



Doping substances in dietary supplements

ORIGINALARTIKKEL

CHRISTINE HELLE

Oslo

She has contributed to the idea, design, interpretation of data, literature search and preparation of the manuscript

Christine Helle, cand.scient. and registered dietitian. She is self-employed and has worked as consultant for Anti-Doping Norway in this project.

The author has completed the ICMJE form and declares no conflicts of interest.

ANNE KRISTI SOMMER

Norwegian Food Safety Authority

She has contributed to the idea, data analysis and revision of the manuscript.

Anne Kristi Sommer, food scientist. She works in the Norwegian Food Safety Authority, mainly in the area of dietary supplements.

The author has completed the ICMJE form and declares no conflicts of interest.

PER VIDAR SYVERSEN

Department of Reliable Supply

Norwegian Medicines Agency

He has contributed to the analysis of data and revision of the manuscript.

Per Vidar Syversen, PhD in biochemistry, responsible for analyses in cases of quality failure and special analysis projects.

The author has completed the ICMJE form and declares no conflicts of interest.

FREDRIK LAURITZEN

E-mail: fredrik.lauritzen@antidoping.no

Department of Prevention and Public Health

Anti-Doping Norway

He has contributed to the idea, design, data analysis and preparation and approval of the manuscript.

Fredrik Lauritzen, sports physiologist with a PhD in neuroscience, head of department.

The author has completed the ICMJE form and declares no conflicts of interest.

BACKGROUND

International studies have shown that 12–58 % of all dietary supplements intended for people who exercise and engage in sports contain substances prohibited by the World Anti-Doping Code (WADC). In some cases, the doping substances are not declared on the product label, and the consumer may therefore be unaware of what he/she ingests. Many of the substances may cause adverse health effects, and sale of such products is illegal in Norway.

MATERIAL AND METHOD

To investigate the prevalence of doping substances in dietary supplements sold on the Norwegian market, a total of 93 high-risk products from online shops targeting Norwegian consumers were analysed for substances on the WADC Prohibited List and pharmaceutical drugs. All supplements were marketed as able to boost energy levels and/or having a muscle-building or fat-burning effect. The products were selected on the basis of tips received, online forums and/or international lists.

RESULTS

Altogether 21 of 93 (23 %) products analysed contained prohibited substances, pharmaceutical drugs and/or illegal amounts of caffeine. Substances on the WADC Prohibited List were detected in 8 of the 93 (9 %) dietary supplements. All products containing doping substances were declared as containing one or more banned substances.

INTERPRETATION

The results show that using apparently legal dietary supplements purchased in online shops targeting Norwegian consumers involves a risk of inadvertent doping and adverse health effects.

In recent years, a number of international studies have reported findings of substances prohibited by the World Anti-Doping Code (WADC) and pharmaceutical drugs in dietary supplements marketed to people who exercise or engage in sports (1) (see definitions in Box 1). Unintentional intake of doping substances in the form of dietary supplements may cause athletes who compete under the World Anti-Doping Code to be sanctioned for an anti-doping rule violation. Moreover, many of the substances found in dietary supplements may cause serious adverse health effects.

Box 1 Definitions

DOPING SUBSTANCES

Drugs that are included in the Prohibited List in the World Anti-Doping Code and used with an intention to boost performance. These drugs are also used to alter the body's physical appearance.

DIETARY SUPPLEMENTS

Products that are intended to supplement a regular diet. The products must be concentrated sources of vitamins and minerals or other substances with a nutritional or physiological effect. They must be sold in pre-packaged form in appropriate dosages, and taken in small, measured quantities (17).

PHARMACEUTICAL DRUGS

Substances, drugs or preparations that are intended for or dispensed to prevent, cure or alleviate illness, symptoms or pain, affect physiological functions in humans or animals, or for internal use to detect illness (18).

It has been estimated that 6–9 % of all anti-doping rule violations (ADRV) internationally are caused by the use of contaminated dietary supplements (2). Positive doping tests caused by use of dietary supplements became a major problem in elite sports around the year 2000. At that time, a study from the Cologne doping laboratory found that 14.8 % of 634 dietary supplements purchased from 13 countries contained undeclared doping substances, so-called contaminated supplements (3). Later studies have shown that 12–58 % of all dietary

supplements are contaminated with anabolic steroids, stimulants and/or beta-2 antagonists (1). The concentration of such contaminating doping substances is usually low, but still traceable in a sample, because the analyses are extremely sensitive (4).

In a study of dietary supplements on the US market, Judkins et al. found that 25 % and 11 % of high-risk supplements were contaminated with undeclared anabolic steroids and stimulants respectively (5). The risk of contamination by doping substances was highest in supplements claimed to boost physical or cognitive performance and/or would help modify the body's appearance. However, doping substances have also been detected in vitamin supplements (6). The latter is usually caused by cross-contamination during manufacturing. It is also assumed that some contamination is caused by companies who deliberately add doping substances to dietary supplements to enhance their effect and thus boost sales (4).

The US anti-doping organisation (USADA) has published a list of dietary supplements with a high risk of containing doping substances on the website www.supplement411.org. The list includes supplements where doping substances have been detected or where such substances are declared on the product (7). The list is updated on a regular basis. In 2014, the Dutch anti-doping organisation investigated the prevalence of contamination in a sample of such high-risk supplements. They found contamination by doping substances in 25 of 66 (38 %) dietary supplements sold through Dutch websites (8). In three (5 %) of these products, doping substances were detected in concentrations that could cause serious adverse health effects.

There have also been cases of ADRV caused by dietary supplements containing where the doping substance was declared on the product label. In recent years, Norway has seen several ADRV involving the stimulant methylhexanamine. This is a pharmaceutical drug which is not permitted to be sold as a dietary supplement in Norway. In the US, several cases of serious health injury and death are reported to have been caused by supplements containing methylhexanamine (9).

Designer steroids and selective androgen receptor modulators (SARM) are also sold as dietary supplements in a number of countries, even though they are pharmaceutical drugs still undergoing clinical testing (10). Sale of such products is illegal in Norway.

The Norwegian Food Safety Authority (NFSA) is a governmental body whose remit includes monitoring of dietary supplements sold in Norway. The aim is to reveal any content of illicit substances such as pharmaceutical drugs, heavy metals and other substances that may pose a health risk. Dietary supplements containing illegal substances and/or excessive concentrations of certain substances are withdrawn from the market.

In 2015, the Norwegian Food Safety Authority collaborated with Anti-Doping Norway to investigate the prevalence of substances on the WADC Prohibited List in dietary supplements marketed to people who exercise and engage in sports. The inspectors from the NFSA collected 116 dietary supplements, most of them purchased in shops. No doping substances were detected, but some supplements contained pharmaceutical drugs and excessive concentrations of caffeine (unpublished data).

In this study, we wished to investigate the prevalence of doping substances and pharmaceutical drugs in dietary supplements purchased anonymously from online shops, and investigate whether the prevalence was higher than in dietary supplements purchased in regular shops.

Material and method

Only dietary supplements sold by online shops targeting Norwegian consumers were included. To identify relevant online shops we searched for supplements from brands included in USADA's high-risk list (7). Online shops that sold any of these products were included. In addition, we selected online shops after searching through web forums where

suspicious supplements are discussed by the members, and online shops suspected of selling illegal supplements according to tips received by Anti-Doping Norway. Products were collected from a total of nine online stores, eight of which were registered in Norway and one in Sweden.

In the selection of supplements we prioritised products that were marketed with one or more of the following effects: boosting energy levels/stimulating effect; fat-burning/weight loss effect; muscle-building effect; and/or increased testosterone level/hormone-regulating effect. All identified products that complied with these criteria were included in the study.

The supplements were purchased anonymously. All products were paid by credit card. Two containers of each product were collected to enable reanalysis and confirmation of any detection of prohibited substances.

ANALYSES OF THE SUPPLEMENTS

The samples were analysed by the laboratory of the Norwegian Medicines Agency. They were primarily analysed by gas chromatography linked to a mass spectrometer (GC-MS). The results were assessed against a substance database (NISO7), with additional manual analysis. Samples that tested positive for doping substances and pharmaceutical drugs, as well as suspicious samples with no concrete findings, were further analysed by liquid chromatography linked to a high-resolution mass spectrometer.

Results

A total of 93 dietary supplements were collected for analysis (Table 1). These dietary supplements came from 49 different manufacturers. The products had been manufactured in the following countries, with the number of products in brackets: USA (68), Sweden (7), Canada (6), EU (4), Norway (2), Denmark (2), UK (2), Belgium (1) and Poland (1). Of the 93 supplements, 51 (55%) were brands included in USADA's high-risk list. Altogether 21 of the 93 (23%) products analysed contained substances on the WADC Prohibited List, pharmaceutical drugs or illegal amounts of caffeine.

Table 1

Distribution of categories of dietary supplements among selected high-risk products from online shops that target Norwegian consumers

Category of dietary supplement	Number of products
Pre-workout supplement	25
Muscle-building	20
Fat-burning	19
Amino acids, proteins	19
Creatine	5
Hormone regulator	4
Inflammation inhibitor	1
Total	93

FINDINGS OF SUBSTANCES ON THE WADC PROHIBITED LIST IN DIETARY SUPPLEMENTS

Doping substances were detected in 8 of the 93 supplements, whereof seven were in the category muscle-building and one was a pre-workout supplement (Table 2). In addition, one supplement was declared to contain a SARM, but this was not detected in the analysis.

Table 2

Eight dietary supplements with doping substances detected among 93 high-risk products from online shops that target Norwegian consumers

Category of dietary supplement	Doping substance detected	Category of doping substance	Doping substance declared
Muscle-building	Methylstenbolone	Anabolic androgen steroid	Methylstenbolone
Muscle-building	Trendione	Prohormone for trenbolone	Trendione
Muscle-building	Trendione	Prohormone for trenbolone	Ostarine
Muscle-building	a) Ostarine b) Ibutamoren	a) Selective androgen receptor modulator b) Growth hormone secretagogue	Ibutamoren
Muscle-building	6-beta-bromoandrostendione	Aromatase inhibitor	6-beta-bromoandrostendione
Muscle-building	Androsta-3,5-dien-7,17-dione	Aromatase inhibitor	Androsta-3,5-dien-7,17-dione
Muscle-building	Androsta-3,5-dien-7,17-dione	Aromatase inhibitor	1,4,6-androstadriendione
Pre-workout supplement	Higenamine	Beta-2 antagonist	Higenamine

A total of seven different substances on the WADC Prohibited List were detected (11). All supplements in which illegal substances were detected had declared the doping substances on the product label (11). However, the analysis revealed that two of the products contained a doping substance different from the one that was declared (Table 2).

Seven of eight supplements containing doping substances were brands included in USADA's high-risk list (7). All the supplements containing identified substances were purchased from the online shop registered in Sweden, and all were manufactured by US companies.

PHARMACEUTICAL DRUGS IN DIETARY SUPPLEMENTS

Another nine of the 93 dietary supplements analysed contained substances that are classified as pharmaceutical drugs in Norway and are illegal ingredients in dietary supplements (Table 3). Three of the products contained synephrine, a stimulant included in the World Anti-Doping Agency's Monitoring Program (12). Two of these supplements also contained caffeine, which in combination with synephrine may cause cardiovascular disorders, osteoporosis and damage to the central nervous system (13). One product contained phenethylamine as well as synephrine and caffeine. Two of the supplements contained yohimbine. Other findings of drugs included hordenine, berberine, ecdysterone and evodiamine, all of which are found naturally in certain herbs, but may also have been added illegally. These substances were not quantified.

Table 3

Nine dietary supplements with pharmaceutical drugs detected among 93 selected high-risk products from online shops that target Norwegian consumers

Category of dietary supplement	Drug detected
Pre-workout supplement	Synephrine
Fat-burning	Phenethylamine, synephrine and caffeine
Fat-burning	Synephrine and caffeine
Pre-workout supplement	Yohimbine
Fat-burning	Yohimbine
Fat-burning	Hordenine
Muscle-building	Berberine
Muscle-building	Ecdysterone
Fat-burning	Evodiamine

FINDINGS OF ILLEGAL AMOUNTS OF CAFFEINE IN DIETARY SUPPLEMENTS

Four dietary supplements contained an excessive concentration of caffeine (Table 4). Dietary supplements sold in Norway may not contain more than 300 mg caffeine per daily dose (14). These products had a caffeine content of 400–520 mg per daily dose.

Table 4

Four dietary supplements with excessive caffeine content among 93 high-risk products from online shops that target Norwegian consumers

Category of dietary supplement	Caffeine concentration detected (mg/daily dose)
Pre-workout supplement	520
Fat-burning	510
Fat-burning	480
Pre-workout supplement	400

Of the 13 dietary supplements that contained pharmaceutical drugs or excessive concentrations of caffeine (Tables 3 and 4), six were brands included in USADA's high-risk list. Nine of the products were purchased from the online shop registered in Sweden, while four were purchased from Norwegian online shops. Twelve of the dietary supplements were manufactured in the USA and one in Sweden.

Discussion

Altogether 21 of the 93 (23 %) dietary supplements analysed contained substances prohibited by the WADC, illegal pharmaceutical drugs or illegal concentrations of caffeine. We detected substances on the WADC Prohibited List in 8 out of 93 supplements. Two of these products were declared to contain a prohibited substance other than the one that was detected. However, we did not detect prohibited substances in any supplement that had not declared a prohibited substances on the product label.

Unintentional doping may occur in three ways as a result of dietary supplement use: the doping substance is not declared on the product label; the doping substance is declared, but with a name that differs from the one on the WADC Prohibited List; or the doping substance is declared with its correct name, but the consumer is unaware that it is included in the Prohibited List. In our study, the doping substances detected were declared on the product label, and there is thus less risk that they may unintentionally cause a positive doping test. The supplements that contained doping substances were marketed as having a stimulating and muscle-building effect.

This illegal online sale of doping substances in the form of dietary supplements represents a problem. Since 2002, different variants of anabolic steroids have been detected in as much as 20 % of all sports supplements traded on the world market, and many of these substances are declared on the product label (15).

When compared to findings of doping substances by similar studies conducted in the USA

(5) and the Netherlands (8), a smaller proportion of the supplements included in our study contained doping substances, pharmaceutical drugs or other illegal concentrations and combinations of ingredients. This may indicate that there is less commerce in dietary supplements containing doping substances on the Norwegian market, when compared to the countries mentioned. Still, it is worth noting that the results of such investigations will largely depend on the selection of dietary supplements that are analysed.

We identified substances from the same Prohibited List categories as those in the review by Martinez-Sanz et al. (1), i.e. anabolic steroids, prohormones, growth hormones, selective androgen receptor modulators, aromatase inhibitors and beta-2 antagonists. As in the studies reviewed, we detected doping substances in supplements marketed as having a stimulating and muscle-building effect, and we detected pharmaceutical drugs in fat-burning supplements.

Even though Norway has one of the world's strictest national regulations for sale of dietary supplements, parts of the industry still engage in questionable practices. This was confirmed by two incidents that occurred during our collection of dietary supplements. The first occurred when we contacted the online shop registered in Sweden to enquire whether the supplements might be seized by the Norwegian customs. In an email, the company replied that they had established a system to avoid customs inspections. When the packages arrived, they all turned out to have been mailed from Oslo.

The second incident occurred when we were contacted by telephone by two companies from whom we had ordered supplements and who offered us a product with a stronger stimulating effect. The caller informed us that he also sold synephrine, a possibly addictive central nervous system stimulant that structurally resembles ephedrine, as well as other illegal supplements. The caller told us that these products were not advertised in the online shop, because the Norwegian Food Safety Authority did not permit their sale. We asked how to use the product, and were advised to double the recommended dose, because this would greatly improve the effect with no risk of adverse effects.

The method of collecting supplements anonymously is the most likely reason we were able to reveal sales of dietary supplements containing doping substances in 2016, after having failed in 2015. On several occasions, the Norwegian Food Safety Authority has seen that the rumour spreads when they undertake their monitoring programmes, and possibly, distributors dealing in illegal dietary supplements act more cautiously during these periods.

Legal dietary supplements shall not have any adverse effects when used by a healthy person in the recommended daily dose. Doping substances and pharmaceutical drugs detected in dietary supplements, however, may cause adverse health effects (9, 16). The level of risk will depend on the dosage and the length of time over which the substance has been used. There may also be individual differences between users with regard to their physiological tolerance for the various substances and possible medical contraindications. In addition, simultaneous use of other drugs and dietary supplements may affect the health risk (9). The effect of some dietary supplements is enhanced if they are ingested prior to or during exercise, and possible adverse effects of such supplements may thus be augmented.

New substances are constantly added to the market for dietary supplements without sufficient assessment of health risk. Examples include the selective androgen receptor modulators and designer steroids that we detected in two of the supplements. SARMs have been under development for 10–15 years, but few studies of positive and adverse effects have been undertaken on humans. SARMs were added to the WADC Prohibited List as far back as 2008, but they are not yet approved as pharmaceutical drugs. Because these substances are new, they may have deleterious effects that are as yet unknown. Moreover, we have little evidence regarding the long-term effects of such substances or the effects of high dosages in both the short and long term.

Conclusion

Dietary supplements declared to contain substances prohibited by the WADC are openly sold on the Norwegian market. Supplements that contain doping substances, pharmaceutical drugs and other illegal concentrations and combinations of ingredients may cause positive doping tests as well as health harms. The results highlight the importance of studying the product label of dietary supplements. If the label lists unknown substances or terms, the consumer should seek professional advice. This applies to all those who use dietary supplements, including recreational as well as elite athletes, but also coaches, doctors and other support personnel.

MAIN MESSAGE

Dietary supplements containing substances on the Prohibited List in the World Anti-Doping Code, pharmaceutical drugs and/or illegal amounts of caffeine are sold openly through online shops targeting Norwegian consumers

Use of dietary supplements may result in a failed doping test and adverse health effects

REFERANSER:

1. Martínez-Sanz JM, Sospedra I, Ortiz CM et al. Intended or unintended doping? A review of the presence of doping substances in dietary supplements used in sports. *Nutrients* 2017; 9: E1093. [PubMed][CrossRef]
2. Outram S, Stewart B. Doping through supplement use: a review of the available empirical data. *Int J Sport Nutr Exerc Metab* 2015; 25: 54–9. [PubMed][CrossRef]
3. Geyer H, Parr MK, Mareck U et al. Analysis of non-hormonal nutritional supplements for anabolic-androgenic steroids - results of an international study. *Int J Sports Med* 2004; 25: 124–9. [PubMed][CrossRef]
4. Maughan RJ, Shirreffs SM, Vernec A. Making decisions about supplement use. *Int J Sport Nutr Exerc Metab* 2018; 28: 212–9. [PubMed][CrossRef]
5. Judkins C, Hall D, Hoffman K. Investigation into supplement contamination levels in the US market. Cambridgeshire: HFL Ltd, 2007. <https://trustedsupplement.typepad.com/Informed-Choice-Sports-Supplement-Research.pdf> (14.1.2019).
6. Geyer H, Parr MK, Koehler K et al. Nutritional supplements cross-contaminated and faked with doping substances. *J Mass Spectrom* 2008; 43: 892–902. [PubMed][CrossRef]
7. USADA. Supplement 411 – High Risk Dietary Supplement List. Colorado Springs, USADA. <http://www.supplement411.org/hrl/#HighRiskListDui> (8.5.2016).
8. Duiven E, de Hon O, Spruijt L et al. Upper limit of the doping risk linked to sports supplements. Capelle aan den IJssel: Anti-Doping Authority Netherlands, 2015. https://www.dopingautoriteit.nl/media/files/2015/Upper_limit_of_the_doping_risk_linked_to_sport_s_supplements_20151120_DEF.pdf (12.10.2018).
9. Hatton CK, Green GA, Ambrose PJ. Performance-enhancing drugs: understanding the risks. *Phys Med Rehabil Clin N Am* 2014; 25: 897–913. [PubMed][CrossRef]
10. Rahnema CD, Crosnoe LE, Kim ED. Designer steroids - over-the-counter supplements and their androgenic component: review of an increasing problem. *Andrology* 2015; 3: 150–5. [PubMed][CrossRef]
11. World Anti-Doping Agency. The Prohibited List. <https://www.wada-ama.org/en/what-we-do/the-prohibited-list> (1.3.2018).
12. World Anti-Doping Agency. Monitoring program. <https://www.wada-ama.org/en/resources/science-medicine/monitoringprogram>(1.3.2018).

13. Mattilsynet. Advarer mot farlige slanke- og sportsprodukter med synefrin og koffein. http://www.matportalen.no/matvaregrupper/tema/diverse_retter_produkter_og_ingredienser/advarer_mot_farlige_slanke_og_sportsprodukter_med_synefrin_og_koffein (1.3.2018).
 14. Statens legemiddelverk. Klassifisering av koffeinholdige produkter. <https://legemiddelverket.no/godkjenning/klassifisering/ klassifisering-av-koffeinholdige-produkter> (1.3.2018).
 15. Mathews NM. Prohibited contaminants in dietary supplements. *Sports Health* 2018; 10: 19–30. [PubMed][CrossRef]
 16. Relis. Funn av nimesulid i kosttilskuddet Fortodol kjøpt i Norge! https://relis.no/Bivirkninger/Nytt_om_bivirkninger/2009/Funn_av_nimesulid_i_Fortodol/ (1.3.2018).
 17. FOR-2004-05-20-755. Forskrift om kosttilskudd. <https://lovdata.no/dokument/SF/forskrift/2004-05-20-755> (14.1.2019).
 18. LOV-1992-12-04-132. Lov om legemidler. <https://lovdata.no/dokument/NL/lov/1992-12-04-132> (14.1.2019).
-

Publisert: 25 februar 2019. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.18.0502

Received 11.6.2018, first revision submitted 16.10.2018, accepted 14.1.2019.

© Tidsskrift for Den norske legeforening 2019. Lastet ned fra www.tidsskriftet.no