

RISKY DIETARY SUPPLEMENTS

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KEY POINTS

- Dietary supplements-unlike medicines and other drugs-do not undergo rigorous testing and screening for efficacy and safety.
- Some products sold as dietary supplements, especially those containing ephedrine, are associated with serious-and sometimes deadly-adverse side effects. Additional risky supplements include androstenedione and other “prohormone” precursors to testosterone, yohimbine, and products that contain kava.
- Even supplements like vitamins, caffeine, creatine, and protein powders that are safe when taken in recommended doses could be harmful if taken in large doses for a long time.
- Dietary supplements may contain substances not shown on the package label that may be harmful or can lead to a positive doping test in sport competitions.
- How do you know if a product is safe? You don’t. However, vitamin and mineral supplements labeled USP (United States Pharmacopoeia) have passed tests for dissolution, disintegration, potency, and purity. In addition, nationally known food and drug manufacturers generally make supplements under the strict quality control procedures they already have in place. Finally, Supplement Watch (www.supplementwatch.com) and Consumer Lab (www.consumerlab.com) provide independent test results and information to help people evaluate and select dietary supplements.

INTRODUCTION

Millions of people rely on dietary supplements for everything from enhancing their sex lives to improving their athletic performances. There is essentially no systematic regulation of the dietary supplement industry, so there is no guarantee that a given supplement will live up to its claims. More important, there is no guarantee that any supplement is safe. We asked a panel of experts to discuss the relative safety of dietary supplements. Each of these

experts, Priscilla Clarkson, Ellen Coleman, and Christine Rosenbloom, has authored numerous publications and given many public presentations on various sports nutrition topics - including dietary supplements. Their comments should be carefully weighed by athletes and non-athletes alike who may be considering the use of a dietary supplement.

Which dietary supplements do you think have the most potential for harm? What is the evidence that each of them might be potentially dangerous?

Coleman: I think the riskiest of the popular supplements are herbs that contain ephedrine, e.g., Ma Huang (Chinese Ephedra, Ephedra Sinica), Mormon Tea, and Sida Cordifolia. Ephedrine is structurally similar to the amphetamines and increases heart rate and blood pressure. The adverse effects of ephedrine range from heart attack, stroke, seizures, psychosis and death to less serious but nevertheless worrisome effects such as dizziness, headache, tremor, nervousness, gastrointestinal distress, irregular heartbeat, and heart palpitations. In susceptible persons, serious adverse effects can occur with low doses. Combining caffeine (from coffee, Guarana, or Kola nut) with ephedrine-containing products, e.g., the “ephedrine-caffeine-aspirin (ECA) stack,” greatly increases the potential for adverse effects of ephedrine. Two years ago Haller and Benowitz reviewed records from 140 ephedra users who experienced complications (heart attack, stroke, seizure, and death) between 1997 and 1999. The researchers found that one-third of the patients’ complications were “definitely or probably” caused by ephedra use and another third of the problems were “possibly” caused by ephedra. They noted that most of the people studied were healthy young people, some of whom had been taking ephedra for only a few days. The National Collegiate Athletic Association (NCAA), the International Olympic Committee (IOC), and the National Football League (NFL) have banned the use of ephedrine.

Androstenedione is another risky supplement. It is a “prohormone” steroid that can be converted to testosterone and is marketed as a supplement that can increase muscle mass and strength. But these effects were not confirmed in a study by King and col-

leagues, who evaluated the effects of androstenedione supplementation (300 mg/day) in untrained men during eight weeks of resistance training. There were no differences in serum testosterone, muscle size and strength, or body composition between the androstenedione and placebo group. However, the androstenedione group had decreases in HDL cholesterol and increases in serum estrogen levels, which may have adverse health consequences during long-term supplementation. The NCAA, IOC, and NFL all ban androstenedione.

Yohimbine, another risky supplement, is extracted from yohimbe bark. It supposedly increases serum testosterone levels (thereby increasing muscle mass), decreases body fat, and serves as an aphrodisiac; none of these effects has yet been substantiated. Reported side effects from yohimbe use include minor complaints such as headaches, anxiety, and psychological tension, plus more serious effects such as high blood pressure, elevated heart rate, heart palpitations, and hallucinations. Anyone who uses yohimbine should be careful to avoid all tyramine-containing foods, e.g., red wine, liver, and cheese, and nasal decongestants or diet aids containing phenylpropanolamine, all of which could contribute to dangerous blood pressure fluctuations.

Clarkson: Ephedrine would be at the top of my list of popular risky supplements, too. Of the 140 adverse reactions between 1997 and 1999 that Ellen described, 10 resulted in death and 13 resulted in permanent disability. However, judging the relative risk of weight-loss supplements containing the ephedrine-caffeine-aspirin stack may depend on whether or not the person is obese. This combination of drugs is a moderately effective weight loss agent because it can speed up metabolism and decrease appetite. In obese people, the risks associated with obesity possibly outweigh the risks of taking the drugs, but in someone who is overweight but not obese, the risk of taking these drugs almost certainly outweighs the weight-loss benefits.

I also agree with Ellen that androstenedione and other so-called “prohormones” are potentially dangerous, especially if used for a prolonged period and in high doses.

Although not very popular, there are even more dangerous supplements on the market, like those that contain gamma butyrolactone (GBL), gamma hydroxybutyric acid (GHB), and 1,4 butanediol (BD). Such supplements are illegally marketed, unapproved drugs and have been associated with serious illnesses and deaths.

Rosenbloom: Products containing ephedra also concern me. Ephedra is found in at least 25 over-the-counter dietary supplements, and many of them don’t identify ephedra by name as the stimulant in the product. So, even if an athlete is aware that ephedra is a potentially dangerous substance and is banned by a sport-governing body, the athlete may not know that a product promoted to boost energy contains ephedra. And while the supplement manufacturers who do identify ephedra as an active ingredient warn athletes not to take more than the recommended dose, the potential for overuse is great. I have heard athletes say that because they are bigger and have more lean tissue than the “average” person, they need more of a supplement to get the desired effect.

I also fear that the rising use of prohormones, especially by young athletes, will result in many adverse effects. A survey by Blue Cross and Blue Shield conducted in 2001 showed that androstenedione, creatine, and ephedra were the three most popular supplements with teenage athletes, with close to a million teens taking sports supplements.

Supplements that contain kava may also be risky. The FDA recently advised consumers of the potential risk of severe liver injury associated with the use of kava-containing dietary supplements. Kava (*Piper methysticum*) is an herb included in supplements purported to promote relaxation, to reduce sleeplessness, and to relieve menopausal symptoms. Whether or not kava actually does any of these things has not been adequately substantiated. Regulatory agencies in Europe have warned consumers about the potential risks of kava use and in some cases have removed kava-containing products from the marketplace. Kava-containing products have been associated with hepatitis, cirrhosis, and liver failure in over 25 reports of adverse events in other countries. Four of these patients required liver transplants. In the U.S., the FDA has received a report of a previously healthy young female who required liver transplantation, as well as several reports of liver-related injuries associated with the use of kava.

Are there some dietary supplements that are probably safe and effective if consumed according to the manufacturer’s instructions but are likely to be harmful if the consumer ingests substantially more of the product than is recommended?

Clarkson: A good example is the traditional use of vitamin and mineral supplements. While the recommended doses can improve a deficiency resulting from a poor diet, megadoses can have toxic effects. For instance, iron deficiency can negatively affect an athlete’s endurance performance, and this deficiency can be improved by taking an iron supplement, which will also improve performance. However, taking megadoses (10 times the recommended level) of iron can create imbalances in other minerals, particularly copper, because high iron intake affects copper absorption. Moreover, research has shown that high levels of iron in the body increase the risk of cardiovascular disease. Thus, taking an iron supplement for a long period of time could result in cardiovascular disease later in life.

Rosenbloom: I think creatine and protein supplements probably fit into this category, too. Creatine has been around long enough that if there were serious risks to health they should have surfaced by now. However, I would caution athletes about using more than the suggested amounts and inform them that a “loading” phase is probably not needed. It also seems likely that well-trained athletes whose protein intakes are less than about 2.8 grams of protein per kilogram of body weight per day (~1.3 g/lb daily) will not harm the function of their kidneys, although higher protein intakes may.

Coleman: Caffeine and Ginkgo biloba come to mind. Caffeine seems to improve endurance performance with minimal side effects when used in doses of 6 mg/kg (3 mg/lb) or less. Higher doses more often resulted in dizziness, headache, insomnia, and gastrointestinal distress. Also, the use of doses greater than 6 mg/kg is progressively more likely to cause excretion of caffeine in the urine that would lead to a positive doping test according to the rules of the International Olympic Committee, which considers urinary caffeine levels above 12 micrograms/ml to be evidence of doping.

Ginkgo biloba appears to be effective in treating ailments associated with decreased cerebral blood flow, particularly in older individuals. Ginkgo enhances blood flow to the brain by promoting vasodilation. For the elderly, Ginkgo may improve concentration

and memory, absent-mindedness, headaches, and tinnitus (ringing in the ears). It may also aid leg circulation. Very large doses may cause restlessness, diarrhea, nausea and vomiting. Ginkgo can act as a blood thinner and may be contraindicated when an individual is using anticoagulants drugs (e.g., Coumadin or aspirin) or dietary supplements such as vitamin E or fish oil, which also have anticoagulant properties.

Do dietary supplements sometimes contain substances not listed on the package that might cause an athlete who used the supplement to fail a drug test for sport competition?

Rosenbloom: Oh yes! Trace contamination of androstenedione and nor-androstenedione supplements was found in one study to be sufficient to cause positive urine tests for 19-norandrosterone. In another report, it was shown that several prohormone supplements contained substances that were not indicated on the label, and two products claiming to be “mental enhancers” contained ephedra that was not indicated on the label. And, of course, there is always the possible waste of money when purchasing supplements—some products don’t contain any active ingredients.

Coleman: I’d like to expand on Chris’ response with a few details of the studies she mentioned. Researchers from the UCLA Olympic Analytical Laboratory found that men who took either 100 or 300 mg of androstenedione for one week tested positive for 19-norandrosterone, a metabolic by-product of nandrolone. The researchers also found that some brands of androstenedione were grossly mislabeled with respect to potency and purity and contained the illegal anabolic steroid, testosterone. In another report, Kamber and colleagues found different substances than indicated on the labels, including testosterone, in seven out of 17 prohormone products. In two out of seven “mental enhancer” products, the authors found caffeine and ephedrine that were not clearly declared on the labels. One product contained a high enough concentration of ephedrine that an athlete would fail a doping test if only one capsule was consumed just before competition.

Clarkson: Because dietary supplements are not regulated by the FDA, there is no guarantee that what is stated on the label is actually in the supplement. In addition to the scientific articles mentioned by Chris and Ellen, there are many other anecdotal reports in which athletes who have tested positive for drugs claimed that the banned substance was not listed on the label of a supposedly legal supplement they had been using.

What tips do you have for increasing the confidence of the consumer that a given dietary supplement actually contains the appropriate amounts of the ingredients listed on the package and only those ingredients?

Coleman: The USP (United States Pharmacopoeia) designation on the label of a vitamin/mineral supplement indicates that the product passes tests for dissolution, disintegration, potency, and purity. Nationally known food and drug manufacturers generally make supplements under the strict quality control procedures they already have in place. Supplement Watch (www.supplement-watch.com) and Consumer Lab (www.consumerlab.com) provide

independent test results and information to help people evaluate and select dietary supplements. Products that pass Consumer Lab’s testing are eligible to bear the CL Seal of Approval.

Clarkson: The more reputable the company, the more likely the supplement contains what it is purported to contain. Still, there is no guarantee.

Rosenbloom: I think Ellen’s advice to check the Consumer Lab evaluation is on target, but as Priscilla suggested, athletes should know it is a “buyer beware” market when it comes to supplements.

It seems that most dietary supplements have never undergone rigorous scientific testing to determine the efficacy and potential side effects of the supplements. Why is there not more published research on these supplements?

Rosenbloom: I think there is a lack of published research on dietary supplements for two reasons. First, a supplement manufacturer is not likely to spend money on research when the laws regulating supplements do not require them to do so. Second, the nature of the supplement industry is always changing—by the time investigators study a dietary supplement and publish the data, twenty new supplements will have hit the scene. It is a fickle industry with new supplements entering the market all the time. Until regulatory agencies require it, I don’t believe we are apt to see more research on supplements.

Clarkson: Research costs money. Who will fund the research? In the case of drugs, where extensive proof of efficacy and safety are required before the drugs can be approved, the drug companies fund the appropriate clinical trials. To provide a fair test of a drug, the clinical trials must incorporate a large population of subjects, and the study controls must be rigorous. Although one might suppose that the supplement companies should fund the research, few companies provide resources for such research projects. The reason for this is that a supplement company must pass along high research costs to the consumer. Thus, their supplement would cost more than a competitor’s supplement, and they would lose market share to the competitor, who would undersell them. Furthermore, the public has shown by their power of purchase that they more often than not believe the manufacturer’s claims without any research proof. So, what is the incentive for the supplement manufacturer to prove a claim and take the chance that the research will show that the supplement does not meet the claim?

Coleman: The burden is now on the FDA to prove that supplements are dangerous instead of on the manufacturers (who profit from sales) to prove that supplements are safe. Adequate research won’t be conducted until supplement companies are held financially and legally responsible for their claims.

Should the US government regulate dietary supplements? If so, what type of regulation would you like to see? What do you think of the regulations passed by Congress in 1994, i.e., the Dietary Supplement Health and Education Act (DSHEA), which liberalized what manufacturers could claim about their supplements and placed the burden on the FDA to prove that a supplement was harmful?

Clarkson: When the DSHEA was passed, there were relatively few supplements on the market, with most of these being the traditional vitamins and minerals. DSHEA opened the door to a vast array of supplements with tempting and appealing claims to improve performance. These supplements have no proof of safety or efficacy. As Ellen said, the burden of proof rests with the FDA to prove that the supplement is unsafe or does not have the performance enhancing effects as claimed. With the number of supplements now available, this burden has proven too large.

Those who voted for or supported the DSHEA did not predict that passing this act would spawn an industry rich with unproved, likely ineffective, and possibly dangerous supplements. Yes, I believe that the FDA should regulate supplements in the same way that it regulates drugs. Before any drug reaches the consumer, it should be tested in a prescribed, rigorous manner to prove both safety and efficacy. Such testing would make supplements more expensive because the research costs would be passed on to the consumer. However, that consumer would have the assurance of efficacy and safety, which should be well worth the extra cost.

Coleman: I agree totally with Priscilla's comments. Congress passed the DSHEA after the supplement lobby used their financial clout and pressed for legislation that hampered the regulation of dietary supplements. The end result was a law that greatly weakened the FDA's ability to protect consumers.

Rosenbloom: I, too, would like to see more regulation of the supplement industry, but it will take a literal act of Congress to do so. That is unlikely to happen given the climate in Washington and the consumer's indifferent attitude toward regulation of industry.

SUGGESTED ADDITIONAL RESOURCES

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Food and Drug Administration Center for Food Safety and Applied Nutrition. Tips for the savvy supplement user: Making informed decisions and evaluating information. <http://www.cfsan.fda.gov/~dms/ds-savvy.html>

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HOW SAFE ARE DIETARY SUPPLEMENT?

Contrary to what you may think, products marketed as dietary supplements and claimed to be effective as aids to weight loss, weight gain, relaxation, strength improvement, mental concentration, endurance performance, and even sexual stamina are basically unregulated by the Food and Drug Administration (FDA) or any other agency of the federal government. What this means is that the consumer has no assurance that any particular dietary supplement works as intended, is safe, or contains what is listed on the package label. It is certainly true that some types of supplements—vitamins and minerals, protein powders, carbohydrate supplements, and others—have been used for many years with no apparent life-threatening effects when used according to the manufacturer's recommendations. But in the last few years there has been an explosion of supplements offered to the public, and concern has been raised about some of these products.



- The FDA has received many reports of serious side effects and even deaths strongly associated with the use of products that contain ephedrine, which is found in herbs such as Ma Huang (also known as Chinese Ephedra, Ephedra Sinica, Ephedra Equisetina, desert herb, and herbal ephedrine), Mormon Tea, and Sida Cordifolia, among many others. Ephedrine has amphetamine-like effects; because it can accelerate the body's use of energy (calories) and depress appetite, it is often a component of weight-loss products. It is especially dangerous when taken in larger-than-recommended doses and when combined with caffeine and aspirin.
- Consumer warnings have also been issued by the FDA about using dietary supplements containing kava, another herbal extract. Kava depresses brain function and is claimed to improve relaxation and reduce anxiety. Kava use, especially in Europe, has been associated with hepatitis, cirrhosis, and liver failure, sometime leading to the need for a liver transplant.
- Androstenedione and other "prohormone" supplements used in hopes of promoting muscle growth can decrease the blood levels of HDL cholesterol (the "good" cholesterol) and raise the levels of LDL (the "bad" cholesterol) and estrogen (female sex hormone), potentially increasing the risk of cardiovascular disease.
- Yohimbine, extracted from yohimbe bark, supposedly increases blood testosterone (thereby increasing muscle mass), decreases body fat, and serves as an aphrodisiac. Among the reported

side effects of yohimbine use are high blood pressure, elevated heart rate, heart palpitations, and hallucinations.

- There are even more dangerous supplements on the market, like those that contain gamma butyrolactone (GBL), gamma hydroxybutyric acid (GHB), and 1,4 butanediol (BD). Such supplements are illegally marketed, unapproved drugs and have been associated with serious illnesses and deaths.
- Supplements may contain potentially dangerous ingredients—ephedrine, for example—without listing them on the package label.
- Supplements may contain non-listed substances—such as anabolic steroids—that are banned by sports governing bodies and have resulted in failed doping tests.
- Even generally safe supplements like vitamins and minerals can be toxic if taken in huge doses.
- Information about the safety and efficacy of dietary supplements can be found at www.supplementwatch.com and www.consumerlab.com.
- Athletes and non-athletes alike should be very cautious before using any supplement. Investigate all supplements thoroughly and consult with a knowledgeable health professional before you buy.

SUGGESTED ADDITIONAL RESOURCES

Catlin, D.H., B.Z. Leder, B. Ahrens, B. Starcevic, C.K.Hatton, G.A. Green, and J.S. Finkelstein. Trace contamination of over-the-counter androstenedione and positive urine test results for a nandrolone metabolite. *JAMA*. 284:2618-21, 2000.

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