Quality Assurance Issues in the Use of Dietary Supplements, with Special Reference to Protein Supplements

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Abstract
The use of dietary supplements is widespread in the general population, in athletes and recreational exercisers, and in military personnel. A wide array of supplements is available, but protein-containing products are consistently among the most popular, especially among those who engage in resistance training. There are significant risks associated with the use of unregulated dietary supplements. Risks include the absence of active ingredients, the presence of harmful substances (including microbiological agents and foreign objects), the presence of toxic agents, and the presence of potentially dangerous prescription-only pharmaceuticals. There is ample evidence of athletes who have failed doping tests because of the use of dietary supplements. There is also growing evidence of risks to health and of serious adverse events, including a small number of fatalities, as a result of supplement use. The risk associated with the use of protein powders produced by major manufacturers is probably low, and the risk can be further reduced by using only products that have been tested under one of the recognized supplement quality assurance programs that operate in various countries. Nevertheless, a small risk remains, and athletes, soldiers, and other consumers should conduct a cost-benefit analysis before using any dietary supplements. J. Nutr. doi: 10.3945/jn.113.176651.

Introduction
The use of dietary supplements (DSs) is widespread in the general population (1,2), in those who participate in sports (3), and in military populations (4). A comprehensive review of evidence from several surveys of supplement use in military personnel was published in 2008 (4). This review reported that the 2005 Department of Defense Survey of Health Related Behaviors found that 60% of active-duty personnel reported using a DS at least once a week over the previous 12 mo (5), whereas 85% of those entering Special Forces and Ranger training reported current or previous use of DSs, and 64% reported current usage (6). Jacobsen et al. (7) analyzed self-reported data from active-duty, Reserve, and National Guard participants of the Millennium Cohort Study. Data on supplement use and physical activity were collected in 2007–2008 from 106,698 soldiers and were linked with deployment and demographic data. This survey revealed that 47% of all participants reported using at least 1 type of supplement; 22% reported the use of multiple supplements. A more recent survey on the use of DSs among active-duty U.S. Army soldiers at various locations around the world reported that 53% of those surveyed used DSs at least once per week (8). These reports suggest that the prevalence of use in various military groups is higher than that in the general population, where a reported prevalence of use of 39% has been reported in U.S. adults aged 19–30 y and 49% in adults aged 31–50 y (9).

Users of supplements cite many different reasons for consuming DSs, although these reasons are more often based on unfounded beliefs than on any understanding of the issues at stake: in the general population, consumption of nutritional supplements is often driven by a belief that they confer health benefits above and beyond those that can be achieved by eating normal foods (10). A recent review suggested that these beliefs may be erroneous and concluded that “With the possible exceptions of vitamin D and omega-3 fatty acids there is no data to support the
widespread use of dietary supplements in Westernized populations; indeed, many of these supplements may be harmful” (11). Although the quality of the evidence base on which these conclusions were based was often poor and the analysis of the evidence was perhaps not as rigorous as it might have been, this review does raise concerns regarding the widespread assumption that supplement use is always both beneficial and safe.

The same beliefs about the need for supplementation exist among athletes, physically active individuals, and soldiers, but added to the health concerns are issues related specifically to the physical and mental aspects of exercise performance. Reported reasons for DS use in a survey of active-service personnel were to improve health (64%), provide more energy (31%), increase muscle strength (25%), and enhance performance (17%) (8). Among competitors at the 2004 Summer Olympic Games, almost half (45%) of those selected for drug testing declared the use of food supplements (12), with vitamins (43%) and proteins/aminos acids (14%) being the most widely used supplements. In military personnel, the most commonly used DSs were multivitamins or multiminerals (38%), protein and amino acids (19%), individual vitamins and minerals (18%), combination products (9%), and herbal supplements (8%) (8). A large-scale analysis of elite track and field athletes (a review of 3887 doping control forms undertaken during 12 International Association of Athletics Federations World Championships and 1 out-of-competition season) found 6523 declarations of use of nutritional supplements, giving an average rate of use of 1.7 supplements per athlete (13). Similar high rates of supplement use were found in elite-level football players competing in the Fédération Internationale de Football Association World Cup competitions of 2002 and 2006 (14). In military populations, there is also evidence of the use of multiple supplements by some individuals: this may exceed 5 separate supplements per day (8). These high levels of use require a substantial financial investment as well as raising other concerns.

The use of performance-enhancing substances seems to be endemic in the athletic population, and the use of these substances seems to begin at a young age. A recent large-scale survey of U.S. youth suggested that the use of all performance-enhancing substances ranged from 5 to 17% at different locations across the United States (15). Among elite young German athletes, the prevalence of DS use was estimated to be 80% (16), which is markedly higher than data from the German National Nutrition Survey II, which showed that 16–19% of all German adolescents (aged 14–18 y) reported using DSs and that use among 18- to 24-y-old Germans was more common (21%) and increased further with age (17).

In surveys of supplement use in active or athletic populations, protein supplements are consistently among the most popular, especially among those performing resistance training (18). Similar findings were reported among male soldiers, although weight-loss supplements were more frequently used by female military personnel (5).

**Supplement Contamination and Quality Assurance Issues**

Consumers expect that supplements purchased are fit for purpose: there is a reasonable expectation that a supplement contains the ingredients listed on the label in the stated amounts and that it does not contain anything else. There is some evidence, however, that this is not always the case and evidence for poor quality control in the manufacture and storage of supplements has been growing over the past 10–20 y, with some clear examples of both poor quality control and of fraudulent practices (19). It is difficult, however, to assess the extent of these problems, because there is no comprehensive testing program for DSs.

In a 2010 review of protein supplements, ConsumerLab reported that tests carried out on 24 commercially available protein supplements found that 31% of products tested failed their quality assurance test (20). One product was found to contain only a small fraction of the stated protein content. Their review of protein powders and drinks also revealed lead contamination in 2 protein supplements: at the levels of contamination found, these products would deliver a daily dose of 6 to 18 μg of lead, which may be sufficient to pose a risk to some consumers (21). Four grams of extra sugar was found in 1 serving of a product. Whereas a small excess of sugar may be fairly trivial, the cumulative effects of lead intake may not be so benign: even though the typical dose provided by these supplements may not be excessive when the recommended intake is consumed, it is recognized that many consumers far exceed the recommended amounts. Another similar organization has also reported problems with heavy metal contamination of protein supplements: ConsumerReports.org reported results of analysis of 15 protein powders and drinks, which were purchased mainly in the New York metropolitan area or online and were tested for the presence of arsenic, cadmium, lead, and mercury: 3 products were found to contain levels of heavy metals in excess of the safe levels proposed by the USP (22).

These problems are consistent with poor quality control in manufacture and storage processes, and there is no other obvious explanation for the presence of these contaminants. A more significant concern is raised by reports from the FDA about supplement contamination. The FDA website contains frequent reports of problems with supplements, with many of these reports relating to the presence of undeclared allergens or microbial contamination or foreign objects in a wide range of supplement products. Only rarely is action taken, and that action seldom amounts to more than a product recall. The extent of these recalls is apparent, however, from the FDA website. Occasionally, more serious action is taken: in 2010, an FDA investigation resulted in a U.S. District Court order that required 2 U.S. supplement companies to shut down all manufacturing and distribution of food products because of violations (23). In addition to the presence of food allergens in products without these being declared, on the label of protein products FDA investigators observed a dead rodent (cut in half) on a blender motor platform, a dead rodent surrounded by rodent excreta pellets in an area used to store near-finished product, and, on 2 occasions, a live rodent running through the blending room. The FDA complaint also alleged that investigators observed bags of raw ingredients that were gnawed through by rodents and covered in rodent urine and feces. The companies and their owner were found guilty, but the penalties applied are small relative to the industry profits.

In cases in which relatively expensive ingredients are involved, it seems that some products contain little or no active ingredient (24). This applies to some protein supplements in which it has been shown that melamine is added as a low-cost substitute for the more expensive protein ingredients (25).

**Sports Doping Issues**

A series of claims by athletes that positive doping outcomes—in particular for the anabolic-androgenic steroid nandrolone—were the result of their use of DSs led to an investigation commissioned by the Medical Commission of the International Olympic
Committee. In an initial investigation, the ingestion of supplements containing nandrolone precursors that were not declared on the label was found to result in the presence of the diagnostic metabolites for nandrolone in the urine of healthy volunteers (26). In a related survey of products on sale to athletes, they purchased a total of 634 nonhormonal nutritional supplements from 215 different suppliers in 13 different countries in 2000–2001 (27). Of these supplements, 289 were from prohormone-selling companies and 345 supplements came from companies that did not offer prohormones. On analysis, 11 different anabolic-androgenic steroids, mainly prohormones of testosterone and nandrolone, were detected. Ninety-four samples (14.8%) contained prohormones. No reliable data were obtained for 66 samples (10.4%) because of matrix effects. Twenty-three samples contained prohormones of nandrolone and testosterone, 64 contained only prohormones of testosterone, and 7 contained only prohormones of nandrolone.

In a similar, more recent survey, an analysis of 58 supplements purchased through standard retail outlets in the United States in 2007 found that 25% of the purchased products contained low levels of steroid contaminants and 11% were contaminated with stimulants (28). Other reports showed the presence of a wide range of prohibited substances in DSs, and there are now many reports of the contamination of supplements with a wide range of agents that are prohibited by the antidoping regulations, including many that are potentially harmful to health (26,29–32). In some cases, the amounts are small, and it seems likely that accidental cross-contamination during manufacture, processing, or packaging may be responsible. Some of these cases may be inadvertent contamination due to poor quality control, but other cases seem more likely to involve deliberate adulteration. There can be little doubt that adulterants are added by some unscrupulous manufacturers to many supplements to enhance their efficacy or to make otherwise ineffective products into extremely effective products. An analysis of the reasons for recalls of DSs by the FDA reveals a clear pattern (Table 1). The undeclared pharmaceuticals present in many supplements make these products effective in achieving their stated aims; this cannot simply be coincidence. Where high doses of potent pharmaceuticals are present, these may be sufficient to cause adverse health effects (33).

Small amounts of testosterone are unlikely to result in a positive doping result, but even small amounts of 19-norsteroids are likely to result in a positive test for nandrolone. In a study by Watson et al. (34), 20 volunteers ingested 500 mL of water containing 5 g of creatine monohydrate (which was analyzed and shown to be free of steroids) and 1.0, 2.5, or 5.0 μg of 19-norandrosterone; subsequent urine samples were collected and analyzed for 19-norandrosterone (19-NA), the diagnostic metabolite for nandrolone, which also results from the metabolism of 19-norandrosterone. Ingestion of the supplement resulted in mean peak urinary 19-NA concentrations of 0.7, 1.6, and 3.9 μg/L in the 1.0-, 2.5-, or 5.0-μg trials, respectively. Under current World Anti-Doping Agency regulations, ingestion of the 1.0-μg dose produced no positive doping tests, 5 subjects (20%) tested positive in the 2.5-μg trial, and 15 subjects (75%) had urinary 19-NA concentrations ≥2 μg/L after ingesting 5.0 μg of the steroid. The strict liability principle that applies in sports means that the offense lies in the presence of the prohibited substance in the athlete’s sample; it is not necessary that there was intent, so many innocent athletes may have registered positive results due to the presence of contaminants in supplements they had been using. Of course, this explanation offers a possible excuse for the guilty athlete, so the situation is complex. Other possible complications include the presence of dimethylamylamine, also known as methylhexaneamine, in many DSs, resulting in false-positive tests for amphetamines in the military screening program (35).

### Adverse Health Outcomes from Supplement Use

Some supplements may actually cause harm to health, but these can be difficult to identify and products are usually withdrawn from the market only after a significant number of adverse events have occurred. In 2009, a range of products containing hydroxycitric acid were withdrawn from sale in the United States: according to the FDA, this action was based on 23 reports of serious health problems ranging from jaundice and elevated liver enzymes, to liver damage requiring liver transplant and 1 death linked to liver damage (36). In these cases, the adverse outcomes can be related to the known presence of harmful agents in the supplements. In cases in which the presence of potentially toxic agents is not declared on the label, the likelihood of a link being established between supplement use and adverse outcomes is much more remote. However, in addition to numerous case reports linking supplement use to adverse health outcomes, a recent report has described the development of hepatitis in a group of 20 Iranian male bodybuilders taking a cocktail of DSs (37).

Even when adverse health outcomes of anabolic steroid use are well recognized by those who consume them, however, use of these agents continues in more than half of users (38). It is likely that similar responses will be observed with supplements, so education alone is unlikely to prevent the use of harmful supplements.

### Quality Assurance Programs

Various quality assurance programs for sports nutrition supplements are available. Unlike the testing carried out by the FDA, which is primarily concerned with consumer protection issues such as the presence of the active ingredients in the stated amounts and the absence of substances that may be harmful to health, the focus of these programs is on the testing of samples provided by

### Table 1

<table>
<thead>
<tr>
<th>Product category</th>
<th>Undeclared ingredients</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle building</td>
<td>Anabolic androgenic agents</td>
<td>Methandienone, desoxymethyltestosterone, 4-chlorodehydrotestosterone</td>
</tr>
<tr>
<td>Tonics</td>
<td>Stimulants</td>
<td>Ephedrine, amphetamine analogs</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Anorectic agents</td>
<td>Sibutramine, fenfluramine, ephedrine, phentermine</td>
</tr>
<tr>
<td>Sexual enhancement</td>
<td>Phosphodiesterase type 5</td>
<td>Sildenafil, tadalafil, aminodiol inhibitors</td>
</tr>
</tbody>
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1 Data are from the FDA (http://www.fda.gov/Safety/Recalls/default.html).
manufacturers or distributors for the presence of World Anti-Doping Agency–prohibited substances. These sports-related programs are not complete quality assurance programs in that the presence of active ingredients is not usually verified.

Although athletes and those who are responsible for their care often see these programs as a guarantee of the integrity of products that have been tested, it is important to recognize that a limited panel of substances is tested for and that the tests have limited sensitivity. In supplements tested through the Informed-Sport program in the United Kingdom, for example, the level of detection is set at 10 ng/g for steroids and at 100 ng/g for stimulants (39). Some other schemes operate at different levels, and it is important to recognize this. For supplements that are consumed in large amounts, such as protein powders or drinks, a much more sensitive test is required than for supplements taken as small pills or capsules. If a protein powder contained 90 ng/g of a steroid such as nandrolone or one of its precursors, this would appear as a negative test if the limit of detection was set at 100 ng/g. However, a 25-g portion of this product would deliver a dose of 2.3 μg of the steroid, and there is a good chance that this might result in a positive test for nandrolone if a sample was collected within a few hours of ingestion of the supplement (34,40). Even when a product batch is tested before release for sale, there may therefore still be a risk, albeit a very low risk. Consumers must recognize that although supplement quality assurance schemes do offer considerable protection, these schemes are not an absolute guarantee of quality.

Supplements or Food?

Unlike the situation with many DSs, food can easily and cheaply provide protein and all of the essential amino acids that proteins contain. This calls into question the use of dietary protein supplements, especially given the observation that these are consistently among the best-selling supplement products. The use of food sources of protein is discussed elsewhere (41,42) and is not discussed in detail here. However, it is appropriate to consider some of the issues because they affect the cost-benefit analysis relating to supplemental protein use.

It is generally agreed that an intake of ~20–25 g of high-quality protein soon after a resistance-training session will promote net protein synthesis in the succeeding few hours, although it is not at present entirely clear that these acute effects will translate into a greater protein accretion or better muscle performance in the longer term (41). Of the various protein supplements available, whey products in the form of concentrates, isolates, and hydrolysates are particularly popular. Whey protein concentrate contains a variable amount of whey protein, and commercial samples typically contain from 29 to 89% whey protein by weight. Whey protein concentrate is also likely to contain significant amounts of lactose, fat, and other milk components, reflecting its origin as a by-product of cheese production. Whey protein isolate is produced by filtration of milk proteins produced as a by-product of commercial cheese-making. Whey isolates should contain at least 90% whey protein, and the filtration process should ensure that they are virtually free from the presence of lactose fat and cholesterol. Whey protein hydrolysates are produced by partial enzymatic hydrolysis of whey proteins, resulting in a high content of peptides and free amino acids. Each form can be selected to give the desired amount of protein, but buyers should be aware of these differences when comparing costs of commercial products and when selecting the amount to be ingested. Other protein products may be less effective. Hydrolyzed collagen protein, for example, has been heavily marketed to the strength-training community in recent years, but it is a low-quality protein, entirely lacking in tryptophan, so will not, by itself, stimulate protein synthesis.

The financial costs of protein products are highly variable, as are the costs of protein-containing foods, and a financial comparison that has meaning on a global scale is impossible. Protein powders, however, are not expensive, and a daily dose taken after training will cost only a few U.S. dollars per week. Most foods will contain a range of other nutrients that will contribute to the individual’s nutrition goals, and this consideration must also be included in any financial comparison.

Athletes often cite the convenience of protein supplements as a major factor in their use, and they also value the assurance that a standard measure will provide a known amount of protein. Ascertaining the protein content of foods requires greater effort and, in cases in which product composition details are not listed on labels, also requires a greater nutrition knowledge. It is somewhat ironic that poor quality assurance means that some supplements may mislead athletes as to what they are actually consuming.

It must also be recognized that some foods also suffer from poor quality control in manufacture and distribution, and problems similar to those cited above are not uncommon in the food industry. The use of anabolic pharmacologic agents as growth promoters in the farming industry may lead to residues in meat products that can cause an athlete to fail a drug test in the same way as can happen with contaminated supplements (43,44). The recent (2013) revelations that substantial numbers of beef products (burgers, ready meals, etc.) sampled across Europe contained varying amounts of horse meat and that some also contained pig meat (based on DNA testing) have raised awareness of the existence of serious problems in the food supply chain. Although trace levels were most commonly present, in some cases, all of the meat in some products was horse, and in others, products labeled as suitable for consumption by Muslims were found to contain traces of pig DNA (45). These revelations have raised the level of awareness among the general public of difficulties and dishonesty in the food supply chain, making it easier for the public to accept that similar issues exist with DSs.

In conclusion, although it is clear that some companies take great care to supply high-quality products, problems with the integrity of commercially available DSs are well documented. Unsanitary and unsafe manufacturing environments mean that some supplements contain microbiological contaminants or hazardous foreign objects. Expensive ingredients may be added in less than the declared amounts or may be omitted altogether. Athletes have failed doping control tests due to the presence of undeclared ingredients in supplements they have consumed. There is also growing evidence of risks to health and of serious adverse events, including a small number of fatalities, as a result of supplement use. The risk associated with the use of protein powders produced by major manufacturers is probably low, and the risk can be further reduced by using only products that have been tested under one of the recognized supplement quality assurance programs that operate in various countries. Nevertheless, a small risk remains, and athletes, soldiers, and other consumers should conduct a cost-benefit analysis before using any DSs. The absence of vital parts of the equation, however, means that such an evaluation cannot be completed with confidence.

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