

Summary of Major Modifications and Explanatory Notes

2023 Prohibited List

SUBSTANCES AND METHODS PROHIBITED AT ALL TIMES (IN- AND OUT-OF-COMPETITION)

PROHIBITED SUBSTANCES

S1. Anabolic Agents

- Androst-4-ene-3,11,17-trione (11-ketoandrostenedione, adrenosterone) is now listed as an example. In the body, it is converted to 11-ketotestosterone and both are androgens already prohibited as metabolites of androstenedione and testosterone, respectively.
- The substance 17 α -methylepithiostanol (commonly referred to as epistane) is the 17-methylated analog to thiodrol (Shionogi, Japan) and converts *in vivo* to the prohibited anabolic agent desoxymethyltestosterone. Hence, per definition, 17 α -methylepithiostanol is also prohibited under S1. In order to unequivocally document the prohibited status of 17 α -methylepithiostanol, the substance was added as an additional example.
- Ractopamine, a beta-adrenergic agonist approved in some countries as a growth promoter for animals, was added to the list of examples under S1.2.
- S-23 and YK-11 were listed as examples of SARMs in S1.2.

S4. Hormone and Metabolic Modulators

- S4.3 was updated to include antibodies of precursors of myostatin and as example, apitegromab was added.
- The numbering was reformatted for clarity but there was no change in classification.

S5. Diuretics and Masking Agents

- The introductory language of the section was revised to harmonize with other sections of the List.
- Torasemide is added as an example of a diuretic and is already named in a *WADA Technical Document* (TD MRPL) and a *WADA Technical Letter* (TL24).
- It was clarified that a *Therapeutic Use Exemption* is not required for topical ophthalmic administration of a carbonic anhydrase inhibitor (e.g. dorzolamide, brinzolamine) or for local administration of felypressin in dental anesthesia in conjunction with a threshold substance.

PROHIBITED METHODS

M1. Manipulation of Blood and Blood Components

- Voxelotor was added as an example, as it alters the ability of hemoglobin to release oxygen in the body, thereby enhancing arterial oxygen saturation. As a side effect, it increases serum erythropoietin, which has been shown to result in higher hemoglobin concentration in healthy individuals.

SUBSTANCES AND METHODS PROHIBITED IN-COMPETITION

PROHIBITED SUBSTANCES

S6. Stimulants

- 1,3-dimethylamylamine and 1,3 DMAA were added as alternative common names for 4-methylhexan-2-amine, while 1,4-dimethylamylamine and 1,4-DMAA were included as synonyms of 5-methylhexan-2-amine.
- Solriamfetol was included in S6b due to its activity as a dopamine and norepinephrine reuptake inhibitor resulting in increases in brain levels of these neurotransmitters and consequent stimulant behavioral effects in preclinical species and in humans.
- Tetryzoline was added as an imidazoline derivative under Exceptions. In addition, it is clarified that otic administration of imidazoline derivatives is not prohibited.

S7. Narcotics

- Tramadol has been on the *WADA* Monitoring Program since 2012. Monitoring data has indicated significant *Use* in sports including cycling, rugby and football. Tramadol abuse, with its dose-dependent risks of physical dependence, opiate addiction and overdoses in the general population, is of concern and has led to it being a controlled drug in many countries. Research studies funded by *WADA*¹ have confirmed the potential for tramadol to enhance physical performance in sports. Consequently, the LiEAG recommends that the *Use* of tramadol should be prohibited *In-competition* effective 2024. A one-year delay in implementation will allow *Athletes* and medical personnel to better prepare for the new rule, Laboratories to update their procedures, and sports authorities to develop educational tools.

S9. Glucocorticoids

- It was clarified that otic administration of glucocorticoids is not prohibited.

P1. Beta-Blockers

- At the request of the World Mini-Golf Federation (WMF), it was agreed to include mini-golf as a sport where beta-blockers are prohibited. The skills required for mini-golf are similar to others found in sports disciplines where beta-blockers are prohibited.
- At the request of the World Under Water Federation (CMAS) beta-blockers will be prohibited *Out-of-competition* as well as *In-competition* in all subdisciplines of freediving, spearfishing and target shooting.

¹ a) Holgado D, Zandonai T, Zabala M, Hopker J, Perakakis P, Luque-Casado A, Ciria L, Guerra-Hernandez E, Sanabria D. Tramadol effects on physical performance and sustained attention during a 20-min indoor cycling time-trial: A randomised controlled trial. *J Sci Med Sport*. 2018 Jul;21(7):654-660.
b) Mauger L, Thomas T, Smith S, Fennell C. (2022). Is tramadol a performance enhancing drug? A randomised controlled trial. British Association of Sport and Exercise Medicine Conference, 26-27 May 2022, Brighton, UK.

MONITORING PROGRAM

- Dermorphin and its analogs were added to detect patterns of use in sport *In-competition*.
- GnRH analogs in females under 18 years were added to detect patterns of use in sport *In- and Out-of-competition*.
- Hypoxen (polyhydroxyphenylene thiosulfonate sodium) was added to evaluate misuse in sport *In- and Out-of-competition*.

* For further information on previous modifications and clarifications, please consult the *Prohibited List* Frequently Asked Questions at <https://www.wada-ama.org/en/prohibited-list#faq-anchor>.

ADDENDUM

S8. Cannabinoids

Background

- Following receipt of requests from a small number of stakeholders to remove (three national anti-doping organizations and one sports federation) or review (two anti-doping organizations) the prohibited *In-competition* status of cannabis from the *Prohibited List*, the WADA Executive Committee endorsed, during its meeting of September 2021, a recommendation of the WADA List Expert Advisory Group (LiEAG) to initiate a scientific review of the status of cannabis in 2022.
- At present, the main psychoactive component of cannabis, delta9-tetrahydrocannabinol (THC), is prohibited *In-competition* and is reported as an *Adverse Analytical Finding (AAF)* by WADA-accredited laboratories when the urinary concentration- of carboxy-THC exceeds a threshold of 150 ng/mL with a *Decision Limit* of 180 ng/mL. This threshold was significantly increased in 2013 from 15 ng/mL in order to minimize the number of *AAFs In-competition* due to potential *Use of THC Out-of-competition*. This means that with the current threshold, *Athletes* most at risk of testing positive are those who have consumed significant quantities of THC close to *In-competition Doping Control* or are chronic users.
- The 2021 World Anti-Doping Code (*Code*) incorporated the new Article 4.2.3 on *Substances of Abuse* for purposes of sanctioning under *Code* Article 10. *Substances of Abuse* are specifically identified on the *Prohibited List* because they are frequently abused in society outside of the context of sport. In this regard, the LiEAG identified THC as a *Substance of Abuse* for the 2021 *Prohibited List*, meaning that if the *Athlete* can establish that the THC use occurred *Out-of-Competition* and was unrelated to sport performance, the standard period of *Ineligibility* is three months, which may be reduced to one month if the *Athlete* satisfactorily completes an approved *Substance of Abuse* treatment program. While it is too early to evaluate the full impact of this new rule on sanctions for THC, preliminary data from 2021 indicates an increase in one- and three-month sanctions, suggesting that this provision is being applied.
- Under the World Anti-Doping Program, the approach to cannabis on the *Prohibited List* has therefore evolved chronologically as follows:

2013: The urinary threshold increased from 15 ng/mL to 150 ng/mL with a *Decision Limit* of 180 ng/ ml. This significantly affected the number of *AAFs*, from an average of between 400-500 per annum in the years 2009-2012 to fewer than 100 in 2021.

2018: Cannabidiol (CBD) was removed from the *Prohibited List*, allowing *Athletes* who wish to use it to have access to the non-psychoactive component of cannabis.

2021: The inclusion of the *Substance of Abuse* provision in the *Code* significantly reduced the length of *Ineligibility* sanctions from a potential two (or even four) years previously to three (or even one) month(s) today for *Athletes* that can establish that the THC use occurred *Out-of-Competition* and was unrelated to sport performance. Under Article 9 of the *Code*, the *Athlete* will still lose their medal, prize and result.

The Review Process:

- Since September 2021, the LiEAG, which is composed of external, international experts in pharmacology, forensic toxicology, drugs of abuse, analytical science, pharmacy, sports medicine, chemistry, endocrinology, internal medicine, regulatory affairs, peptides and growth factors and hematology embarked on a full *de novo* review of the status of delta9-tetrahydrocannabinol (THC) in sport. This extensive review focused on the three criteria set forth by Article 4.3 of the 2021 *Code*, namely:
 - a. Medical or other scientific evidence, pharmacological effect or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or enhances sport performance;
 - b. Medical or other scientific evidence, pharmacological effects or experience that the *Use* of the substance or method represents an actual or potential health risk to the *Athlete*;
 - c. *WADA*'s determination that the *Use* of the substance or method contravenes the spirit of sport described in the introduction to the *Code*.
- Under *Code* Article 4.3, a substance or method must meet at least two of these three criteria to be considered for inclusion in the *Prohibited List*.
- Two subgroups of members of the LiEAG were formed, one to evaluate the effects of THC on performance enhancement (LiEAG-PE) and the other to assess the health risks (LiEAG-H). All existing scientific and medical publications related to these two topics were reviewed, as well as testimonials from *Athletes* who were/are cannabis users, available publicly, including in published surveys.
- This scientific literature review was subsequently discussed with four world-renowned independent, external international experts (Ad-Hoc THC Expert Group) specialized in the pharmacology, toxicology, psychiatry and behavioral properties of THC and cannabinoids, to ensure that all relevant publications had been included and that all relevant scientific and medical aspects had been appropriately evaluated. The experts confirmed that the information review had been extensive and that all relevant data and aspects of the impact of THC on health and performance enhancement had been properly examined.
- With respect to the Spirit of Sport criterion, the LiEAG Chair consulted with the *WADA* Ethics Expert Advisory Group (Ethics EAG). The Ethics EAG considered cannabis *Use*, at this time, to be against the Spirit of Sport across a cluster of areas listed in the *Code*, in particular:
 - Health
 - Excellence in Performance
 - Character and *Education*
 - Respect for rules and laws
 - Respect for self and other participants

They also noted that:

- Further research should be undertaken or supported in relation to *Athletes*' perceptions of cannabis *Use* but also in relation to its potential (including placebo-induced) enhancing effects. These are areas of uncertainty owing to a lack of robust evidence.

- Levels to trigger an *Anti-Doping Rule Violation In-competition* are such that they would be problematic on medical grounds for a competing *Athlete*, or indicative of a chronic habitual user. The present rule is not, as sometimes perceived or represented, an excessive incursion into private lifestyles. Nevertheless, and mindful of shifting public attitudes and laws in certain countries, the weight of evidence and argument, along with broad international restrictive regulatory laws and policies, supports the continuance of cannabis on the *Prohibited List* at this time.
- The LiEAG Chair also consulted with the members of the *WADA Athlete* Committee to seek their opinions on the *Use* of cannabis in sport. The meeting reflected the range of opinions and views of the *Athlete* community.
- In total, there were 10 consultative meetings held prior to the latest meeting of the LiEAG on 25-26 April 2022:
 - three by the LiEAG-PE
 - two by the LiEAG-H
 - one between the LiEAG Chair and the *Athlete* Committee Chair
 - one between the LiEAG Chair and the *Athlete* Committee
 - one between the LiEAG Chair and the Ethics EAG
 - one between the Ad-Hoc THC Expert Group and the LiEAG-PE
 - one between the Ad-Hoc THC Expert Group and the LiEAG-H

Conclusions:

After a thorough assessment and discussion under *WADA Code* Article 4.3, the LiEAG concluded that:

- a. There is compelling medical evidence that *Use* of THC is a risk for health, mainly neurological, that has a significant impact on the health of young individuals, a cohort which is overrepresented in *Athletes*.
- b. The current body of objective evidence does not support THC enhancement of physiological performance, while the potential for performance enhancement through neuropsychological effects still cannot be excluded.
- c. In consideration of the values encompassed by the Spirit of Sport as outlined by the Ethics EAG, and noting in particular that respect for self and other participants includes the safety of fellow-competitors, the *Use* of THC In-competition violates the Spirit of Sport.

Based on these three criteria defined by the *Code*, on the scientific evidence available, THC meets the criteria to be included on the *List*.

Future considerations:

- These conclusions are based on the currently available scientific literature. From the extensive review conducted, it was evident that there is a lack of robust studies evaluating the performance enhancing effects of THC at both the physical and mental level. While anecdotal, self-reported evidence is available, further clinical studies are required to rigorously determine the neuropsychological impact of THC on performance. However, it is also acknowledged that such studies may be difficult to design. For example, it would require enrolling volunteers actively consuming THC, which in most countries is illegal; it would not be a truly blinded placebo study because the subject would feel the effect of THC leading to possible positive bias (to show it has performance enhancing effects and thus should be prohibited) or negative bias (to support exclusion from the *List*); it would be difficult to re-create the stress of a competition; and it is very unlikely that high level *Athletes* could be included as volunteers. Therefore, only those using cannabis and in regions where THC use is legal could be recruited, and in an *Out-of-competition* setting, with a risk of positive or negative bias.
- As with all substances that are prohibited *In-competition* only, *Athletes* in regions where cannabis use is legal are advised to refrain from consuming cannabis for a number of days before the start of competition.