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REVIEW

The continuing story of nutritional supplements and doping infractions

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Nutritional supplements can be a source of positive doping cases as some supplements contain prohibited substances without showing this on their label. This problem has existed for some time and has been extensively studied in the past 8 years. The sport of tennis has played a particular role in this problem because of some peculiar doping cases within its community. This article focuses on this particular doping problem, explaining the background and reviewing the available literature. It presents the first 3 years of experience within the Netherlands Security System Nutritional Supplements Elite Sports ("Nederlands Zekerheidssysteem Voedingssupplementen Topsport" or NZVT) and explains the most extensive system established to combat this particular doping problem. The NZVT experience has shown that paper-based quality systems are still prone to possible contaminations, which leads to the conclusion that the best possible solution for athletes who wish to use nutritional supplements must include laboratory-based analysis for doping substances, preferably repeated for every new batch. The most important educational message, however, is to use a nutritional supplement only if it is deemed of benefit by a nutritional expert.

The consequences of testing positive for a doping substance are severe. The sanctions for doping infractions, laid down in the World Anti-Doping Code, allow for mitigating circumstances to lower the standard 2-year ban.¹ But the use of unknown contaminated nutritional supplements is very seldom accepted as a reason to reduce a sanction, and the result of the particular competition is always nullified, which is a severe sanction in itself.

This has led to a situation where most international sports bodies advise athletes to abstain from using any nutritional supplements. This advice is deemed unsatisfactory by most athletes and nutritional experts, as supplements can help athletes to meet their nutritional needs.^{2–3} Many studies have shown that supplements like carbohydrate drinks, creatine, and glucosamine can help some athletes to perform at their highest level.^{4–10} It must be said, though, that the expectations of athletes tend to exceed the actual effects.

This article will review all relevant aspects of the relationship between supplement use and doping infractions. It will also present the results of the approach that has been taken in the Netherlands, often acknowledged to be the most all-encompassing effort to tackle this particular problem.¹¹ Finally, advice will be given for athletes and their support team (such as coaches, physical therapists, nutritionists and physicians) on how to reduce the risk of an unintentional doping infraction.

For more than a decade, it has been known that nutritional supplements can be "contaminated" with doping substances, which means that the contents of the supplements are not identical to the list of ingredients on the label. Tennis has played a particular role in this debate because of the complexity of the cases of Bohdan Ulihrach and Greg Rusedski, who tested positive for nandrolone or nandrolone prohormones in 2002 and 2003, respectively. In June 2007, Guillermo Coria sued an American nutritional company for the financial damages he suffered during his 2-year suspension after also testing positive for nandrolone in 2001. This problem is of major concern to elite athletes, who can test positive in a doping test without knowingly taking banned substances. This so-called "inadvertent doping use" has resulted in an unknown number of positive cases because doping tests often rely on the presence of metabolites of banned substances in urine, and cannot discern between intentional and inadvertent use. In this article, doping is defined as substances that are included on the list of prohibited substances of the World Anti-Doping Agency (WADA) or (before 2003) the International Olympic Committee (IOC).

THE DOPING RISK OF SUPPLEMENTS

In the 1990s the IOC issued a public warning when certain supplements appeared to contain unlabelled pseudo-ephedrine, at that time a prohibited substance. This issue was brought to a head by sprinter Linford Christie, who tested positive for pseudo-ephedrine during the Olympic Games of 1988, but (as a rare exception) was not sanctioned because the likely source was a cup of ginseng tea.¹² Contamination of ginseng is often cited as a potential hazard.¹³

Christie also tested positive for nandrolone in 1999. In the UK, the number of nandrolone

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Abbreviations: BCAA, branched-chain amino acids; CLA, conjugated linoleic acid; DHEA, dehydroepiandrosterone; DSHEA, Dietary Supplement Health Education Act; HACCP, hazard analysis critical control points; IOC, International Olympic Committee; MDMA (or XTC), methylenedioxymethylamphetamine; NOC*NSF, Netherlands Olympic Committee/Netherlands Sports Confederation; NZVT, Nederlands Zekerheidssysteem Voedingssupplementen Topsport; OKG, ornithine-alpha-ketoglutarate; WADA, World Anti-Doping Agency

Box 1: Examples of nutritional supplements that have been contaminated with doping substances (in alphabetical order)

- Branched-chain amino acids (BCAAs)
- Carnitine
- Chrysin
- Conjugated linoleic acid (CLA)
- Creatine
- Glutamine
- Guarana
- Minerals
- Ornithine-alpha-ketoglutarate (OKG)
- Proteins
- Pyruvate
- Ribose
- Saw palmetto
- Tribulus terrestris
- Vitamins
- Zinc

positives jumped from an average of 3.4 in the years 1994–1998 to 17 in 1999; an increase from 0.08% to 0.29% of all the samples analysed.¹⁴ A possible cause of this increase was the ingestion of contaminated nutritional supplements. A few years later, it was concluded that this statistical increase appeared to have been exceptional and was only present within the UK in 1999,¹⁵ but from 2000 onwards the subject of nutritional supplements and doping entered the limelight. In subsequent years, more and more studies were published that confirmed the hypothesis that supplements could indeed cause unintentional doping infractions.^{16–22} Other publications showed that unlabelled doping substances can be found in a variety of products^{23–26} and thoroughly discussed the risks for elite athletes.^{27–30}

The information on this issue came mainly from the WADA-accredited laboratory in Cologne that conducted an IOC-sponsored study in 2004.¹⁸ This study showed that 14.8% of 634 freely available substances contained anabolic agents that were not declared on the label. These products were partly selected because the producers of these substances also sold pro-hormone containing products. The risk of buying a contaminated supplement is about twice as high in products from such companies. The amounts that were found varied from 10 ng/g or parts per billion (ppb) to 190 µg/g or parts per million (ppm). Later studies found even higher and profoundly dangerous amounts of anabolic agents, up to 17 mg of unlabelled metandienone per tablet.^{31–33}

The sport of tennis has had its own experiences regarding this subject. Bohdan Ulihrach and Greg Rusedski are rare examples of athletes who tested positive in a doping case, but were exonerated because they might have used contaminated supplements. The complexity in these cases lies in the fact that the source of their positive tests might have been supplied by the testing authority itself: the Association of Tennis Professionals (ATP). The tribunals, special enquiries, and task forces that studied these cases all named the nutritional supplements provided by the ATP organisation as the most likely source of the nandrolone metabolite. However, many minerals and vitamins that were available on the ATP tour have actually been tested, and the true source has never been confirmed. Because there were more (anonymous) cases within

the ATP that were all linked, as demonstrated by an analytical anomaly noticeable in the mass spectrogram of the urine analysis, all of these tennis players have been cleared. Such exoneration by an anti-doping tribunal is extremely rare.

CHARACTERISTICS OF CONTAMINATION

The fact that nutritional supplements can lead to a positive urine test has been consistently found in various studies. The risk of producing a positive doping test can be present for hours to days after the ingestion of one single supplement, depending on the substance, dose, and individual variation in metabolism.^{16–18 21 24 34 35}

The difficulty of finding possible contaminations of a nutritional supplement was shown in one of the very first studies addressing this problem. A group from an anti-doping laboratory in Los Angeles, California, USA proved the existence of tablet-to-tablet variation in contaminations.²⁴ This variation was confirmed later that year¹⁷ and is still likely to exist. The experiences from the laboratories show that contaminations can be present in the raw materials that are used, both in the active ingredients and in the substances used to make tablets or capsules. This type of contamination is often referred to as “cross-contamination”. A second source of contamination might result from a lack of sufficient hygiene in the machinery that is being used during the production process.

Contamination problems in nutritional supplements can be found in any country. It concerns all types of nutritional supplements (box 1) and all forms, including powders, pills, capsules, and liquids. Likewise, experience shows that contaminations can occur with a multitude of doping substances (box 2).

Even though these lists might not be complete, the variety of substances found indicates the magnitude of the problem. It also shows that contaminations in nutritional supplements are most likely to occur with substances that are part of the groups of anabolic agents or stimulants.

The problems surrounding nutritional supplements that contain unlabelled doping substances have often been attributed to the Dietary Supplement Health Education Act (DSHEA)

Box 2: Examples of contaminations found in nutritional supplements (in alphabetical order)

- 4-Androsten-3,17-diol
- 4-Androsten-3,17-dion
- 5-Androsten-3,17-diol
- 19-Nor-4-androsten-3,17-diol
- 19-Nor-4-androsten-3,17-dion
- 19-Nor-5-androsten-3,17-diol
- 19-Nortestosterone (nandrolone)
- Benzylpiperazine
- Caffeine (off the WADA doping list since 1 January 2004)
- Dehydroepiandrosterone (DHEA)
- Ephedrine
- Methandienone
- Methylenedioxymethylamphetamine (MDMA or XTC)
- Nor-pseudo-ephedrine
- Sibutramine
- Stanozolol
- Testosterone

that was passed in the USA in 1994. The DSHEA has often been accused of introducing a system where quality control is lacking.^{13 28 36 37} This Act has undoubtedly played a large role in creating the problem of contaminated substances, because of the strong influence of the USA on the global market and the consequent spread of (traces of) anabolic agents and strong stimulants. But this problem does not only originate from the USA. Any facility that is part of the production or storage process of nutritional supplements, or that handles doping substances in addition to doping-free products, could be a source of the eventual downfall of an ignorant athlete. Globally there is a great difference in the quality procedures surrounding pharmacological medications and nutritional supplements, but the difference between these two groups is not always as clear as it should be.^{7 38-40}

In 2004 a new law was introduced in the USA, the Anabolic Steroid Control Act, which goes some way to recognising that there were flaws in the original legislation. It is not to be expected, however, that the chance of contamination will diminish rapidly. Not only is DHEA still freely available under the new law, but there are also many other countries and many other substances that can still cause doping problems. The Directorate for Health in the Netherlands, for example, has already found traces of designer steroids in regular supplements.

INITIATIVES TO REDUCE THE RISK OF USING CONTAMINATED SUPPLEMENTS

Over the years different approaches have been used to address the problem of contamination. Countries such as Norway, Switzerland, and the UK have tried to help the athletes and their nutritional advisors to choose supplements from companies that are deemed to be reliable. WADA has organised two symposiums to address the issue, but is primarily waiting for the industry to solve the problem that stems from their own production lines. The ATP is the only sports organisation that is actually involved in a system to provide athletes with nutritional supplements that are as doping-free as possible. After their unfortunate experiences, they started a system whereby a strict selection of tested supplements can be provided to athletes. The ultimate responsibility, however, still lies with the athlete.

Initiatives in Australia, Austria, France, Germany, and North America also include laboratory analyses in order to aid athletes in their decision when choosing between the large variety of available supplements. However, these systems do not always incorporate batch-by-batch analysis or the involvement of anti-doping organisations. As well as these official initiatives, some nutritional supplement companies conduct their own testing, but these results are not supervised by an independent third party and sometimes have considerably higher limits of detection. It is encouraging to note that in one study of 201 supplements, all produced under pharmaceutical guidelines, no unlabelled anabolic steroids were detected;⁴¹ however, without confirmation on a larger scale it is too early to conclude that such supplements do not pose any risks to athletes.

THE DUTCH EXPERIENCE

The Cologne study, performed in 2001, showed that the Netherlands faced one of the biggest contamination issues in Europe.¹⁸ Together with some high-profile doping cases, this finding prompted a preliminary study, which would serve as an extra service to the Dutch athletes in their preparation for Salt Lake City 2002 and as an opportunity for the participating partners to devise a structural solution to the problem.

In November 2001, the athletes nominated to go to the Winter Olympics in Salt Lake City 2002 were given an

opportunity to have their supplements tested for doping substances. They were asked to buy a supply of the nutritional supplements they were going to use during their preparation for the Olympics from a controlled sample of one batch. From this supply, a random selection of supplements was tested for several anabolic steroids, their precursors, and several stimulants.

The results of this preliminary study gave a clear insight of the seriousness, size, and scope of the problem. Of the 69 supplements that were submitted (mainly vitamins, minerals and creatine), 13 (19%) contained unlabelled doping substances.⁴² Most products showed traces of caffeine and/or ephedrine, one product contained a small amount of 3,4-methylenedioxyamphetamine (better known as MDMA or XTC), and five products contained anabolic steroids. By pure chance, two different batches of one single product were tested as well, yielding one positive and one negative finding.

These results were reported to the relevant public authorities. The local authorities took appropriate steps to eradicate the amphetamine traces from the public food supply, but concluded that this particular issue is not a concern from a public health perspective but is first and foremost a sport and a doping problem, as the trace amounts found in supplements would not endanger general health.

NZVT: MAXIMAL RISK REDUCTION

The results and experiences of this preliminary study were used to develop a structural solution to the issue of nutritional supplements and doping. The branch organisation for supplements producers and providers in the Netherlands (NPN), the Netherlands Olympic Committee**Netherlands Sports Confederation (NOC*NSF)*, and the Anti-Doping Authority of the Netherlands set up the Netherlands Security System Nutritional Supplements Elite Sports ("Nederlands Zekerheidssysteem Voedingssupplementen Topsport" or NZVT). This was strongly supported by the Ministry for Health, Welfare and Sports (VWS), the NOC*NSF Athletes Commission, and the National Institute of Public Health and the Environment (RIVM). All parties are involved on a not-for-profit basis; the producers pay only for the analysis. The NZVT consists of four elements:

- Criteria enriched hazard analysis critical control points (HACCP) system. The companies and producers joining the NZVT system have to follow special procedures for the purchase of raw materials, production, and labelling of nutritional supplements. For quality control, a specific HACCP system has been developed by the branch organisation NPN, in which extra criteria is incorporated into the various stages of the production process to eliminate the risks of cross-contamination with doping substances. HACCP is an extensive set of regulations that ensures that any type of food is safe to be consumed.
- Laboratory analyses. Laboratory analyses are conducted on every batch of nutritional supplements that wish to become part of the NZVT system. For this purpose, the NZVT Standard Analytical Procedure has been developed in co-operation with the participating laboratories. This procedure consists of sample taking, analytical processing, and the listing of relevant doping substances and their threshold levels relating to the doping list. Testing is performed for stimulants and anabolic steroids because these are the most likely sources of contamination.
- Security analysis. The National Institute of Public Health and the Environment randomly conducts extra, double analyses as an extra security. This is performed by taking the same samples originally selected from the batches of nutritional

supplements or by taking consumer units from these batches on the market. The security analyses are also conducted according to the NZVT Standard Analytical Procedure.

- Communication to athletes. The batches of nutritional supplements that have been produced according to the NZVT HACCP system standards are communicated to the athletes through a secured website (<http://antidoping.nl/nzvt>). Visitors to the website are informed that all statements regarding security guarantees are only applicable to the specified product/batch combination and that the "strict liability" rule, as applied in anti-doping cases, is not lifted. Website users are warned that other products and all other batches of the same product might not fulfil the NZVT requirements.

TESTING RESULTS FROM NZVT

The NZVT was launched in November 2003 and the results of the laboratory tests are presented in table 1. It is striking to see that despite the HACCP-plus system and 3 years of experience, there are still some positive cases. Apparently, a quality system that is infallible on paper is still not a guarantee that doping-free supplements will be produced. This is the reason why batch-by-batch analysis is still a prerequisite for producers to join the NZVT.

The six positive test results consist of two ephedra positives and four steroid positives (DHEA and 5-androsten-diol). The sources of these positives, as far as could be traced, were either raw ingredients or the material used to make capsules. In the production facilities of the end product, no doping substances are allowed, which prohibits cross-contamination at this stage. Naturally, the batch numbers of these positive cases were not posted on the NZVT-website, and the producers were free to bring these particular batches onto the market as they did not pose a major health risk to the general public.

The fact that contaminations easily occur was also shown in the early stages of the NZVT. Of the 96 products tested, 10 were shown to contain traces of (unlabelled) caffeine. As caffeine is an ingredient that is often used by the supplement industry, the presence of this substance in products where it is not intended to be an ingredient is another clear indication that cross-contamination between different products made in the same production facility can easily occur. This underpins the necessity of producing legal supplements via completely separate production lines.

The NZVT is considered a success by athletes, their support personnel, and the parties involved in running the system. It gives willing producers of nutritional supplements the platform to express their commitment to a doping-free sport and shows their eagerness to go great lengths to produce a doping-free product. Despite the positive cases that sometimes still occur, the percentage of contaminated products is far lower than the previously found percentages in the Netherlands.^{18 42} Most of all, the system gives athletes an opportunity to choose those products that can truly be called "athlete friendly". The website has been frequented daily by scores of visitors, which is

satisfactory for a small country like the Netherlands with relatively few elite athletes. An evaluation during the Olympic Games in Athens showed that of all Dutch athletes who used supplements, 78% chose NZVT supplements. This amounts to 65% of all Dutch Olympic athletes, indicating that the primary message of the NZVT ("only use those products that are really useful") is also catching on.

ANALYTICAL ISSUES

All NZVT analyses were conducted by one of four possible institutions: the laboratories accredited for the analysis of doping substances in nutritional supplements in Ghent (Belgium) and Cologne (Germany), the National Institute of Public Health and the Environment (RIVM) in Bilthoven (the Netherlands), and TNO Nutrition and Food Research in Zeist (the Netherlands). The methods used by the laboratories in Ghent, Cologne, and Bilthoven have been published elsewhere.^{18 43-46}

Based on the published facts that a precursor of an anabolic steroid in an amount between 1–10 µg can cause a positive doping test,^{18 24} and based on the fact that athletes easily use 50 g of supplements per day or more, a reporting threshold value of 10 ng/g or 10 ppb for all anabolic steroids is used in all tests. This value also allows for individual variations in metabolism. Excretion studies for stimulants are rare, but similar considerations led to the conclusion that for stimulants, a reporting threshold value of 100 ppb is opportune.

NO 100% GUARANTEE

The only way athletes are able to enjoy a 100% guarantee is when they decide not to take any supplements at all. But there are certainly some circumstances when dietary supplements provide an added benefit to diet and, in the world of elite sport where the ultimate goal is to reach one's best, it is not fair to deny athletes the use of legal substances that could improve their health, such as anti-oxidants and multivitamins. Although there are some studies that suggest that there is a relationship between (legal) supplement use and (illegal) doping use, these are only based on epidemiological data and causality has never been established.^{47 48}

Two types of contamination can be identified. The first type is from malpractising producers who do not care about consumer health or even deliberately spike products with known effective substances such as anabolic steroids or their precursors. Generally, such companies change identity quickly and most often sell their products over the Internet. Occasionally, the products might emerge in regular shops, but a country's health directorate is highly likely to pick up such products and take them off the market. Most of the time this type of company uses advertisements with unrealistic claims, and athletes and their support personnel should be able to avoid this type of supplement easily.

The second type of contamination is more subtle and more difficult to detect, and thus more of a concern to athletes with good intentions. The nature of the origin of such contaminations (mostly cross-contamination from other products, frequently not in the facility where the end-product is made and packed and therefore always unexpected) makes it very difficult to pick up such contaminations, even for well intentioned producers who follow strict quality procedures. Experience shows that such supplements can contain doping substances despite these extra efforts. Even though the level of such contaminations might be low, even very low amounts of doping substances can suffice to cause a positive urine sample for a window of several hours after the consumption of such a product.

Table 1 Testing results of NZVT from 2003–2006

Year of analysis	No. of completed analyses	Positive cases
2003	99	1 (1.0%)
2004	72	3 (4.2%)
2005	53	0 (0.0%)
2006	72	2 (2.8%)
Total	296	6 (2.0%)

Even athletes who are careful can test positive for doping because of a contaminated nutritional supplement. This is a discomfoting thought, but an unavoidable consequence of the current situation in the nutritional supplement industry. However, 8 years after the sudden rise in nandrolone positives in the UK and the wealth of experience with this issue in the mean time, ignorance is no excuse for today's elite athletes.

Athletes should rethink whether there is an actual positive balance for them when determining the cost/benefit ratio of taking a particular supplement. Such an evaluation should preferably be performed with the aid of a nutritional expert. If it is concluded that supplementation could be beneficial, the athletes, with the aid of their support team, should select a product that has the slimmest possible chance of being contaminated.

HOW TO DEAL WITH SUPPLEMENTS IN THE FIELD OF PRACTICE

Many athletes tend to take supplements for a variety of reasons.⁴⁹⁻⁵³ The first rule in any educational effort regarding supplements is that athletes should be cautioned against their indiscriminate use. Supplements can play a role in an athlete's diet, but confirmation of their added benefit should be sought with an appropriate expert before using them.

The second step is to try and identify those supplements that have the slimmest chance of being contaminated with doping substances. Companies that sell products containing doping substances should definitely be avoided, and it is prudent to disregard companies with unrealistic claims in their advertisements. This includes advertisements that mention "IOC approved" or "WADA tested" on their label, as no such approvals exist. The basic anti-doping rule remains that at all times athletes are responsible for the substances that are within their bodies, and a simple appeal based on an advertisement does not lift this rule of strict liability.

Athletes and their support personnel should be aware that no system is able to provide a 100% guarantee of doping free supplements. Contaminations can occur in many ways, which leads to possible package-to-package or even tablet-to-tablet variation. No sampling protocol is able to cater for all these possibilities. However, there are protective systems that can be used to bring down the chances of ingesting contaminated supplements to very close to 0%. Such athlete-friendly systems

should address the problems surrounding possible contaminations mentioned in this article, and well intentioned producers should acknowledge that contaminations can occur outside their control. Generally speaking, any system that ensures that the particular product is produced in a "doping-free environment", meaning that all parts of the production process are free of any substances prohibited by WADA, will provide an athlete with a trustworthy product. But as the NZVT experience has shown, even quality systems that are foolproof on paper cannot prevent contaminations with doping substances. Therefore, the best available option for athletes is to only use supplements that have been analysed in a knowledgeable laboratory on a batch-by-batch basis.

CONCLUSIONS

The problem of nutritional supplements and doping infractions is an issue that every sport organisation, including anti-doping organisations, has been obliged to address over the past 8 years. Tennis is a prime example of a sport where some trips and subsequent strides forward have eventually led to a practical solution that seems to serve athletes well. In the end, a situation where the strict liability rule in anti-doping is compromised is harmful to the entire anti-doping fight. The rulings on the cases of Rusedski and Ulihrach should remain very rare exceptions. It is precisely for this reason that some form of support system, preferably one with batch-by-batch analyses, is imperative for athletes and their support personnel. All organisations and individuals that love sport owe it to themselves to try and remedy the potentially disastrous situation of a well intentioned athlete unintentionally testing positive.

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What is already known on this topic

- Nutritional supplements can contain unlabelled substances that are on the List of Prohibited Substances as published yearly by the World Anti-Doping Agency.
- They are a potential source for unintentional doping violations, leading to severe sanctions for well-intentioned elite athletes.

What this study adds

- This article reviews 8 years of experience on this topic, and adds the results and experiences of the Netherlands Security System Nutritional Supplements Elite Sports (better known by its Dutch acronym "NZVT").
- Guidelines for athletes, nutritionists, physicians, and others on how to choose a low-risk supplement are provided.

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COMMENTARY

This paper highlights the issues arising from the use of nutritional supplements in relation to doping control. The authors draw attention to the risks associated with the use of untested supplements for athletes that can be subjected to doping control. In addition, they describe a quality system set up in The Netherlands to supply athletes with information about 'low-risk' dietary supplements. They also demonstrate the necessity for laboratory-based testing in addition to the HACCP procedures that are of utmost importance in ensuring the quality athletes expect. However, as stated in the article, additional efforts by governments, the industry and anti-doping organisations have to be made to reduce (un)intentional malpractice in the supplement industry.

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