weight (Berdanier and Zempleni, 2009). Symptoms of this severe acute toxicity can include headache, phobia and anoxia, skin-related lesions (exfoliation), problems of long bones (osteoporosis), and problems with closure of long bones in children. For vitamin D, the dose for acute toxicity has not been established; however, chronic toxicity has been demonstrated at 50,000 IU/day for adults (Hathcock et al., 2000). Toxicity may be manifested by hypercalcemia, muscle weakness, headache, and nausea. Longer term use may also produce constipation, cramps, polyuria, and polydipsia.

For vitamin C, no acute toxic dose has been established but chronic toxicity can occur in those with hereditary glucose-6-phosphate dehydrogenase deficiency given doses of 2 g/day; problems include kidney stones, diarrhea, nausea, and red blood hemolysis (Berdanier and Zempleni, 2009). There is also the possibility of dental decalcification and rebound scurvy in infants born to women consuming large concentrations of vitamin C and estrogen changes in women. Although calcium is essential, massive doses can promote atherosclerosis and other related problems. Acute high doses of iron can cause problems in iron storage in individuals with the genetic disease of hemachromatosis. Chronic massive (higher concentration than the Dietary Reference Intake) doses of iron in those genetically affected can cause iron being deposited in various internal organs. Other common symptoms of iron-related toxicity include hepatomegaly, skin pigmentation, joint diseases, and lethargy (Berdanier and Zempleni, 2009).

Although consumption of vitamin and mineral supplements is generally safe in moderation, in 2008, over 69,000 calls were made to poison control centers for toxicity complaints relating to acute overdosing with vitamin or mineral supplements (Poison Control Centers). Toxicity because of vitamin and mineral supplement ranked 15th among all the substances reported to poison control and seventh among all pediatric substances. Fortunately, no deaths were attributed to overdosing.

Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality (E. R. Miller)

The findings of the meta-analysis of vitamin E supplementation and mortality were published in 2005 (Miller et al., 2005). There have been numerous reports supporting the beneficial effects of vitamin E in CVDs. Vitamin E is a lipid soluble vitamin, which has been known to protect lipids from free-radical damage. This is relevant to atherosclerosis and CVD, as Steinberg in 1989 put forward the “oxidation modification hypothesis of atherosclerosis” whereby the oxidation of low-density lipoproteins (LDL) cholesterol was proposed as an obligatory step in the formation of atherosclerotic plaques and that vitamin E and other dietary antioxidants protect against oxidative damage of lipids (Parthasarathy et al., 1989). In their model of atherosclerosis, circulating LDL crosses the endothelium layer, where oxidation by free-radical activity forms oxidized LDL. Oxidized LDL is picked up by receptors on macrophages and is accumulated in the intimal layer of arteries. According to the Steinberg model, LDL oxidation is obligatory for initiation of the early phase of atherosclerosis, and dietary antioxidants can prevent such damage. In vitro studies using isolated human LDL cholesterol show that antioxidants, such as beta-carotene and vitamin E supplementation, prevent the oxidation of LDL, as illustrated by indices, such as resultant decreased formation of conjugated dienes or malondialdehyde. In addition, studies from our laboratory whereby subjects were supplemented with vitamin E, vitamin C, or both, for 2 months, resulted in reduced concentrations of urinary isoprostanes, which are markers of oxidative damage of arachidonic acid. These studies in total indicate, in principal, that supplementation in laboratory-based studies, with vitamin E for 2 months, can decrease oxidative stress. Going from laboratory-based studies to human epidemiological-based studies, it has been shown in multiple studies that there is a strong inverse association between serum or dietary intake of vitamin E and risk for atherosclerosis. The Nurse’s Health Study is an example of an observation study (i.e., no intervention), published in the early 1990’s, reported that the upper age quartile of nurses followed for 5 years had a 34% reduction in CVDs in those reported to be taking vitamin E supplements (Stampfer et al., 1993). Although such studies do not show cause and effect, they did provide strong justification for randomized trials. Subsequently, there have been numerous randomized trials completed, including hundreds of thousands of individuals. Thus, in total, this provided the incentive for 2005 meta-analysis. The inclusion criteria for meta-analysis was a randomized trial design, inclusion of a placebo group, more than 10 deaths in the trial, and a follow-up for more than 1 year; a dose-response analysis, as well. There were 19 randomized trials that included over 136,000 people and 12,500 deaths. Doses ranged between 17 and 2000 IU/day. Typical intake for vitamin E from food is 10 IU per day. Average age was 64 years, and the median length of follow-up was 4 years. Overall, there were more deaths in the vitamin E supplement group compared
with the placebo group. Conclusions of the meta-analysis are that there is a significant increase in mortality in participants in those trials that used high-dose vitamin E (> 400 IU/day). At low doses of vitamin E and related to populations with vitamin E deficiency, vitamin E was associated with lower mortality.

Based on current research findings, suggested reasons for increased mortality with high vitamin E supplementation include the following: pro-oxidant effects at high doses, displacement of other important antioxidants, vitamin E interference with essential defense mechanisms, such as apoptosis, damage to essential lipids, and competition for absorption of other essential compounds. Possible explanations for a lack of benefit of vitamin E are that natural vitamin E may be more important, need for studying combination of antioxidants, and perhaps the duration of trials are too short.

Subsequently, the results from several additional trials have been published and have evaluated the consistency of new, independent evidence with findings. The high risk for CVD (HOPE-TOO, 2005) trial included 7000 people, and follow-up of 7 years found a relative risk of mortality of 1.02 or 2% higher risk for the vitamin E–supplemented group compared with placebo controls (Lonn et al., 2005). The Women’s Health study (2005) included 40,000 women with follow-up of 10 years and found that the relative risk was 1.03 or 3% higher risk of mortality compared with the placebo group. A cancer prevention trial, which looked at the recurrence of cancers in those who had a history of cancer, reported that the death rate was 30% higher in those assigned to vitamin E, vitamin C supplementation, and follow-up for 6.5 years (Bairati et al., 2006). The Women’s Antioxidant Cardiovascular Study (Cook et al., 2007; WACS, 2007), a secondary prevention trial where women had a higher rate of CVD, reported a relative risk of mortality of 1.02 or 2% higher risk in the vitamin E–supplemented group. In the Prevention of Progression of Arterial Disease and Diabetes (Belch et al., 2008) trial, the relative risk for the group provided with vitamin E was 1.43 for 6.7 years or a 43% increased risk of death. The pooled relative risk, 1.09 (0.99–1.20) for these new trials, was consistent with findings in the original meta-analysis results for high-dose trials (pooled relative risk for mortality of 1.04; confidence interval 1.01–1.07, p = 0.035) for those assigned to vitamin E versus those using a placebo.

Based on recent CDC data, as people age, there is a tendency for increased use of vitamin E by the general population. However, there is no evidence from randomized trials that high dose vitamin E supplementation is beneficial; in fact, numerous long-term clinical trials and the meta-analysis report the opposite that there is an increased risk of mortality with higher doses.

Beta-Carotene Supplementation: Example of when Lifestyle Habits Can Increase Risk Factors (T. Spriggs and A. Bendich)

The objectives of this review were to present some basic information on beta-carotene, clinical data from beta-carotene trials, examples where lifestyle habits appear to increase risk factors, and highlight the paradox, i.e., supplements of beta-carotene should be useful. Beta-carotene is one of a variety of some 100 carotenoid compounds found in richly colored fruits and vegetables. Beta-carotene and four other carotenoids are classified as pro-vitamin A carotenoids. In theory, beta-carotene can be metabolically cleaved into two molecules of vitamin A (Bendich, 2004). The typical American diet will provide between 1 and 3 mg/day beta-carotene. If people are prudent in their consumption of five or more fruits and/or vegetables per day, they can obtain 3–6 or even 8 mg/day. Beneficial examples of beta-carotene functions include antioxidant properties and specific immune cell functions, such as increasing natural killer cell activity. Beta-carotene is also associated with improved physiological functions, such as enhanced lung function (Krinsky and Johnson, 2005). Beta-carotene was also an approved drug. Solatene was sold by Hoffman-LaRoche for use in an inherited disease of photosensitivity, erythropoetic protoporphyria. Preclinical toxicity studies in rodents show that consumption of this compound at high doses up to 100 mg/day over a lifetime is not mutagenic, carcinogenic, or a reproductive toxicant (Bendich, 1988). Epidemiological data have shown that in diets rich in beta-carotene, there is decreased incidence of cancer compared with those with normal diets. When people have less beta-carotene in their blood, there is an increased incidence of cancer. Additionally, smokers have consistently low serum levels of beta-carotene. Thus, based on these data, it has been suggested that beta-carotene should be helpful in preventing cancer.

ATBC Cancer Prevention Study Group (1994) was a randomized placebo control study of approximately 30,000 male subjects of age 50–69 years who were heavy smokers. There were four treatment groups: 50 mg vitamin E alone, 20 mg of beta-carotene alone, combination of the two, and a placebo group. Subjects received their respective treatment for 5–8 years. The results were that those who were treated with beta-carotene had an increased incidence of lung cancer (16–18%) and increased rate of mortality by 8% (ATBC Cancer Prevention Study Group, 1994). In addition, the Beta-Carotene and Retinol Efficacy Trial (CARET) study, another randomized placebo control study, included smokers and former smokers who were exposed to asbestos (Omenn et al., 1996). These subjects received 20 mg of beta-carotene in combination with 25,000 IU of retinol (vitamin A) for an average of 5 years. There was a 28% increased incidence in lung cancer versus placebo, increase in overall mortality of 17% versus placebo, and an increase in CVD mortality of 26% versus placebo. The CARET trial was stopped when the ATBC trial results were reported.

In contrast to the ATBC and CARET studies, the Women’s Health Study, conducted in approximately 20,000 subjects who received 50 mg of beta-carotene every other day for 2 years (or a placebo), did not demonstrate a negative effect of beta-carotene supplementation (Lee et al., 1999). There was no
significant increase in incidence of cancer, CVD, or total mortality. Of the 13% of subjects who were smokers, there was no difference in number of cancers or CVD. In support of the findings of the Women’s Health Study, a 12-year trial was conducted with approximately 22,000 male physicians, where intake of 50 mg beta-carotene on alternate days had no impact on incidence of cancer or total mortality, regardless if they were smokers or not (Hennekens et al., 1996).

Furthermore, an intervention study conducted in Linxian, China, where there is a high incidence than normal of esophageal cancers, demonstrated a decrease in mortality in subjects who received 15 mg of beta-carotene plus 30 mg of vitamin E and 50 μg of selenium for 4–5 years (Blot et al., 1996). Whereas it has been suggested that a possible adverse effect of high levels of beta-carotene was on blood concentrations of vitamin E, Nierenberg et al. (1997) demonstrated no impact on serum concentrations of either vitamin E or other carotenoids following supplemental intake of 25 mg/day for 4 years.

Primary prevention lung cancer clinical trials demonstrate a potential risk of increased lung cancer and overall mortality associated with beta-carotene supplementation for smokers or individuals exposed to asbestos. It is possible that treatment with beta-carotene in those studies was not long enough to show lung cancer prevention in high-risk people. The paradox is that whereas many dietary intake studies have shown an association of increased intake of beta-carotene with decreased risk of lung cancer, intervention studies with high-dose beta-carotene supplementation have shown an increased risk of lung cancer in smokers and workers exposed to asbestos. Further research is needed to define the biologically plausible explanation for the possible association between beta-carotene supplementation and increase in lung cancer rates in individuals at high risk for lung cancer.

Supplements: Pro-oxidant versus Antioxidant Effects or Beneficial versus Adverse Effects (S. T. Omaye)

Sixteen years have elapsed since investigators reported the results from the ATBC Cancer Prevention Trial study (Heinonen and Albanes, 1994). Their findings that supplements of beta-carotene increased lung tumors in smokers surprised many. The predominant thinking of the time was that nutrient antioxidants should be beneficial, particularly to those who are being exposed to a variety of oxidants. Perhaps, this was less of a surprise to toxicologists, likely because of “Paracelsus” and the guiding principal of “dose makes the poison.” These, as well as other studies dealing with antioxidants, aroused widespread scientific debate and raised the suspicion that antioxidants may even have adverse effects when taken inappropriately or excessive amount. In an attempt to provide some science-based understanding to this apparent paradox, a symposium was presented at the 36th Annual Meeting for the Toxicology Society (Omaye et al., 1997). Potential mecha-
Experiments with cell-free systems, isolated membrane systems, and underculture conditions indicate that, in the presence of transition metals, ascorbic acid can readily switch from an antioxidant to a pro-oxidant. The concentrations at which this occurs will depend on the concentrations of metal and ascorbic acid in the solution. Potentially, in low ascorbate situations, this could lead to superoxide and other ROS generation. High concentration of transition metals will bind up with protein (Halliwell and Gutteridge, 1989). There are usually no free transition elements because of being bound up with protein (Halliwell and Gutteridge, 1989).

Patients with iron overload and healthy people of Northern Africa often have abnormal low contents of ascorbic acid in blood and tissues. Feeding them with ascorbate in the absence of desferrioxamine can produce deleterious and lethal consequences. It is estimated that 10% of non-African background and up to 30% of African heritage have a gene disorder for iron overload (hemochromatosis), where the iron may be available unbound either to transferrin or ferritin, thus exerting adverse catalytic reactions. Thalassemic patients with conditions of iron overload have died after ingestion of high vitamin C (Herbert et al., 1996). Food scientists have known about the potential for vitamin E compounds to act as pro-oxidants. Oxidation of food vegetable oils can occur when the vitamin content becomes greater than 2000 ppm (Peers and Coxon, 1983; Terao and Matsushita, 1986). This can be accelerated by the presence of metal ions or pigments containing metal ions and high vitamin E (Kamal-Eldin and Appelqvist, 1996). In suspension of LDL isolated from human blood, vitamin E can accelerate the peroxidation of polyunsaturated fatty acids. LDL oxidation is most likely initiated by various attacking aqueous radicals, and vitamin E residing at or near the surface of the membranes would form vitamin E radicals. The antioxidant effects may well be controlled by various antioxidants working in concert. It has been described as aqueous antioxidants exerting antioxidant action in aqueous phase and lipid antioxidants working in lipid materials. This is what Stocker and Keaney (2004) have referred to as “co-antioxidants,” illustrated in Figure 1. Interactions between various antioxidants would be expected to occur based on the order of reactivity of their oxidation-reduction potentials (Omaye et al., 1996). Several phenolic antioxidants can accelerate oxidative damage of macromolecules, such as, protein, carbohydrates, and DNA (Aruoma et al., 1993), and accelerate LDL oxidation (Bonet et al., 1996). However, mixtures of polyphenol compounds displayed antioxidant effects compared with their respective individual compounds, which displayed either antioxidant or pro-oxidant effects when loaded into human LDL suspensions. Such results were consistent with coantioxidants of various polyphenols (Cirico and Omaye, 2005).

Other antioxidant compounds can be demonstrated to exert pro-oxidant effects. There is evidence that lipidic acid and dihydrolipoic acid can exert pro-oxidant properties in vitro. Dihydrolipoic acid accelerated iron-dependent hydroxyl radical generation and lipid peroxidation in liposomes, probably by reducing Fe$^{3+}$ to Fe$^{2+}$, and it increased the loss of creatine kinase activity in human plasma exposed to gas phase cigarette smoke. These compounds also promote mitochondrial permeability transition in permeabilized hepatocytes and isolated rat liver mitochondria. Likewise, coenzyme Q is involved in superoxide production by the respiratory chain by the ubisemiquinone radical (James et al., 2004).

Whether subcellular environments favor the production of antioxidant or pro-oxidant species of such compounds could have profound effects on the diseases driven by such processes. It is imperative that we develop a better understanding of such reactions so that such disease is managed with better predictive efficacy. Interactions between antioxidants are expected and do occur in many biological systems.

It is unlikely that a single food component from the many hundreds that make up one’s diet will be the answer to any disease. Given its dynamic nature, we would postulate that no single constituent of antioxidant defense network would be able to produce a maximum possible reduction of adverse oxidative stress situations. Another consideration that we should make is in all nutrient interventions, new dose-response data must be generated when an antioxidant is used in combination with other antioxidants. Also, it behooves us...
when embarking on further studies to consider the growing confounding factors of polypharmacy and potential confounding factors of drug-nutrient interactions. Thus, as has been noted by health and nutrition scientists, variety, moderation, and balance are the pillars of nutrient intake. Imbalance of nutrients, which likely occurs for antioxidant supplements, may lead to subcellular discord.

ROUNDTABLE DISCUSSION AND CONCLUSIONS

It is clear that scientists must apply the very best science in characterizing the safety of vitamin and mineral supplements. For the past few decades, the consumer has experimented with a variety of these substances for a multitude of reasons, e.g., protection, prevention, longevity, and therapy. Early research suggested that because of demonstrated health benefits of fruits and vegetables, specific nutrients from such sources should be as useful as nutritional supplements. Regulation of dietary supplements within the FDA is under the DSHEA passed in 1994 (DSHEA, 1994). Coincidently, in that same year, the ATBC Cancer Prevention Trial reported a higher incidence of lung cancer in heavy smokers in the beta-carotene arm of the study. More recently, the potential for adverse effects, including death, has been further demonstrated in many studies, and there is a strong suggestion that contributing lifestyle/environmental factors, such as smoking and exposure to asbestos, other oxidants, and carcinogens, may accentuate adverse outcomes. The typical consumer perspective is that supplements are safe at any dose; however, these individuals are either unaware of or fail to take into consideration the basic premise of toxicology whereby dose makes the poison. As our science base continues to make strides toward determining the mechanism of action for these substances, we will be better able to extrapolate to provide effective regulation to insure more safety for the consumer.

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