

A Review on Doping in Elite Sport : Prevalence, Method, and Governance

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Abstract: *The global effort to maintain fair play in competitive sports faces continuous challenges from the misuse of performance-enhancing drugs (PEDs). This review summarizes recent developments and persistent analytical hurdles across several key classes of substances prohibited by the World Anti-Doping Agency (WADA). Anabolic Agents and Peptide Hormones continue to dominate adverse analytical findings. The review highlights the significant health risks, particularly cardiovascular damage, associated with Anabolic-Androgenic Steroids (AAS). For Erythropoietin (EPO), the challenge remains the unambiguous distinction between endogenous and exogenous forms, especially with the practice of evasive microdosing. Advancements in detecting Growth Hormone (GH) misuse have been achieved through the GH Isoform Differential Immunoassay, while the verification of Chorionic Gonadotropin (CG) now relies on robust mass spectrometry (MS) techniques to tackle complex isoforms. Hormone and Metabolic Modulators present dual challenges, as exemplified by formestane, which is both a natural metabolite and an exogenous doping agent. The analytical gap is being addressed by incorporating Isotope Ratio Mass Spectrometry (IRMS) and lowering reporting thresholds. Beta-2 Agonists, though therapeutic for asthma, carry an anabolic potential, necessitating strict controls and analysis of specific routes of administration to prevent abuse. Furthermore, the paper addresses substances used to mask doping, such as the plasma-expanding properties of Glycerol, a Diuretic and Masking Agent. The detection of Cannabinoids, specifically Δ^9 -tetrahydrocannabinol (THC), is focusing on THC-glucuronide as a reliable urinary marker for recent inhalation. Finally, the difficulty in interpreting findings for Glucocorticosteroids (GCs) stems from distinguishing between permitted localized administration and prohibited systemic use, suggesting a need for analysis of unique metabolic signatures. Collectively, these challenges underscore the necessity for continual improvement in anti-doping tests, specifically focusing on techniques that can reliably establish exogenous origin, detect repetitive microdosing, and accurately determine the route of administration to ensure a level playing field and uphold the 'true spirit of sportsmanship.*

Keywords: WADA (World Anti-Doping Agency), Performance-Enhancing Drugs (PEDs), Anabolic-Androgenic Steroids (AAS), Erythropoietin (EPO), Microdosing, Adverse Analytical Finding (AAF), Isotope Ratio Mass Spectrometry (IRMS), GH Isoform Differential Immunoassay, Dietary Supplements (containing prohibited substances), Masking Agents (e.g., Glycerol), Beta-2 Agonists, Glucocorticosteroids (GCs), Prevalence of Doping (likely a "double-digit figure"), Analytical Hurdles, Athlete Biological Passport.

I. INTRODUCTION

The actual prevalence of doping in elite sports is a frequent subject of debate. Although various methods are used to study how common doping is, recent information shared by several elite cyclists has highlighted a significant difference between the true numbers and the results of official positive doping tests. This suggests that the current testing methods may be underestimating the real extent of the problem.[1,2] This article aims to explore the pros and cons of the main ways we currently try to figure out how many elite athletes are doping.



These methods include:

- (1) chemical tests done in laboratories,
- (2) surveys and questionnaires,
- (3) analyzing performance data for unusual patterns, and
- (4) drawing conclusions from "ego documents" (like diaries or letters).

A secondary goal is to look at all the available scientific data—since the last big review in 1997—to get a better idea of the actual rate of doping in elite sports today.[3] Sport is widely considered a microcosm of society, meaning the world of athletic competition and organizations serves as a smaller-scale reflection of the larger societal structure, values, and issues. Scholars like Adlthukhov and Nauright and Aduval emphasize that the dynamics seen in sports—such as competition, cooperation, economic disparity, power struggles, and social inequality (including race and gender bias)—mirror those present in the broader culture. Therefore, by studying sport, researchers can gain valuable insight into the dominant norms and conflicts within a particular society.[4,5] The text essentially suggests that sports have a powerful ability to unite people from diverse backgrounds, fostering a communal society built on the principles of sportsmanship. However, it also points out a key relationship between law and society: the law is fundamentally a mirror reflecting the values and norms held by that society, as supported by the research of Harrel and Hanstad and Houlihan.[6,7] Sports were originally created to help improve relationships between different countries around the world. To make sure this goal was achieved, it was crucial to maintain a strong sense of fairness and harmony throughout every competition. Because of this need for a level playing field, strict rules, regulations, and laws were established—specifically, those that ban the use of performance-enhancing drugs. This ban is designed to uphold the true spirit of sportsmanship.[8]

Doping is the use of any substance or method that is either dangerous to an athlete's health or improves their performance unnaturally.[9] The World Anti-Doping Agency (WADA) was founded in 1999 to spearhead a global push for clean, doping-free sport. It's an independent international body equally funded by the world's governments and the sports movement itself. To formalize this fight, WADA introduced the WADA Code in 2004. This Code serves as the universal rulebook against doping and has been adopted by nearly 700 sports organizations, including major bodies like the IOC, IPC, International Federations, and various national and regional anti-doping groups. WADA also ensures the rules stay current by yearly updating the List of Prohibited Substances and Methods.[10] Even though we all know that eating a balanced diet is key to performing at our best, competitive sports and really tough exercise push our bodies much further than they normally go. Because athletes subject themselves to such strenuous physical activity, their bodies have unique demands that go beyond normal biology. Simply put, regular healthy eating is the starting line, but serious training requires special attention to fuel and recovery to handle the extreme stress placed on the system.[11] The pervasive issue of doping in sport has become significantly more complex than it once was. It's no longer a simple discussion about rule-breaking; rather, it presents numerous multifaceted standpoints and opinions. Consequently, the debate surrounding doping is now informed by, and approached from, all possible conceivable perspectives, involving athletes, scientists, governing bodies, and fans alike. This complexity means that finding unified solutions or simple answers is increasingly challenging.[12,13] The annually updated World Anti-Doping Agency (WADA) edited Prohibited List represents the central document detailing substances and methods of doping in sport.[14] The core issue remains a subject of ongoing debate: how much evidence is required to prove that a prohibited substance actually enhances athletic performance. This discussion focuses primarily on defining the necessary extent or certainty of proof for a banned substance to justify its status as performance-enhancing.[15,16]

II. CLASSIFICATION

3.1 Anabolic agents

3.1.1 Anabolic-androgenic steroids :

Despite the continuously growing body of evidence concerning the adverse health effects associated with anabolic androgenic steroids (AAS), this specific class of anabolic agents was the most frequently reported substance responsible for adverse analytical findings in doping control samples during 2013. This indicates that even with increasing awareness and documentation of the significant health risks involved, anabolic steroids remained the primary illicit substance



detected in competitive sports that year.[17] Misuse of Anabolic Androgenic Steroids (AAS) has been frequently linked to concerning cardiovascular issues. Specifically, numerous reports indicate that individuals misusing these substances often exhibit impaired post-exercise heart rate recovery. This reduced ability of the heart to return to its resting state after physical exertion serves as a critical indicator of potential underlying cardiac dysfunction.[18] Autopsy Findings Confirm AAS-Related Organ Damage Autopsy results from individuals whose sudden or unnatural deaths were linked to Anabolic- Androgenic Steroid (AAS) use (confirmed by toxicology) consistently validated the most commonly reported health concerns. Specifically, the post-mortem examinations confirmed significant damage to key organs, including:

3.1.2 Testicular Health: Findings such as testicular atrophy (shrinkage) and testicular fibrosis (scarring) were present, often accompanied by arrested spermatogenesis (failure of sperm production).

3.1.3 Cardiovascular System: Left ventricular hypertrophy (abnormal thickening of the heart's main pumping chamber) was also substantiated, highlighting the severe, and potentially fatal, impact of AAS use on the heart.[19]

3.2 Peptide hormones, growth factors and related substances

3.2.1 Erythropoiesis-stimulating agents (ESAs)

When we talk about erythropoiesis-stimulating agents (ESAs), one name stands above the rest: erythropoietin, or EPO. It's a key substance, but it carries a complicated legacy. Despite the well-documented cases of athletes misusing EPO to gain an unfair advantage, research continues to explore its legitimate medical potential. Scientists are still trying to fully grasp its therapeutic value in clinical settings, precisely how it boosts endurance in healthy individuals, and the core mechanisms behind that effect.[20,21] The Continuing Challenge of Detecting EPO Doping: Despite advancements, there remains an unmet and critical need to test for the use of xenobiotic (synthetic) Erythropoietin (EPO) in sports. It is essential to develop methods that can unambiguously distinguish between the naturally occurring EPO produced by the body (endogenous) and EPO administered externally for doping (exogenous). Furthermore, testing methods must be continuously improved to effectively counter the latest doping trends, particularly the practice of repetitive microdosing (administering small, frequent doses to evade detection). Consequently, timely review papers are necessary to: Summarize recent developments and key accomplishments in EPO detection. Clearly outline the future goals and strategic needs for improving anti-doping tests.[22,23]

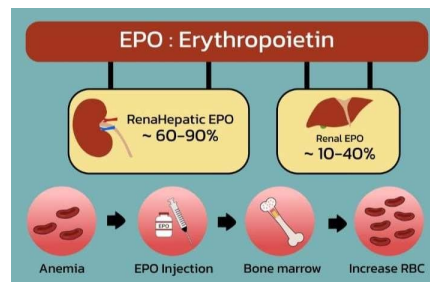


Fig.no.1: Erythropoiesis-stimulating agents (ESAs)

3.2.2 Chorionic gonadotropin (CG) and luteinizing hormone (LH):

Chorionic gonadotropin (CG) was the most common peptide hormone, growth factor, or related substance on the WADA Prohibited List to be identified in Adverse Analytical Findings (AAFs) and Atypical Findings (ATVs).[24]

3.2.3 Advancements in Confirmatory Testing:

The need for highly reliable confirmation of CG (Chorionic Gonadotropin) levels has driven researchers to develop mass spectrometry (MS) techniques over the past decade. MS offers superior specificity, making it the gold standard for verification.



3.2.4 A Breakthrough MS Procedure:

A significant recent development was presented by Woldemariam and Butch, who introduced a robust MS-based method. Their procedure tackles the complexity of CG isoforms by:



Fig.no.2: A Breakthrough MS Procedure

3.2.5 Two-Step Immuno-Extraction: This crucial initial step selectively isolates and purifies the target CG forms from the sample, significantly enhancing the accuracy of the subsequent analysis.

3.2.6 Bottom-Up Quantification: Using this approach, the researchers quantified the three most prevalent and clinically relevant isoform of CG:

Intact CG (the complete molecule) The free β -subunit

The β -subunit core fragment

This method represents a major step forward, providing a precise and comprehensive "signature" of the active CG forms present.[25]

3.2.7 Growth hormone, Insulin-like growth factor-1 (IGF-1), and other growth or releasing factors:

The challenge of detecting growth hormone (GH) misuse in sports has been a major focus of anti-doping science, necessitating extensive research investment spanning over 15 years. This sustained effort has been successful, culminating in the World Anti-Doping Agency (WADA) approving two distinct methodologies for use in official doping control procedures.[26,27] The GH Isoform Differential Immunoassay serves as a critical methodology in anti-doping efforts to detect the misuse of pharmaceutical (synthetic) Growth Hormone (GH) preparations. The test's underlying principle exploits the fact that administering external GH significantly influences and disrupts the natural distribution and ratios of circulating GH isoform (molecular variants) within the body. To accurately interpret the assay results and report an Adverse Analytical Finding (AAF), laboratories require precisely calculated decision limits (cut-off values). These decision limits were derived from an extensive analysis of GH isoform ratio variations across a large cohort of 21,943 serum samples collected and analyzed between 2009 and 2013. By establishing these assay-specific values, laboratories are enabled to confidently report an AAF whenever the measured isoform ratios in a sample exceed the defined non-natural threshold.[28]

3.3 Beta-2-agonist

β_2 -agonists (β_2 -agonists) are a class of drugs that have long been at the center of debate concerning their performance-enhancing potential in athletic competition. While their primary therapeutic role is in managing conditions like asthma—by promoting the relaxation of bronchial smooth muscle—their chemical properties also raise concerns. The potential for β_2 -agonist to influence anabolic processes (muscle building) and body



composition (e.g., in livestock, they are known to promote cattle fattening) has led to their strict regulation. Current Prohibitions and Exceptions

Under current anti-doping regulations, all β_2 -agonist are prohibited for use by athletes, with only three specific exceptions granted for therapeutic purposes:

Salbutamol, Formoterol, Salmeterol

Even for these three allowed drugs, their use is heavily restricted. Athletes must adhere to specified routes of administration (typically inhaled) and maximum permissible dosages to ensure their use remains strictly therapeutic and does not cross into the realm of potential performance enhancement.[29]

3.3.1 Muscle Fatigue and Strength :Research by Decorte et al. investigated the impact of inhaled salbutamol (at doses of 200 μg and 800 μg) on quadriceps muscle fatigue. The placebo-controlled studies revealed that salbutamol did not alter the maximum voluntary contraction (MVC), meaning the drug didn't boost the absolute peak strength a person could generate. However, a significant performance-enhancing effect was observed: the athletes could perform a greater number of maximal contractions until fatigue after salbutamol application.

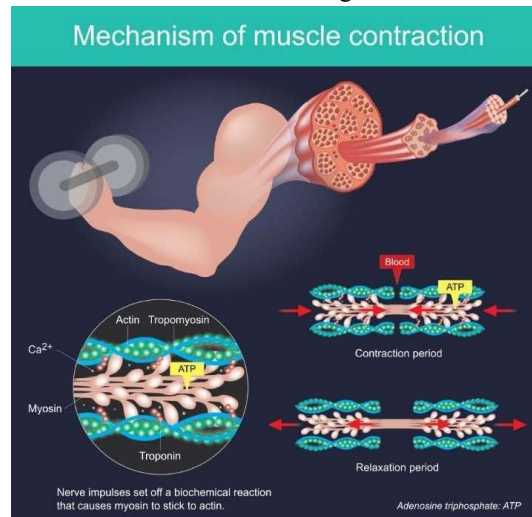


Fig.no.3: Muscle Fatigue and Strength

While the exact mechanism behind this anti-fatigue phenomenon is currently unclear, the study clearly points to a beneficial effect of inhaled salbutamol on muscle endurance.

Endurance Exercise Performance :In a complementary line of investigation, Dickinson et al. specifically examined the acute effects of inhaled salbutamol on endurance athletes' performance during a 5-kilometer time trial run.[30,31]

3.4 Hormone and metabolic modulators

The World Anti-Doping Agency (WADA) classifies aromatase inhibitors (AIs) as a critical class of hormone and metabolic modulators (Category 1) due to their potential for performance enhancement by altering hormone balance. A key substance in this category is formestane.

3.4.1 The Dual Challenge: Natural Origin and Exogenous Abuse

The analytical challenge associated with formestane is its dual origin. While it can be administered exogenously as a doping agent (often monitored alongside anabolic- androgenic steroids (AAS) using highly sensitive techniques like GC-MS/MS), it is also a naturally occurring substance in human urine. This natural presence necessitates the use of a reporting threshold to distinguish between endogenous levels and doping. Historically, a relatively high threshold of 150 ng/mL has been applied. However, this high value presents a dilemma: while it minimizes false positives, it potentially allows athletes abusing formestane at lower, but still performance-enhancing, concentrations to escape detection.



3.4.2 A Smarter Approach: Incorporating IRMS and Lowered Thresholds To address this gap, anti-doping science requires a more sophisticated approach. Isotope Ratio Mass Spectrometry (IRMS) is the preferred method for confirmation, as it can unequivocally determine whether the formestane detected is of synthetic (exogenous) or natural (endogenous) origin. To trigger these resource-intensive IRMS confirmatory analyses on a sensible basis, a new, lower action level was proposed. Based on a comprehensive study of a large reference population ($n = 3031$) and controlled elimination studies following the administration of testosterone and androst-4-ene-3,17-dione, a revised threshold of 25 ng/mL has been suggested. This new, significantly lowered threshold represents a crucial compromise. It maintains sufficient sensitivity to detect the abuse of formestane at lower doping levels while simultaneously providing a scientifically justified filter to limit the burden of unnecessary confirmatory IRMS analyses on samples exhibiting only low endogenous concentrations.[32] Tamoxifen, a cornerstone in the treatment of estrogen-sensitive cancers, is a prominent member of the selective estrogen receptor modulator (SERM) class. Its widespread clinical use was evident in 2013, when it was the most frequently monitored drug within the therapeutic category S.4.[33]

3.5 Diuretics and other masking agents and stimulants

Glycerol has become a significant focus in doping control studies, primarily because of its potential use as a plasma-volume expanding substance to mask doping. Research, particularly meta-analyses, has confirmed that when glycerol is administered alongside fluids, it does successfully increase plasma volume due to its osmotic properties. However, despite this confirmed dilutional effect, the overall impact on the crucial hematological parameters used in the Athlete Biological Passport (ABP), such as hemoglobin and hematocrit, has been found to be modest. This suggests that while glycerol can expand the plasma compartment, its ability to significantly alter the key markers used to detect blood manipulation within the anti-doping framework is relatively minor.[34]

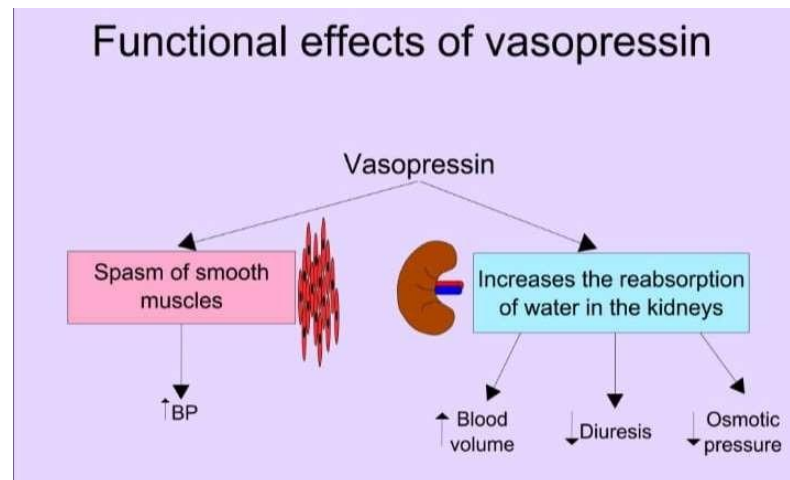


Fig.no.4: Diuretics and other masking agents and stimulants

Building upon the findings of this meta-analysis, a subsequent placebo-controlled study investigated the effects of glycerol pre-loading (administration prior to exercise). Researchers assessed changes in blood parameters and measured the corresponding urinary glycerol concentrations.[35]

3.6 Stimulants

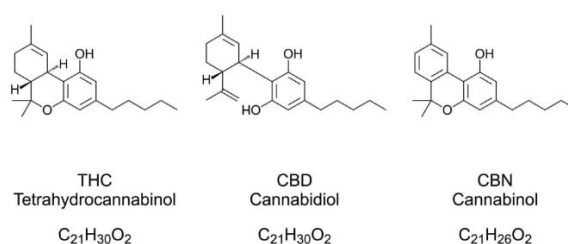
Following its established structure, the WADA Prohibited List continues to categorize stimulants into two main groups: non-specified and specified compounds. This distinction helps in managing the penalties associated with a positive test, as non-specified substances generally carry harsher sanctions than specified substances.[36] In regulatory and forensic contexts, a stimulant is typically presumed to be specified unless explicitly categorized as non-specified. While our understanding of traditional stimulants is well-established, the continuous proliferation of designer (psycho)stimulants presents a significant, complex challenge across multiple fields, including legal, forensic science, toxicology, and anti-



doping control. Since 2012 alone, hundreds of these new chemical entities have been documented, complicating detection and regulation efforts.[37,38]

3.7 Cannabinoids

The core compound from which all cannabinoids originate, Δ^9 tetrahydrocannabinol (THC), has been extensively researched across various contexts. In the field of sports drug testing, a long-standing focus has been on detecting the recent use of THC (specifically, shortly before competition). This is crucial for anti-doping authorities to accurately interpret urinary concentrations of Adverse Analytical Findings (AAFs), because THC is prohibited in-competition only. Furthermore, the body's processing of THC (its metabolic fate) is complex and is known to be affected by numerous variables, including physical exercise. Against this background, a study by Desrosiers et al. explored the potential of THC-glucuronide as a specific marker in urine to reliably indicate the recent inhalation of THC.[39]



Desrosiers et al. sought to validate THC-glucuronide as a reliable urinary marker capable of pinpointing the recent use (inhalation) of cannabis, suggesting a potential improvement over existing screening methods.[40]

Classes of doping agents

Prohibited at all times (in- and outside competition)






Class	Example	Exemplary structure	Used in sport...
Anabolic agents	Androgenic steroids <i>Testosterone</i>		Bodybuilding, Cycling, Football, Boxing, Martial arts...
Peptide hormones, growth factors and related	Erythropoiesis-Stimulating Agents <i>EPO (erythropoietin)</i>		Endurance sports: Cycling, distance running, Bi-/Triathlon...
Beta-2 agonists	(<i>R</i>)- <i>Salbutamol</i>		
Hormone antagonists and other modulators	Aromatase inhibitors <i>Aminoglutethimide</i> , Antiestrogens		Female bodybuilders
Diuretics and other masking agents	<i>Acetazolamide</i>		Athletes in general
Non-Approved	Any Substance not addressed, with no approval for medical use

Fig.no.5: Classification

3.8 Glucocorticosteroids

Glucocorticosteroids (GCs) are banned in sports when administered systemically via oral, intravenous, intramuscular, or rectal routes. However, distinguishing the exact route of administration analytically poses a significant challenge. Notably, localized injections of certain GCs, like triamcinolone acetonide in intra-articular or intratendinous treatments, can result in high urinary drug concentrations, sometimes reaching up to 200 ng/mL . This overlap in urinary concentration makes it difficult to ascertain if an athlete received a prohibited systemic dose or a permitted local injection. To help resolve this ambiguity and support the identification of the drug administration regimen, researchers, such as Matabosch et al. in their work on methylprednisolone, have suggested that analyzing the metabolic pattern of corticosteroids following different routes—specifically topical versus oral—could provide useful differentiating evidence. This approach aims to leverage the unique metabolic signatures produced by various application methods to better determine the origin of the detected substance.[41,42]



IV. METHODS


4.1 Doping Control Test Results

Since 2003, the World Anti-Doping Agency (WADA) has routinely released annual summaries detailing the number of Adverse Analytical Findings (AAFs). These findings—which represent positive test results—are compiled from data reported by all official WADA-accredited laboratories worldwide. These published data are fundamental for researchers and policymakers assessing the scale of doping in sports.[43] Clearer and more engaging (less dense academic jargon).Flow better for the reader. Use stronger, more active verbs (avoiding passive voice where possible). Tell the story of the research and findings.Example:"We then focused on creating new catalysts to significantly speed up the reaction."[44,45,46]The challenge of detecting doping is significantly complicated by the use of substances characterized by very short detection windows. When administered in micro-doses, these effective performance-enhancing drugs (PEDs) can become virtually untraceable within a matter of hours or even less, making them undetectable just days after administration. Intentional users are well aware of this pharmacological limitation and strategically exploit the gaps in testing protocols. They leverage the fact that athletes are not subjected to daily testing, timing the administration of these transient substances to fall between scheduled or potential anti-doping controls, thereby successfully evading detection.[47,48,49]The initial limitations in laboratory techniques mean that a doping offense might not be detected at the time the sample is first tested. To address this, current anti-doping regulations permit the re-analysis of collected samples for a significant period—up to 8 years after the initial collection date. This provision is crucial as it allows anti-doping agencies to benefit from advances in analytical science that have occurred since the samples were first collected.Impact of Re-analysis, While this strategy has been successfully deployed in high-profile cases involving substances like methoxy polyethylene glycol-epoetin beta (CERA) and methandienone, leading to new doping convictions, the overall number of new cases identified through re- analysis has been relatively small. Nonetheless, these retrospective cases are often very high profile, demonstrating the long-term commitment to catching athletes who cheated in the past and underscoring the continuously evolving nature of anti-doping science.[50,51]

Prohibited methods

Table 2. Prohibited methods¹⁵

M1. Manipulation of blood and its components	Administration of products containing red blood cells in the circulatory system	Increasing the amount of oxygen or its transport
M2. Physical and chemical handling	Altering the integrity and validity of the sample collected during anti-doping control	Intravenous infusions or injections of more than 50 mL for 6 hours
M3. Genetically doping	Transfer of polymers of nucleic acids or their analogs	Use of normal or genetically modified cells



The diagram below illustrates the four categories of prohibited methods and the specific substances or techniques associated with each:

- Skill** (Speed, reflexes, limb-eye co-ordination, concentration): Skill sports (driving/riding, target shooting). Out of competition Training. In competition Beta-blockers. Stimulants: amphetamine, alkaloids, glucocorticoids.
- Strength** (Lifting, throwing, boxing, sprinting): Power sports (lifting, throwing, boxing, sprinting). Androgen doping Direct: natural, synthetic, designer, nutraceutical & non-steroidal androgens. Indirect: hCG, LH, anti-estrogens, GnRH analogs.
- Stamina** (Endurance sports, long distance or duration events): Endurance sports (long distance or duration events). Blood (Hb) doping Direct: blood transfusion. Indirect: heterologous, autologous, erythropoietin, biosimilars & analogs, hypoxia-mimetics.
- Recovery** (Basic repair after injury & training): Contact sports & intense physical training. GH. GH releasing peptides (GHRH, Ghrelin analogs). Growth factors.

Fig.no.6: Prohibited Methods

4.2 Population Estimates Based on Biological Parameters

Indirect estimation methods, particularly those focusing on the distribution of specific biological parameters, offer a valuable strategy for assessing the prevalence of doping within athlete groups.



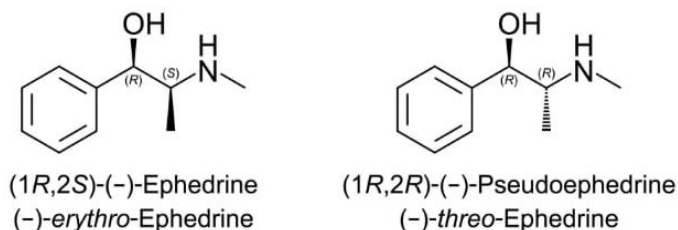
Utilizing Blood Parameters for Haematological Doping: The analysis of blood parameters has been a key area of research in this domain, providing insights into the prevalence of blood-related doping techniques. This includes the misuse of substances like erythropoietin (EPO) and other forms of haematological manipulation aimed at enhancing oxygen-carrying capacity.

Trends in Elite Cycling: A notable example of the effectiveness of this monitoring approach is seen in elite cycling. the percentage of athletes exhibiting 'extreme' (and thus suspect) haematological values experienced a significant reduction, dropping sharply from 11% to 2%. This decline suggests that improved testing and monitoring protocols may have successfully deterred or reduced the reliance on blood-doping methods within the sport.[51]The observed changes in individual blood parameters (i.e., markers used to assess blood composition) during this period may be interpreted as an indication that the prevalence of hematological doping—or the use of more aggressive, "extreme" doping methodologies—has decreased. This approach of correlating blood parameter shifts with potential doping activity has also been employed in investigations across other sports.[52,53] A significant advancement in anti- doping science was introduced by Sottas et al. through the development of a sophisticated Bayesian model.This innovative method moves beyond traditional testing by employing a comprehensive statistical framework that incorporates several relevant biological and analytical parameters. Critically, the model is built upon empirically validated data gathered from both athletes known to have doped and those who are clean.The core mechanism of this approach is its ability to analyze large, population-wide datasets and statistically determine the expected distribution of biological markers within a clean population. By calculating the proportion of data that falls outside this expected, 'natural' range, the model effectively identifies the segment of the population whose blood profiles are statistically 'unnatural'. The final output is a powerful, evidence-based estimate of the prevalence of blood manipulation within the tested population. This provides a more holistic and quantitative perspective on doping than individual test results alone.[54,55,56]

V. DIETARY SUPPLEMENTS CONTAINING PROHIBITED SUBSTANCES

5.1 Ephedrine and pseudoephedrine

Despite the ease of detection in modern laboratories, the use of stimulants remains a persistent issue in competitive athletics. While the full list of both permitted and banned substances is extensive, a notable concern centers on the unintentional ingestion of prohibited compounds through dietary supplements. Numerous studies have documented that various supplements contain undeclared or hidden stimulants, including ephedrine and its analogues (such as pseudoephedrine and methylephedrine), caffeine, and even more potent, illicit compounds like 3,4- methylenedioxy-N-methylamphetamine (MDMA or 'ecstasy') and other amphetamine-related substances. This demonstrates a significant risk for athletes, as they may face anti-doping sanctions due to products that often fail to accurately disclose all ingredients on their packaging labels.[57]



5.2 Sibutramine

The weight-loss supplement market has seen the emergence of products adulterated with sibutramine, an anti-obesity drug. This ingredient is deliberately omitted from the product labels.Sibutramine has been discovered in products falsely advertised as 'pure herbal' slimming capsules and 'natural' tea. This constitutes a significant consumer risk, as users are unknowingly consuming a pharmaceutical agent.The presence of sibutramine is not fleeting. In a study, urinary metabolites (breakdown products) of sibutramine were still detectable 50 hours after a volunteer consumed a single "dose" of one of these adulterated teas.This highlights the drug's persistence in the human body, which is critical information



given the potential for adverse health effects associated with sibutramine, especially for individuals with underlying health conditions.[58,59]

5.3 Methylhexaneamine

Methylhexaneamine, a stimulant initially developed for use as a nasal decongestant, has become a substance of significant concern within the dietary supplement industry. Despite its original pharmaceutical intent, it has been widely detected as an ingredient in commercially available supplements, marketed primarily for its performance- enhancing and fat-burning properties. Due to serious safety concerns, the World Anti- Doping Agency (WADA) declared it a prohibited compound in 2009. The severe adverse cardiovascular effects of this stimulant have been tragically highlighted by case reports, including one detailing the deaths of two U.S. soldiers. Both individuals, who were consuming dietary supplements containing methylhexaneamine, suffered cardiac arrest during periods of physical exertion and ultimately succumbed to the effects. This underscores the critical risk of combining potent stimulants like methylhexaneamine with strenuous physical activity.[60,61]

VI. DISCUSSION

The prevalence of true doping among elite athletes is likely to be significantly higher than officially reported figures. As WADA's Director General, David Howman, projected, the actual doping rate is anticipated to be a "double-digit figure"—suggesting a minimum prevalence of 10% or more among the elite sporting population.[62]

VII. CONCLUSION

The presented information outlines the critical advancements and persistent challenges in the field of anti-doping control, reflecting the continuous effort to ensure fair play in competitive sports.

REFERENCES

- [1]. Waddington I. Changing patterns of drug use in professional cycling: implications for anti-doping policy. InDoping in Cycling 2018 Dec 7 (pp. 31- 44). Routledge.
- [2]. Sorgdrager W, Van Bottenburg M, Goedhart E. Joining or Quitting [Original Title:'Meedoen of Stoppen']. Arnhem, The Netherlands. 2013.
- [3]. Laure P. Epidemiologic approach of doping in sport. A review. The Journal of sports medicine and physical fitness. 1997 Sep 1;37(3):218-24.
- [4]. Altukhov S, Nauright J. The new sporting Cold War: implications of the Russian doping allegations for international relations and sport. InGlobal Markets and Global Impact of Sports 2020 Apr 28 (pp. 36-52). Routledge.
- [5]. Duval A. The Russian doping scandal at the court of arbitration for sport: lessons for the world anti-doping system. The International Sports Law Journal. 2017 Apr;16(3):177-97.
- [6]. Harrell EJ. How 1% performance improvements led to Olympic gold. Harvard Business Review. 2015 Oct 30;30:1-7.
- [7]. Vidar Hanstad D, Houlihan B. Strengthening global anti-doping policy through bilateral collaboration: The example of Norway and China. International journal of sport policy and politics. 2015 Oct 2;7(4):587-604.
- [8]. Scanlan Jr JA, Cleveland Sr GE. The Past as Prelude: The Early Origins of Modern American Sports Law. Ohio NUL Rev.. 1981;8:433.
- [9]. Cox RW. Dictionary of Sports Studies.
- [10]. Terreros JL, Manonelles P, López-Plaza D. Relationship between doping prevalence and socioeconomic parameters: an analysis by sport categories and world areas. International journal of environmental research and public health. 2022 Jul 30;19(15):9329.
- [11]. Zadik Z, Nemet D, Eliakim A. Hormonal and metabolic effects of nutrition in athletes. Journal of Pediatric Endocrinology & Metabolism. 2009 Sep 1;22(9).



- [12]. Delanghe JR, Maenhout TM, Speeckaert MM, De Buyzere ML. Detecting doping use: more than an analytical problem. *Acta Clinica Belgica*. 2014 Feb 1;69(1):25-9.
- [13]. Dvorak J, Baume N, Botré F, Broséus J, Budgett R, Frey WO, Geyer H, Harcourt PR, Ho D, Howman D, Isola V. Time for change: a roadmap to guide the implementation of the World Anti-Doping Code 2015. *British journal of sports medicine*. 2014 May 1;48(10):801-6.
- [14]. Davoren AK, Rulison K, Milroy J, Grist P, Fedoruk M, Lewis L, Wyrick D. Doping prevalence among US elite athletes subject to drug testing under the World Anti-Doping Code. *Sports Medicine-Open*. 2024 May 20;10(1):57.
- [15]. Heuberger JA, Cohen AF. Review of WADA prohibited substances: limited evidence for performance-enhancing effects. *Sports Medicine*. 2019 Apr;49(4):525-39.
- [16]. Simon P, Dettweiler U. Current anti-doping crisis: the limits of medical evidence employing inductive statistical inference. *Sports Medicine*. 2019 Apr 12;49(4):497-500.
- [17]. World Anti - Doping Agency. 2013 Anti - Doping Testing Figures Laboratory Report.
- [18]. Dos Santos MR, Dias RG, Laterza MC, Rondon MU, Braga AM, de Moraes Moreau RL, Negrão CE, Alves MJ. Impaired post exercise heart rate recovery in anabolic steroid users. *International journal of sports medicine*. 2013 Oct;34(10):931-5.
- [19]. Darke S, Torok M, Duflo J. Sudden or unnatural deaths involving anabolic - androgenic steroids. *Journal of forensic sciences*. 2014 Jul;59(4):1025-8.
- [20]. Cernaro V, Lacquaniti A, Buemi A, Lupica R, Buemi M. Does erythropoietin always win?. *Current medicinal chemistry*. 2014 Mar 1;21(7):849-54.
- [21]. Hardeman M, Alexy T, Brouwer B, Connès P, Jung F, Kuipers H, Baskurt OK. EPO or PlacEPO? Science versus practical experience: panel discussion on efficacy of erythropoietin in improving performance. *Biorheology*. 2014 Mar;51(2-3):83-90.
- [22]. Reichel C. Detection of peptidic erythropoiesis-stimulating agents in sport. *British Journal of Sports Medicine*. 2014 May 1;48(10):842-7.
- [23]. Citartan M, Gopinath SC, Chen Y, Lakshmipriya T, Tang TH. Monitoring recombinant human erythropoietin abuse among athletes. *Biosensors and Bioelectronics*. 2015 Jan 15;63:86-98.
- [24]. World Anti - Doping Agency. 2013 Anti - Doping Testing Figures Laboratory Report.
- [25]. Woldemariam GA, Butch AW. Immunoextraction–tandem mass spectrometry method for measuring intact human chorionic gonadotropin, free β -subunit, and β -subunit core fragment in urine. *Clinical chemistry*. 2014 Aug 1;60(8):1089-97.
- [26]. Holt RI. Detecting growth hormone misuse in athletes. *Indian journal of endocrinology and metabolism*. 2013 Oct 1;17(Suppl1):S18-22.
- [27]. Green GA. Drug testing in sport: hGH (human growth hormone). *AMA Journal of Ethics*. 2014 Jul 1;16(7):547-51.
- [28]. Hanley JA, Saarela O, Stephens DA, Thalabard JC. hGH isoform differential immunoassays applied to blood samples from athletes: decision limits for anti- doping testing. *Growth Hormone & IGF Research*. 2014 Oct 1;24(5):205-15.
- [29]. Fragkaki AG, Georgakopoulos C, Sterk S, Nielen MW. Sports doping: Emerging designer and therapeutic β 2-agonists. *Clinica chimica acta*. 2013 Oct 21;425:242-58.
- [30]. Decorte N, Bachasson D, Guinot M, Flore P, Levy P, Verges S, Wuyam B. Effect of salbutamol on neuromuscular function in endurance athletes. *Medicine and science in sports and exercise*. 2013 Oct 1;45(10):1925-32.
- [31]. Dickinson J, Hu J, Chester N, Loosemore M, Whyte G. Acute impact of inhaled short acting β 2-agonists on 5 km running performance. *Journal of Sports Science & Medicine*. 2014 May 1;13(2):271.
- [32]. Polet M, Van Renterghem P, Van Gansbeke W, Van Eenoo P. Profiling of urinary formestane and confirmation by isotope ratio mass spectrometry. *Steroids*. 2013 Nov 1;78(11):1103-9.



- [33]. World Anti - Doping Agency. 2013 Anti - Doping Testing Figures Laboratory Report.
- [34]. Koehler K, Thevis M, Schaenzer W. Meta - analysis: Effects of glycerol administration on plasma volume, haemoglobin, and haematocrit. *Drug testing and analysis*. 2013 Nov;5(11-12):896-9.
- [35]. Koehler K, Braun H, de Marees M, Geyer H, Thevis M, Mester J, Schaenzer
- [36]. W. Glycerol administration before endurance exercise: metabolism, urinary glycerol excretion and effects on doping - relevant blood parameters. *Drug testing and analysis*. 2014 Mar;6(3):202-9.
- [37]. Görgens C, Guddat S, Orlovius AK, Sigmund G, Thomas A, Thevis M, Schänzer W. "Dilute-and-inject" multi-target screening assay for highly polar doping agents using hydrophilic interaction liquid chromatography high resolution/high accuracy mass spectrometry for sports drug testing. *Analytical and bioanalytical chemistry*. 2015 Jul;407(18):5365-79.
- [38]. King LA. New phenethylamines in Europe. *Drug Testing and Analysis*. 2014 Jul;6(7-8):808-18.
- [39]. Glennon RA. Bath salts, mephedrone, and methylenedioxypyrovalerone as emerging illicit drugs that will need targeted therapeutic intervention. *Advances in pharmacology*. 2014 Jan 1;69:581-620.
- [40]. Wong A, Montebello ME, Norberg MM, Rooney K, Lintzeris N, Bruno R, Booth J, Arnold JC, McGregor IS. Exercise increases plasma THC concentrations in regular cannabis users. *Drug and Alcohol Dependence*. 2013 Dec 1;133(2):763-7.
- [41]. Desrosiers NA, Lee D, Concheiro-Guisan M, Scheidweiler KB, Gorelick DA, Huestis MA. Urinary cannabinoid disposition in occasional and frequent smokers: is THC-glucuronide in sequential urine samples a marker of recent use in frequent smokers?. *Clinical chemistry*. 2014 Feb 1;60(2):361-72.
- [42]. Chang CW, Huang TY, Tseng YC, Chang-Chien GP, Lin SF, Hsu MC. Positive doping results caused by the single-dose local injection of triamcinolone acetonide. *Forensic science international*. 2014 Nov 1;244:1-6.
- [43]. Matabosch X, Pozo OJ, Monfort N, Pérez-Mañá C, Farré M, Marcos J, Segura J, Ventura R. Urinary profile of methylprednisolone and its metabolites after oral and topical administrations. *The Journal of steroid biochemistry and molecular biology*. 2013 Nov 1;138:214-21.
- [44]. Botrè F, De La Torre X, Donati F, Mazzarino M. Narrowing the gap between the number of athletes who dope and the number of athletes who are caught: scientific advances that increase the efficacy of antidoping tests. *British journal of sports medicine*. 2014 May 1;48(10):833-6.
- [45]. Hatton CK. Beyond sports-doping headlines: the science of laboratory tests for performance-enhancing drugs. *Pediatric Clinics of North America*. 2007 Aug 1;54(4):713-33.
- [46]. Bowers LD. The analytical chemistry of drug monitoring in athletes. *Annual review of analytical chemistry*. 2009 Jul 19;2(1):485-507.
- [47]. Catlin DH, Fitch KD, Ljungqvist A. Medicine and science in the fight against doping in sport. *Journal of internal medicine*. 2008 Aug;264(2):99-114.
- [48]. Waddington I. Changing patterns of drug use in professional cycling: implications for anti-doping policy. *InDoping in Cycling 2018 Dec 7* (pp. 31- 44). Routledge.
- [49]. Lentillon - Kaestner V. The development of doping use in high - level cycling: From team - organized doping to advances in the fight against doping. *Scandinavian journal of medicine & science in sports*. 2013 Mar;23(2):189- 97.
- [50]. Voet W. Prikken en slikken [original title: Massacre a la chaine]. Roeselare: Roularta Books NV. 1999.
- [51]. De Hon O, Kuipers H, Van Bottenburg M. Prevalence of doping use in elite sports: a review of numbers and methods. *Sports medicine*. 2015 Jan;45(1):57- 69.
- [52]. Zorzoli M, Rossi F. Implementation of the biological passport: the experience of the International Cycling Union. *Drug Testing and Analysis*. 2010 Nov;2(11 - 12):542-7.
- [53]. Videman T, Lereim I, Hemmingsson P, Turner MS, Rousseau - Bianchi MP, Jenoure P, Raas E, Schönhuber H, Rusko H, Stray - Gundersen J. Changes in hemoglobin values in elite cross - country skiers from 1987 to 1999. *Scandinavian journal of medicine & science in sports*. 2000 Apr;10(2):98-102.



- [54]. Manfredini F, Carrabre JE, Litmanen H, Zhukovskaja L, Malagoni AM, Dal Follo D, Haberstroh J. Blood tests and fair competition: the biathlon experience. *International journal of sports medicine*. 2003 Jul;24(05):352-8.
- [55]. Sottas PE, Robinson N, Saugy M, Niggli O. A forensic approach to the interpretation of blood doping markers. *Law, probability and risk*. 2008 Sep;7(3):191-210.
- [56]. Sottas PE, Robinson N, Saugy M. The athlete's biological passport and indirect markers of blood doping. *Doping in sports: Biochemical principles, effects and analysis*. 2009 Sep 17:305-26.
- [57]. Sottas PE, Saudan C, Saugy M. Doping: a paradigm shift has taken place in testing. *Nature*. 2008 Sep 11;455(7210):166-.
- [58]. Geyer H, Parr MK, Koehler K, Mareck U, Schänzer W, Thevis M. Nutritional supplements cross - contaminated and faked with doping substances. *Journal of mass spectrometry*. 2008 Jul;43(7):892-902.
- [59]. Jung J, Hermanns-Clausen M, Weinmann W. Anorectic sibutramine detected in a Chinese herbal drug for weight loss. *Forensic Science International*. 2006 Sep 12;161(2-3):221-2.
- [60]. MESTER J, SCHÄNZER W. RECENT ADVANCES IN DOPING ANALYSIS (15).
- [61]. Thevis M, Sigmund G, Geyer H, Schänzer W. Stimulants and doping in sport. *Endocrinology and Metabolism Clinics*. 2010 Mar 1;39(1):89-105.
- [62]. Eliason MJ, Eichner A, Cancio A, Bestervelt L, Adams BD, Deuster PA. death of active duty soldiers following ingestion of dietary supplements containing 1, 3-dimethylamylamine (DMAA). *Military medicine*. 2012 Dec 1;177(12):1455-9.
- [63]. De Hon O, Kuipers H, Van Bottenburg M. Prevalence of doping use in elite sports: a review of numbers and methods. *Sports medicine*. 2015 Jan;45(1):57- 69.

