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The forensic response after an adverse analytical finding (doping) involving a selective androgen receptor modulator (SARM) in human athlete

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ABSTRACT

Selective androgen receptor modulators (SARMs) are a class of drugs presenting identical anabolic properties to anabolic steroids in addition to marked reduced androgenic effects. These drugs have emerged in the doping area within the early 2000′s. Ligandrol, ostarine, RAD-140 and andarine are the most popular agents belonging to this class. According to the world anti-doping agency (WADA) prohibited list, SARMs are prohibited at all times (i.e. in and out-of-competition) and are listed under the section S1.2 (other anabolic agents).

The compilation of the WADA testing figures reports from 2015 to 2019 has indicated a regular increase of adverse analytical findings (AAF) due to SARMs, particularly with ostarine and ligandrol. The implementation of highly sensitive chromatographic anti-doping analyses has induced high-profile challenges of anti-doping rules violations as athletes have claimed in numerous occasions that contamination was the reason for their AAF.

Since the early 2000′s, it has been accepted by the Court of Arbitration for Sports (CAS) in Lausanne (Switzerland) that, under some specific circumstances, unusual explanations can be provided to the Panel to explain an AAF. This was the open door for forensic investigations, as it is done in criminal Courts.

A forensic approach can include testing for SARMs in food, drinks, but mostly in dietary supplements. As most anti-doping rules violations are only known several weeks after urine collection, this biological matrix is seldom use for further tests, despite the fact that most SARMs can be detected for several weeks in urine.

Luckily, hair or nail testing can be a complement to document the claim of the athlete but of course, it cannot be considered as an alternative to urinalysis. This is because a negative hair or nail result cannot exclude the use of the detected drug and cannot overrule the urine result.

To date, all methods for SARMs identification in various matrices involve liquid chromatography coupled to tandem mass spectrometry or high-resolution mass spectrometry.

The aim of this paper is to review the scientific literature on the analytical possibilities of testing SARMs in dietary supplements, urine and hair or nail clippings after an AAF to document the claims of an athlete or his/her legal team.

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1. Introduction

Selective androgen receptor modulators (SARMs) are a class of drugs presenting identical anabolic properties to classic anabolic steroids, such as testosterone, stanozolol, or nandrolone but with reduced androgenic effects. This last property is very important as it decreases the usual side-effects of steroids, such as liver toxicity. This is because SARMs selectively bind to androgen receptors in some specific tissues, but not in others [1–3].

Initially, SARMs were proposed by pharmaceutical companies as therapeutic drugs to treat osteoporosis, hypogonadism or muscle-wasting pathology such as muscular dystrophy but none has been yet approved by the health authorities in any country of the world [4].

SARMs have emerged in the doping area within the early 2000′s. Ligandrol, ostarine (enobosarm), RAD 140 and andarine are the most

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Table 1
WADA statistics about SARMs identification in sport.

Year	Total AAF	Ostarine AAF	Ligandrol AAF	RAD 140 AAF	Other AAF
2015	3809	28	2	0	2
2016	4822	30	6	2	1
2017	4596	47	9	6	3
2018	4896	45	26	5	1
2019	4180	74	62	4	2

AAF: adverse analytical finding.

popular agents belonging to this class. These drugs are also known by a code, such as LGD-4033 for ligandrol, S-22 or MK-2866 for ostarine or S-4 for andarine. From the dozen of compounds listed as SARMs, ostarine and ligandrol are the more frequently identified.

According to the world anti-doping agency (WADA) prohibited list, SARMs are prohibited at all times (i.e. in and out-of-competition) and are listed under the section S1.2 (other anabolic agents), a section that also contains clenbuterol [5].

It is in 2010, that the Swiss laboratory for doping analyses reported the first case of SARMs abuse (it was andarine) during in-competition testing [6]. SARMs have the potential to be misused for performance enhancement in sport due to their anabolic properties. In the recent years, SARMs have been increasingly observed in anti-doping rules violation (ADRV) as they can be purchased very easily on the Internet. Table 1 lists some statistics about adverse analytical findings (AAF) involving SARMs. Animal doping, mostly equine doping, has also been described with SARMs [7,8].

In case of challenging an AAF, an athlete (who has the burden of proof in doping control) is in his right to produce evidence for his/her defence. This has prompted athletes to get closer to the forensic side to produce alternative admissible elements to confirm their claims of unintentional doping. Very recently, in 2020, a series of publications [9], presenting investigations performed by WADA accredited laboratories have demonstrated that the forensic approach can be useful to document unusual adverse finding. For example, it was retrospectively demonstrated that the AAF of Dieter Baumann, in 1999, could be the consequence of a contaminated toothpaste with norandrostenedione, a prohormone of the anabolic drug nandrolone [10]. This clearly indicates that there is room for additional proofs in sports, despite a very strong regulation of evidence admissibility.

2. The strategy to document an adverse analytical finding

From the author's point of view, based on 25 years of experience with anti-doping rules violation, including the 1998 Tour de France, acceptance by sport federations or the Court of Arbitration for Sports (CAS) in Lausanne (Switzerland) of third-party contamination to account for an AAF has some prerequisites [11], which include, at least, the following points:

1. To support incidental exposure, only minute amounts of prohibited drug or metabolite(s) must be present in the urine collected for control. High concentrations that are observed after recreational abuse or for doping purposes cannot account for contamination. The possible dose, estimated after indication by the athlete of the moment of the exposure, has to be too small to have any recreational or performance-enhancing effect.
2. The athlete head hair test, which can support either 1. a negative results (with a suitable limit of detection) to confirm incidental exposure or 2. a result that can support external or environmental contamination, must be presented. This hair test must cover the period of time where the specimen was collected for doping control (alternatively, body hair or nail clippings have to fit to the requested window of detection).
3. The athlete's legal team must present verified circumstances of contamination or evidence of drug possession. The source of contamination must be established, as, on a balance of probability, the indicted athlete bears the burden of persuading the judging body that the occurrence of the circumstances on which he / she relies is more probable than their non-occurrence or more probable than other possible explanations of the doping offence.
4. There must be verified claims of the athlete about the fact that he/she did not knowingly take the prohibited substance, i.e. that the violation was not intentional, although no test exists that can positively and definitively exclude the intentional use of a drug prior to the collection of a specimen for doping control
5. An experienced pharmacologist or toxicologist has to perform a pharmacological verification of the athlete's claims. This means that pharmacokinetic and pharmacodynamics parameters of the specific drug must fit with the submitted scenario and the athlete must establish how the prohibited substance entered his or her system.
6. A third-party positive hair test to support the claims of drug use by the partner and therefore being the source of contamination during an intimate moment, must be presented when the "kissing scenario" or the "sex scenario" is advocated [12–14].

As indicated in this protocol, the source of contamination must be identified, the dose to which the athlete was exposed should be estimated and a hair test must confirm the absence of long-term SARM exposure. These 3 items will be developed in the following lines.

3. Dietary supplements contaminated by SARMs

To the best of the author's knowledge, up to now, there is no case where an athlete or his/her legal team has challenged an AAF due to meat contamination. This has been described after animal administration of anabolic steroids [15] or ractopamine, zeranol and clenbuterol [16], but does not seem applicable for SARMs.

In the recent years, it has been increasingly published that dietary supplements can be falsified [17]. They may contain no active ingredient or other active ingredient(s). In addition, the announced active ingredient can be associated to other active substances or present a variable doses. These supplements can produce numerous adverse events, ranging from absence of therapeutic efficacy up to serious health effects, which can involve deaths [18]. In sport, contaminated supplements can lead to adverse analytical findings, with complicated consequences for the athletes to justify their behaviour [19,20]. Although theoretically all doping agents can contaminate supplements, in most cases, anabolic steroids, stimulants, selective androgen receptor modulators, clenbuterol or diuretics have been identified. Low doses of SARMs have been found in pre-workout, fat burner/thermogenic, brain/cognitive booster, and hormone/testosterone booster. Back in 2008, Thevis et al. [21] reported for the first time the presence of a contaminated supplement with the identification of andarine.

In their paper [22], Walpurgis et al. have demonstrated that an oral administration of 10 µg (which is minimal, less than one grain of salt) of ostarine can produce a urine concentration up to 5.77 ng/mL, which is of course a concentration that constitutes a doping offence. Given WADA accredited laboratories can have limits of detection of 10 pg/mL for SARMs, these micro doses can influence the future activities of any athlete. The same authors have reported that 1 µg of ostarine can be detected for up to 9 days by monitoring ostarine glucuronide.

Despite their lack of safety approval, SARMs are often illegally marketed as dietary supplements, available for consumers after online purchase. In these products, discrepancies can range from a

supplement in which no active ingredient was found to supplements containing undeclared prohibited agents. Sometimes, discrepancies were observed between the concentrations measured and those detailed on the product packaging [23]. In the laboratory of the author, a wide range of items, from various companies, were tested and in most cases a lower dosage was found when compared to what was labelled. It also can happen that a specific SARM can be replaced by another one, without informing the customer. For example, we bought liquid ostarine that was, after analysis, andarine [24]. This can have an influence on the claims of an athlete as he can confirm not knowingly taking one product while in fact his/her supplement has been switched to another agent. Of course, cheaters can use this situation, but the final outcome, evidenced by a hair test, remains the same, as it constitutes a doping violation.

Because the use of dietary supplements can be risky, several national anti-doping agencies have advertised, on several occasions that safety can be breached due to contamination [25]. For example, Supplement 411 is USADA's dietary supplement safety education and awareness resource [26].

Very recently, Lee et al. [27] tested 60 dietary supplements obtained in 2020 by on-line and direct purchase from international vendors. Various SARMs were identified in 20 products at high concentration, including for example one product containing andarine at 7.2%. The authors concluded that a continuous control and supervision of dietary supplements is necessary.

On an analytical point of view, as these products are generally presented as tablets, capsules or oral liquid solutions, a simple dilute (with methanol) and shot approach is generally achieved.

4. Urine testing for SARMs

Urine is the standard specimen for anti-doping control. It can be easily collected by trained collectors but must be stored at low temperature to avoid drug degradation. Ventura et al. [28] have published that the stability of SARMs in urine at +4 °C (two weeks) and – 20 °C (four weeks) has been verified. These authors concluded that the long-term stability testing data ensure confidence in findings from anti-doping processes.

If it was complicated to obtained authentic reference material for SARMs in the early 2010, this is no more the case today. One can easily purchase pure standards from suitable manufacturers without buying material from the Internet. However, this is not the case for SARMs metabolites. On numerous occasions, the Anti-Doping Administration and Management System (ADAMS) has issued an anti-doping rules violation based on the identification of a metabolite, for example di-OH-ligandrol. Generally, these specific metabolites have a longer window of detection when compared to the parent compound. Unfortunately, metabolite(s) are not available for forensic laboratories for a reasonable delay as they are only available for WADA accredited laboratories. For some metabolites, it can take more than 6–9 months to get the permission of purchase, after tedious administrative investigations that verify the final use of the material. This is to avoid internal cheating approaches by verifying that the urine of an athlete is clean.

As SARMs have not been investigated in controlled large studies due to the lack of clinical interest, most data about metabolism are available after experimental tests involving human liver microsomes (HLMs) or administration of a specific drug to a single subject followed by urine collection over a long period [29].

All methods for SARMs identification in human urine involve liquid chromatography coupled to tandem mass spectrometry or high-resolution mass spectrometry. Briefly, methods involve hydrolysis with ß-glucuronidase and sometimes arylsulfatase, liquid-liquid extraction, separation on a reverse phase and mass spectrometric detection [30]. Typical limits of quantitation are lower than 1 ng/mL.

5. Hair testing for SARMs

In 2013, the President of the World Anti-Doping Agency (WADA), Sir Craig Reedie, wished for new approaches other than urine and blood in doping control. Indeed, he declared that hair testing "will create tremendous opportunities for advances in anti-doping and allow our scientists to look at alternative approaches to sample testing for banned substances" [31].

Although hair is not a routine specimen for the WADA, its use as a specimen of investigation is accepted in most criminal courts of justice in the world.

Hair testing is a useful measure of drug intake of an individual, in any situation in which a history of past rather than recent drug use is expected, as it reflects consumption over a long period of time. For practical purposes, it is commonly accepted that each cm of head hair represents the growth, and therefore drug accumulation, for one month. Using segmental hair analysis, statements about the course of drug intake and chronological correlations are possible. While a constant regular profile along the hair shaft is in favour of permanent drug use, any variation of concentration indicates a change in drug intake [32].

The Society of Hair Testing (SoHT) has established in 1999 [33] a consensus on hair testing for doping agents. This statement includes that hair specimens are not suitable for general routine doping control and that a negative hair test result cannot exclude the administration of the detected drug and cannot overrule an adverse analytical finding (AAF), identified in blood or in urine.

The World Anti-Doping Code has already addressed how the "no fault" plea should be considered. In the 2021 version [34], article 10.6 "reduction of the period of ineligibility based on no significant fault or negligence" and its explanatory footnotes, describe what is acceptable or not. In particular, at footnote 66 [Comment to Article 10.6.1.2: "In order to receive the benefit of this Article, the Athlete or other Person must establish not only that the detected Prohibited Substance came from a Contaminated Product, but must also separately establish No Significant Fault or Negligence".

Applications and limitations of hair tests in doping control have been extensively reviewed in several papers during the last years. In particular, it must be emphasised that a single exposure to some drugs, such as anabolic steroids, SARMs or diuretics is not detectable in hair [35]. The advantages of hair testing for active substances over blood and/or urine testing include non-invasive and ease of collection to prevent adulteration or substitution. Hair test results allow establishing a retrospective calendar of drug exposure over weeks to months based on a standard head hair growth rate of 1 cm per month.

Given the author has 30 years experience in hair testing, particularly for doping agents, it has been suggested to test for SARMs in this alternative specimen [24,36,37]. A comprehensive review of papers published with the key words "SARMs" and "hair" only produced one additional citation with respect to the identification of SARMs in human hair [38].

The first paper dealing with SARMs identification in human hair was published in 2019 [24]. Since this initial method by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), the authors have implemented a confirmation procedure by liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS) for both hair and nail clippings [36].

Briefly, the method involves decontamination with dichloromethane, segmentation as per request, incubation in pH 9.5 buffer in presence of bicalutamide-d_4, used as internal standard and extraction in a mixture of organic solvents. Separation is achieved on an Acquity HSS C18 column and detection performed by MS/MS on a Waters XEVO TQS micro.

Rading et al. [38] identified GSK2881078 at 1.7 pg/mg in human hair collected 3 weeks after a single 1.5 mg oral administration. After

cutting the hair into pieces of approx. 1 mm size, these authors incubated 50 mg in 3 mL of methanol followed by an ultrasonic disintegration for 6 h at approx. 50 °C. After evaporation of the methanol and solubilisation of the residue in an organic solvent, the drug was separated on a Kinetex C18 column and detected on a QTRAP 6500+ from Sciex. The limit of detection was 0.1 pg/mg.

Kintz et al. [24] identified ostarine at 12 and 138 pg/mg, in the 2×3 cm hair segments of a male athlete (mixed martial fighter) who returned an AAF for ostarine. In this case, the hair test results confirmed the ADRV. In the hair of a subject arrested by the customs for trafficking, Kintz et al. [36] identified ostarine at 146, 168, 93, and 101 pg/mg in the 4×3 cm sections, clearly demonstrating long-term use.

Finally, the same group [37], in 3 separate cases, identified ligandrol (14–42 pg/mg), andarine (0.1–0.7 pg/mg) and ostarine (3–21 pg/mg), offering new biological perspectives in SARMs abuse detection.

According to the WADA's international standard for laboratories [39] hair tests are approved, but must not be used to counter analytical findings from urine or blood.

A potential use of hair analysis when challenging a urine result is to verify accidental or unintentional ingestion of food or liquids that has been contaminated with drugs. However, in case of a single use, the hair will not test positive for SARMs as these compounds are poorly incorporated into hair [38]. While analysis of urine specimens cannot distinguish between repetitive use and single exposure, hair analysis can make this distinction, when several segments of hair, irrespective of their length, are positive.

The toxicological significance of the measured concentrations is difficult to determine because there is no controlled study about SARMs incorporation into hair and single dose detection tests have produced controversial results. It is therefore not possible to interpret the data in terms of dosage and frequency of abuse.

It is accepted by the authors that some parameters that must be evaluated during the validation phase are not yet assessed: dose necessary to give a positive result, influence of gender, variable incorporation into hair according to hair colour, external factors that may have an impact, cosmetic treatment(s), etc. The minimum dose that had to be ingested by the athlete in order to get a "positive" detection in one of his/her hair sections is unknown for ostarine, ligandrol and other SARMs, although there are abused by many athletes.

Given in hair, the target analyte is the parent compound, identification of SARMs administration is obviously facilitaed in this matrix when compared to urine, a specimen which mostly contains metabolites.

6. Nail testing for SARMs

Nails can stably accumulate substances for long periods of time, thus providing retrospective information regarding drugs of abuse and pharmaceutical use. As it is the case for hair, nails have several advantages over conventional matrices, including a longer detection window, non-invasive sample collection, and easy storage. These aspects make nails a very interesting matrix for forensic and clinical toxicology.

Incorporation of substances into nails mainly occurs through diffusion from the rich blood supply, which deposits substances to both the germinal matrix and the nail bed on the underside of the nail plate, thus allowing incorporation in both a vertical and horizontal way during nail formation. Other mechanisms of incorporation that have been proposed are incorporation through diffusion from biological fluids such as sweat, sebum, and saliva, and incorporation through diffusion from the external environment. Distribution patterns have indicated that drugs are not only deposited at the germinal matrix, but also along the length of the nail bed.

Nails grow at a continuous rate. The average growth rate of fingernails is 3.0 mm per month, while toenails grow at an average rate of 1.1 mm per month. The regeneration time (i.e., the time to grow from the germinal matrix to the nail's free edge) is 3–5 and 8–16 months for finger- and toenails, respectively. Compared to blood and urine, nails have a longer window of detection from which information on xenobiotic exposure or ingestion can be retrieved. There is no agreement on the exact time frame nail clipping can represent and each laboratory has its own window of detection.

Interestingly, nails provide some additional advantages over hair. Firstly, when hair is not (sufficiently) available (e.g., subjects with short hair, in case of alopecia, during chemotherapy, or during the first weeks or months after birth), nail analysis can be an important tool to gain retrospective information on xenobiotic use. Secondly, in contrast to hair, nails do not contain melanin. Since drug incorporation may be influenced by melanin concentrations, hair pigmentation can be an important source of bias when interpreting detected drug concentrations. Thirdly, nails grow slower than hair, which provides the opportunity to detect smaller exposure levels and/or to investigate longer periods of time. Fourthly, while hair is characterised by a cyclic growth rate with different stages, nails grow at a constant rate, which facilitates the interpretation of results.

Finally, compared to hair sampling, nail collection is aesthetically more acceptable, easier, and less intrusive. Taken together, these advantages underline the potential of nails as an interesting and useful matrix for the retrospective detection of drug and pharmaceutical use.

To date, only one publication has presented some results for the identification of ostarine in human nail clippings [36].

7. A famous example: the case of Laurence Vincent Lapointe

To illustrate the forensic approach of an AAF involving a SARM (here ligandrol), it is possible to summarise the case of the Canadian canoe star Laurence Vincent Lapointe. This is possible because the athlete has given all details during numerous press releases [40]. Briefly, late in July 2019, the athlete failed an anti-doping control when minute amounts (4 pg/mL) of ligandrol, a SARM, were identified in her urine. She strongly denied any use of the molecule. A first set of dietary supplements analyses was unable to find any trace of ligandrol. Hair specimens were collected mid-September, and tested for ligandrol in 6×1 cm segments. This covered the period of the urine control. The hair test results were negative (limit of detection at 5 pg/mg). Further investigations by her legal team revealed that her partner was repetitively using a product manufactured under the trade name SR9011. It is a liquid, containing a Rev-ErbA agonist (a protein that regulates the circadian rhythm, modulates glucose and lipid metabolism and regulates the inflammatory response). However, when analysed, ligandrol was identified in the liquid at approximately 6 mg/mL in addition to traces of ostarine, another SARM. The hair test of the partner was positive, both in head hair and chest hair. Later, he confessed having used the product some hours before intimate moments at the time of the urine control. After taking into consideration scientific expert evidence provided by Ms Vincent Lapointe's legal team, and also the miniscule traces of ligandrol found in the athlete's sample, an anti-doping panel convened by the International Canoe Federation (ICF) has accepted that Ms Vincent Lapointe did not knowingly take the illegal substance. The ICF has accepted Laurence Vincent Lapointe's evidence, which supports that she was the victim of third-party contamination, and has cleared her to return to training and competition immediately [41].

The final decision was based on investigations that support a forensic approach, including minute amounts of the drug in urine, negative hair test, no deliberate exposure to the drug, and identification of the source of contamination.

8. Conclusion

The recent widespread of new drugs all over the world via Internet has demonstrated that there is a need of analytical approaches to document these new habits of consumption. Therefore, implementing tests for SARMs seems of great importance, not only for anti-doping purposes, but also for clinical toxicologists or poison centres, in order to correctly establish a diagnosis of addiction or to document unusual side-effects. Given the increasing popularity of SARMs abuse, vigilance and identification of new cases are required. As hair and nail clippings allow retrospective and long-term investigations, these specimens present all suitable properties to be qualified for SARMs detection.

The difficulties in interpreting results of hair analysis for new drugs, such as SARMs, must be highlighted. In particular, little is known about the incorporation of SARMs into the keratin matrix after intake and the correlation between dose, frequency of use and hair or nail clippings concentrations. For example, answering to the following question remains, to date, impossible: if one were to have a hair analysis performed to detect traces of a specific SARM and the results were negative, what conclusion can be made with respect to the amount of SARM he/she had been exposed to? Is it possible to conclusively say that he/she had consumed less than (for example) one dose of SARM?

Therefore, hair or nail clippings tests results for SARMs should be interpreted with caution by experienced forensic toxicologists.

Conflict of Interest

No conflict of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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