

prescribed for comparable medicines. For the synthetic amphetamine-like β -methylphenethylamine and N, β -dimethylphenethylamine we used Attention Deficit Hyperactivity Disorder medicines Dexedrine and Ritalin as comparison (Catalent Pharma Solutions, 2017; Novartis Pharmaceuticals Corporation, 2017). Their maximum daily dose is set at 60 mg. For oxilofrine we used Carnigen as comparison. For this outdated medicine (1950-2010) the maximum daily dose was 40 mg of oxilofrine a day (Cohen et al, 2017).

Table 1. Maximum dose of medicines containing doping substances

WADA Doping Class	Substance	Maximum dose
Anabolic agents	testosterone	1000 mg*
	nandrolone	50 mg*
Stimulants	dexamphetamine	40 mg**
	methylphenidate	60 mg**
	ephedrine	50 mg**
Beta-2 agonists	salbutamol	40 mg*
	salmeterol	100 μ g**
	formoterol	72 μ g**
Beta-blocker	bisoprolol	10 mg**

* Maximum single dose ** Maximum daily dose (WADA, 2015)

Results

Screening results

Of the 66 sports nutrition supplements, 25 products (38%) tested positive for the presence of doping substances, 38 products (58%) tested negative, and the results of 3 products (4.5%) were inconclusive (Figure 2).

The positive products contained 5 different anabolic steroids (21 findings), 9 different stimulants (25 findings), 1 beta-2 agonist (4 findings) and 1 beta-blocker (1 finding) (Figure 3).

Three products (4.5%) contained high levels of synthetically produced stimulants. Two products contained oxilofrine as well as β -methylphenethylamine (BMPEA) and N, β -dimethylphenethylamine (NBDMPEA). One product contained only high levels of oxilofrine (Table 2).

During low level screening, the anabolic steroid boldione was detected the most (11 findings) followed by the anabolic steroid 5-androstene-3 β ,17 α -diol (17 α -AED) and the stimulant 4-methylhexan-2-amine (both 6

findings), The beta-2 agonist higenamine was detected 4 times.

The beta-blocker detected was bisoprolol (Figure 3).

Doping control risk assessment

Based on the results of this survey, the use of some sport nutrition supplements pose a significant risk of doping violations (Table 3).

Only for the three products with high level screening findings does this risk seem obvious. Maximum daily intake of the product with the highest risk is estimated to cause urine levels up to 20,000 times higher than the amount needed to provide a positive doping test. Of the products with only low screening findings only one product containing stimulants has the theoretical potential to do the same, but only if contamination levels are assumed to be at the high end of the ng·g⁻¹ range. The risk is predominantly caused by the product's high maximum recommended daily dose of 89 g. At the time of the study, the 4 products containing higenamine would also cause a clear potential risk for doping tested athletes. However, in September 2017 WADA introduced a reporting level for higenamine, which indicates that the laboratories are expected not to report higenamine urine levels below 10 ng·mL⁻¹ (WADA, 2018a). Since then, the four detected higenamine findings are unlikely to cause doping violations anymore.

Health risk assessment

Only the three high level screening findings give maximum ingestion levels well above the previous established threshold level of 1 mg (Table 4).

Table 4. Maximum intake compared to prescribed maximum dosages

Product	Compound	Maximum intake	Prescribed Maximum dosage	Factor
F1	BMPEA	0.39 g	60 mg	6.5
	NBDMPEA	15 mg	60 mg	0.3
	oxilofrine	0.17 g	40 mg	4.3
F3	BMPEA	0.98 g	60 mg	16
	NBDMPEA	0.48 g	60 mg	8.0
	oxilofrine	0.80 g	40 mg	20
G3	oxilofrine	0.17 g	40 mg	4.3

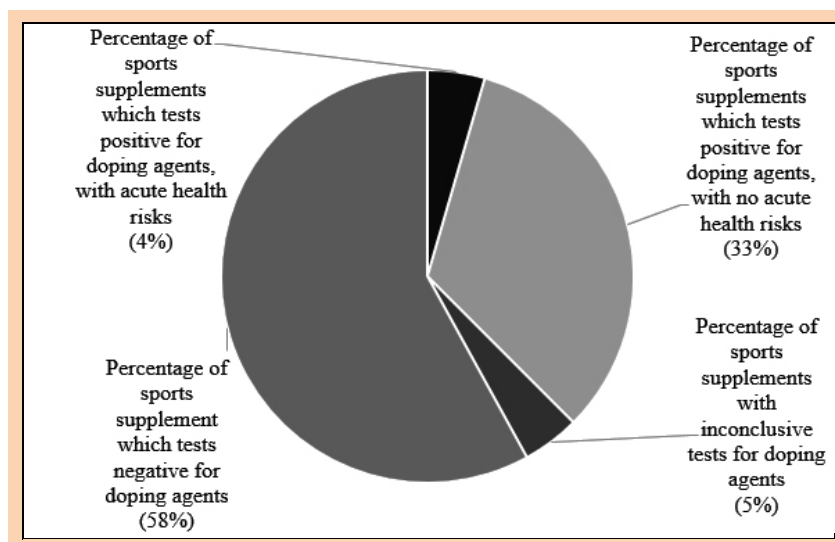


Figure 2. Overview of the main screening results.

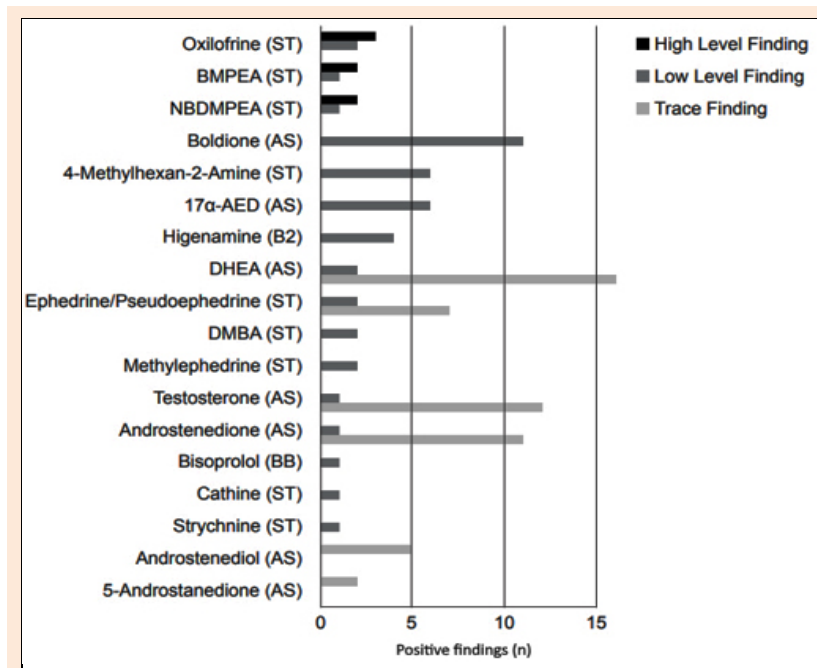


Figure 3. A vertical bar chart showing the detected doping agents, organized by number of hits.

Table 2. High level findings.

Supplement	Compound	Equation	X	Weight (g)	Estimated concentration (mg·g ⁻¹)
F1	BMPEA	Y=0.00254X - 0.07	27.6	1.08	26
	NBDMPEA	Y=0.0133X - 0.0141	1.06	1.08	1
	oxilofrine	Y=0.00177X - 0.0209	11.8	1.08	11
F3	BMPEA	Y=0.00704X - 0.407	57.8	1.19	49
	NBDMPEA	Y=0.0262X - 0.735	28.1	1.19	24
	oxilofrine	Y=0.0173X - 0.82	47.4	1.19	40
G3	oxilofrine	Y=0.00172X - 0.102	59.3	1.07	55

Table 3. Maximum doping substance intake and doping control risk

Supplement	Weight maximum daily dose	Compound (class)	Contamination calculation	Positive doping control threshold	Estimated potential risk
B5	1.5 g	higenamine	1.5 μ g	10 μ g	NO ²⁰¹⁷
F1	15 g	BMPEA †	0.39 g	50 μ g	YES
		NBDMPEA †	15 mg	50 μ g	YES
		Oxilofrine †	0.17 g	50 μ g	YES
F3	20 g	BMPEA †	0.98 g	50 μ g	YES
		NBDMPEA †	0.48 g	50 μ g	YES
		Oxilofrine †	0.80 g	50 μ g	YES
G2	3.0 g	Endogenous AAS (1)	3.0 μ g	1 mg	NO
		higenamine	3.0 μ g	10 μ g	NO ²⁰¹⁷
		oxilofrine	3.0 μ g	50 μ g	NO
		testosterone	3.0 μ g	1 mg	NO
G3	3.0 g	cathine	3.0 μ g	5 mg	NO
		ephedrine	3.0 μ g	10 mg	NO
		methylephedrine	3.0 μ g	10 mg	NO
		oxilofrine †	0.17 g	50 μ g	YES
		strychnine	3.0 μ g	50 μ g	NO
		testosterone	3.0 μ g	1 mg	NO
H2 ³	4.8 g	Endogenous AAS (6)	29 μ g	1 mg	NO
		ephedrine	4.8 μ g	10 mg	NO
		higenamine	4.8 μ g	50 μ g	NO ²⁰¹⁷
O2	4.8 g	higenamine	4.8 μ g	10 μ g	NO ²⁰¹⁷
Q1	89 g	DMBA	89 μ g	50 μ g	YES
		oxilofrine	89 μ g	50 μ g	YES

†= high level finding, 2017 = before September 2017 this product was estimated to potentially cause a positive doping test, 3=this product contained 3 components which were tested separately

Discussion

This study demonstrates that 38% of the selected high-risk sports nutrition supplements sold online contain undeclared doping substances. Based upon the recommended dose, the ingestion of some of these products could result in doping violations. The prescribed use of 3 products (4.5%) could impose general health risks.

In the present study we assessed the current prevalence of doping contamination in a range of high-risk sports nutrition supplements with specific functional claims. We selected 216 sports nutrition supplements claiming to modulate hormone regulation, stimulate muscle mass gain, increase fat loss, and/or boost energy. As we were interested in the unreported presence of doping substances, 32 products (15% preselection) were excluded for declaring a doping substance on the label and/or giving a specific warning for doping controlled athletes (Figure 1). Nevertheless, these products may pose significant risks for athletes concerning unintentional doping violations and general health.

We purchased and analyzed 66 products, 25 (38%) of which contained undeclared doping substances. As in previous prevalence studies 15-24% of high-risk sport supplements contained doping agents (Geyer et al., 2003; Judkins et al. 2007) (Table 5), the sports supplements industry doesn't appear to be solving its contamination and spiking problem. Table 5 may at first sight give the impression that the situation is deteriorating, but Chi-Squared testing indicates this is not the case (data not shown).

Table 5. Comparison of prevalence rate studies.

Study	Anabolic steroids	Stimulants	Other	All
Geyer et al. (2004)	15%	-	-	15%
Judkins et al. (2007)	22%	10%	0%	24%
Duiven et al. (2018)	21%	15%	6%	38%

The difference can probably be best explained by the more extensive testing screen used in this study. Also the stronger focus on selecting products emphasizing performance enhancing claims, which are potentially higher risk products, is felt to be of influence.

The positive products contained 5 different anabolic steroids (21 findings), 9 different stimulants (25 findings), 1 beta-2 agonist (4 findings) and 1 beta-blocker (1 finding) (Figure 3). Three products were reported to contain high levels of contamination (Table 2). One contained oxilofrine (at least 55 mg·g⁻¹), two others were shown to contain oxilofrine (40 and 11 mg·g⁻¹) as well as β-methylphenethylamine (BMPEA, 49 and 26 mg·g⁻¹) and N,β-dimethylphenethylamine (NBDMPEA, 24 and 1 mg·g⁻¹). When taking the prescribed maximum daily dose of these products, the maximum intake of contaminants would exceed the maximum prescribed dose of referenced medication 6 out of 7 times. For each product as a whole, the three supplements exceeded the maximum prescribed doses of referenced medication by 4 to 44 times (Table 4). Ingestion of such excessive amounts could potentially lead to adverse health effects, including cardiac arrest (Novartis

Pharmaceuticals Corporation, 2017) and coma (Catalent Pharma Solutions, 2017; Novartis Pharmaceuticals Corporation, 2017). Oxilofrine is a synthetically produced hydroxyl derivate of ephedrine. It was produced and sold as a medicine under the name Carnigen to treat low blood pressure from 1950 to 2010. It has been reported in nutritional supplements before (Cohen et al., 2017). The synthetically produced β-methylphenethylamine (BMPEA), an isomer of amphetamine, was also detected in nutritional supplements before (Cholbinski et al., 2014). As far as we know, and at the time of this study, the detection of the synthetically produced N,β-dimethylphenethylamine (NBDMPEA) in supplements is a first. It is isomeric with synthetic methamphetamine.

During low level screening, the anabolic steroid boldione was detected the most (11 findings) followed by the anabolic steroid 5-androstene-3β,17α-diol (17α-AED) and the stimulant 4-methylhexan-2-amine (both 6 findings). The beta-2 agonist higenamine was detected 4 times. During this screening, the beta-blocker bisoprolol was also detected once. Next to the high level findings, the stimulant oxilofrine was detected two more times and the stimulants BMPEA and NBDMPEA were both detected one more time.

The use of some sport nutrition supplements could lead to doping violations. Based on the data from this study and the available reference data, it is not possible to state exactly how many. Only for the three products with high level screening findings this risk seems obvious. WADA states that most stimulant urine levels should not be reported below 50 ng·g⁻¹. According to data from excretion studies (Van Eenoo et al., 2006; Koehler et al., 2007; Perrenoud et al., 2009), we expect that at least a single dose of 50 μg should be ingested to obtain this minimum urine level. However, when the maximum recommended daily dose is taken, the ingestion of the 7 high level contaminants (found within 3 products - Table 2) is expected to range between 15 mg - 0.98 g. This is 300 - 20,000 times higher than potentially needed to cause a positive doping test. Of the products with only low screening findings only one product containing stimulants has the theoretical potential to do the same, but only if contamination levels are assumed to be at the high end of the ng·g⁻¹ region. The risk is then predominantly caused by the product's high maximum recommended daily dose of 89 g. The assumptions made seem to infer that testing sport nutrition supplements at levels of 10-100 ng·g⁻¹ are a good measure for elite athletes to mitigate the risk of accidentally infringing doping regulations.

Four products were reported to contain higenamine (norcoclaurine). Higenamine is a natural constituent of several botanicals (Chung et al., 2006; Patil et al., 1991). The four products containing higenamine all contained complex botanical ingredients, making it possible that the presence was due to natural presence instead of product contamination. At the time of the study, ingestion of these products would be a clear potential risk for doping tested athletes. Laboratories had a limit of detection as low as 2 pg·mL⁻¹ and there was no reporting limit (Thevis et al., 2017). Based on data of excretion studies, we calculate that the ingestion of a single dose of 2 ng higenamine already

had the potential to cause this level. However, WADA acknowledged this risk and introduced a reporting level of $10 \text{ ng}\cdot\text{mL}^{-1}$ for higenamine in September 2017 (Perrenoud et al., 2009). Since then, the four detected higenamine findings are unlikely to cause doping violations anymore. Hence, the introduction of the reporting levels for higenamine seems an adequate response from WADA to protect the good-willing athletes and to prevent honest mistakes.

The complex nature of botanical based products has potentially played part in most of the findings within this study. The most common compounds observed are steroids such as boldione and 5-androstene- $3\beta,17\alpha$ -diol (17 α -AED). It is not fully understood as to why these observations are occurring. They may be the result of suboptimal production processes in the supplement chain. Another explanation may be the possible microbial conversion of plant sterols into low levels of anabolic steroids or natural presence (Patil et al., 1991; Saraphanchotiwiththaya and Sripalakit, 2016). The same explanations may apply to the findings of the natural occurring stimulants ephedrine (and/or pseudoephedrine), methylephedrine, norpseudoephedrine and strychnine (Behpour et al., 2012; Dingerdissen and McLaughlin, 1973; Medana et al., 2013). Since we were already aware of this risk before this study, we used minimum reporting levels for a number of doping substances related to microbial conversion or natural presence (Figure 3). Reporting levels were set at $10\text{ng}\cdot\text{g}^{-1}$ for related anabolic steroids and $100\text{ng}\cdot\text{g}^{-1}$ for pseudoephedrine/ephedrine. Findings below these levels were not considered positives. However, without the use of these reporting levels, another 8 products would have been regarded positive, bringing the total positive products up to 50%. The number of findings (doping substances detected) would have risen from 51 to 104.

Product 'spiking' (the deliberate action of a manufacturer to add undeclared substances to a product) could be considered an obvious explanation for the seven high level findings. For the low level findings of synthetic stimulants 4-methylhexan-2-amine (6 findings), 1,3-dimethylbutylamine (DMBA, 2 findings) and oxilofrine (2 findings) and beta-blocker bisoprolol (1 finding) cross-contamination seems more plausible. The complex nature of botanical based products was also felt to have played part in the three products which produced inconclusive results.

The present study shows that the current self-control strategy for the production of nutritional supplements is insufficient. A small amount of sports nutrition supplements are likely 'spiked' with newly developed designer compounds and may continue to cause health related sports incidents. Better regulation and controls are needed to prevent potential health issues amongst athletes and the general consumer alike. The possible natural presence of - and microbial conversion of plant sterols into - low levels of doping substances in botanical ingredients should be studied more extensively. Next to higenamine, it may also explain several other low level findings.

The problems outlined in this paper may be more serious than our estimates and calculations suggest. We have not taken into account the habit of some sports supplement users to use higher doses than the manufacturer

specifies. In a study of users of pre-workout formulas, 14% of them admitted to exceeding the recommended maximum amount by a factor of two or more (Jagim et al., 2019).

Conclusion

In conclusion, many sports nutrition supplements sold online still contain undeclared doping substances. The prescribed use of such products significantly increases the risk of unintentional doping violations and may even impose general health risks. Food regulation authorities, doping controlled athletes, and WADA are advised to take appropriate actions.

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Key points

- In this study, 38% of 66 high-risk sports supplements tested (which claimed to intensify workouts, promote muscle growth and fat loss) were found to contain doping agents.
- 4.5% of the products tested were found to contain doping agents in concentrations which can have acute negative health effects, and may result in a positive doping test.
- The problem regarding the presence of undeclared doping agents in sports supplements has not diminished in recent decades.

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