

## Protocol to reduce the risk of unintentional doping caused by dietary supplements ingestion

### Protocolo de redução de risco de Doping não intencional causado por consumo de suplementos alimentares

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#### ABSTRACT

**Introduction:** Dietary supplements is considered the main cause of unintentional doping among athletes. However, the prevalence of supplement use by elite athletes is almost 100%, and awareness of the risk of unintentional doping does not seem to be effective. The scientific literature point out some possible factors related to the poor quality of products on the market. However, it does not propose any protocol that objectively guides health professionals and athletes in reducing the risk of doping and damage to health caused by supplements contaminated with prohibited substances not listed on the label. **Objectives:** to propose a protocol to reduce the risk of unintentional doping based on a narrative review of studies that have discussed regulatory factors related to dietary supplements, the prevalence of contamination of supplements, their main contaminants, possible adverse effects on human health, awareness of athletes about the indications for supplement use and the risks of unintentional doping. **Results:** A six-step protocol was developed, which proposes methods capable of reducing the risk of unintentional doping. **Conclusion:** It is believed that this instrument is highly relevant in sports, especially among elite athletes; however, without excluding the importance for any consumer of this type of product, since high prevalences of contamination of food supplements and consumption of this product were identified, as well as an insufficient level of awareness on the part of its consumers.

**Keywords:** dietary supplements; doping in sports; athletic performance; security measures.

#### RESUMO

**Introdução:** A suplementação alimentar é considerada a principal causa de doping não intencional entre atletas; no entanto, a prevalência de consumo de suplementos por atletas de elite é próxima à 100%, e a conscientização sobre o risco de doping não intencional não parece ser efetiva. A literatura científica aponta alguns possíveis fatores relacionados à má qualidade dos produtos disponíveis no mercado; no entanto, não propõe qualquer protocolo que oriente, objetivamente, profissionais da área da saúde e atletas quanto à redução de risco doping e danos à saúde causados por suplementos contaminados com substâncias proibidas não listadas no rótulo. **Objetivo:** propor um protocolo de redução de risco de doping não intencional, a partir de uma revisão narrativa sobre estudos que tenham discutido os fatores regulatórios relacionadas aos suplementos alimentares, prevalência de contaminação de suplementos, seus principais contaminantes, possíveis efeitos adversos à saúde humana, conscientização de atletas sobre as indicações para uso de suplementos e os riscos de doping não intencional. **Resultados:** Foi elaborado um protocolo de seis passos, que propõe métodos potencialmente capazes de reduzir o risco de doping não intencional. **Conclusão:** Acredita-se que este instrumento seja de elevada relevância no âmbito esportivo, especialmente entre atletas de elite, no entanto, sem excluir a importância para outros consumidores deste tipo de produto, uma vez que foram identificadas elevadas prevalências de contaminação de suplementos alimentares e de consumo deste produto, bem como insuficiente grau de conscientização por parte de seus consumidores.

**Palavras-chave:** suplementos nutricionais; doping nos esportes; desempenho atlético; protocolo de segurança.

## Introduction

Elite athletes are constantly submitted to challenges in which sports performance improvement stands out as a central objective, either during training sessions or competitive events [1]. In this scenario, any evolution in performance, even if minimal, can be enough to significantly influence an athlete's result in a championship [2].

Among the factors capable of promoting performance improvement in athletes, nutritional status stands out, although some international positions mention that most of an athlete's nutritional needs can be achieved through simple food adjustments in their routine [3]. Stellingwerff *et al.* [4] clarify that some athletes may face difficulties making such adjustments viable.

In this sense, the two main types of difficulties faced by athletes can be summarized as: a) limitations in the consumption of adequate amounts of food, as athletes often mention not eating enough due to gastrointestinal discomfort during training sessions or competitions or because they experience reduced appetite and even changes in their eating routine, due to constant international travel [4]; b) supply limitations of specific ergogenic compounds, such as creatine, beta-alanine, caffeine, nitrate, and sodium bicarbonate, considered safe and effective by the International Olympic Committee (IOC), provided they are consumed in adequate doses, which are not reached exclusively through food [5].

Faced with the difficulties of meeting nutritional needs and specific ergogenic effects exclusively through food, the use of dietary supplements has been increasing among elite athletes, ranging from 78 to 100% of this population, depending on the modality studied [6,7]. However, it is essential to clarify that not all athletes face such difficulties, which highlights the importance of individual nutritional assessment [8].

For those athletes who need food supplementation to achieve specific ergogenic effects and/or to maintain an adequate nutritional status; and consequently prevent negative outcomes resulting from malnutrition, such as overtraining syndrome and relative energy deficiency in sport (REDS), it is necessary to clarify that this strategy is considered the greatest risk factor for unintentional doping [9], being responsible for approximately 6.4 and 8.9% of all adverse analytical findings (positive doping) [10].

Doping has been defined as the presence of prohibited substances and/or their metabolites in blood or urine samples, and it is considered an unsportsmanlike crime, with the consequences of losing titles, banning participation in competitions, compromising reputation, and damage to health [11].

According to the principle of "Strict Liability" provided for in Art. 14, paragraph III of the World Anti-Doping Code [12], "it is not necessary that intent, fault, negligence or knowing Use on the Athlete's part be demonstrated in order to establish an anti-doping violation". In this way, when consuming a poor-quality food

supplement contaminated with substances prohibited by the World Anti-Doping Agency (WADA) without any identification on the label, the athlete obtains performance advantages in relation to his opponents, even if unintentionally. Therefore, when presenting adverse analytical findings, they may suffer the sanctions provided for this type of crime, as well as be exposed to the risk of developing potential adverse health effects caused by prohibited substances.

The scientific literature has pointed out some possible factors related to the poor quality of products available on the market [11]. However, it does not propose any protocol that objectively guides health professionals and athletes in reducing the risk of doping and health damage caused by supplements contaminated with prohibited substances not listed on the label.

Therefore, the first objective of the present study was to carry out a narrative review of studies that have discussed regulatory factors related to dietary supplements, the prevalence of contamination of supplements, their main contaminants, possible adverse effects on human health, awareness of athletes about the indications for supplements use and the risks of unintentional doping. Based on this narrative review, the second objective of the present study was to propose a protocol to reduce the risk of unintentional doping.

## Methods

The study consisted of a narrative review and document analysis, in which conclusions culminated in a protocol proposition to reduce the risk of unintentional doping.

The narrative review was carried out through scientific articles indexed in the databases: PubMed, Google Scholar, Science Direct and Web of Science, and Portal de Periódicos CAPES, without language restrictions, through the terms “dietary supplements”, “banned substances”, “contamination”, “cross-contamination”, “doping”, “unintentional doping”, “involuntary doping”. Other relevant sources were found in the references of related articles. No additional filters have been added, and the last search was performed in February 2023.

For the document analysis, the websites of governmental organizations and international agencies related to the anti-doping policy were consulted, such as the World Anti-Doping Agency (WADA) and the Brazilian Doping Control Authority (ABCD), and the last search was carried out in February 2023.

## Results and discussion

### *Regulatory factors related to dietary supplements*

Unlike the rigid processes that regulate the registration and marketing of a new drug, in much of the world, the quality of food supplements is not tested before these products reach the market [11].

In Europe and the United States (USA), the producers themselves are responsible for “guaranteeing” the safety of dietary supplements, with no need for proof before the product reaches the market, which increases the risk of marketing poor-quality products [13].

In the US, the dietary supplement industry is overseen by two federal agencies, the FDA and the Federal Trade Commission (FTC), in which the first is in charge of the safety and proper labeling of products, and the second of their advertising and promotional claims. In the case of the FDA, its action is governed by the Dietary Supplement Health and Education Act (DSHEA) of 1994, which classified these products as food and, therefore, exempted them from proving their safety before being marketed [14]. In this country, drugs are considered unsafe until evidence shows otherwise; food supplements are considered safe until proven they are not [15].

Thus, since manufacturers are not required to submit safety information before marketing dietary supplements in the US, the FDA depends on adverse event reports, product sampling, and information from the scientific literature as evidence of risk. Consequently, for an inappropriate product to be withdrawn from circulation in the US, it must first have documented victims and be brought to the attention of health authorities [15].

It is noteworthy that US supplement manufacturers must comply with Good Manufacturing Practices (GMP) requirements, which state that they “must establish - for each component and the finished dietary supplement - specifications as to identity, purity, strength, composition, and limits of contaminants, to assure its quality”. However, the US GMP guidelines do not specify which tests and methods must be adopted, which allows manufacturers to decide which methodologies they will base their quality controls on. As a consequence, problems such as the presence of impurities, microorganisms, toxins, and toxic elements such as lead, mercury, arsenic, and cadmium in the products may occur, as well as the poor characterization and replacement of declared components by cheaper alternatives, of lower quality and even the inclusion, not informed on the label, of active ingredients prohibited by WADA.

In Brazil, the regulation of the dietary supplements sector is similar to the American and European ones, being governed by the Resolution of the Collegiate Board (RDC) number 243 of July 26, 2018, of the National Health Regulatory Agency (Anvisa), which provides for “the requirements for the composition, quality, safety, and labeling of dietary supplements and for updating the lists of nutrients, bioactive substances, enzymes, and probiotics, use limits, claims and complementary labeling of these products” [16], plus the lists of permitted and prohibited ingredients of Normative Instruction number 28 also of July 26, 2018, later modified by Normative Instruction number 76 of November 5, 2020.

As in the US, Brazil also regulates dietary supplements more as food than as medicine, which translates into milder and simpler standards and requirements for their registration and marketing, and a lower degree of inspection. Unlike what happens in the USA; however, Brazilian manufacturers must previously submit to

Anvisa information on the safety and efficacy of their products, which may include scientific evidence such as clinical trials, endorsement by health authorities or recognized regulatory bodies in other countries; in addition to of pharmacopeias or other specific codes for the sector in Brazil or abroad [14].

In Brazil, until 2018, there was no legal definition for dietary supplements. At that time, most of the products used as dietary supplements were classified into different regulatory categories: (I) Food for athletes; (II) Vitamin and/or mineral supplements; (III) New foods and/or new ingredients; (IV) Foods with functional and/or health properties; (V) Specific drugs; and (VI) Herbal Medicines. However, in recent years, Anvisa has promoted a series of debates, which led to RDC Anvisa nº 243/2018, which defines the health requirements of dietary supplements and is characterized as a regulatory framework in the country. Anvisa also established food additives and technology adjuvants authorized for use in food supplements through RDC Anvisa nº 239, of July 26, 2018 [17] and published Normative Instruction nº 76, which provides for the updating of lists of constituents, use limits, claims and complementary labeling of food supplements; including minimum and maximum limits of nutrients, bioactive substances, enzymes, and probiotics that may be contained in food supplements, based on the daily recommendation for consumption of the product for certain population groups indicated by the manufacturer [18].

RDC nº 243 [16] deals with regulating the requirements for composition, quality, safety, and labeling of food supplements, both for the industrial environment of large-scale production and commercialization and for compounding pharmacies. Among several standards established in this Resolution, the need to identify ingredients on the product label stands out. More specifically, article 7 defines that “substances considered as doping by the World Anti-Doping Agency are not allowed in the composition of food supplements” (Table I). However, except for products containing enzymes or probiotics, it is not mandatory to carry out analyzes of food supplements before they are placed on the market, and the manufacturer is solely responsible for declaring that he complies with the rules and communicating the start of manufacture or importation of the product to the local health surveillance agency. Added to this is the scarcity of official methodologies in Brazil for carrying out this type of analysis, making the quality and safety of these products questionable.

Cross-contamination is usually attributed to errors in production in situations in which supplements and other products containing substances prohibited by WADA are manufactured on the same production line; in this case, containers or benches previously used in handling prohibited substances are improperly cleaned and then reused for the transport or storage of raw materials and food supplements, culminating in contamination. There is also the hypothesis that the inclusion of the prohibited substances in dietary supplements is intentional to increase the effectiveness of the products and build consumer loyalty [20]. Additionally, the Brazilian Doping Control Authority (ABCD) warns that, for the most part, contaminated products are those often listed as possibly capable of reducing body weight and promoting

increased muscle anabolism [21], which corroborates with the hypothesis of intentional contamination.

**Table I** - World anti-doping agency list of prohibited substances and methods for the year 2023

Identification No.	Prohibited substance/method	Type	When prohibited
S0	Unapproved substances	Substance	Always
S1	Anabolic agents	Substance	Always
S2	Peptide hormones, growth factors, related substances, and mimetics	Substance	Always
S3	Beta-2 agonists	Substance	Always
S4	Hormonal and metabolic modulators	Substance	Always
S5	Diuretics and masking agents	Substance	Always
S6	Stimulants	Substance	In competition
S7	Narcotics	Substance	In competition
S8	Cannabinoids	Substance	In competition
S9	Glucocorticoids	Substance	In competition
M1	Handling blood and blood components	Method	Always
M2	Chemical and physical manipulation	Method	Always
M3	Genetic and cellular doping	Method	Always
P1	Beta-blockers	Substance	In specific sports

Source: WADA - World Anti-Doping Agency [19]

Therefore, as the food supplements industry continues to grow and athletes continue to consume them, the review and modernization of the regulation of this industry are extremely necessary to prevent both acute and chronic damage to health, as well as unintentional doping [11]. However, while the legislation is not changed, the need to create mechanisms to reduce the risk of unintentional doping is clear.

#### *Prevalence of contamination of food supplements, their main contaminants and possible adverse effects on human health*

Passive exposure to prohibited substances, caused by the consumption of dietary supplements, in addition to causing damage to health, also makes elite athletes susceptible to unintentional doping [22,23].

In a study by Kozhuharov, Ivanov, and Ivanova [11], 50 studies were gathered and published between 1996 and 2021, in which 875 dietary supplements were analyzed as possible sources of unintentional doping. The dietary supplements studied came from practically all parts of the world, predominantly from the USA, Holland, United Kingdom, Italy, and Germany, followed by products manufactured in China and Southeast Asia. The authors found that of all the supplements analyzed, about 28% had a high risk of unintentional doping due to the substances present but not declared on the label.

Among these substances, the most common was sibutramine in 248 con-



taminated food supplements (28.34%), followed by testosterone and other anabolic steroids in 228 products (26.06%), fluoxetine in 192 products (21.37%), 1,3-dimethylamylamine (DMAA) in 58 products (6.62%) and hygenamine in 15 (1.71%) of the 875 food supplements analyzed. Other substances such as diuretics and Selective Androgen Receptor Modulators (SARMs) not declared on the labels and prohibited by WADA were also identified in the products, but to a lesser extent (Table II) [11].

**Table II** - Main contaminants found in dietary supplements, and their frequency, not identified on the label

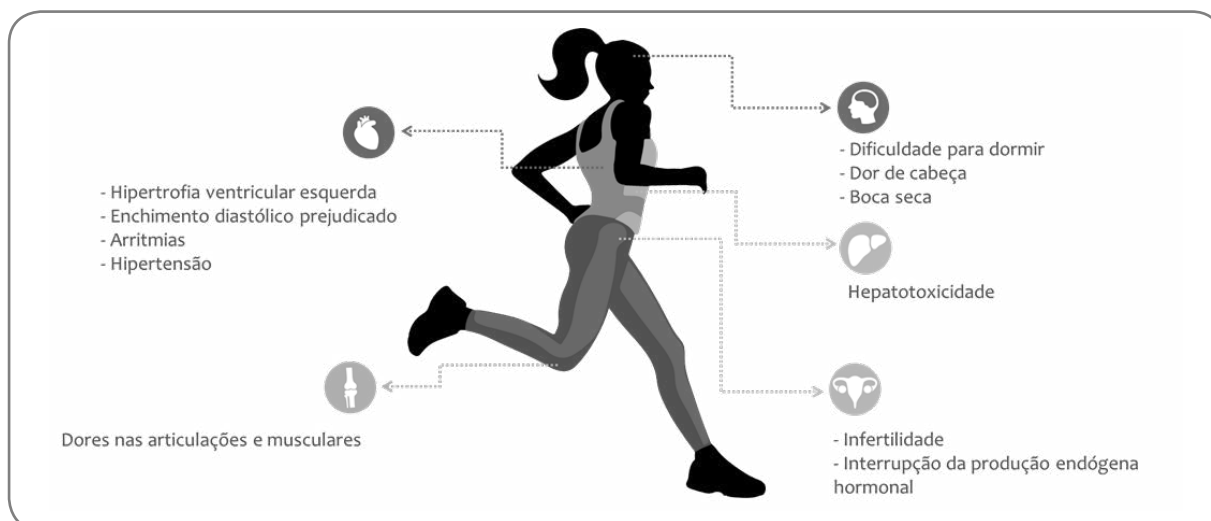
Contaminants prohibited by WADA	Absolute and relative frequency
Sibutramine	248 (28.3%)
Testosterone or other anabolic steroids	228 (26.0%)
Fluoxetine	192 (21.4%)
1,3-dimethylamylamine	58 (6.6%)
Hygenamine	15 (1.71%)

Source: Adapted from Kozhuharov, Ivanov and Ivanova [11]

Food supplements, in general, are used chronically, some even very frequently throughout the day. And if they are contaminated with pharmacologically active substances, they can expose consumers to serious side effects due to the accumulation of prohibited substances without the slightest control of the ingested dose. Therefore, the unexpected consumption of adulterated supplements can cause adverse effects such as allergies, and cardiovascular, liver, and kidney problems, among others, depending on the level of adulteration and the consumer's tolerance to such substances [24].

According to Kozhuharov, Ivanov, and Ivanova [11], the most recurrent substance in dietary supplements as a contaminant was sibutramine. This substance poses serious health risks both for elite athletes and for other individuals. Its ingestion can cause several side effects, such as increased blood pressure, arrhythmias, dry mouth, difficulty sleeping, headache, or joint and muscle pain [25-27].

Another type of substance that stood out in the study by Kozhuharov, Ivanov, and Ivanova [11] as a contaminant of food supplements was the category of anabolic steroids; its adverse effects are correlated with prolonged use, which may lead to interruption of the endogenous production of these hormones, as well as infertility and gynecomastia. Additionally, they are associated with cardiovascular side effects such as left ventricular hypertrophy, impaired diastolic filling, hypertension, thrombosis, and hepatotoxicity [28-30].



Source: Florentin *et al.* [25]; James *et al.* [26]; Scheen [27]; Torrisi *et al.* [28]; Karila *et al.* [29]; Ivanova *et al.* [30]

**Figure 1** - Major adverse health effects caused by contaminants predominantly found in dietary supplements, such as sibutramine, testosterone or other anabolic steroids, 1,3-Dimethylamylamine, and hygenamine

As previously mentioned, the study by Kozhuharov, Ivanov, and Ivanova [11] analyzed 50 studies published between 1996 and June 21, 2021, and found a prevalence of 28% of contamination among food supplements. After this period, in our searches, using the same descriptors and research platforms, we found four more studies [31–34] whose objective was to evaluate the contamination of sports food supplements.

Duiven *et al.* [31] evaluated the prevalence of doping substances in a variety of sports food supplements available in Dutch online stores. A total of 66 sports supplements - identified by the study authors as “potentially high-risk products” as their advertising claimed to modulate hormone regulation, stimulate muscle mass gain, enhance fat loss, and/or increase energy - were selected from 21 different brands and purchased in 17 virtual stores. All products were analyzed for the presence of prohibited substances by a company with extensive experience in anti-doping control. A total of 25 of the 66 products (38%) contained substances prohibited by the WADA, not declared on the label, which included high levels of the stimulants oxylphrine,  $\beta$ -methylphenethylamine and  $N,\beta$ -dimethylphenethylamine, the stimulant 4-methylhexan-2-amine (methylhexaneamine, 1,3-dimethylamylamine, DMAA), the anabolic steroids boldenone (1,4-androstadiene-3,17-dione) and 5-androstene- $3\beta,17\alpha$ -diol (17 $\alpha$ -AED), the beta-2 agonist higenamine and the beta-blocker bisoprolol. The authors concluded that the ingestion of some products identified in this study, in the concentrations found, could represent a significant risk of unintentional doping violations and to consumers’ health.

Leaney *et al.* [32] carried out a study on the consumption of hygenamine through products made from beetroot, currently evidenced as an ergogenic strategy because it is a source of nitrate. To investigate this relationship, concentrated beetroot beverages were consumed by six individuals, and this compound was quanti-



fied in the urine. Hygenamine was confirmed to be present in the majority of beet-derived foods and supplements tested in this study, with experimental evidence that it can arise in beet extracts upon heating. The results of this study demonstrate the first evidence of a relationship between beetroot and hygenamine, a substance prohibited by WADA.

It is noteworthy that, although free hygenamine was detected in the urine of all individuals tested in the study by Leaney *et al.* [32], its concentration was significantly low, representing about 1% of the acceptable limit described in the current WADA report. However, although the risk of inadvertent doping violation by consuming the products investigated in this study is low, beetroot as a source of hygenamine should be considered by athletes, especially those who consume amounts higher than those recommended by the manufacturers.

In the third study found in our searches, after the publication of the systematic review by Kozhuharov, Ivanov, and Ivanova [11], Zhang *et al.* [33] proposed a new analytical method for the detection of anabolic steroids, also prohibited by WADA, in samples of food supplements. The method was considered sensitive and accurate, and when analyzing 300 liquid and solid food supplements, it detected a positive sample for testosterone and three suspected drugs (4-hydroxyandrostenedione, DHEA, and 6-Br androstenedione) in three food supplements purchased on the internet.

Finally, in the last study found in our searches, after the publication of the systematic review by Kozhuharov, Ivanov, and Ivanova [11], Rodriguez-Lopez *et al.* [34] analyzed 52 “sports supplements” made of protein available in physical and online stores in Spain with several objectives, among them, to identify possible contamination with substances prohibited by the WADA. No ingredients banned by WADA were found, except for colostrum in one of the supplements, and consumption of colostrum is currently discouraged by WADA, as it may contain growth factors (IGF-1), among others, which are prohibited and can lead to doping.

When analyzing data from Zhang *et al.* [33] and Rodriguez-Lopez *et al.* [34], it is possible to observe a prevalence of contamination (1.33% and zero, respectively) lower than the 38% reported by Duiven *et al.* [31] and the 28% mentioned in the review by Kozhuharov, Ivanov, and Ivanova [11]. However, in the first case, only one type of prohibited substance (steroids) was evaluated, while in the second case, only protein supplements marketed in a single country. While in the studies by Duiven *et al.* [31] and Kozhuharov, Ivanov, and Ivanova [11], there was an investigation of numerous types of prohibited substances, specifically, in the case of Kozhuharov, Ivanov, and Ivanova [11], it is a systematic review with meta-analysis, which brought together supplements from all over the world, which reinforces the need for extreme vigilance concerning the consumption of food supplements by athletes.

### *Athletes' awareness of dietary supplements and the risk of unintentional doping*

The most cited motivations for dietary supplements use by athletes around the world have been improvements in performance, health, and recovery. Additionally,

women are more likely to consume supplements for health reasons, while men more often report using them to enhance sports performance [6,35]. However, according to Walpurgis *et al.* [20], most athletes using dietary supplements are not aware of the consequences of consuming contaminated dietary supplements, such as unpredictable health risks and adverse analytical discovery in routine doping controls.

Studies have found that athletes' main sources of information on the subject tend to be of low quality, as they mostly come from their coaches, team partners, friends, or even family members [35–37]. According to Dodge [38], consumers of dietary supplements mistakenly believe that if dietary supplements are approved by the government, then they are tested for safety and efficacy, as well as have their content analyzed in the laboratory, and manufacturers are obliged to disclose adverse effects on consumers. However, this is not observed in practice since the laws of several countries do not require such procedures.

A study by Braun *et al.* [39] found that only 36% of the participating athletes knew that food supplements could have some type of contaminant. Following by Torres-McGehee *et al.* [40], in which only 9% of 400 North American athletes had adequate knowledge about sports nutrition, including supplementation. Another study with college athletes showed that 86% were unaware that food supplements could have potential adverse effects [37]. In addition to these, a study carried out with Australian athletes on the same subject showed that 62% of respondents did not know the active ingredient(s) of the supplement(s) they consumed, 57% did not know about the possible adverse effects, 54% were unaware of the mechanism of action, and 52% were unaware of the recommended dose [41].

Chan *et al.* [42] evaluated 410 young athletes (17.7 years old  $\pm$  3.9), Australian, from regional, national, and international levels, from modalities such as Athletics, Badminton, Swimming, Gymnastics, Swimming, Triathlon, Basketball, Cricket, Football, Rugby, hockey and water polo. Such athletes received a lollipop free of charge while waiting for the completion of a questionnaire. Among the various findings of the study, it was observed that only 40.6% refused to eat an unknown food given to them and that among all those who consumed the product, only 16.1% read the list of ingredients before making it. This study suggests that young athletes had a low level of concern about exposing themselves to new food products and the possible risks of unintentional doping.

Some countries, such as Germany, France, the United Kingdom, Austria, and Holland, have databases available for athletes, which catalog dietary supplements tested for ingredients [20]. Specifically, in Holland in 2003, the Dutch Safeguards System for Dietary Supplements in Elite Sport, known as NZVT, was created [43]. Thus, Wardenaar *et al.* [44] tested the knowledge and attitudes of 601 Dutch athletes with Olympic and non-Olympic status towards the NZVT system. The authors showed that, although the majority (68%) of athletes were aware that dietary supplements can lead to an adverse analytical finding, and 87.8% of these athletes considered fraud due to incomplete labeling unacceptable, there is still a reasonable portion of

these athletes (32%) who are unaware of such risks. Of the athletes who were aware of the NZVT system, those with Olympic status reported using it more frequently than non-Olympic athletes (81.7% vs. 50.0%,  $p < 0.001$ ). Additionally, women were more familiar with and used the system more frequently when compared to men. In conclusion, the authors report that although doping warnings and regulations have been in place, considering the risk of unintentional use of doping for more than two decades, knowledge of the Olympic and non-Olympic status of high-level athletes still needs to be improved.

The studies cited above show that even athletes from countries with programs or systems that guide the purchase of safe products are still insufficiently aware of the risk of unintentional doping caused by the consumption of contaminated food supplements. According to our searches, there is no robust investigation on the subject in Brazil, but considering that in this country there is no governmental system to protect athletes in this sense, it is believed that the level of awareness is even lower, which raises the question of the need for educational programs in this regard and the proposition of risk reduction protocols.

#### *Proposal for a “Protocol to reduce the risk of unintentional doping through dietary supplements”*

Considering that the risk of unaware athletes consuming dietary supplements contaminated with substances prohibited by WADA is high, but also considering that the use of these products may be indispensable in certain elite sports scenarios and that changes in regulatory factors are unlikely to occur in the short term, the proposal of a risk reduction protocol becomes fundamental. In this way, our proposal will be exposed in 6 steps:

#### **1<sup>st</sup> Step: Consume only food supplements that are strictly necessary and that present scientific evidence of efficacy and safety.**

Few commercially available products claiming ergogenic benefits are supported by solid evidence. Research methodologies on the effectiveness of sports supplements are often limited by small sample sizes, the inclusion of untrained individuals, low representation of specific subpopulations of athletes (women, older athletes, athletes with disabilities, etc.), performance tests that are unreliable or irrelevant, poor control of confounding variables, by not including control of the athletes' diet during the study or by not considering the interaction with other supplements [45,46].

The International Olympic Committee, in a position released recently [5], categorized food supplements according to the purpose of use and the degree of evidence regarding safety and efficacy. Following these criteria, the following categories emerged: supplements whose purposes are: (a) Practically providing energy and nutrients, (b) Preventing and/or treating nutritional deficiencies, (c) Promoting

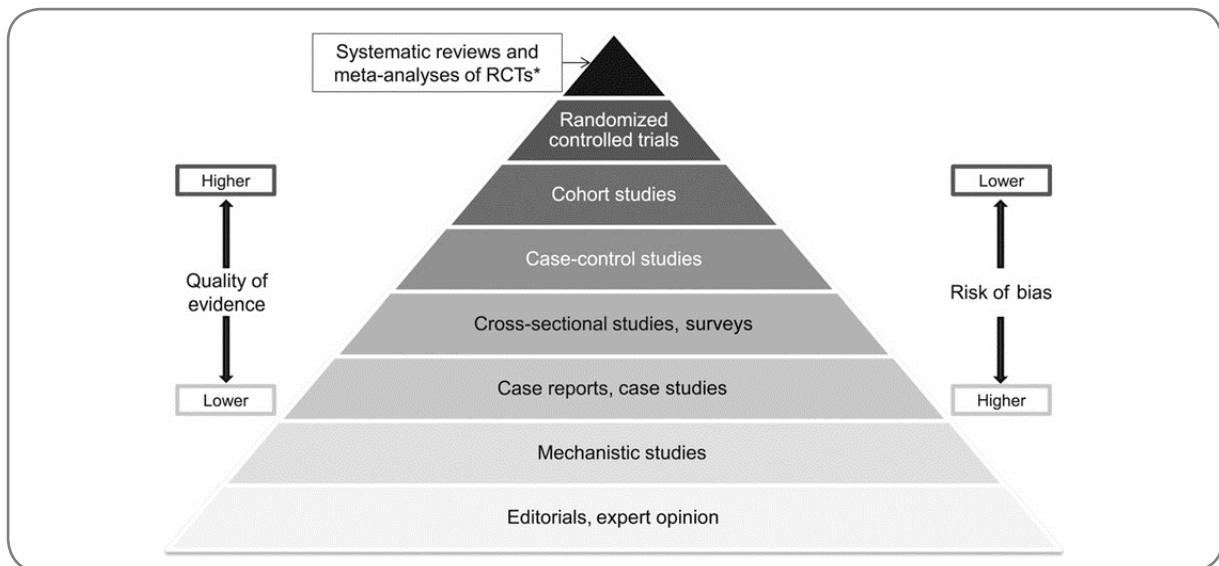
muscle mass gain, (d) Promoting weight loss, (e) Promote performance improvement indirectly, through injury prevention and immunity improvement, (f) Promote performance improvement directly.

According to Table III, in the category “supplements whose purpose is to directly promote performance improvement”, for example, there is evidence that only five dietary supplements - creatine, sodium bicarbonate, beta-alanine, caffeine, and nitrate - could promote gains in performance margins, as long as they are used in specific scenarios [5]. Thus, in practice, the athlete should stick to just such possibilities, also considering the guidance of a nutritionist to assess the feasibility of use according to the specific scenario, such as training periodization, the specificity of each sport modality, and the biological individuality of the athlete.

**Table III** - Categorization of food supplements according to purpose of use and degree of evidence regarding safety and efficacy

Purposes	Strong evidence	Moderate evidence	Small/trivial/limited evidence	No evidence/ further studies
<b>Improve performance directly</b>	Creatine, caffeine, sodium bicarbonate, beta-alanine, nitrate.			
<b>Gain lean mass</b>	Proteins			Leucine
<b>Slimming</b>			Protein, green tea, CLA, chitosan, glucomannan fiber, omega 3, lipoic acid.	
<b>Injury prevention</b>				Vitamin D, Calcium, Curcumin, Cherry Juice, Hydrolyzed Collagen, Vitamin C
<b>Improvement of immunocompetence</b>		Vitamins D and C, Carbohydrates, Probiotics, Zinc, Polyphenols		Glutamine, Omega 3, Caffeine, Vitamin E, B-glucans
<b>Prevention/treatment of deficiencies</b>	Vitamin D, iron and calcium; BE-: low-dose multivitamins and minerals			
<b>Practical supply of energy and nutrients</b>	sports drinks; energetic drinks; sports gels; protein powder; liquid meals; sports bars; protein-added foods			

Source: Adapted from Maughan *et al.* [5]



\*RCTs = Randomized clinical trials. Source: Pereira and Veiga [48]

**Figure 2** - Hierarchy of evidence used to establish good health practices

Finally, if there is still no systematic review with meta-analysis available for a given dietary supplement and for the desired population, clinical trials can be useful in decision-making, as long as they are interpreted critically, considering criteria such as sample type, type of performance testing, study design, supplement quality, study funding, and conflict of interest, among others, as discussed by Porrini and Del Bo [49].

Thus, the nutritionist responsible for prescribing dietary supplements must be able to interpret such studies, base their conduct on scientific evidence, and guide athletes to use only what is strictly necessary.

## **2<sup>nd</sup> step: Analyze the quality of the product available on the market**

### *Evaluate ingredient list*

The first type of analysis refers to something that precedes unintentional doping; that is, at first, the athlete must be aware of the fact that it is his responsibility to analyze all the compounds present in the list of ingredients, even though the marketing is more directed to only one ingredient. In this case, if the prohibited substance is described in the list of ingredients, it will no longer be characterized as unintentional doping.

### *Analyze in the laboratory the substances present in the food supplement, regardless of not being present in the list of ingredients*

Considering that about 28% to 38% of the products available on the market contain substances prohibited by WADA, without these being described in the list of ingredients, step 2.1. is essential, but not enough. To ensure that the product is free of contaminants, it would be necessary to send a sample of it for laboratory analysis [11], and if the result points to the presence of a contaminant, the athlete should discard it and look for another option on the market.

However, such procedures are often significantly costly for the athlete. Analyzing each product reduces the speed of the process and can represent an unfeasible cost for most athletes. Thus, to reduce such obstacles, there are two distinct initiatives, but still not very effective in global terms: a) companies that sell food supplements tested in batches (batch-tested) and certify such products, including seals on the packaging, so that the consumer can identify it. However, they are rare on the market and therefore difficult to access; b) Government programs aimed at analyzing supplements and disclosing to athletes a list of tested and approved products and their respective batches. However, according to our searches so far, only five countries have this type of program: Germany, the United Kingdom, France, Holland, and Austria [11].

It is important to point out that each new batch of food supplement produced by the same company must be tested again since it was probably handled at different times and perhaps under different circumstances.

#### *Investigate the history of the manufacturing company*

In the impossibility of performing analysis of a dietary supplement in the laboratory, either on the athlete's initiative, by laboratories that perform analysis and disclose the seal on the product label, or by governmental initiatives, Kozhuharov, Ivanov, and Ivanova [11] suggest that, if the use of the product is crucial for the health and performance of the athlete, before acquiring it, the athlete must investigate the history of the manufacturing company, in search of possible previous accusations. In this same line of reasoning, it is common for elite athletes from the same team to share experiences, the most experienced ones report to the most novices the brands that they have been using for years and never generated adverse analytical findings in the constant anti-doping controls to which they are submitted. The fact that a company has never been denounced or caught in cases of contamination does not prevent it from committing possible fraud in the future; however, according to Kozhuharov, Ivanov, and Ivanova [11], it is a reasoning of reduction of probabilities. And for that reason, in parallel with this strategy (step 2.3 of our protocol), more preventive measures should be taken, as described in the following steps.

#### **3<sup>rd</sup> step: Acquisition of dietary supplements preferably produced in large-scale industry**

The risks of contamination in dietary supplements with prohibited substances are real; both in products produced in industry, on a large scale, and in those manipulated in pharmacies. However, according to ABCD [21], there is the possibility that part of the compounding pharmacies does not strictly and consistently follow the criteria required of manufacturers of industrialized products sold on a large scale, and for this reason, they would represent a greater risk for consumers. Additionally, Judkins, Teale, and Hall [50] suggest that some pharmacies that handle medicines and dietary supplements may use contaminated or low-quality raw materials,



and work with unreliable substances, creating unsafe mixtures with ingredients that have not yet been tested in humans [21].

However, our searches found that scientific studies have been dedicated to assessing the presence of prohibited substances in supplements produced on a large scale without necessarily comparing their contamination rates with products handled in pharmacies [51–56]. Therefore, given this scientific gap, it is not possible to state that supplements produced on a large scale are less susceptible to contamination than those manipulated in pharmacies.

While this gap is not filled through new scientific evidence, in compliance with the ABCD and the document still in force [21], our unintentional doping risk reduction protocol will adopt the proviso that the preferential acquisition must be of products produced in industry, without excluding, however, the option of products manipulated in pharmacy. Additionally, if the athlete decides to purchase a product compounded in a pharmacy, it is recommended to verify that the chosen pharmacy follows the rules of good practices for handling magistral and officinal preparations for human use in pharmacies.

#### **4<sup>th</sup> step: Storage of possible evidence of “unintentional” doping by the athlete (WADA, 2021)**

As previously mentioned, the unintentional doping of the athlete does not exempt them from possible punitive consequences because even if unconsciously, this subject obtained advantages over their opponents. However, it has been observed that in cases that athletes claim and prove the absence of intent, sanctions can be mitigated. It is also essential that possible contamination of food supplements can be identified, so that measures can be taken in relation to their manufacturers. Therefore, it is suggested that the following items be stored:

##### *Duplicate of the same batch number of the food supplement*

Given step 1, that is, defining the food supplement(s) essential for the health and/or performance of the elite athlete, and step 2.3, the investigation of the history of the product manufacturer desired (since it is impossible to analyze each product in the laboratory), the next preventive measure consists of purchasing the product together with a duplicate of the same lot number (step 3).

Since the early 2000s, it has been accepted by the Court of Arbitration for Sport in Lausanne (Switzerland) that, in some specific circumstances, unusual explanations can be provided to the Panel to explain an adverse analytical finding (positive doping). This change was considered the “opening of doors” for forensic investigations, as is done in criminal courts. Therefore, a forensic approach may include testing prohibited substances in food and beverages, but especially in dietary supplements [57].



According to WADA [2021], the athlete must keep a sample of the food supplement stored in a safe place, preferably a duplicate with the same batch number and sealed. Thus, if the athlete presents adverse analytical findings (positive doping), such duplicate may be submitted for analysis to detect possible contamination with the substance detected in the sample collected from the athlete. Therefore, this duplicate should not be consumed (Figure 3).

In practice, the sealed duplicate storage orientation may represent a substantial increase in the athletes' monthly budget, as it means doubling the budget allocated to food supplementation. However, when the use of a food supplement is common throughout the season, such as a certain type of carbohydrate for intra-workout consumption, it is possible to predict the amount to be consumed for a longer period (for example, six months) and organize the acquisition of a greater number of packs, all from the same lot, keeping only one duplicate for the six months, which would have less impact on the athlete's budget. In this example, it is essential to observe the product's shelf life.



**Figure 3** - Food supplement storage suggestion: for each product to be consumed, a duplicate with the same batch number must be stored

*Invoice in the name of the athlete, with product description and batch number*

In addition, to store a duplicate of the food supplement consumed by an athlete, it is essential to prove that the product was purchased by them. Therefore, the ABCD [21] guides the athlete to store a copy of the invoice, which describes the name and ID number of the athlete and the batch number of the purchased pro-

ducts. If the invoice is generated automatically by some computerized system of the commercial establishment and does not describe the lot number of the products, it is worth requesting a separate statement listing the name and ID number of the athlete and the lot numbers of the products purchased by them.

In practice, the athlete may receive food supplementation from a sponsor, and the invoice would not be a document involved in the process. In this case, it would be interesting for the athlete to ask the sponsor for a duplicate of the food supplement with the same batch number, accompanied by a signed and dated declaration, certifying that the product, with that batch number, is being donated to the athlete, with the name and ID number identified.

#### *Nutritionist's prescription, with their license number, professional stamp and signature*

Under the World Anti-Doping Code, which outlines the principle of strict liability, athletes are liable even when a doping compound enters their bodies without their knowledge. It is the personal duty of athletes to ensure that non-permitted substances do not enter their bodies, and therefore, when instructed to consume a dietary supplement, they must be aware that they are assuming the risk of unintentional doping.

However, if an athlete is caught with positive doping and claims that the fact is due to supposedly contaminated food supplements, ABCD [21] considers that proof of prescription by a professional can strengthen the athlete's defense in court responsible for this type of process.

#### **5<sup>th</sup> step: Acquisition in physical stores**

According to ABCD [21] guidelines, online sales facilitate the sale and distribution of not safe and/or legal products since, in most cases, sellers can close the company or change the name or the page of the internet from another country. Additionally, the anonymity and ease of opening and closing an online business has made the illegal distribution of steroids, which can contaminate dietary supplements, a serious problem.

On the other hand, in our searches, no studies were found that compared different ways of acquiring food supplements contaminated with substances prohibited by WADA, which suggests that the hypothesis that "products sold online pose a greater risk of contamination than those sold physically" has yet to be scientifically tested.

However, in practice, the dietary supplements acquisition in duplicate, with the same lot number (according to step 4 of the proposed protocol), is more feasible in physical stores, as it is not always possible to choose the lot numbers when making an online purchase.

## 6<sup>th</sup> step: Adequate completion of the specific form when collecting a urine or blood sample for anti-doping analysis

When an athlete undergoes anti-doping tests, in addition to collecting a urine or blood sample for later laboratory analysis, it is also necessary to fill out a form through which some facts are questioned, including the food supplements usage. In this way, it is fundamental that the athlete registers all the food supplements that they are consuming or that they recently have; because if they forget to mention the use of these compounds and are caught with a positive test for prohibited substances, it would be incoherent to claim that the cause of the contamination is the food supplement.

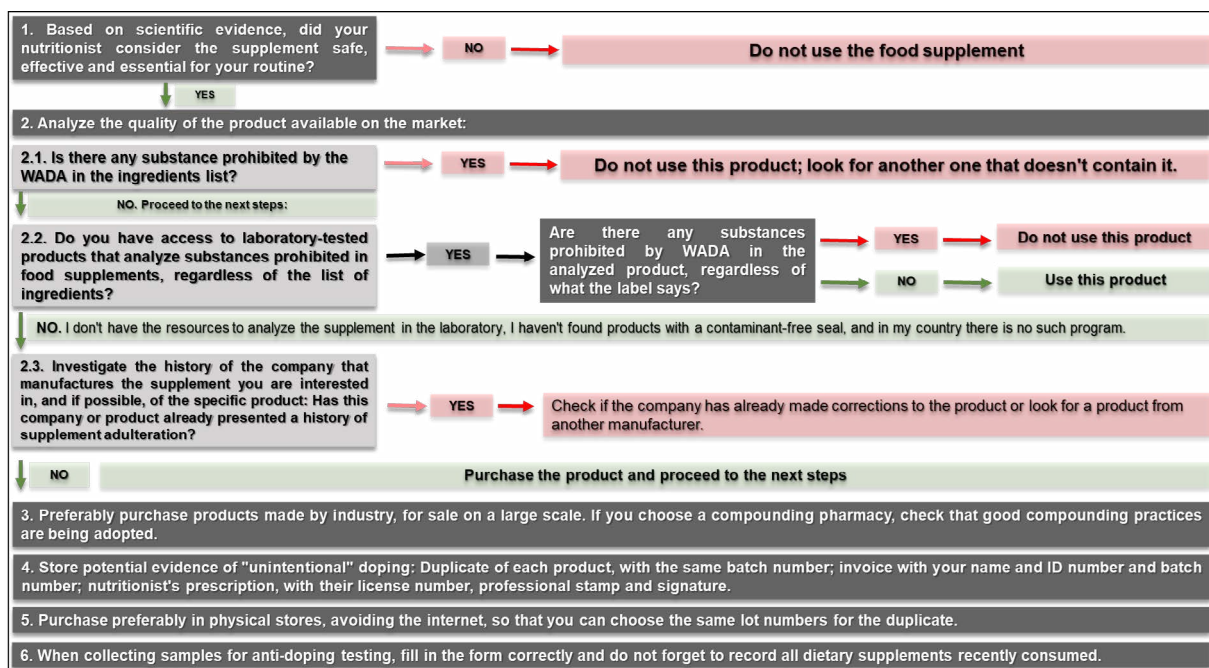


Figure 4 - Unintentional doping risk reduction protocol

## Conclusion

The use of contaminated food supplements is an important predictor of doping, and regulatory factors play a fundamental role in the high availability of poor-quality products on the market. The prevalence of contamination of supplements varies between 28 and 38%, with emphasis on sibutramine, testosterone, and other anabolic steroids, fluoxetine, 1,3-dimethylamylamine, and hygenamine, which, in addition to causing doping, are also capable of causing harm to the health of the consumer. The degree of awareness of athletes about the subject is low, and for this reason, we proposed a risk reduction protocol consisting of six steps:

(1) Seek only strictly necessary food supplements that present scientific evidence of efficacy and safety, guided by a nutritionist;

(2) Analyze the quality of the product available on the market: read the list of ingredients and arrange for the product to be analyzed in the laboratory, either on

your initiative or by companies that test in batches and issue a quality seal, or through programs government, if your country has such a strategy; if laboratory analysis is not feasible, investigate the manufacturer's history, choose companies without cases of adulteration, and move on to the next steps;

(3) Preferably purchase products made by industry, or if you choose a compounding pharmacy, check that good practices are being adopted for handling magistral and officinal preparations for human use in pharmacies;

(4) Store possible evidence of “unintentional” doping: duplicate product with the same batch number; invoice with the athlete's name and product description with the batch number; the nutritionist prescription, with their license number, professional stamp, and signature;

(5) Acquire supplements preferably in physical stores, avoiding the internet, so that you can choose the same batch numbers;

(6) At the time of collecting samples for anti-doping testing, fill in the form correctly and do not forget to record all food supplements consumed recently.

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There are no conflicts of interest.

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#### Authors' contribution

**Research conception and design:** Mendes RR; **Data collection:** Mendes RR, Prado JRS; **Análise e interpretação dos dados:** Mendes RR, Prado JRS; **Statistical analysis:** Mendes RR; **Manuscript writing:** Mendes RR, Prado JRS; **Critical review of the manuscript for important intellectual content:** Mendes RR

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