The Conference on the Science and Policy of Performance-Enhancing Products, held January 8–9, 2002, examined the available scientific evidence that addresses the safety and efficacy of performance-enhancing dietary supplement products. The conference also provided an initial step in broadening a partnership to identify gaps in knowledge, frame research questions, and address major societal challenges in the responsible use of sports nutrition products. The conference was organized by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) and the dietary supplement trade association Council for Responsible Nutrition (CRN), with additional support from the National Institute of Child Health and Human Development, the NIH Office of Research on Women’s Health and Office of Behavioral and Social Science Research, Phoenix Laboratories, Rexall Sundown, and EAS.

As noted in the keynote address by the Olympic gold medal swimmer Donna de Varona, sports supplements are widely used by all types of athletes: male and female, young and old, professional and amateur. Hydration drinks, energy bars, protein powders, and multivitamins are used safely by millions of people. Other sports supplements, however, contain ingredients such as steroid hormone precursors and stimulants, which raise concern. The conference focused on the latter group because there is much confusion about which products are safe, effective, legal, and ethical. Conflicting rules and practices fuel the confusion surrounding performance-enhancing products. For example, androstenedione is allowed in major league baseball, but its use is prohibited by the International Olympic Committee (IOC), National Collegiate Athletic Association (NCAA), and most sports federations. The IOC and NCAA have banned the stimulant ephedrine for many years, but the National Football League just recently prohibited its use and was among the first professional sports league to do so.

REGULATION OF PERFORMANCE-ENHANCING PRODUCTS

On a federal level, the Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) regulate dietary supplements. Christine Taylor, Ph.D., director of the FDA Office of Nutritional Products, Labeling, and Dietary Supplements, explained that the FDA is authorized to regulate dietary supplements through the Food, Drug and Cosmetic Act and the 1994 Dietary Supplement Health and Education Act (DSHEA). A product’s regulatory status, as a food, drug, or dietary supplement, depends on its intended use. For example, caffeine is considered a food ingredient in coffee and soft drinks, a dietary supplement if there is a claims for alertness, and a drug ingredient in over-the-counter (OTC) migraine products.

Consumer safety is protected through regulations for grandfathering, notification procedures, and adulteration. Grandfathered ingredients were those on the market before October 1994 (when DSHEA was signed into law), and they are presumed safe. Postmarketing surveillance tracks their safety. For new ingredients, those introduced to the market after October 1994, the manufacturer must file notification with FDA and submit data supporting the safety of the new ingredient. A dietary supplement is considered adulterated and subject to removal from the market if it presents a significant or unreasonable risk of illness or injury when used according to label directions.

Laura Sullivan, J.D., from the FTC Bureau of Consumer Protections explained that section 5 of the FTC Act prohibits deceptive and unfair acts and practices in commerce. Claims made in advertising, express or implied, must be truthful, not misleading, and substantiated by competent and reliable scientific evidence. The studies must relate to the product, and claims must reflect the strength of the science. Consumer anecdotes are never a substitute for scientific evidence. Advertising must also include any material information that qualifies a claim, such as significant side effects or safety risks, conditions of use, or limits on efficacy. In regards to performance-enhancing products, the FTC has focused its activities on unproven safety claims in advertising.
Several speakers addressed the pattern of use of performance-enhancing products, which can vary by age, gender, level of athletic training, and type of sport. Harrison Pope, M.D., chief of the Biological Psychiatry Laboratory at McLean Hospital in Massachusetts, reported results from a study of performance-enhancing supplement use in which a single-page questionnaire was distributed to 511 clients as they entered five Boston-area gyms (14). Among 334 male respondents, more than half (61%) used some type of protein product, 47% used creatine, and 4% consumed androstenedione for 6 months or longer. Protein and ephedrine products were the most frequently consumed by women, 34% and 13%, respectively. Creatine was used by 7% of women, whereas androstenedione supplementation was reported by 3% of women, but none used it longer than 6 months. Extrapolated to a national level, rough estimates indicate that 4.3 million men and 2.7 million women use protein products, 3.3 million men and 0.5 million women use creatine, 1.8 million men and 1 million women use ephedrine supplements, and 1.3 million men and 240,000 women use products from the androstenedione family. Dr. Pope questioned the long-term effects of supplements such as ephedrine, androstenedione, and creatine, which are used continuously for years by certain subpopulations (e.g., bodybuilders).

Studies by Harris Lieberman, Ph.D., U.S. Army Research Institute of Environmental Medicine, with elite military populations demonstrated that use varies by age or maturity. Dr. Lieberman assessed dietary supplement use among 768 Army Rangers, 152 members of the Special Forces, and 315 officers at the Army War College. Ranger units consist of young enlisted volunteers (aged 23.6 ± 4.3 yr), and the participants’ average time in the Army was 2 yr. The Special Forces are more mature than Rangers (aged 31.3 ± 6.1 yr), and the participants had about 10 yr military experience. Officers at the Army War College represent the middle to upper management level and are typically 40 yr of age or older.

All three military groups reported high levels of supplement use (65–80%), but the type of supplements consumed varied by group. Rangers and Special Forces reported using supplements for muscle or performance enhancement or to increase energy. Among the Rangers, the most frequently used products were carbohydrate-electrolyte drinks (70%), multivitamins (28%), and caffeine (23%). Similarly, the most popular supplements among Special Forces were sports drinks (36%), multivitamins (32%), and creatine and protein powders (each 16%). War College officers, however, tended to take supplements for general health. Vitamins and minerals were the most frequently consumed products, for example, 53% of female officers and 42% of male officers used multivitamins.

Considering the popular use of dietary supplements among these elite military populations, Dr. Lieberman recommended research to assess the benefits and risks of these products. Determining whether supplementation is physiologically required or beneficial among soldiers consuming calorie-dense foods is of particular interest.

Every 4 yr, the NCAA surveys college-student athletes to evaluate the use of drugs, nutritional supplements, cigarettes, and alcohol. Gary Green, M.D., chair of the NCAA Subcommittee on Drug Testing/Drug Evaluation, reported the 2001 survey results (11). Nutritional supplements were used by 29% of respondents in the previous 12 months. Creatine was the most popular supplement (26%), followed by amino acids (10%), androstenedione, chromium, and ephedra (each about 4%). Improving athletic performance and physical appearance were the primary reasons cited for the use of nutritional supplements (27%), followed by weight loss–weight gain and general health (20%), preventing injury (9%), and recovery from illness or injury (6%). Supplement use typically began before college: 57% of respondents began use in high school and 6% in junior high or earlier.

Ann Grandjean, Ed.D., executive director of the Center for Human Nutrition in Omaha, described the use of supplements by elite athletes (18a). Data were collected from 592 American athletes who participated in the 2000 Olympic summer games. Preventing illness is the most frequent reason stated by Olympic athletes who use supplements. Getting sick before Olympic competition is a real threat to ending careers, hopes, and dreams. It follows that multivitamin–multimineral supplements were the most commonly consumed product. Further analysis of the data is ongoing. Dr. Grandjean noted the need to research the benefits of sports supplements among fitness center clientele and their reasons for use.

STIMULANT AND THERMOGENIC INGREDIENTS

Ira Jacobs, Dr. Med. Sc., chief scientist for the Defense and Civil Institute of Environmental Medicine in Toronto, described investigations that assessed the effects of pharmaceutical grade anhydrous caffeine and ephedrine hydrochloride on physical performance across a range of exercise intensities among military personnel. A randomized controlled trial evaluating performance on a cycle ergometer test (2) showed that supplementation with caffeine (5 mg·kg⁻¹ bodyweight) or ephedrine (1 mg·kg⁻¹ bodyweight) extended time to exhaustion by approximately 1.5 min compared with placebo. A combination of caffeine and ephedrine, however, extended time to exhaustion by 5 min, a magnitude of improvement normally achieved after several weeks if not months of physical training.

The effect of caffeine and ephedrine on muscle endurance during weight lifting exercise also was assessed. Thirteen males each ingested the following treatments: 4 mg·kg⁻¹ caffeine, 0.8 mg·kg⁻¹ ephedrine, caffeine plus ephedrine, or placebo. The mean number of repetitions for leg press was significantly higher after using caffeine plus ephedrine (19.8) or ephedrine alone (17.4) compared with placebo (14.0). It would take several weeks of training to accomplish this magnitude of improvement without supplementation.
Because ephedrine and caffeine elevate metabolic heat production, there is concern that this combination could impair body temperature regulation during exercise in the heat. To explore this possibility, 10 subjects exercised at 40°C and 30% relative humidity for 3 h or until rectal temperature reached 39.5°C or heart rate was 95% of maximal heart rate for 3 min (1). The subjects were supplemented with 5 mg·kg⁻¹ caffeine and 1 mg·kg⁻¹ ephedrine or placebo. Tolerance time and rectal temperature were not affected. The mean skin temperature was lower with supplementation, which explains why rectal temperature did not increase. The subjects were likely to evaporate more sweat to balance the extra metabolic heat production. Although heat tolerance was not impaired in this experiment, the results suggest that predisposition to heat illness may be a concern if exertion occurs in an environment where the ability to remove body heat is impaired (e.g., when protective clothing is worn).

Caffeine and ephedrine appear to be effective acute-use ergogenic aids that may be of benefit for certain types of military operations such as those requiring a rapid increased physical work capacity. Dr. Jacobs, however, emphasized the use of pharmaceutical grade caffeine and ephedrine in the studies, and that its bioequivalence to nutritional supplement ingredients should be examined. He also recommended investigation of the health risks and optimal dosing of ephedrine.

Luke Bucci, Ph.D., from Weider Nutritional International in Salt Lake City, reviewed studies using other stimulant ingredients such as synephrine, green tea, guarana, and quercetin. Synephrine, from the plant *Citrus aurantium*, is a direct-acting alpha₁-adrenergic agonist and a weak beta-adrenergic agonist. It causes no significant increase in heart rate, blood pressure, or respiratory exchange ratio and is generally recognized as safe (GRAS) based on its use as bitter citrus flavoring.

A 20-subject study comparing the effect of a synephrine-caffeine combination with ephedrine-caffeine on resting metabolic rate (RMR) showed that the rate increased significantly with both combinations, although to a greater extent with ephedrine and caffeine. Compared with placebo, both combinations increased body core temperature equivalently, indicating its thermogenic action. The ephedrine-caffeine combination increased heart rate by 12%, whereas the synephrine effect was similar to placebo. Ephedrine-caffeine increased arterial blood pressure by 6–8 mm Hg, but the synephrine-caffeine combination had a smaller effect (3–5 mm Hg).

Green tea contains about 250 mg of caffeine per serving. The (−)-epigallocatechin-3-gallate (EGCG) polyphenolic component in green tea works synergistically with caffeine enhancing thermogenesis (7). Green tea also works synergistically with ephedrine by inhibiting the action of phosphodiesterase at the adenosine receptor, preventing the breakdown of epinephrine and norepinephrine, and thus inhibiting the normal feedback mechanism. Guarana is another herbal source of caffeine, containing about 50 mg per serving, and also inhibits phosphodiesterase.

Quercetin is a flavonoid antioxidant commonly found in foods such as onions and apples. *In vitro* evidence suggests that it inhibits prostaglandin A1 for 3–6 h. Potentially, quercetin could inhibit the effect of prostaglandins on the feedback inhibition of epinephrine and norepinephrine. Yohimbe, from the plant *Pausinystalia johimbe*, contains yohimbine, an indolalkylamine. Yohimbine is an alpha₂-adrenergic receptor antagonist and may also inhibit feedback regulation of epinephrine and norepinephrine. Dr. Bucci noted that little is known about stimulant ingredients, particularly those that might serve as substitutes for ephedrine. He encouraged research to characterize alternative thermogenic agents.

**HORMONE PRODUCTS AND ANALYTICAL CHALLENGES**

Greg Brown, M.S., from the Department of Health and Human Performance at Iowa State University, reviewed three studies that examined androstenedione’s purported anabolic effects (15,18,23). Each study demonstrated that daily androstenedione supplementation (100 mg, 1 or 3 times·d⁻¹) did not increase serum total or free testosterone and had no effect on muscle strength, muscle fiber area, muscle protein synthesis, or lean body mass. Mr. Brown suggested that the effect of larger single androstenedione doses (e.g., 300 mg) and alternate modes of delivery (e.g., sublingual) are important areas to explore.

King et al. (4,15) observed significant negative effects in their studies of androstenedione supplementation. Their research showed that androstenedione caused a significant decrease in high-density lipoprotein (HDL) cholesterol, and they noted that lowered HDL-cholesterol could increase cardiovascular disease risk by 10–15%. In addition, they found significant increases in serum estrone and estradiol concentrations. Elevated estrogen levels have been associated with pancreatic cancer and gynecomastia. In addition, Brown et al. (4) found that the serum dihydrotestosterone (DHT) response to androstenedione supplementation was related to age. Mr. Brown recommended further research to examine age-specific effects.

Mr. Brown also noted that androstenedione is combined with herbal extracts in stacking formulas. Various herbal extracts (e.g., saw palmetto), purported to inhibit enzymes related to DHT metabolism or estrogen formation, are added to change the hormonal response to androstenedione. A study (3) of these formulations, however, found that the herbal extracts did not prevent the formation of estrogens, inhibit DHT production, or increase serum testosterone level.

Wendy Kohrt, Ph.D., professor of medicine at the University of Colorado Health Science Center in Denver, explained that dehydroepiandrosterone (DHEA) is the most abundant steroid in human plasma. It is widely distributed in the body, with the highest concentrations found in the brain. DHEA and its sulfur form (DHEA-S) are converted to androstenedione then testosterone, which is metabolized to DHT or estradiol. DHEA-S serves as the precursor to about 50% of the androgens in adult men, perhaps as much as 75% of estrogens in premenopausal women, and nearly all estro-
gens in postmenopausal women (17). DHEA levels decline with age. By age 65 to 75, circulating levels may be 20–30% of peak concentrations, which occur about age 25 yr.

A 1988 placebo-controlled trial (19) tested the effect of 1600 mg DHEA-d⁻¹ for 28 d in 10 young men (aged 22–25 yr). Androstenedione levels increased, but there was no significant increase in free testosterone or estrogens. The DHEA-treated group experienced a 5-kg increase in lean mass and a 31% decrease in fat mass. The decrease in fat mass over the 4-wk period would require an estimated 500 kcal energy deficit-d⁻¹ or an increase in energy expenditure. With a similar design (25), the effect of DHEA was examined among six obese men, with no change in body composition.

The effect of DHEA on resistance training in young men was also explored (5). Nineteen men (aged 19–29 yr) were randomized to daily placebo or 150 mg DHEA over 8 wk. Androstenedione levels increased slightly, but no changes in total or free testosterone or the estrogen profile were observed. There was a tendency for the DHEA-treated group to increase lean body mass (by 30%) and decrease fat mass, but an estimated 50 subjects would be needed to demonstrate statistically significant changes in body composition.

Dr. Kohrt offered several research recommendations. On a basic level, DHEA’s mechanism of action is not understood. Sex- and age-specific responses to DHEA supplementation have not been adequately studied. The potential effects of DHEA supplementation in eugonadal and hypogonadal athletes and DHEA therapy for female athletes with amenorrhea are also worthy research topics.

Dr. Green addressed the issue of product labeling and described a study (10) that examined whether 12 brands of supplements (sold in the Los Angeles area) conformed to labeling requirements of DSHEA. According to DSHEA, a dietary supplement is considered misbranded if the label fails to list the identity and proper strength of the product’s ingredients. Product content was analyzed by high-pressure liquid chromatography, and only one brand was properly labeled. The others failed to list ingredients (e.g., androstenedione, testosterone), listed ingredients that were not detected, or had ingredient concentrations higher or lower than declared on the label. Swiss researchers, who examined 75 products purchased over the Internet, reported similar findings (13).

CREATINE AND OTHER METABOLIC INTERMEDIATES

Creatine is a nonessential compound made in the body from amino acids and can also be obtained in the diet. The primary mechanism for creatine is related to energy dynamics. It is an energy substrate and rephosphorylates adenosine triphosphate (ATP) during high intensity exercise. Jeff Volek, Ph.D., from the Kinesiology Department at the University of Connecticut, Storrs, reported that the majority of studies demonstrate creatine’s ergogenic effect on performance during short duration, high intensity types of exercise. Typically, it provides a small improvement of 5–10%. Several reasons may explain why some studies do not show a favorable effect from creatine supplementation, such as inadequate statistical power, variable muscle creatine concentrations in the normal population, and inappropriate or unreliable performance tests. For example, it may not be possible to detect a 5–10% improvement with a 15% variation in a test measure.

Based on the published literature, Dr. Volek stated that there is no scientific evidence that creatine causes abnormal side effects in healthy individuals, yet anecdotal claims of kidney impairment persist. He also noted the emerging research on creatine’s beneficial effect in different disease states such as Parkinson’s and Huntington’s, which showed promising results in animal studies.

Several human studies have examined the effect of beta-hydroxy-beta-methylbutyrate (HMB) on resistance training (9,12,16,20,21,24,26), and Steven Nissen, Ph.D., professor in the Animal Science Department at Iowa State University, summarized the findings. The studies showed that muscle mass increased 0.14%–0.40%-wk⁻¹ with HMB supplementation. HMB is associated with small changes in systolic blood pressure (3 mm Hg), a 9% decrease in low-density lipoprotein (LDL) cholesterol, no change in HDL cholesterol, no changes in blood hematoloy, and no negative effects on emotional profiles. Safety data, however, are based on 3–12 wk of supplementation, and clinical data on long-term use are needed.

Tim Maher, Ph.D., professor at the Massachusetts College of Pharmacy and Health Sciences in Boston, noted the importance of studying the effects of combining performance-enhancing ingredients in “stacking formulas.” Combinations may produce an additive, synergistic, potentiating, or antagonistic effect. For example, the sympathomimetics amphetamine, ephedrine, and phenylpropanolamine each interact with presynaptic terminals and cause a release of norepinephrine. Compared with a saline control, each of these compounds decreases food intake. If tyrosine is combined with such sympathomimetcs, it enhances the effectiveness of these compounds in decreasing food intake.

Dr. Maher recommended that ingredients should be tested in real-life use patterns. The importance of such testing is exemplified by a study of ibuprofen and aspirin (6), which both have antiplatelet activity. Few people would have suspected that the combination produces a subadditive or antagonistic response.

CHALLENGES FACING SPORTS MEDICINE

Andrew Pipe, M.D., Chair of the Canadian Center for Ethics in Sports (Ottawa), noted that the sports physician has responsibility to the patient, sport, and sports community. The use of supplements among athletes raises a number of questions, including evidence of need and benefit and the potential for harm.

Describing an example of industry–academic research partnership, Grant Pierce, Ph.D., director of the Canadian National Center for Agri-Food Research in Medicine, Winnipeg, addressed the challenge of identifying dietary supplement products that athletes can use without fear of positive doping tests. Using an IOC accredited testing facility,
TABLE 1. Summary of Research Recommendations

- Evaluation of the risks and benefits of performance-enhancing supplements among subpopulations with diverse dietary patterns and nutrient intakes, such as adolescents, body builders, military personnel, and the elderly.
- Monitoring and surveillance of the effects of chronic, prolonged use of performance-enhancing supplements, particularly androstenedione, ephedrine, and creatine.
- Identification and characterization of mechanism(s) of action of performance-enhancing ingredients.
- Characterization of the patterns of use (e.g., type of product, frequency) and psychosocial behavioral aspects of use among various subpopulations in the United States.
- Characterization of dose-response curves for performance-enhancing supplements, particularly those containing ephedrine, alkaloids, and steroid hormone precursors such as androstenedione.
- Characterization of the endocrine effects of performance-enhancing supplements, especially those containing hormonal ingredients such as androstenedione and dehydroepiandrosterone (DHEA), according to age, gender, and physiological life stage (e.g., female athletes with amenorrhea, disordered eating, or at high risk for osteoporosis).
- Comparative studies of analytical grade dietary supplement ingredients (particularly caffeine and ephedrine) with formulations currently in the marketplace.
- Evaluation of the effects of combining performance-enhancing ingredients as in “stacking formulas” or the simultaneous use of multiple sports supplements.
- Comparative studies that examine the frequency and timing of supplementation on physical performance.
- Determining targeted approaches to communicate the risks and benefits of performance-enhancing products to various segments of the U.S. population (professional and lay audiences).
- Determining whether other stimulant and thermogenic ingredients might serve as substitutes for ephedrine alkaloids.

...the Center conducted a study of a CV Technologies cold and flu product, which contains ginseng. Thirty-nine amateur athletes, aged 18–25 yr, ingested the product for 28 d, then urine samples were collected following IOC guidelines. The samples were screened for approximately 200 banned substances within the categories of stimulants, beta-agonists and blockers, narcotic analgesics, anabolic agents, diuretic agents, peptide hormones, local anesthetics, and masking agents. All subjects were found to have acceptable levels of all tested substances: the product did not contain any IOC banned ingredients. By supporting this level of research, industry could use the study results to promote their product as a safe and legal sports supplement.

That several factors affect the dietary needs of athletes and deserve additional research was explained Peter Lemon, Ph.D., professor at the University of Western Ontario. These factors include type of exercise, intensity and duration, continuous versus intermittent exercise, rest and recovery time, degree of training, exercise environment (e.g., temperature and humidity), age, and gender. Several studies support the beneficial effect of calorie supplementation, regardless of source (i.e., carbohydrate, protein or fat) among trained athletes. For example, a study with 16 university-age elite female rowers showed that a carbohydrate or fat supplement (940 kJ·d⁻¹) enhanced performance as measured by the 2000 m ergometer rowing test.

Timing of supplementation is another important factor. Rasmussen et al. (22) showed that postexercise supplementation was most effective when consumed 1–2 h after exercise. In a study of elderly men who participated in a resistance-training program, Esmarck et al. (8) found that a 420 kJ protein supplement had the greatest effect on muscle strength and size when consumed immediately after a weight training session.

Another challenge is providing credible information on substance use to athletes, coaches, parents, and healthcare professionals. In Canada, the Center for Substance Use in Sport and Health (SUSH) was created through federal funding to provide an educational model on substance use. Jonathan Geiger, Ph.D., president and cofounder of SUSH and director of neuroscience research at St. Boniface Research Center in Winnipeg, explained this model. The SUSH message remains consistent, regardless of the audience’s age or level of education: “Just Say Know.” The decision-making model builds from the following seven elements: 1) fair play based on the ethics and rules of sport; 2) legal and illegal substances based on the rules of law; 3) proper dose of performance-enhancing products; 4) health benefits; 5) medical side effects; 6) safety for oneself and others; and 7) financial considerations, cost of the product and consequences if it causes a positive doping result.

The SUSH approach does not use scare tactics. Instead, it stresses knowing the positive and negative effects of a substance to make an informed decision. Dr. Geiger emphasized the need for additional science-based information on the benefits and safety of sports supplements.

RECOMMENDATIONS AND FUTURE STEPS

Among its mandated tasks, ODS is to conduct and coordinate dietary supplement research at NIH. Therefore, the main conference outcomes will be development of an appropriate research agenda and support of industry–academia–government partnerships to advance this research. Each of the conference speakers offered recommendations for future investigation, and audience discussion generated additional suggestions (Table 1). The following research themes emerged: optimal dosing and health risks of performance-enhancing ingredients, particularly ephedrine; reasons for use; interactions with drugs, foods, or other supplements; gender- and age-specific responses, especially to hormone ingredients; long-term health effects of sports supplements; differences between responders and nonresponders to supplement ingredients; mechanism(s) of action; and optimal timing of supplementation.

Additional conference information, a detailed meeting report, speakers’ presentations, and a web-based videocast are available from the following web sites: http://ods.od.nih.gov/news/conferences/pep.html and www.crnusa.org.

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Address for correspondence: Dr. Rebecca Costello, Deputy Director, Office of Dietary Supplements, National Institutes of Health, 6100 Executive Blvd., Room 3B01, MSC 7517, Bethesda, MD 20892-7517; E-mail: CostellB@od.nih.gov.
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