

SARM study

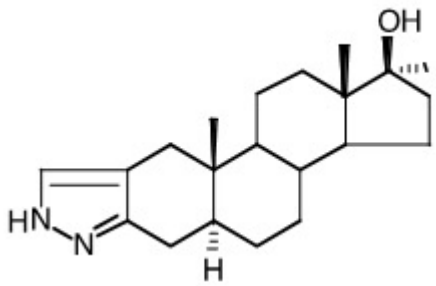
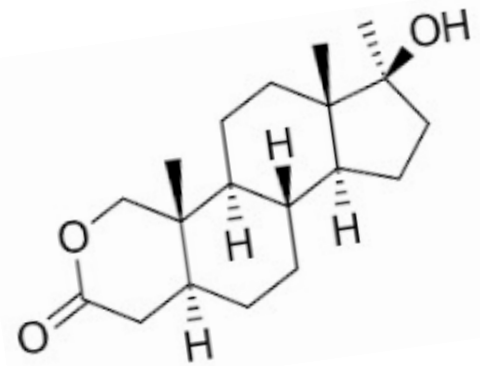
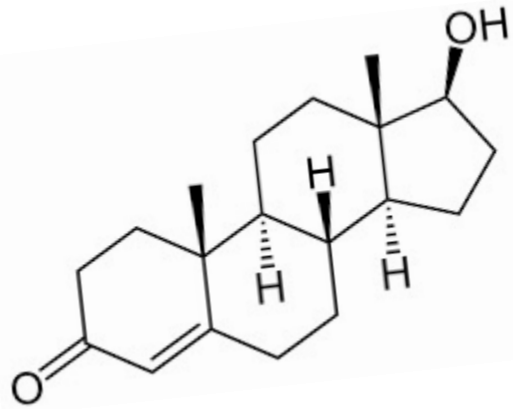
Lena Ekström, sjukhuskemist, adjungerad professor

Kim Pettersson Bohlin, sjukhuskemist, PhD student

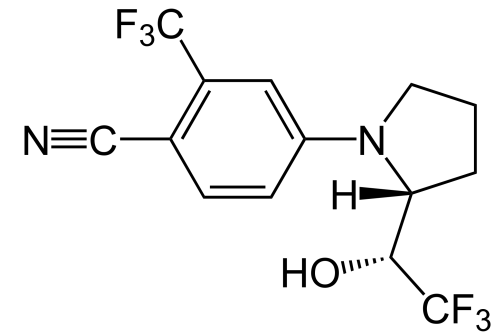
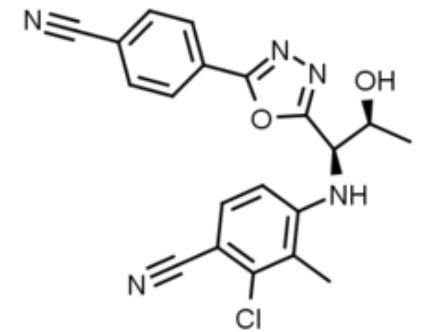
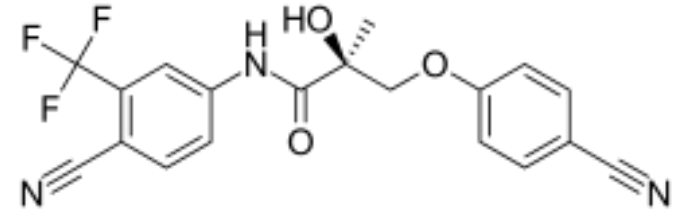
International Conference on DOPING & public health 18 June



AAS



SARM



Androgen Receptor



Example SARMs

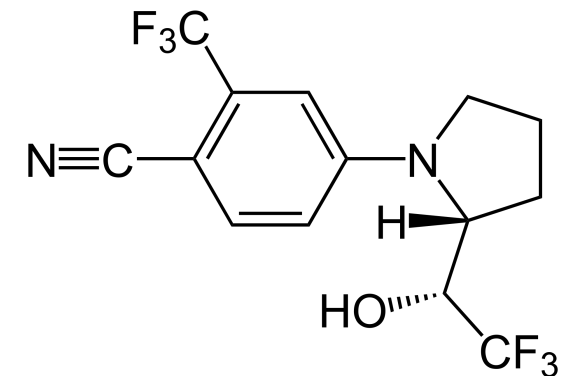
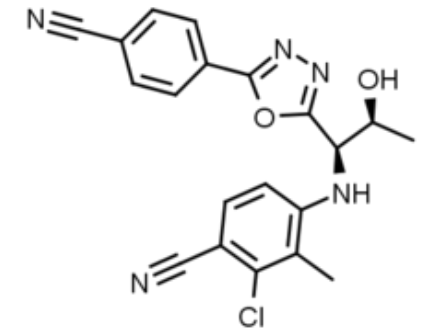
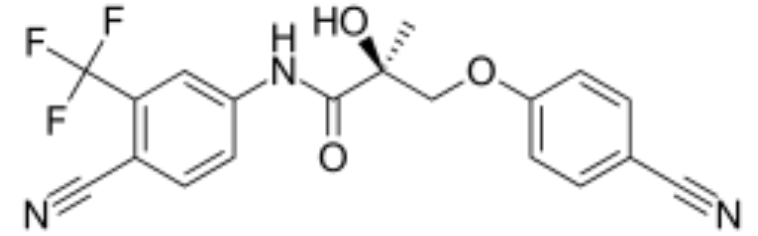
1998

Tested in humans

- Enobosarm, (ostarine, MK2866, S22) – **GTx Inc/Oncernal Therapeutics**
- Ligandrol (LGD-4033, VK5211) – **Viking Therapeutics Inc**
- RAD 140 (testolone) – **Radius Health Inc**
- MK-0773 (PF-05314882) - **Merck**
- GSK2881078 – **Glaxo-Smith-Kline**
- GLPG-0492 (DT200) – **Galapagos NV**

Others

- Andarine (S4), S-1, S-4, S-40503 not tested humans
- S23, TFM-4 AS-1, YK-11 unknown status



SARMs as medicine

Muscle waisting

Hypogonadism

Contraceptive males

Urinary incontinence

Duchenne muscular dystrophy



WADA list since 2008

2. OTHER ANABOLIC AGENTS

Including, but not limited to:

Clenbuterol, selective androgen receptor modulators [SARMs, e.g. andarine, LGD-4033 (ligandrol), enobosarm (ostarine) and RAD140], tibolone, zeranol and zilpaterol.



WORLD ANTI-DOPING CODE
INTERNATIONAL STANDARD
**PROHIBITED
LIST**
2024

Lag (1991:1969) om förbud mot vissa dopningsmedel

1 § Denna lag gäller

1. syntetiska anabola steroider,
2. testosteron och dess derivat,
3. tillväxthormon, och
4. kemiska substanser som ökar produktion eller frigörelse av testosteron och dess derivat eller av tillväxthormon. *Lag (2011:112)*.

2 § Medel som anges i 1 § får inte annat än för medicinskt eller vetenskapligt ändamål

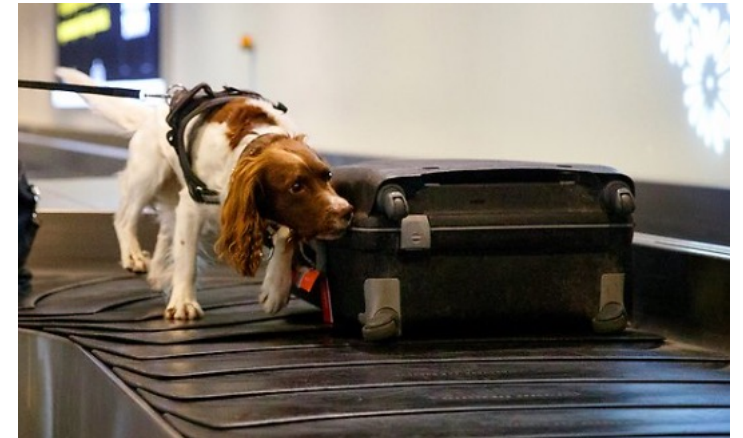
1. införas till landet, 2. överlåtas, 3. framställas, 4. förvärvas i överlåtelsesyfte, 5. bjudas ut till försäljning, 6. innehas, eller 7. brukas. *Lag (1999:44)*.

3 § Den som uppsåtligen bryter mot 2 § 2-7 döms för dopningsbrott till fängelse i högst två år.

Är ett brott som avses i första stycket med hänsyn till mängden dopningsmedel samt övriga omständigheter att anse som ringa, döms till böter eller fängelse i högst sex månader.

How common is SARMs outside WADA testing?

- Customs seizure / waste water
- Self-reporting
- Detection of SARMs in relation to AAS in drug abuse testing



Ostarine and ligandrol 4/779 = **0.5 %**

Ostarine 1000 g/259 000 grams = **0.3 %**

SUBSTANCE USE & MISUSE
2017, VOL. 52, NO. 6, 742–753
<http://dx.doi.org/10.1080/10826084.2016.1263665>



ORIGINAL ARTICLE

Qualitative and Semiquantitative Analysis of Doping Products Seized at the Swiss Border

Christina Weber^a, Oliver Krug^{b,c}, Matthias Kamber^a, and Mario Thevis^{b,c}

^aAntidoping Switzerland Foundation, Berne, Switzerland; ^bCenter for Preventive Doping Research/Institute of Biochemistry, German Sport University Cologne, Cologne, Germany; ^cEuropean Monitoring Center for Emerging Doping Agents, Cologne/Bonn, Germany

ABSTRACT

Background: Substances developed for therapeutic use are also known to be misused by athletes as doping agents and, outside of regulated sport, for image-enhancement. This has generated a market

KEYWORDS

Doping substances; anabolic androgenic steroids; peptide hormones; estrogens

Eur J Clin Pharmacol (2014) 70:1303–1311
DOI 10.1007/s00228-014-1743-5

REVIEW ARTICLE

Identification of black market products and potential doping agents in Germany 2010–2013

Oliver Krug · Andreas Thomas · Katja Walpurgis · Thomas Piper · Gerd Sigmund · Wilhelm Schänzer · Tim Laussmann · Mario Thevis

Emergence and occurrence of performance-enhancing substance use in Australia determined by wastewater analysis

Received: 2 March 2023

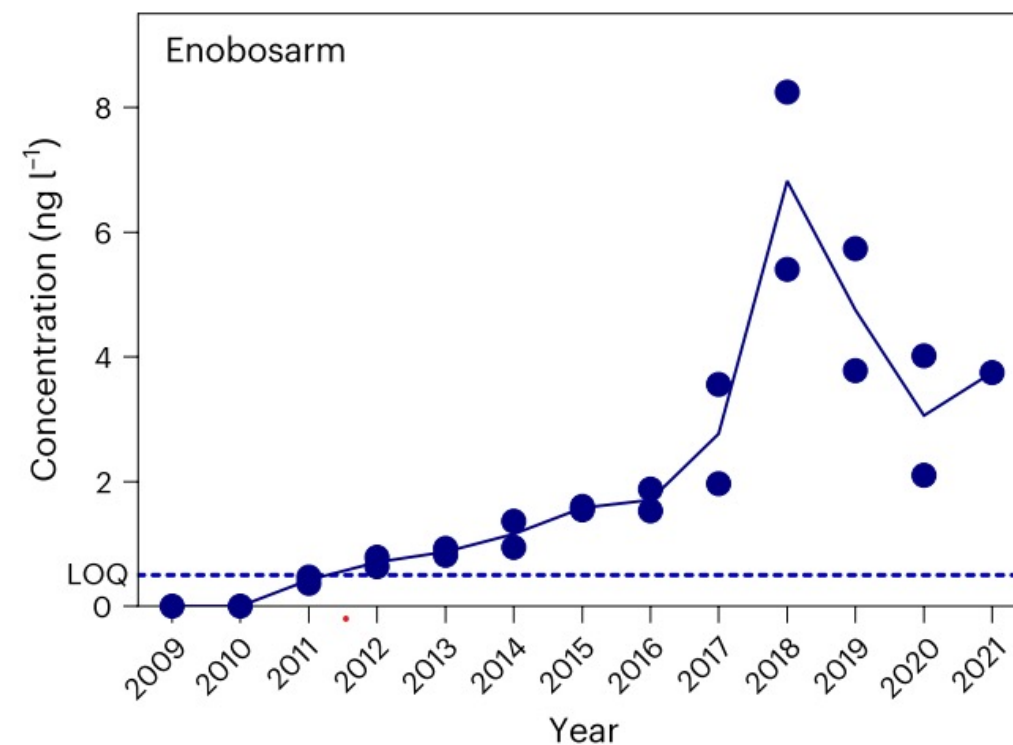
A list of authors and their affiliations appears at the end of the paper

Accepted: 29 August 2023

Published online: 9 October 2023

 Check for updates

Steroidal androgens, non-steroidal androgens and other non-steroidal performance- and image-enhancing drugs that are Schedule III substances under the US Controlled Substances Act as well as Schedule 4 and 10 substances under the Australian Poisons Standard are being used by athletes and non-athletes. Recent data suggest that they are growing in popularity.





A Summary of Online Enquiries Submitted to Anti-doping Hotline 2005–2018

Lena Ekström^{1,2}, Susanne Broström², Marja-Liisa Dahl^{1,2} and Annica Börjesson^{1,2*}

¹ Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, ² Department of Clinical Pharmacology, Karolinska University Hospital, Stockholm, Sweden

Anabolic Androgenic Steroid (AAS) abuse in the society is considered a health problem and has been associated with cardiovascular toxicity, endocrine disruption, as well as psychiatric symptoms such as aggression and cognitive dysfunction. Men and women abusing AAS, as well as persons in close relationship to AAS abusers, may encounter

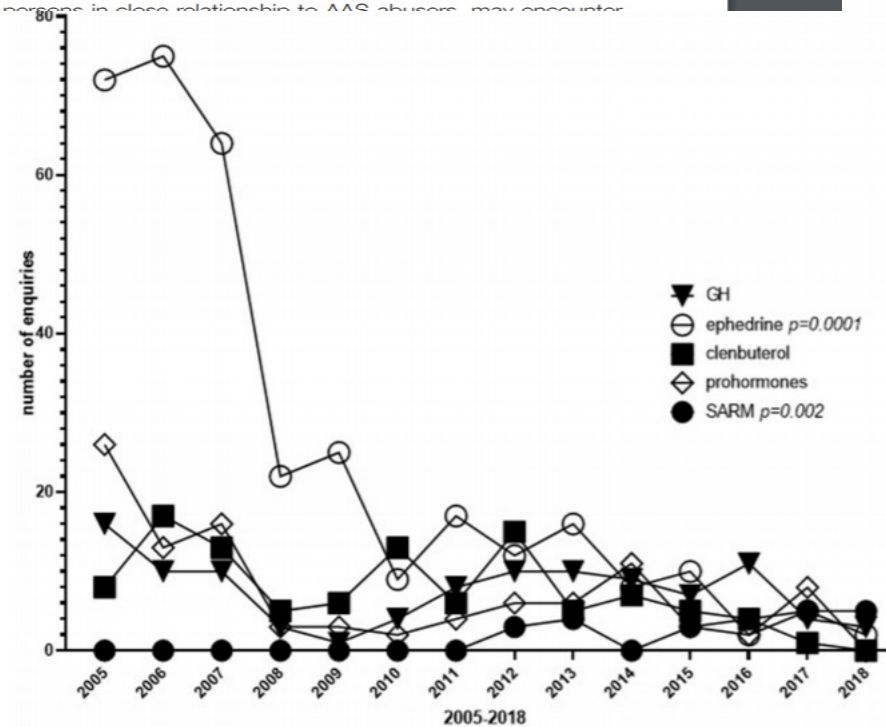


FIGURE 4 | Frequency of questions regarding doping agents other than Anabolic Androgenic Steroids (AAS) between 2005 and 2018. GH, Growth Hormone; SARM, Selective Androgen Receptor Modulator.

Description of SARMs among AAS users

**DOPING
JOURNEN**

Det tar ungefär 2 veckor för dom flesta SARM's att börja verka och ge resultat på styrka och muskelbyggning. En del kan dock börja märka av effekterna innan, och några av tecknen på detta kan vara tex ökad svettning under träningen.

LGD-4033. Potent SARM. Få bieffekter. Bra för att lägga på sig senigare muskler. Testosteronsänkande, men hanterbart för dom flesta användare. Ingen aromatisering så låg risk gynekomasti. Dosering: Låg: 1mg (dos som använts i studier), Mellan: 4/5mg, Hög: 10mg (fördelarna planar ut på den här nivån)

S-4

A few side effects, vision problems is a big one. Good for lean mass gains. Suppressive but manageable. Dosering: Låg: 10mg, Mellan: 50mg, Hög: 100mg

Ostarin/MK-2866

Få bieffekter. Bra för att läka avslitna senor och ligament. Ingen aromatisering så låg risk för gynekomasti. Dosering: Låg: 3mg, Mellan: 20mg, Hög: 50mg

YK-11- Inga mänskliga studier. Det anses och förväntas inte finnas några pålitliga källor på marknaden. Används på egen risk.

[FDA In Brief: FDA warns against using SARMs in body-building products](#)

FDA In Brief: FDA warns against using SARMs in body-building products



For Immediate Release: Oct. 31, 2017

Media Inquiries

[Lyndsay Meyer](#)

240-402-5345

"We are extremely concerned about unscrupulous companies marketing body-building products with potentially dangerous ingredients. Body-building products that contain selective androgen receptor modulators, or SARMs, have not been approved by the FDA and are associated with serious safety concerns, including potential to increase the risk of heart attack or stroke and life threatening reactions like liver damage," said Donald D. Ashley, J.D., director of the Office of Compliance in the FDA's Center for Drug Evaluation and Research. "We will continue to take action against companies marketing these products to protect the public health."

Many Case reports

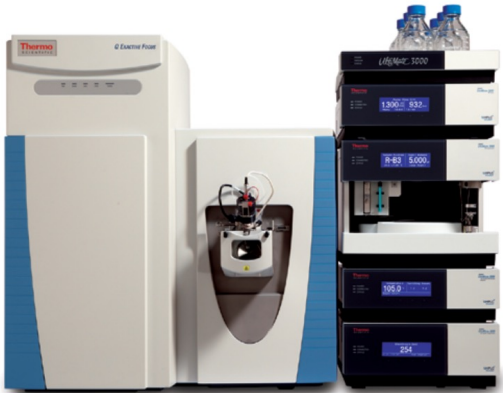
Study samples Urine samples from UAAS testing

- Urine samples from UAAS testing (from drug abuse treatment/drug addiction programs, suspected healthcare). 1000/year
- Enough urine for SARM and AAS analyses
- Anonymization (Male/Female information)



SARM testing Doping lab

- SARM and SARM metabolites



Q Exactive Focus mass spectrometer with Thermo Scientific Dionex Ultimate RSLC 3000

- Included in our big LC-HRMS screening method
 - ~ 500 substances

SARM	Metabolite(s)
AC-262536	
ACP-105	
Enobosarm (ostarine)	M3 (glucuronide), M4a-c (hydroxylated; glucuronide) ^{41,42}
GSK2881078	
LGD-4033 (ligandrol)	M1 (mono hydroxylated), LL metabolite ⁴³
S1	
S4 (andarine)	M3, M8 ^{30,44}
S9	
S-23	
RAD140	
YK-11	

Results

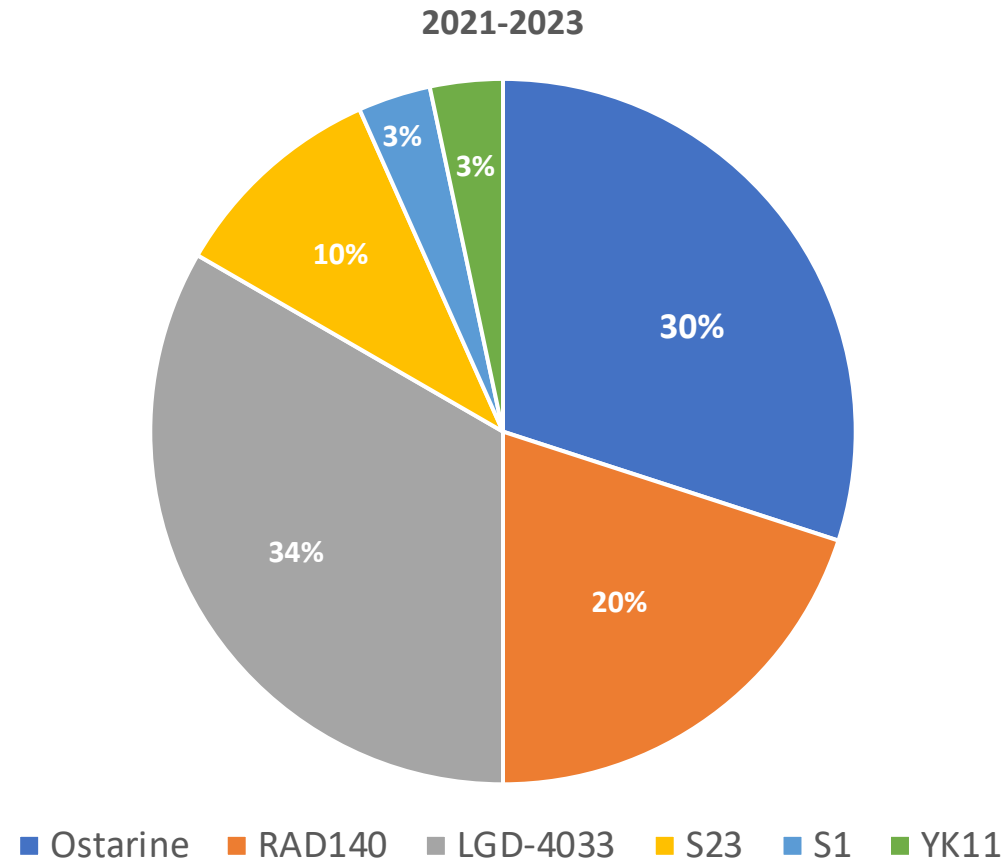
- Sep 2021-Aug 2022 (M542/F100)
- Of the 542 male healthcare samples, 20 male samples contained SARMs, corresponding to a **detection rate of 4% (35 % AAS positive)**.
- Among these 60% also contained an AAS.



Unpublished Results

- Nov 2022 – June 2023
- 269 male healthcare samples 11 contained SARMs corresponding to a **detection rate of 4 %** (35 % AAS positive).
- 1 female sample contained SARMs
- 60 % containing SARMs also contained AAS

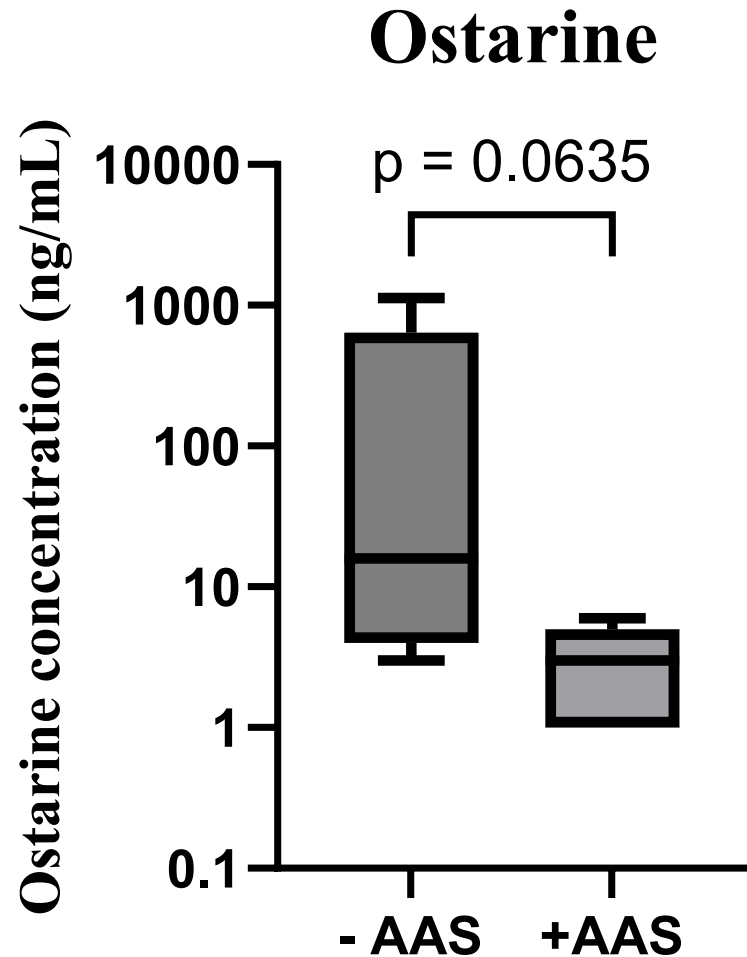
Most common SARMs



- 45 % of SARMs samples two or more SARMs

Concentrations of SARMs

	LGD4033 (ng/mL)	Ostarine (ng/mL)	S23 (ng/mL)	S1 (ng/mL)	AAS
K034	-	147	-	-	-
M031	-	5	-	-	-
M059	-	1	-	-	+
M079	88	-	-	-	+
M101	128	3	2	2	+
M112	46	6	-	-	+
M131	75	1	-	-	+
M135	-	1130	-	-	-
M188	85	16	-	-	-
M230	-	-	131	111	+
M237	-	4	-	-	+
M239	-	3	-	-	-



Lower SARM concentrations in active AAS users

Some individuals may use SARMs instead of AAS

Conclusions

- The prevalence of SARMs is low compared to AAS
- Mostly males
- Alarming - few individuals **high concentrations of SARMs** !!!
- Some may use SARMs instead of AAS

Drug of Abuse Laboratory, Dep Clinical Pharmacology, KUL is setting up a SARM method as a healthcare service



”Livsfarliga” substansen Cardarine säljs i svenska butiker

Publicerad 6 dec 2023 kl 19.52, uppdaterad kl 20.52

Det senaste året har en rad friidrottsstjärnor åkt fast med dopingmedlet Cardarine – eller GW1516 – som stämplas som ”*dödligt och farligt*” av flera stora antidopingbyråer.

Trots det finns det att köpa som kosttillskott på flera svenska hemsidor, något som chockar Jenny Schulze, avdelningschef för dopingkontroller på Antidoping Sverige.

– Det är helt fruktansvärt, säger hon.

Tv-profilen och journalisten Jonas Karlsson, som föreläser om doping och kosttillskott, säger att GW1516 bara är en av många okontrollerade och potentiellt farliga substanser i omlopp.

– Lagstiftning och kontroll i Sverige är bristfällig, säger han.



Cardarine GW501516, 60 caps

Paragon Pharmatech



- 🏋️ The Ostarine Cardarine stack is a powerful combination often used for enhancing muscle growth and fat burning, significantly aiding fitness regimens.

GW1516



- PPAR δ (peroxisome proliferator-activated receptor) agonist
- preclinical and human phase I and phase II trials - positive effect on HDL/LDL, insulin levels, anti-inflammatory, increase fatty acid oxidation in muscles, reduce fat gain treatment

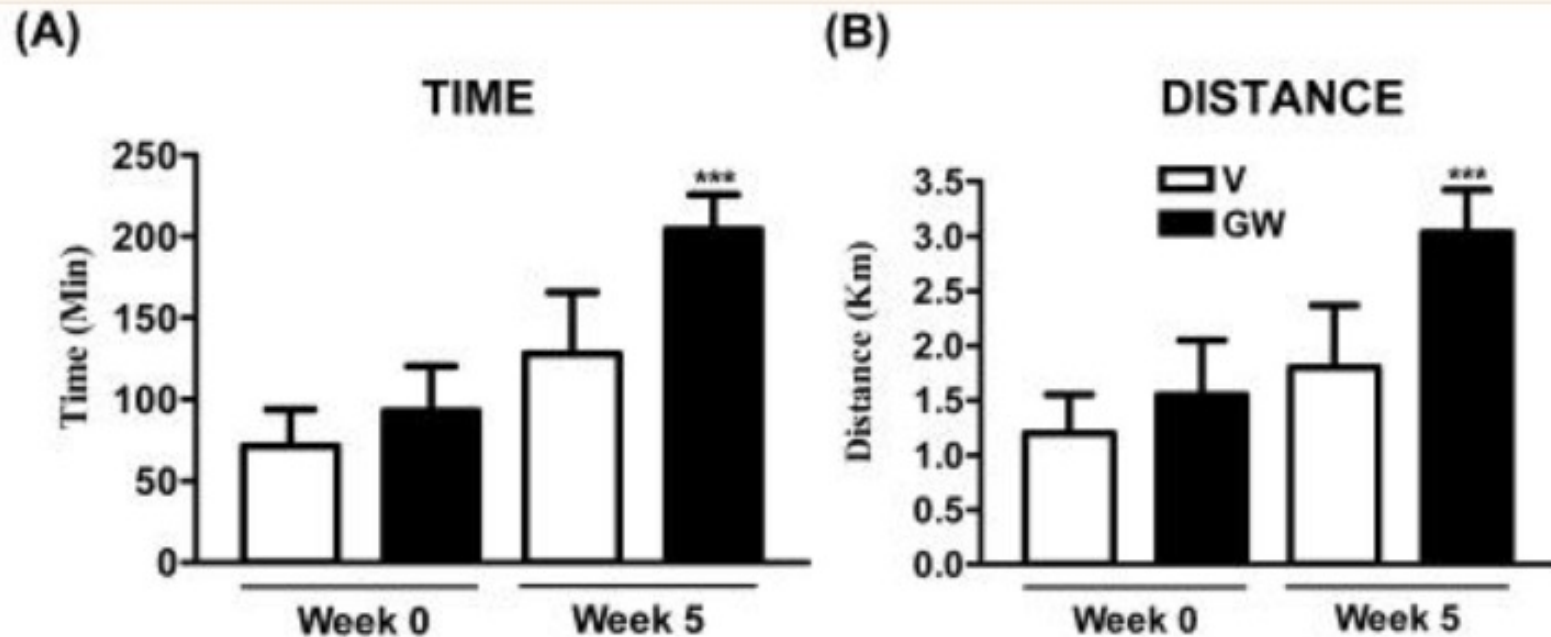


Hälsosfarlig. Produkten kan ge ärftlig genetisk skada, **cancer**, fosterskador eller störa fortplantningen. Används också för produkter som ger



GW1516 was given to mice that concurrently underwent exercise training on a treadmill for 4 weeks.

Significant increase in endurance by about 70% over that seen in exercise-trained control mice.



2009 ✓

WADA



WORLD ANTI-DOPING CODE
INTERNATIONAL STANDARD
**PROHIBITED
LIST**
2024

This List shall come into effect on 1 January 2024.

HOME / NEWS / INTEGRITY BLOG / GW1516 – POPULAR, BUT DEADLY

GW1516 – POPULAR, BUT DEADLY

Integrity Blog

play true magazine

NEWS

NEWS

FEATURES

PROFILES

ABOUT WADA

WADA issues alert on GW501516

🕒 March 21, 2013

It has come to WADA's attention that the black market substance GW501516 is being sold to and used by some athletes.

The side effect of this chemical compound is so serious that WADA is taking the rare step of warning "cheats" to ensure that there is complete awareness of the possible health risks to athletes who succumb to the temptation of using GW501516 for performance enhancement.

GW501516 was a developmental drug that was withdrawn from research by the pharmaceutical company and terminated when serious toxicities were discovered in [pre-clinical studies](#).

Clinical approval has not, and will not be given for this substance.

However, GW501516 has been available for some months on the black market, through the Internet and elsewhere. Anti-Doping authorities have already seen its use by athletes, as there are a number of positive cases.

Please pass this information on to your athletes as soon as possible.



GW1516 outside sport testing

- Only one case study -



Article

Peroxisome Proliferator-Activated Receptor Delta Agonist (PPAR- δ) and Selective Androgen Receptor Modulator (SARM) Abuse: Clinical, Analytical and Biological Data in a Case Involving a Poisonous Combination of GW1516 (Cardarine) and MK2866 (Ostarine)

Pascal Kintz ^{1,*}, Laurie Gheddar ¹, Camille Paradis ², Mickael Chinellato ³, Alice Ameline ¹, Jean-Sébastien Raul ¹ and Magali Oliva-Labadie ²



Research projects

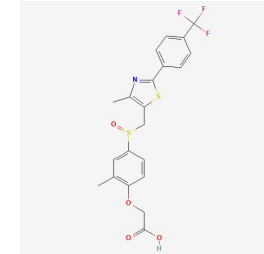
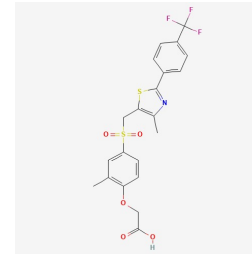
- UAAS samples from drug abuse laboratory (ca 800)

GW1516 not included in drug/doping testing outside sport

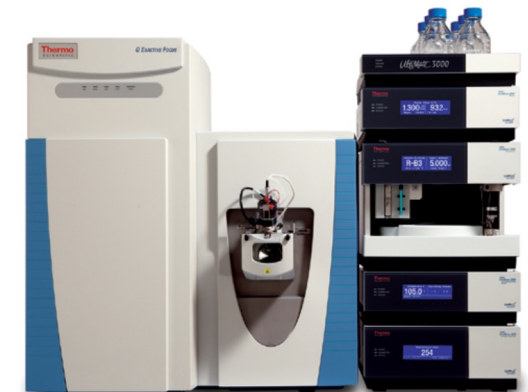
GW1516 testing Doping lab

- GW1516 metabolites sulfone and sulfoxide

- GW1516 sulfone detectable ~ 40 days
- GW1516 sulfoxide detectable ~ 25 days



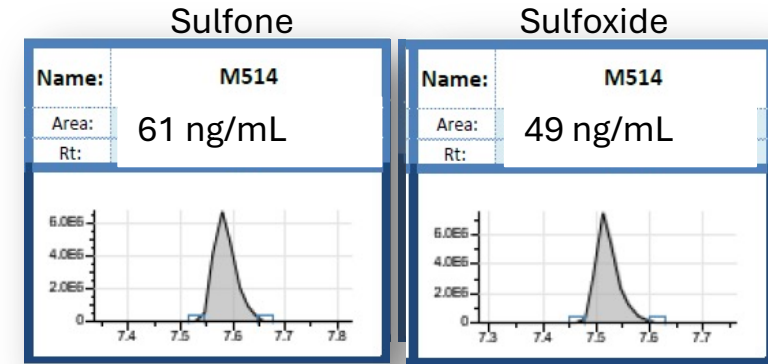
- Included in our big LC-HRMS screening method
 - ~ 500 substances



Q Exactive Focus mass spectrometer with Thermo Scientific™ Dionex™ Ultimate™ RSLC 3000

Preliminary Results

- 4 of 800 samples contained GW1516 metabolites **0.5 %**
(35 % AAS, 4 % SARM)
- 3 samples contained "high concentrations"
- Two samples ostarine and GW1516 combination




Emergence and occurrence of performance-enhancing substance use in Australia determined by wastewater analysis

Received: 2 March 2023

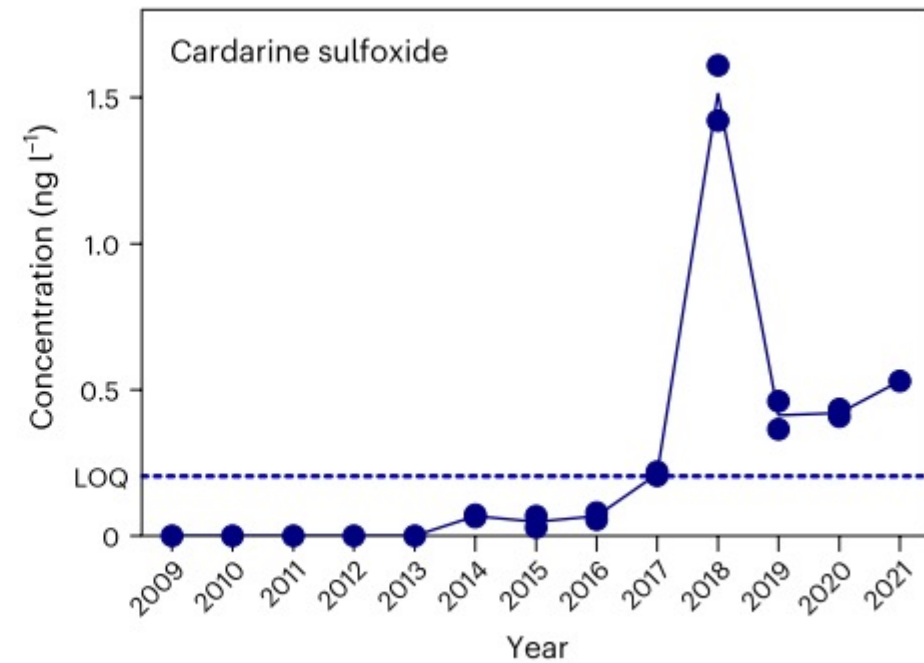
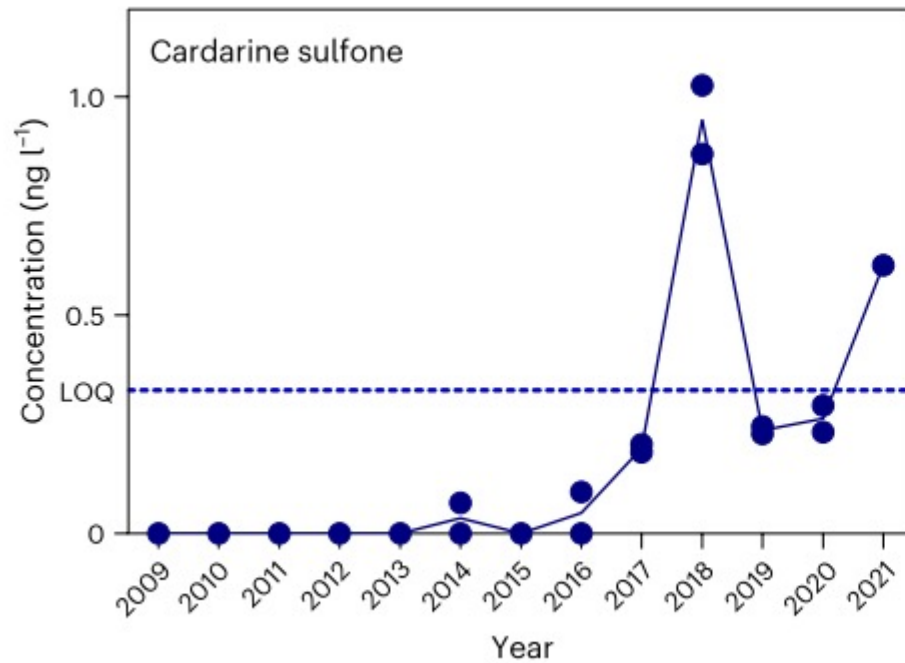
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- GW1516 found at concentrations over LOQ but at lower concentrations than ostarine
- show similar time-pattern as SARM

Summary

Prevalence of SARMs is 10 times less common than AAS – both high and low concentrations (associated with liver toxicity).

Prevalence of "life threatening drug" GW1516 is 70 times lower compared to AAS.



Continue studies SARMS

Continue analyze drug abuse samples for presence of SARMS/GW1516 (and other doping/narcotic agents different AAS, amphetamine etc etc).

Broader understanding of abuse profile outside sport

- what drugs to screen for in future testing panels
- Inform the healthcare and society

Future project: Analyzing supplements

