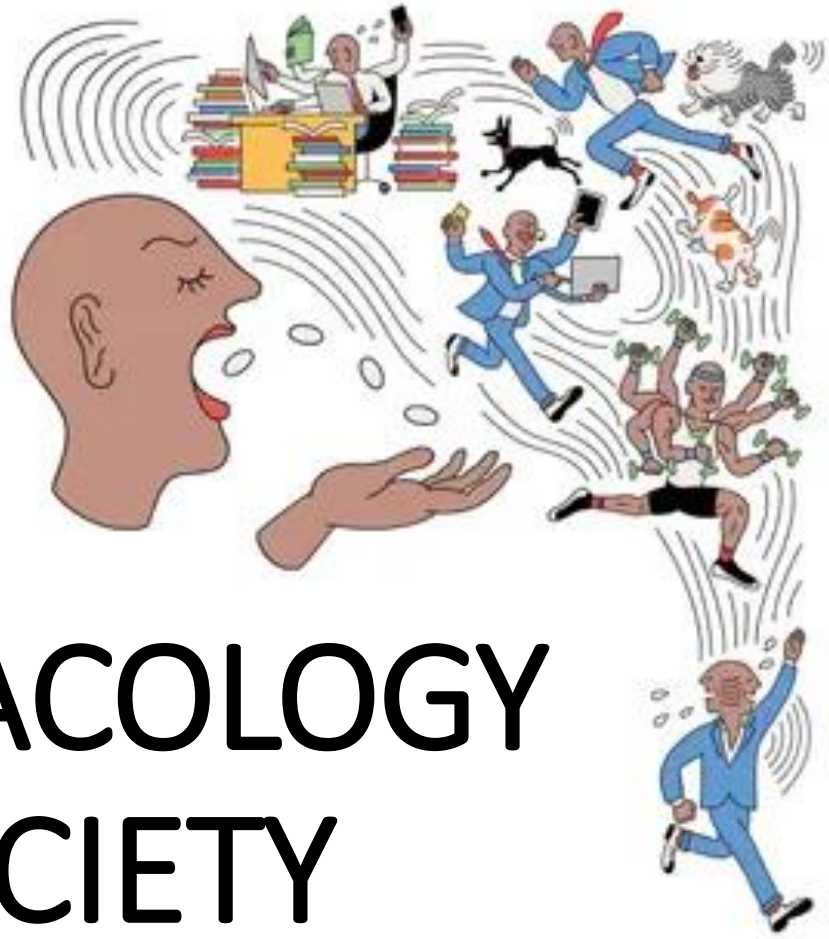


DOPING AND PHARMACOLOGY IN SPORTS AND SOCIETY

Assist. Prof. Lovro Žiberna, PhD MPharm

SLOADO
SLOVENSKA ANTIDOPING ORGANIZACIJA
SLOVENIAN ANTI-DOPING ORGANISATION

Univerza v Ljubljani
Medicinska fakulteta
1919
2019

Doping is a

social phenomenona.

IT IS NOT ONLY A PROBLEM OF SPORT, BUT RATHER A PROBLEM OF SOCIETY.

DRUGS - SUBSTANCES

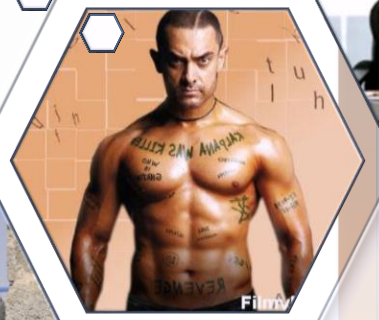
CLASSICAL MUSICIANS

SOLDIERS

ATHLETES

MANAGERS

MOVIE ACTORS



STUDENTS

PERFORMANCE ENHANCING

DRUGS - SUBSTANCES

CLASSICAL MUSICIANS

MANAGERS

MOVIE ACTORS

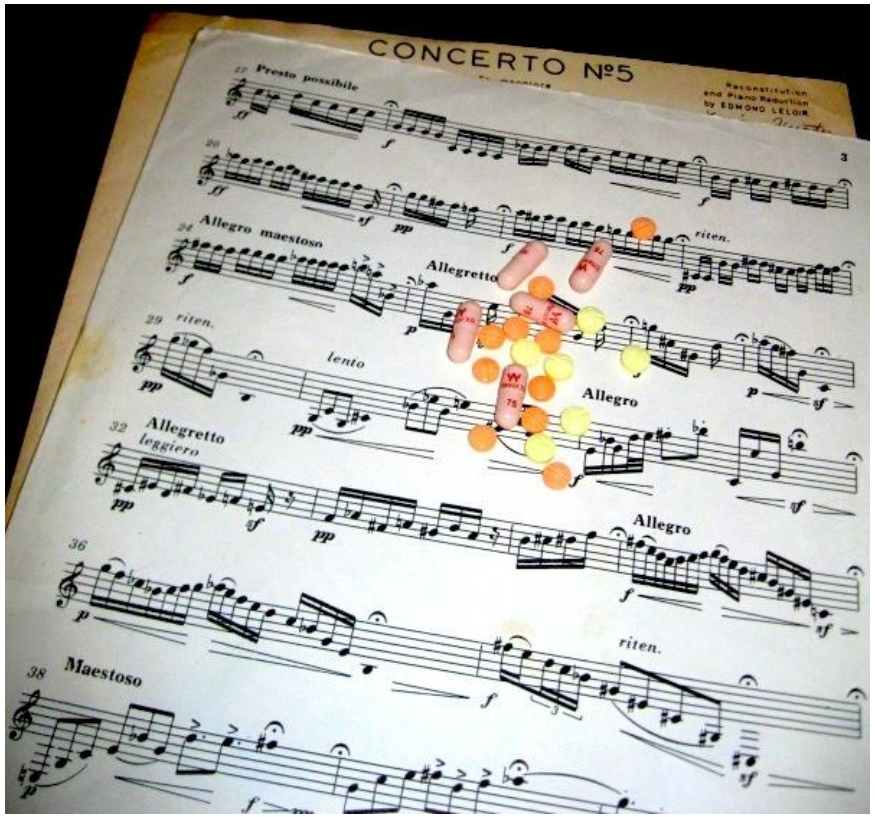
Doping control

SOLDIERS

ATHLETES

STUDENTS

PERFORMANCE ENHANCING



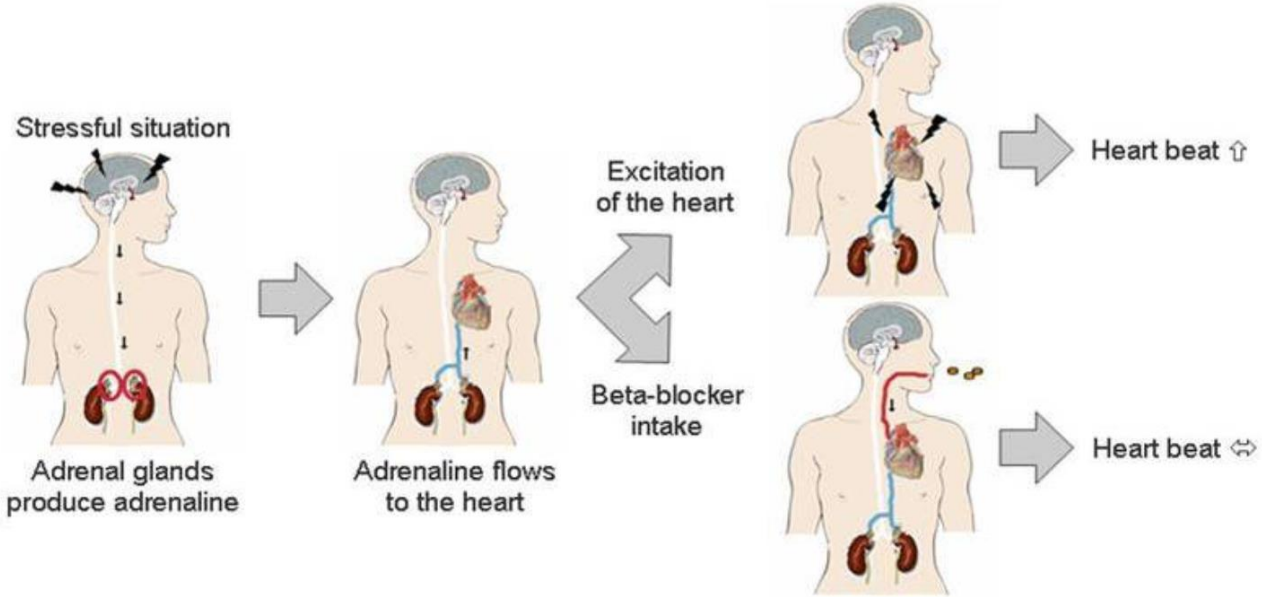
DOPING IN MUSIC?

Can we use certain substances to improve our music performance?

Beta-blockers (reduce the effects of adrenaline and noradrenaline as the consequence of fear, performance anxiety)

- **increased heart rate**
- **tremor**
- **sweating**
- **vibrating voice**
- **dizziness, vertigo**

Example of doping protocol for the musicians:
5-20 mg propranolol/ performance;
60-90 min before (start protocol)



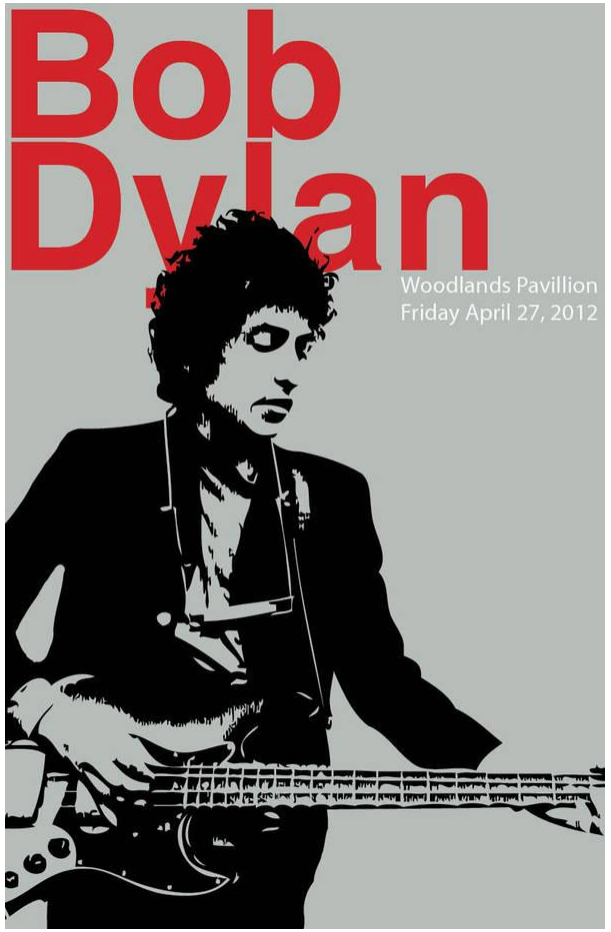
The Musician's Steroid: The Controversy Surrounding Beta Blockers

"Some of my teachers in conservatory days would gladly carry around a flask of Scotch and take it before they went on stage," she said. "But I don't see that in any of the orchestras that I've played in recently."

Instead, Mulcahy and other orchestra musicians increasingly turn to beta blockers. According to Mulcahy and other musicians who spoke with WQXR, in some backstage areas, they're passed around like chewing gum or mints. Mulcahy recalls panicked colleagues calling "Oh my God, does anybody have any Inderal?"

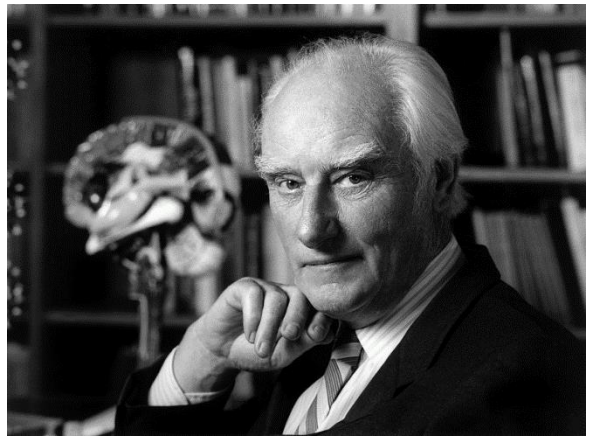
URL: http://www.wqxr.org/#!/story/312920-musicians-use-beta-blockers-relieve-stage-fright/

DOPING IN ART – PSYCHODELIC SUBSTANCES FOR IMPROVED CREATIVITY

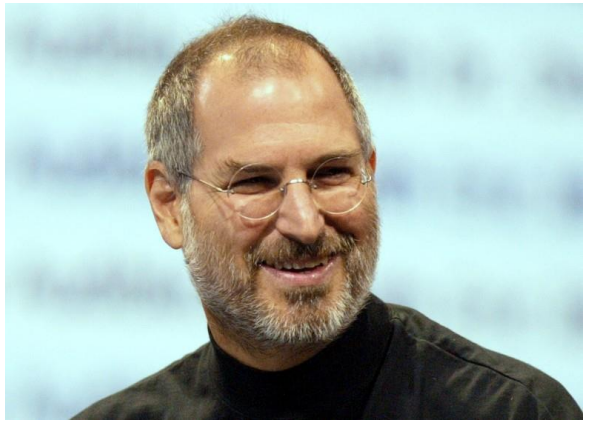


DOPING IN SCIENCE? IN INNOVATION?

Can we increase our creativity and thinking?

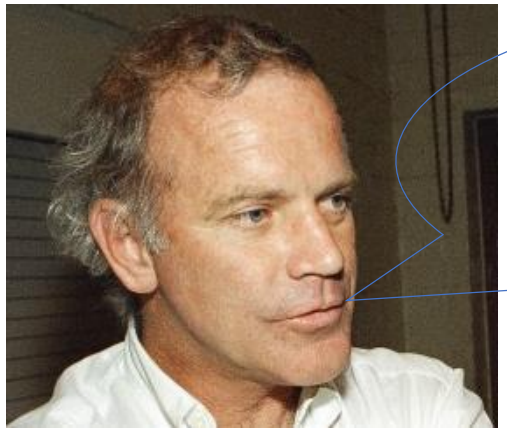


FRANCIS CRICK – discovery of DNA. Nobel Prize in Medicine awarded in 1962. Used **LSD** with researcher at University of Cambridge – also during the discovery.



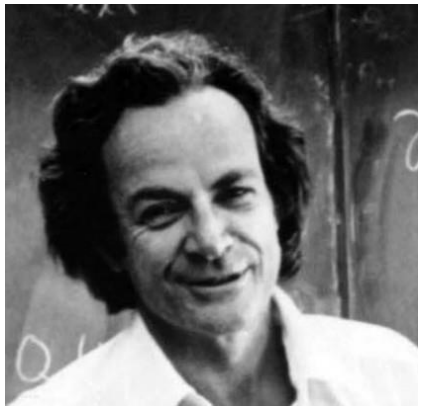
STEVE JOBS – founder of Apple. In years 1972-1974 used **LSD**.

BILL GATES – founder of Microsoft. Used **LSD** in the age <25 years.



KARY MULLIS – developed PCR. Nobel prize in chemistry in 1993. **LSD**

"What if I had not taken LSD ever; would I have still invented PCR? I don't know. I doubt it. I seriously doubt it."



RICHARD FEYNMAN, USA physicist, Nobel prize in physics in1965.
LSD, marijuana, ketamine.

MICRODOSE DOPING TO INCREASE PRODUCTIVITY AS „CREATIVITY ENHANCERS“

Protocol 1:
10-15 µg LSD (10% „normal dose“)

Protocol 2:
taking sub-perceptual doses (6-25 microgram LSD, 0.2-0.5 gram dried mushrooms, 50-75 microgram mescaline HCL

CREATIVITY ENHANCERS

Purpose: to improve „out-of-the-box-thinking“

The Telegraph

Home Video News World Sport Finance Comment Culture Travel Life Women

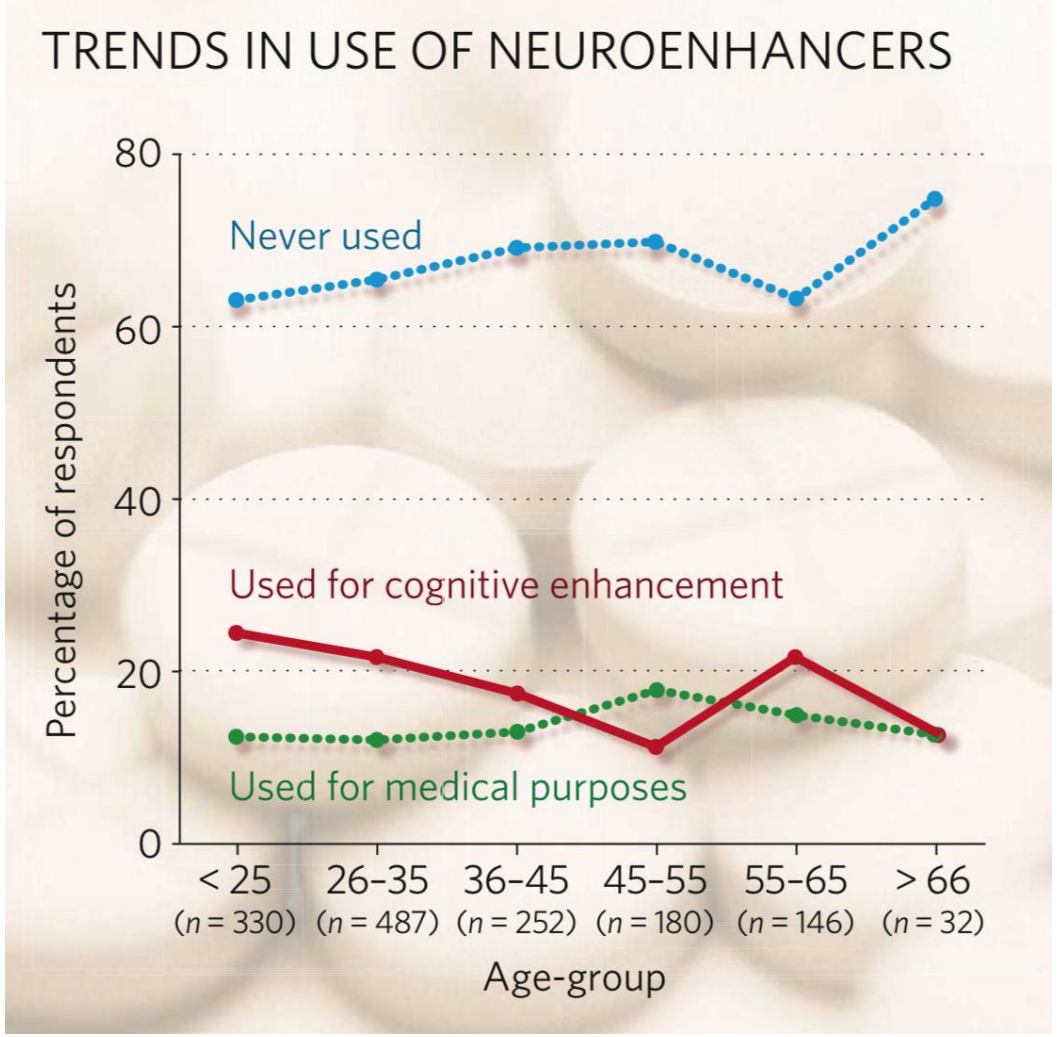
Politics | Investigations | Obits | Education | Science | Earth | Weather | Health | Royal | Celebr

HOME » NEWS » NEWS TOPICS » HOW ABOUT THAT?

Silicon Valley professionals are taking LSD at work to increase productivity

An increasing number of twenty-somethings are reportedly 'micro-dosing' on psychedelic drugs - and they say it's making them better workers

USE IN ACEDEMIC FIELD – ACADEMIC DOPING



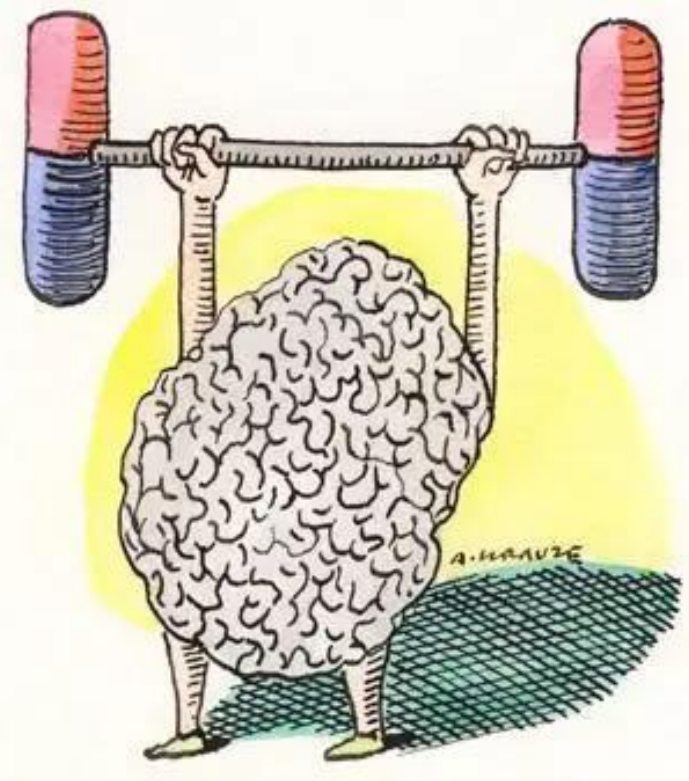
1400 researchers from 60 countries

3 substances as academic doping:

- **modafinil: 62 %**
- **methylphenidate: 44 %**
- **beta-blockers: 15 %**

All 3 are <u>prohibited in sports</u> (by WADA).

Maher, B. (2008, April 10). Poll results: look who's doping. *Nature*, pp. 674–675. Nature Publishing Group. http://doi.org/10.1038/452674a



Taking substances to improve cognitive performance?

STUDENT DOPING AT UNIVERSITY?

PREVALENCE - MEDICAL STUDENTS IN CANADA

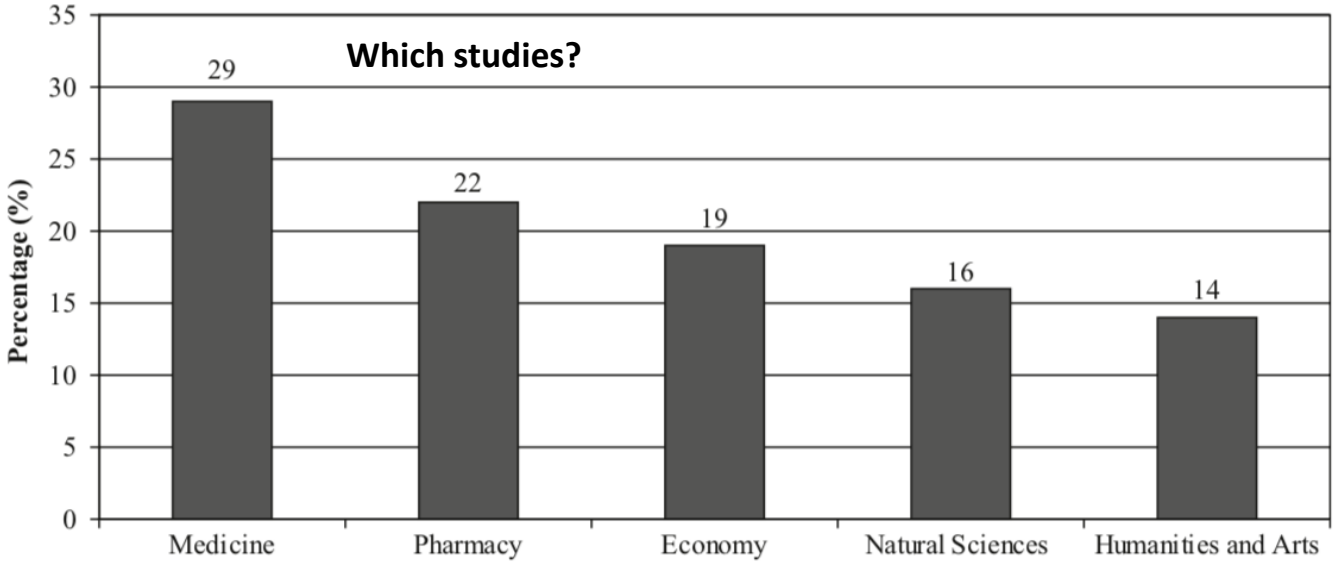
TABLE 2
Prevalence Data

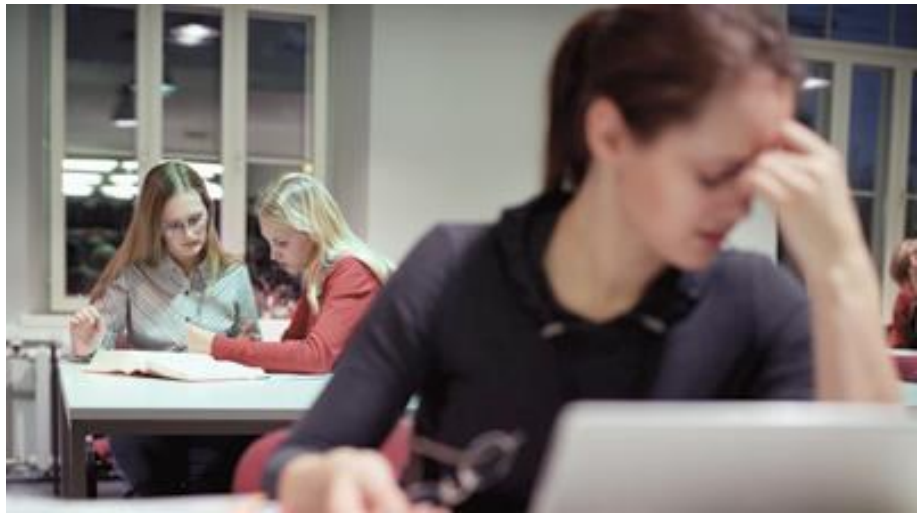
Substance group	Lifetime use	Use within the last year (recent use)
Coffee, tea, cola	300 (92%, *CI: 89%–95%)	271 (83%, CI: 79%–87%)
High-caffeine energy beverages	169 (52%, CI: 47%–57%)	82 (25%, CI: 20%–30%)
Natural supplements (i.e., gingko biloba, omega 3 fatty acids, B vitamins, melatonin, choline)	97 (30%, CI: 25%–35%)	62 (19%, CI: 15%–23%)
Tobacco, decongestants	39 (12%, CI: 8%–15%)	8 (2%, CI: 0.2%–4%)
Stimulant pharmaceuticals (i.e., methylphenidate, modafinil, dextroamphetamine, dextro/levoamphetamine, adrafanil, piracetam)	49 (15%, CI: 11%–19%)	14 (4%, CI: 2%–6%)

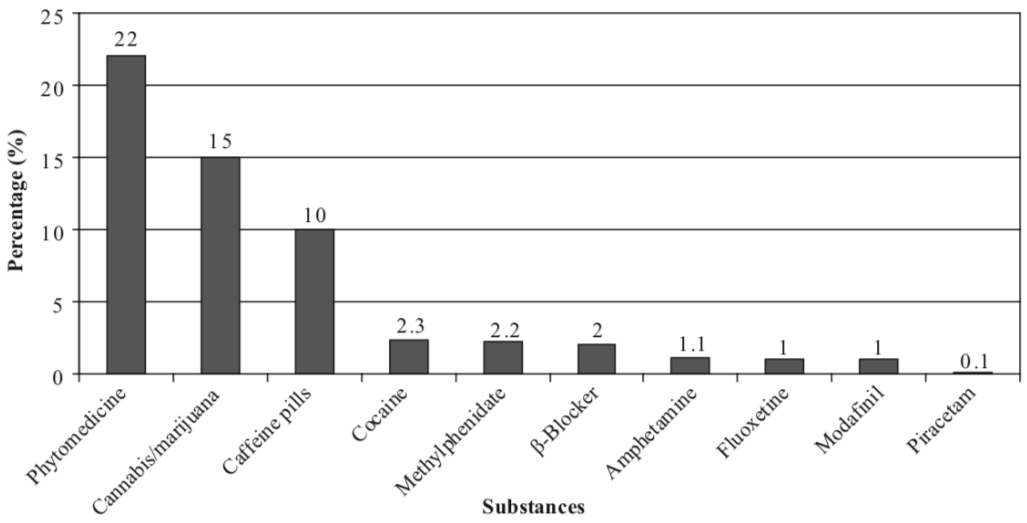
*All 95% CI.

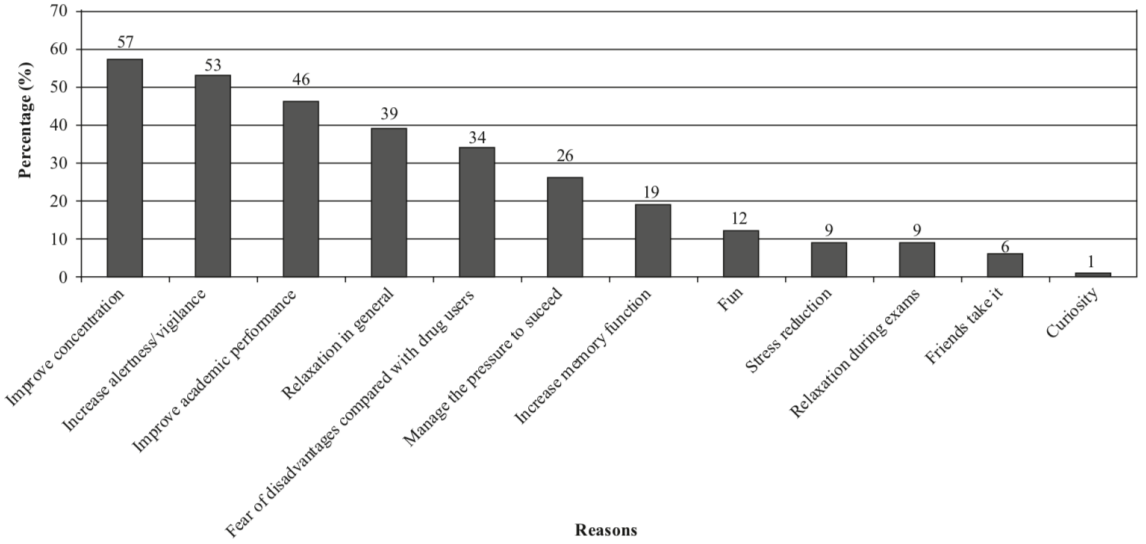
Kudlow, P. A., Naylor, K. T., Xie, B., & McIntyre, R. S. (2013). Cognitive enhancement in Canadian medical students. *Journal of Psychoactive Drugs*, *45*(4), 360–365.

UNIVERSITY STUDENTS in GERMANY





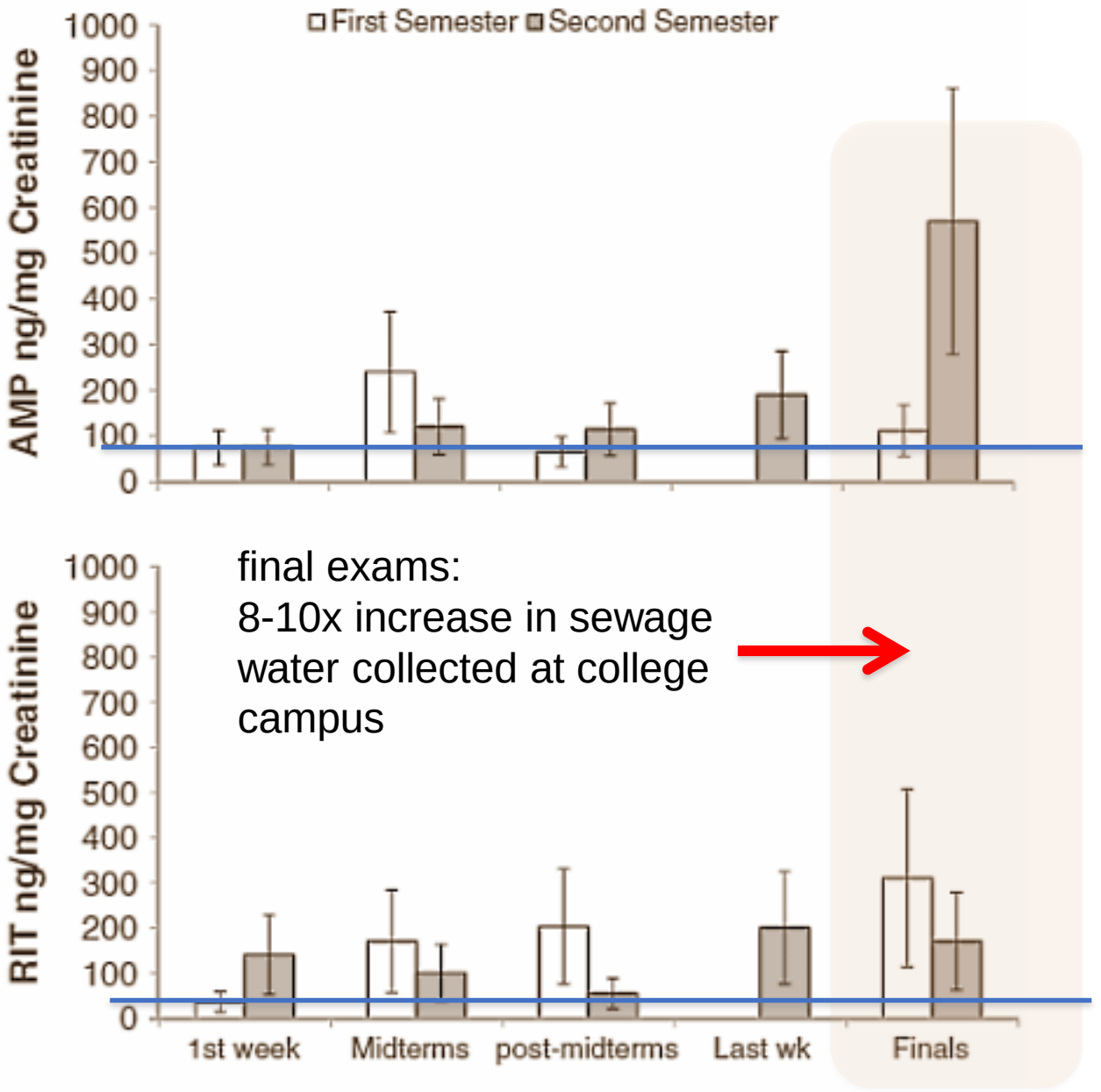




Mache, S., Eickenhorst, P., Vitzthum, K., Klapp, B. F., & Groneberg, D. A. (2012). Cognitive-enhancing substance use at German universities: frequency, reasons and gender differences. *Wiener Medizinische Wochenschrift (1946)*, *162*(11-12), 262–271.

amphetamines

methylphenidate



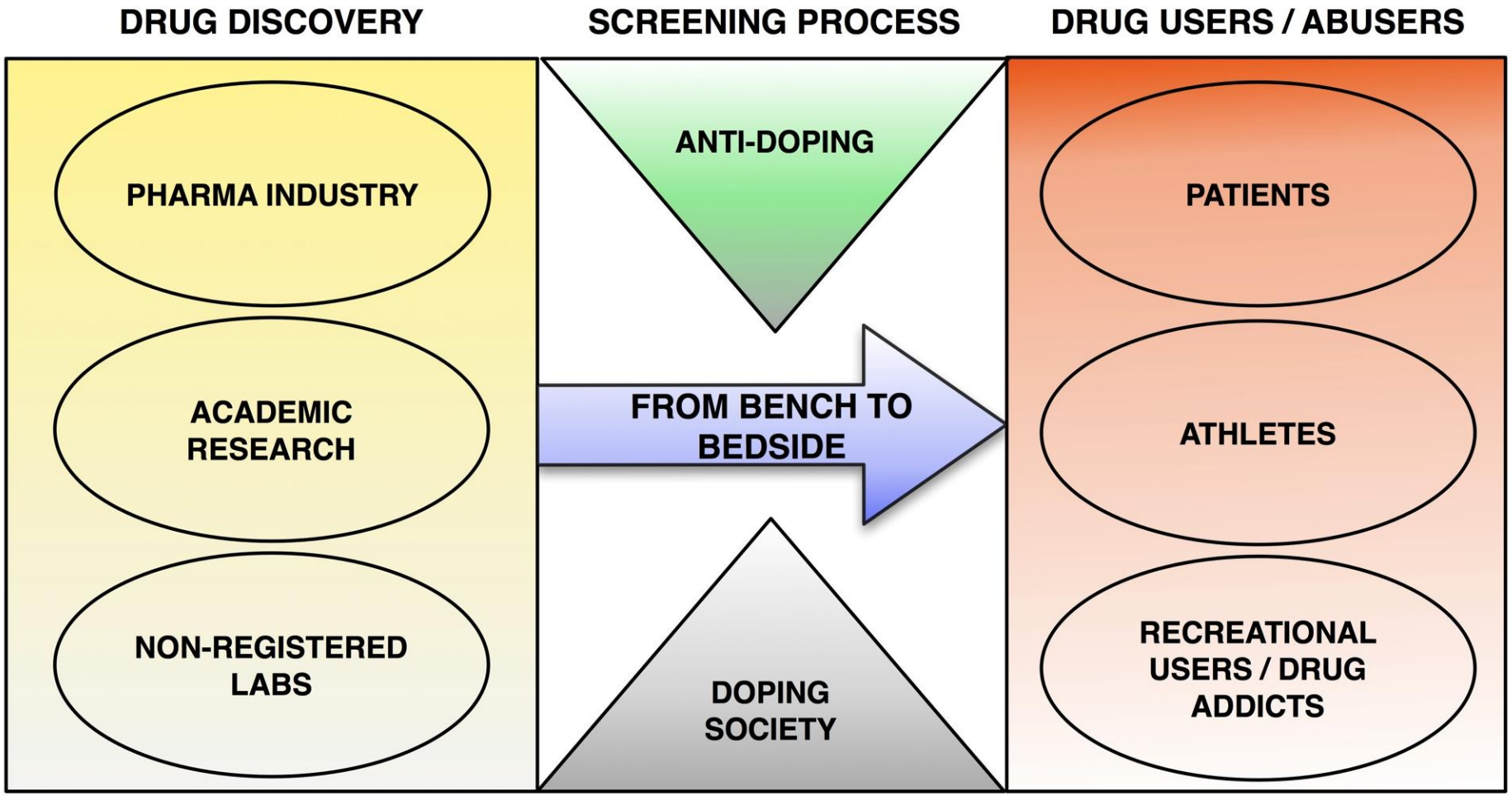
final exams:
8-10x increase in sewage water collected at college campus

Sci Total Environ. 2013 Apr 15;450-451:242-9.

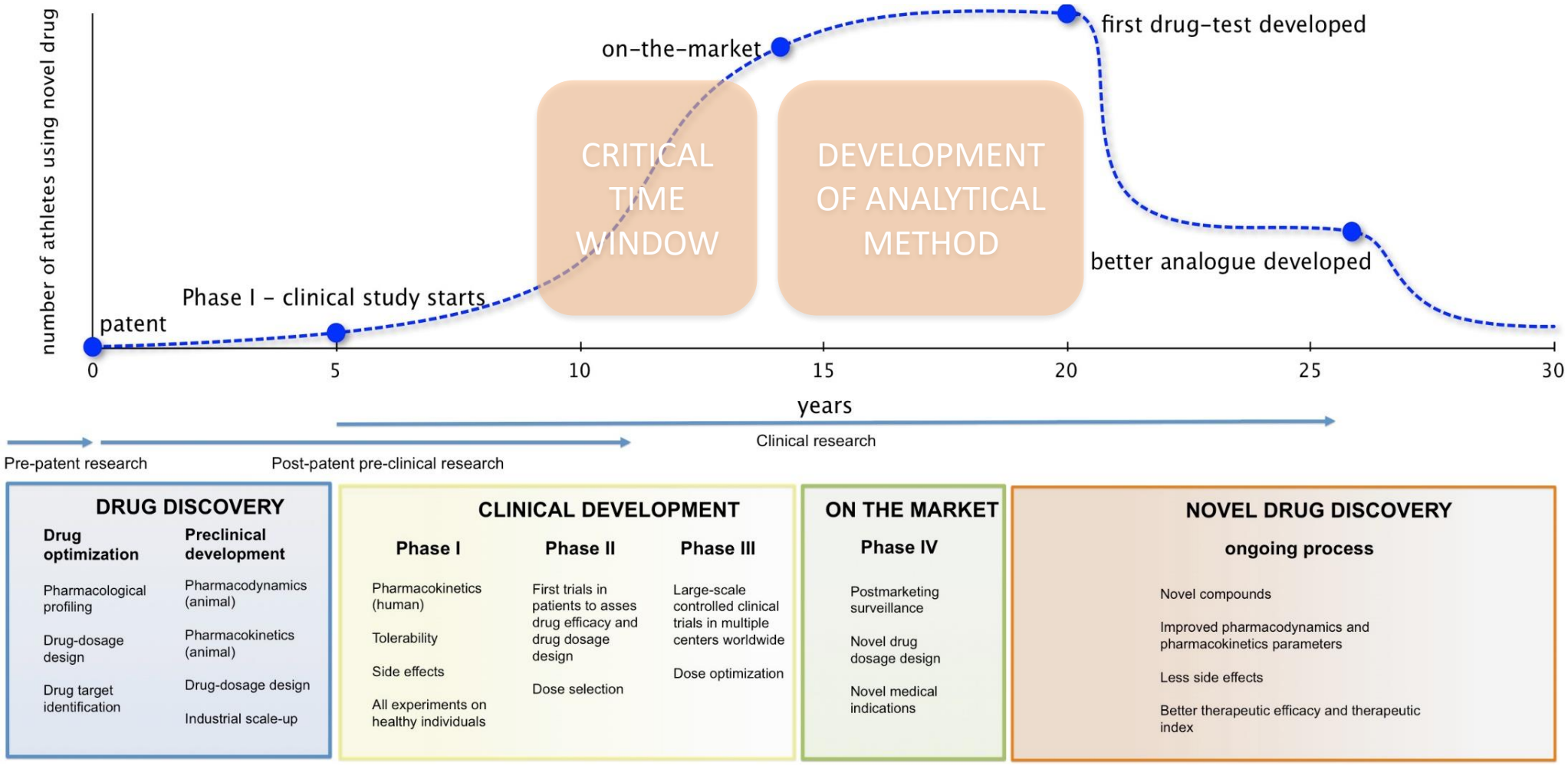
NEW DRUG SUBSTANCES

Therapeutic usage vs. abuse by health individuals as PED

THE ORIGIN OF NOVEL DOPING SUBSTANCES



DRUG DISCOVERY PROCESS AND DOPING



Ziberna L. Drug (Re) Discovery: From Bench to Sport Side. Unfamiliar Journal, 2012, p58-60

COLLABORATION WITH PHARMA INDUSTRY

23rd July 2012 – start of ***Protecting the Integrity of Science and Sport***

IFPMA

Bio
Biotechnology Industry Organization

WORLD ANTI-DOPING AGENCY
play true

1 - International Federation of Pharmaceutical Manufacturers & Associations
2 - Biotechnology Industry Organization (BIO)
3 - World Anti-Doping Agency (WADA)

FIRST COLLABORATION started in **2004** – **Roche Holding AG and WADA**.
EPO 3rd.gen. - **CERA** – in 2007 arrival on the market → in 2008 many athletes tested positive

DOPING IN SPORT

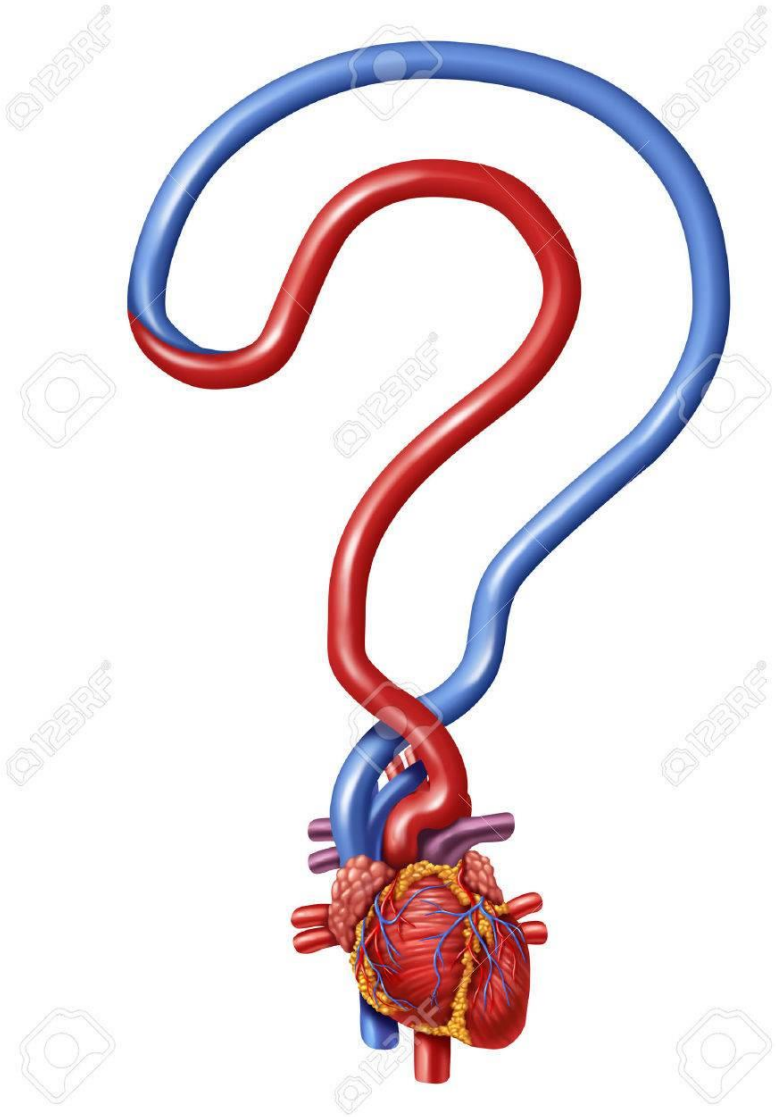
What is doping? Why we fight against doping?

GOLDMAN DILLEMA

"Would you take an illegal performance enhancing drug that was undetectable
Condition 1: "and guaranteed you would win an Olympic gold medal, if it would kill you in five years?" (n = ○125, 64.8% male, mean age

Elite athletes (1984): 52 % YES

General population (2009): 0.8 % YES



Connor, J. M., & Mazanov, J. (2009). Would you dope? A general population test of the Goldman dilemma. *British Journal of Sports Medicine*, *43*(11), 871–872.

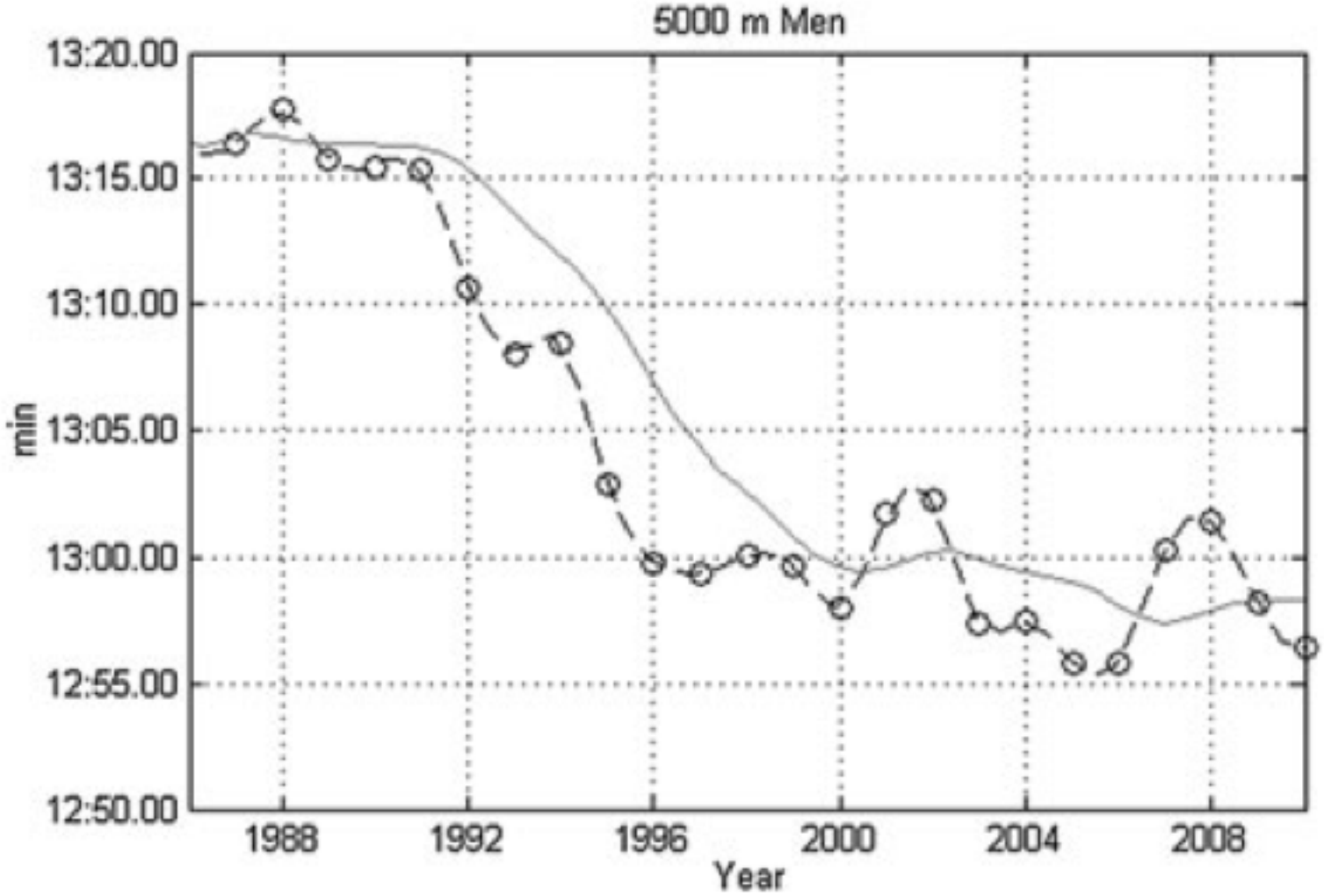
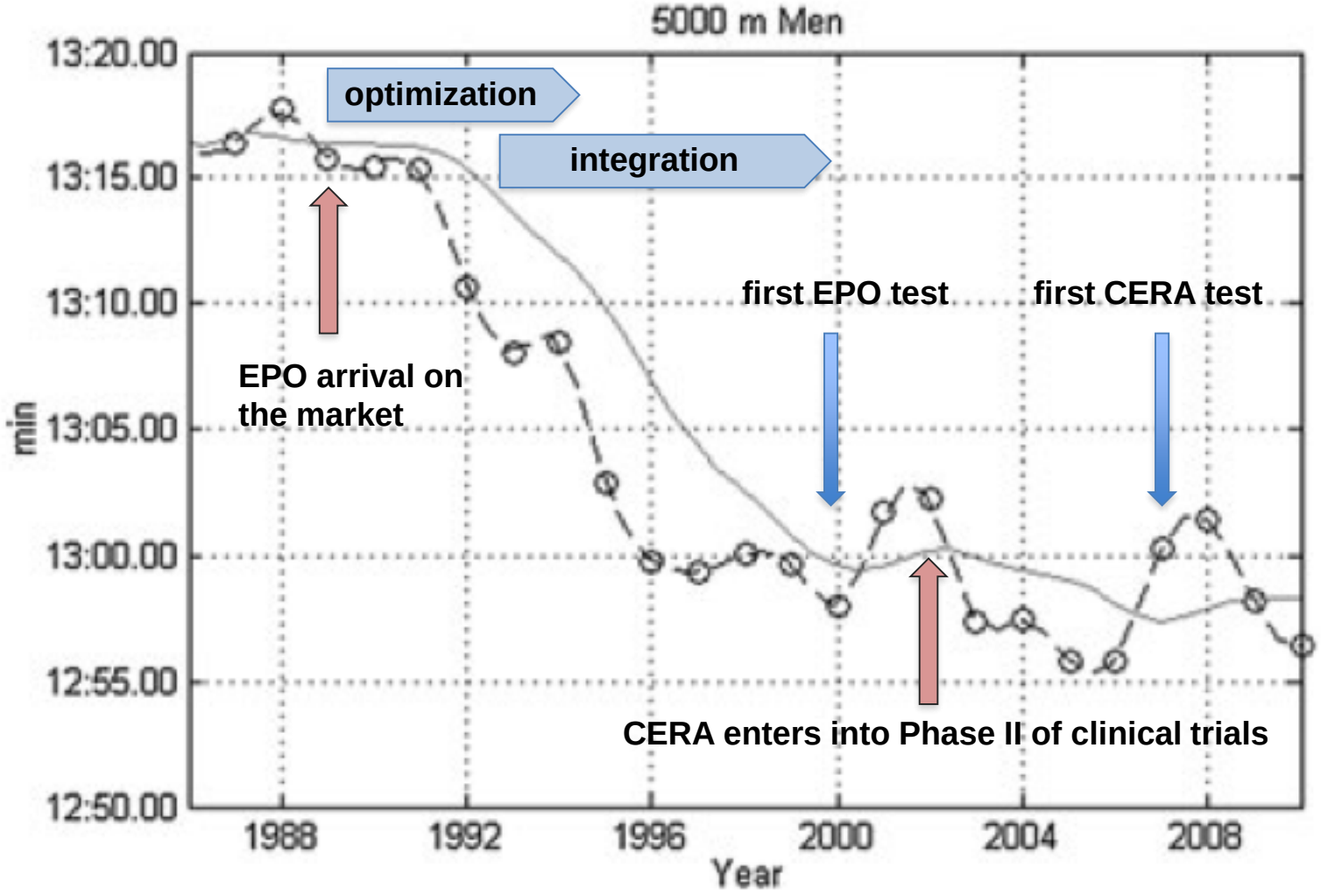


Figure 2. Development of the arithmetical mean of the time of the top 20 athletes on the men's 5000 m from 1985 to 2010 (o) connected through a polynomial spline (– –) and further described with the corresponding moving average (–).

Ernst S, Simon P. Drug Test. Analysis. 2012 Aug.29.DOI:10.1002/dta.1406



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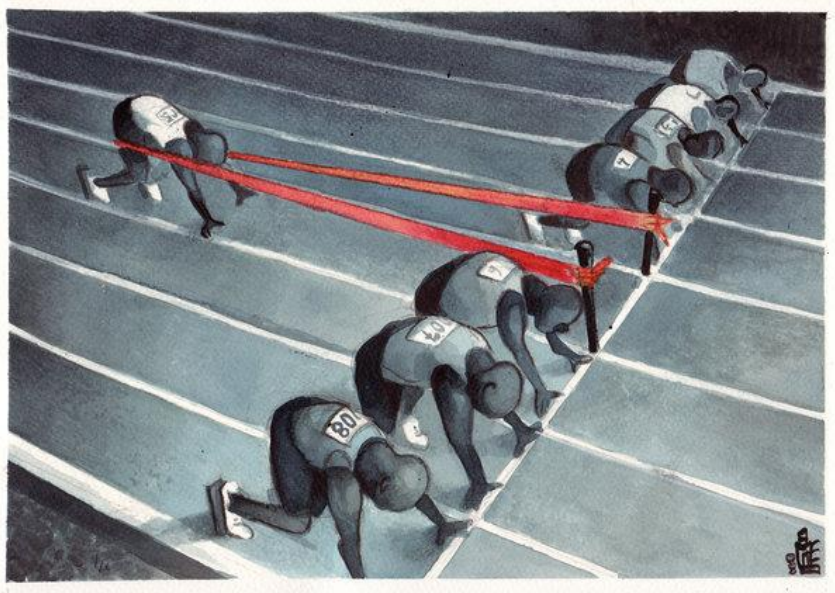
Ernst S, Simon P. Drug Test. Analysis. 2012 Aug.29.DOI:10.1002/dta.1406

WHY ARE (SHALL/MUST BE) SUBSTANCES PROHIBITED?

Fair-play violation – cheating.



Danger to health.

BBC SPORT FOOTBALL

Low graphics | Help

Last Updated: Tuesday, 28 August 2007, 14:50 GMT 15:50 UK

E-mail this to a friend Printable version

Sevilla's Puerta dies in hospital

Spain international Antonio Puerta has died after suffering a heart attack in his club side Sevilla's 4-1 win against Getafe on Saturday.

Puerta helped Sevilla win the Uefa Cup last season

Defender Puerta, 22, collapsed in the first-half and medics prevented him from swallowing his tongue.

But he collapsed again after going off and was given cardiac resuscitation before being taken to hospital.

He was placed in intensive care and doctors said on Tuesday his condition had deteriorated before his death.

Puerta collapsed after jogging back towards his own goal 35 minutes into the opening league game of the season at the Sanchez Pizjuan on Saturday.

CYCLING/BMX

Belgian rider Sermon dies in sleep

Updated: February 15, 2004, 6:39 AM ET

BRUSSELS, Feb 15 - Belgian cyclist Johan Sermon has died in his sleep at the age of 21, news agency Belga reported.

Sermon, of the Daikin team, appeared to have died of natural causes, Belga quoted team manager Ernest De Vuyst as saying.

"An autopsy has been carried out and we are now awaiting the results. But I can already say with certainty it was a natural death," said De Vuyst, who added that he believed Sermon had died of heart failure.

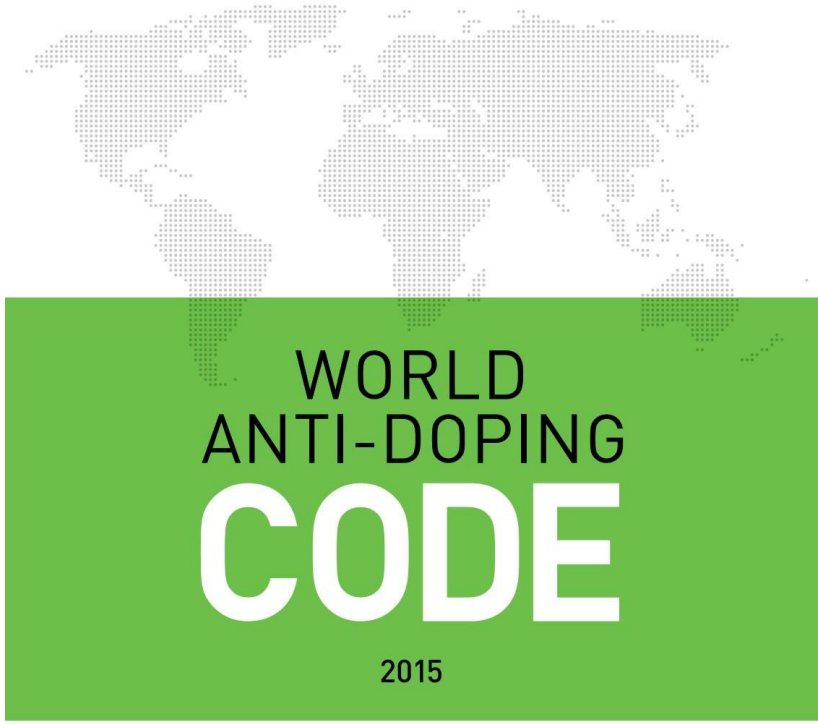
Former Tour de France winner Marco Pantani was found dead in a hotel room in Italy at the weekend.

Belga quoted former French Minister of Youth and Sports Marie-George Buffet as saying: "I am devastated by the announcement of the deaths of Marco Pantani and Johan Sermon."

21 years of age, heart arrest during the sleep – 15th February 2004

What is doping in sports?

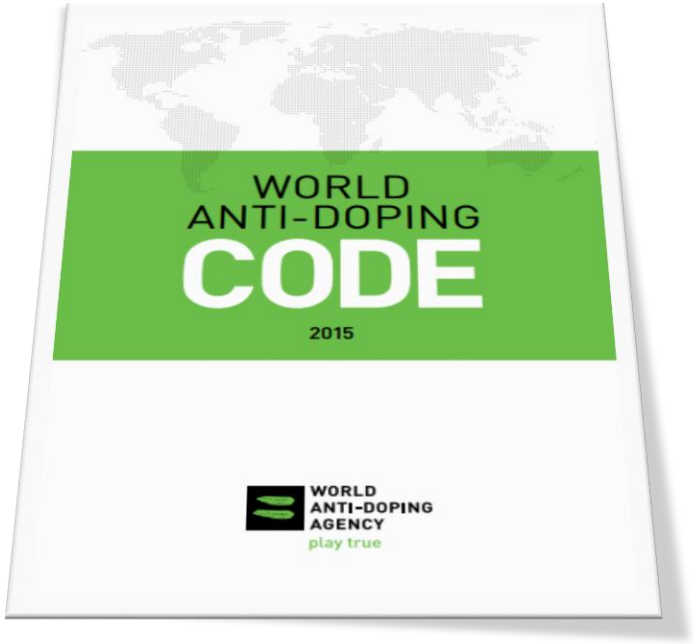
Doping is defined as the occurrence of one or more of the **anti-doping rule violations.**



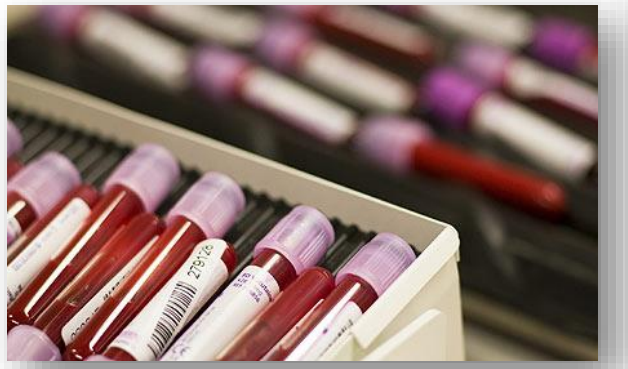
WORLD ANTI-DOPING AGENCY
play true

The current official definition of doping is given based on the World Anti-Doping Code.

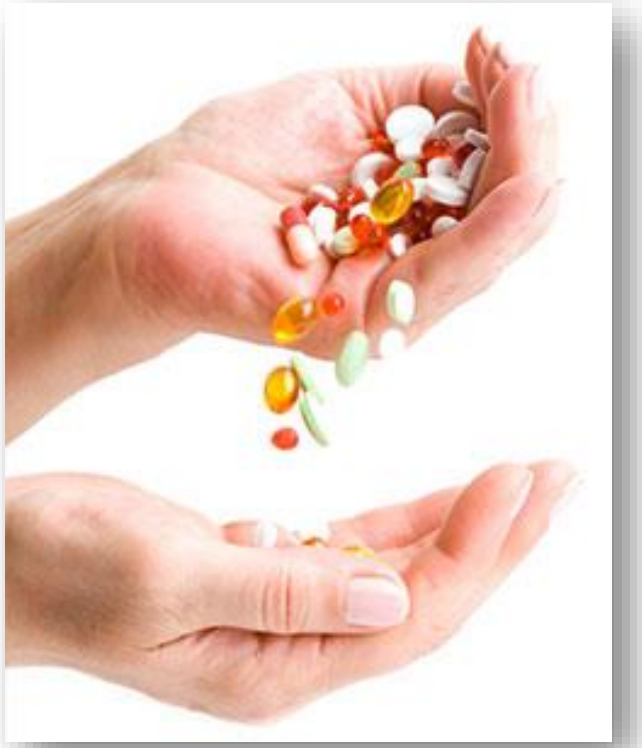
1) Presence of a prohibited substance or its metabolites or markers in an athlete's sample



- substances and methods which have been included on the Prohibited List



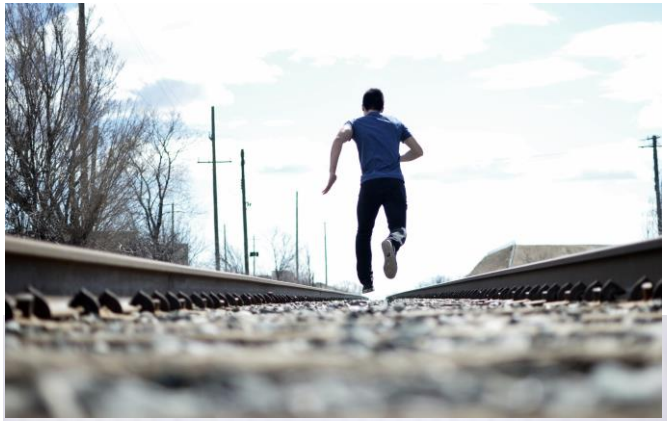
2) Use or Attempted Use by an Athlete of a Prohibited Substance or a Prohibited Method



- it is each athlete's personal duty to ensure that no prohibited substance enters his or her body and that no prohibited method is used
- the success or failure of the use or attempted use of a prohibited substance or prohibited method is not important

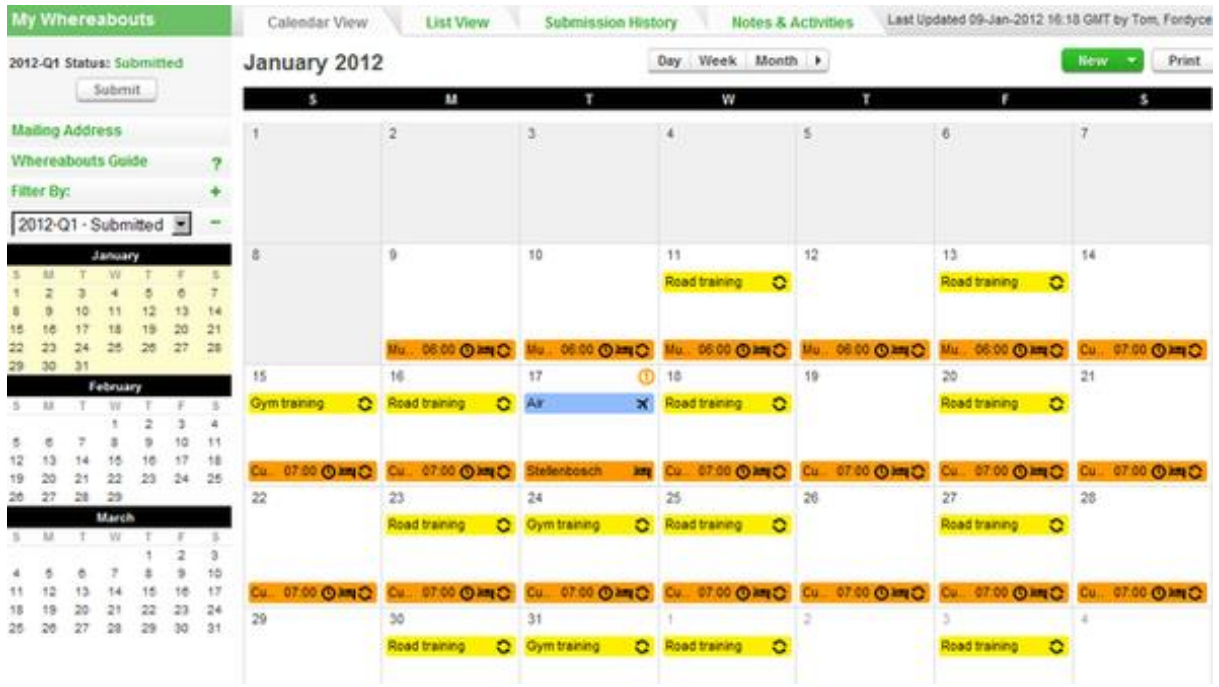
3) Evading, Refusing or Failing to Submit to Sample Collection

- **evading sample collection**, or without compelling justification, **refusing or failing to submit to sample collection** after notification as authorized in applicable anti-doping rules



4) Whereabouts Failures

- Any **combination of three missed tests and/or filing failures**, as defined in the International Standard for Testing and Investigations, **within a 12-month period** by an Athlete in a Registered Testing Pool.



5) Tampering or Attempted Tampering with any part of Doping Control

- intentionally interfering or attempting to interfere with a Doping Control official,
- providing fraudulent information to an Anti-Doping Organization,
- intimidating or attempting to intimidate a potential witness

- Including: altering identification numbers on a Doping Control form during Testing, breaking the B bottle at the time of B Sample analysis, or altering a Sample by the addition of a foreign substance

6) Possession of a Prohibited Substance or a Prohibited Method

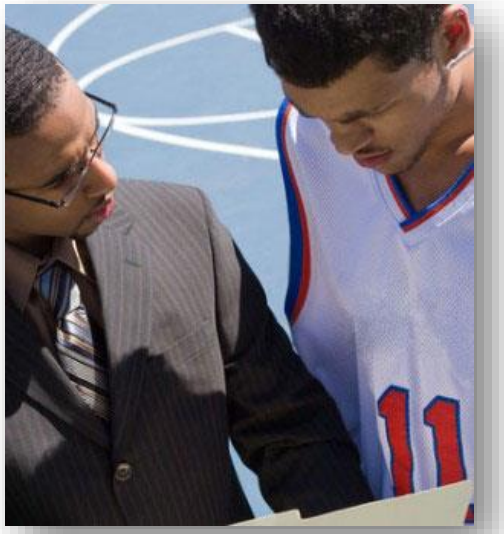
- possession by an athlete of any prohibited substance or any prohibited method on both in-competition and out-of-competition period

- exceptions are substances, which are used *for therapeutic purposes*

- valid for **both athletes and athlete support person**

7) Trafficking or Attempted Trafficking in any Prohibited Substance or Prohibited Method

8) Administration or Attempted Administration to any Athlete of any Prohibited Substance or Prohibited Method



- In-competition, and out-of-competition
- help, advisorory role, induction, covering up, …
- national Crime laws

e.g. in SLOVENIA:

Kazenski zakonik (KZ-1) – 186. člen in 187.člen (od 1.novembra 2008)

9) Complicity

- assisting, encouraging, aiding, abetting, conspiring, covering up or any other type of intentional complicity involving an anti-doping rule violation,

10) Prohibited Association

Association by an Athlete to any personnel, which is:

- serving a period of Ineligibility
- convicted or found in a criminal, disciplinary or professional proceeding to have engaged in conduct which would have constituted a violation of anti-doping rules if Code-compliant rules had been applicable to such Person
- serving as a front or intermediary for an individual described above (intermediary person)


THE SUNDAY TIM

British doctor claims he doped 150 sports stars

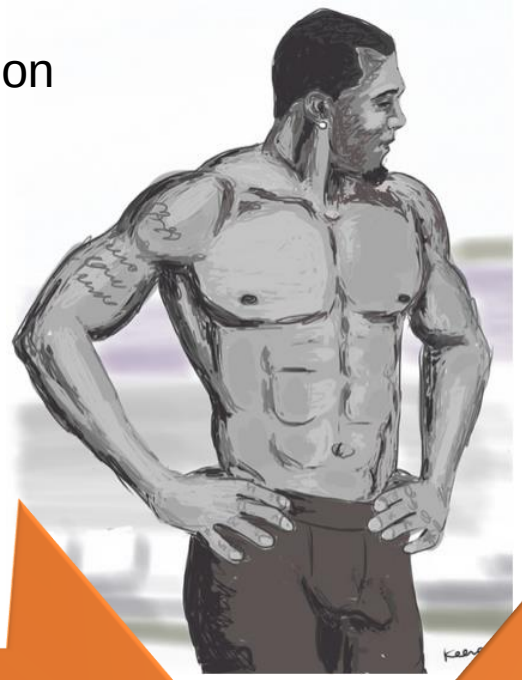
INSIGHT

THE DOPING SCANDAL

PREMIER LEAGUE FOOTBALLERS, AN ENGLAND CRICKETER, BRITISH TOUR DE FRANCE CYCLISTS, A BOXING CHAMPION AND TENNIS PLAYERS ARE AMONG HIS ALLEGED CLIENTS

- suspension from competition
- results are erased
- (UCI – financial penalty)

- prison
- captured material
- financial penalty (depending on national laws)



WADA CODE

KAZENSKI ZAKONIK

SPORT PENALTY

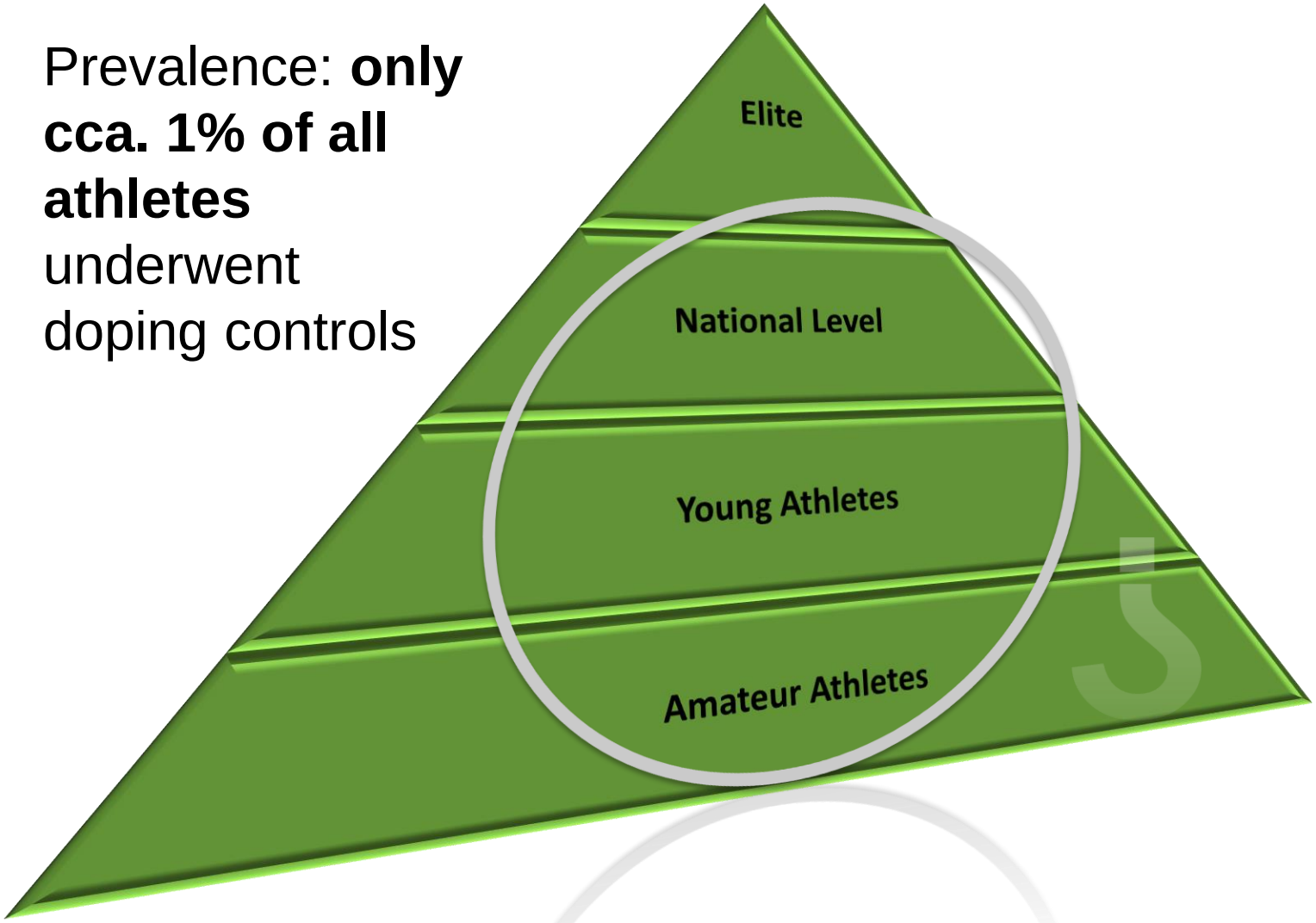
CRIMINAL LAW

- WADA
- national anti-doping organizations (e.g. SLOADO)
- International sports organization (UCI, FIFA, UEFA, FIBA, IAAF, itd.)

- police
- criminal investigaton

DOPING CONTROLS IN SPORT

Prevalence: **only cca. 1% of all athletes** underwent doping controls



DOPING IN AMATEUR SPORTS

Doping for seniors

By: Monika Prell Published: August 10, 2007, 00:00, Updated: April 20, 2009, 21:36 Edition: First Editi

In Italy a 55 year-old was caught for doping in an amateur race. The rider for Team Marlis won a...

In Italy a 55 year-old was caught for doping in an amateur race. The rider for Team Marlis won a race in the category for 55 to 59 year-olds, but CONI, the Italian Olympic committee, announced that the amateur racer was caught for using stimulants, according to *La Gazzetta dello sport*. He is facing a suspension until he turns 57 as well as a revoking of his title.

USA TODAY

90-year-old cyclist stripped of world record after failed drug test

Dana Hunsinger Benbow | Indianapolis Star
Published 4:16 PM EST Jan 7, 2019

PARACYCLING

Sports	Disciplines	Urine						Blood						Sub Total	Total Samples	Total AAFs	% AAF
		IC			OOC			IC			OOC						
		Samples	ATF	AAF	Samples	ATF	AAF	Samples	ATF	AAF	Samples	ATF	AAF				
Cycling	Para-Cycling**	108	-	3	114	1	1	6	-	-	30	-	-	258	561	7	0.5%
	Para-Cycling Road**	126	1	3	79	-	-	-	-	-	7	-	-	212			
	Para-Cycling Track Sprint**	24	-	-	15	-	-	-	-	-	5	-	-	44			
	Para-Cycling Track Endurance**	27	-	-	8	-	-	2	-	-	-	-	-	37			
	CISS Cycling Road	6	-	-	-	-	-	-	-	-	-	-	-	6			
	CISS Cycling	4	1	-	-	-	-	-	-	-	-	-	-	4			

PROFESSIONAL CYCLING

Cycling	Road	6460	30	92	4123	39	18	407	-	-	569	-	1	11559	22,652	244	1.1%
	Cycling	2737	16	60	1880	34	11	176	-	1	293	-	-	5086			
	Mountain Bike	1719	7	33	354	1	2	27	1	-	87	-	-	2187			
	Track	908	3	12	384	3	1	43	2	-	65	-	-	1400			
	Cyclo-Cross	687	-	11	60	-	-	23	-	-	3	-	-	773			
	Track Endurance	374	2	2	172	2	-	9	-	-	37	-	-	592			
	Track Sprint	347	5	-	137	-	-	1	-	-	44	-	-	529			
	BMX	256	-	-	119	-	-	6	-	-	6	-	-	387			
	Trials	103	5	-	-	-	-	2	-	-	-	-	-	105			
	Indoor (Artistic, Cycle Ball) (R)	14	-	-	-	-	-	-	-	-	-	-	-	14			
	Artistic	4	-	-	7	-	-	-	-	-	-	-	-	11			
	Cycle-Ball	7	-	-	2	-	-	-	-	-	-	-	-	9			

AMATEUR CYCLING

Cycling	Amateur (R)	115	-	4	-	-	-	-	-	-	-	-	-	115	127	4	3.1%
	Military Cycling	12	-	-	-	-	-	-	-	-	-	-	-	12			

LIST OF PROHIBITED SUBSTANCES AND METHODS

ADVERSE ANALYTICAL FINDINGS

Table 1: Total Samples Analyzed (All Sports)*

A *Samples* Analyzed

Sport	Analyzed	*AAFs* [1]	(%)	*ATFs* [2]	(%)	*Total Findings* [3]	(%)
Olympic Sports [4]	196,581	1,634	0.83%	1,585	0.81%	3,219	1.64%
Non-Olympic Sports [5]	32,831	888	2.70%	320	0.97%	1,208	3.68%
Non-ADAMS Data [6]	73,957	1,287	1.74%	198	0.27%	1,485	2.01%
TOTAL	**303,369**	**3,809**	1.26%	**2,103**	0.69%	**5,912**	1.95%

Substance Group	Occurrences	% of all ADAMS reported findings
S1. Anabolic Agents	1728	50%
S6. Stimulants	528	15%
S5. Diuretics and Other Masking Agents	428	12%
S9. Glucocorticosteroids	215	6%
S4. Hormone and Metabolic Modulators	152	4%
S8. Cannabinoids	127	4%
S3. Beta-2 Agonists	115	3%
S2. Peptide Hormones, Growth Factors and Related Substances	98	3%
S7. Narcotics	21	1%
P2. Beta-Blockers	19	1%
M2. Chemical and Physical Manipulation	1	0.03%
P1. Alcohol	0	0%
M1. Enhancement of Oxygen Transfer	0	0%
TOTAL*	3432	

Is there a high-risk sport?

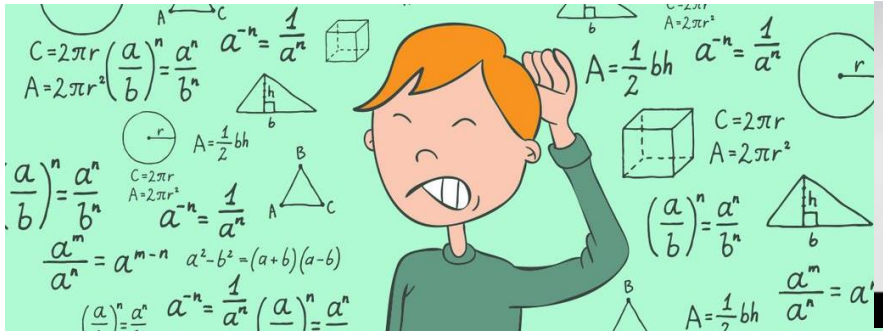
MENTAL (MATH) EXPERIMENT

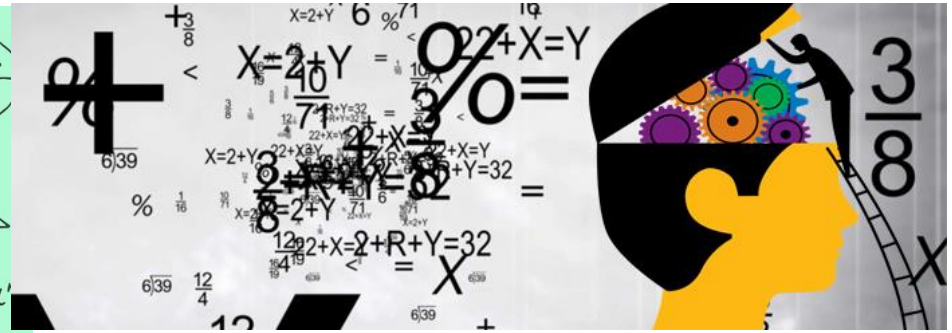
Sport A	Sport B
Prevalence=1%	Prevalence=1%
Testing program = 50,000 samples/year	Testing program = 1,000 samples/year
AAF = 500 samples (athletes)	AAF = 10 samples (athletes)

Which sport is more risky? Which sport has higher prevalence of doping?

MEDIA: Sport A. There are 500 athletes positive each year.

Relative value ≠ Absolute value





WORLD ANTI-DOPING AGENCY
play true

2010 *Adverse Analytical Findings and Atypical Findings* Reported by Accredited Laboratories

Table C Olympic Sport *Sample* Analysis

Sport	Total *Samples* per Sport	A *Sample Adverse Analytical Findings* [1]	A *Sample Atypical Findings* [2]	A *Sample* Total Findings [3]	% *Adverse Analytical Findings* [1]
Aquatics	**13,138**	**90**	65	155	**0.69%**
Archery	**1,156**	**17**	4	21	**1.47%**
Athletics	**25,013**	**196**	242	438	**0.78%**
Badminton	**1,250**	**3**	2	5	**0.24%**
Basketball	**9,575**	**139**	62	201	**1.45%**
Biathlon	**1,967**	**-**	18	18	**0.00%**
Bobsleigh	**1,214**	**2**	17	19	**0.16%**
Boxing	**3,874**	**75**	35	110	**1.94%**
Canoe / Kayak	**3,726**	**15**	35	50	**0.40%**
Curling	**477**	**3**	5	8	**0.63%**
Cycling	**21,427**	**254**	359	613	**1.19%**
Equestrian	**723**	**12**	5	17	**1.66%**
Fencing	**1,916**	**8**	20	28	**0.42%**
Football	**30,398**	**146**	257	403	**0.48%**
Gymnastics	**2,670**	**14**	19	33	**0.52%**
Handball	**4,141**	**37**	30	67	**0.89%**
Hockey	**2,275**	**30**	27	57	**1.32%**
Ice Hockey	**5,370**	**68**	63	131	**1.27%**
Judo	**4,068**	**46**	28	74	**1.13%**

Air Sports	**97**	**3**	-	3	3.09%
Bandy	**199**	**1**	3	4	0.50%
Baseball	**18,402**	**128**	89	217	0.70%
Baseball/Softball[4]	**302**	**6**	6	12	1.99%
Billiard Sports	**330**	**14**	1	15	4.24%
Boules	**304**	**13**	8	21	4.28%
Bowling	**347**	**2**	2	4	0.58%
Bridge	**50**	**3**	-	3	6.00%
Chess	**159**	**2**	2	4	1.26%
Cricket	**943**	**2**	1	3	0.21%
Dance Sport	**405**	**3**	1	4	0.74%
Floorball	**523**	**5**	5	10	0.96%
Golf	**1,619**	**33**	12	45	2.04%
Karate	**1,078**	**10**	7	17	0.93%
Korfball	**86**	**-**	1	1	0.00%
Life Saving	**331**	**3**	-	3	0.91%
Motorcycle Racing	**482**	**20**	5	25	4.15%

Number of AAF in the time period 2003 - 2013

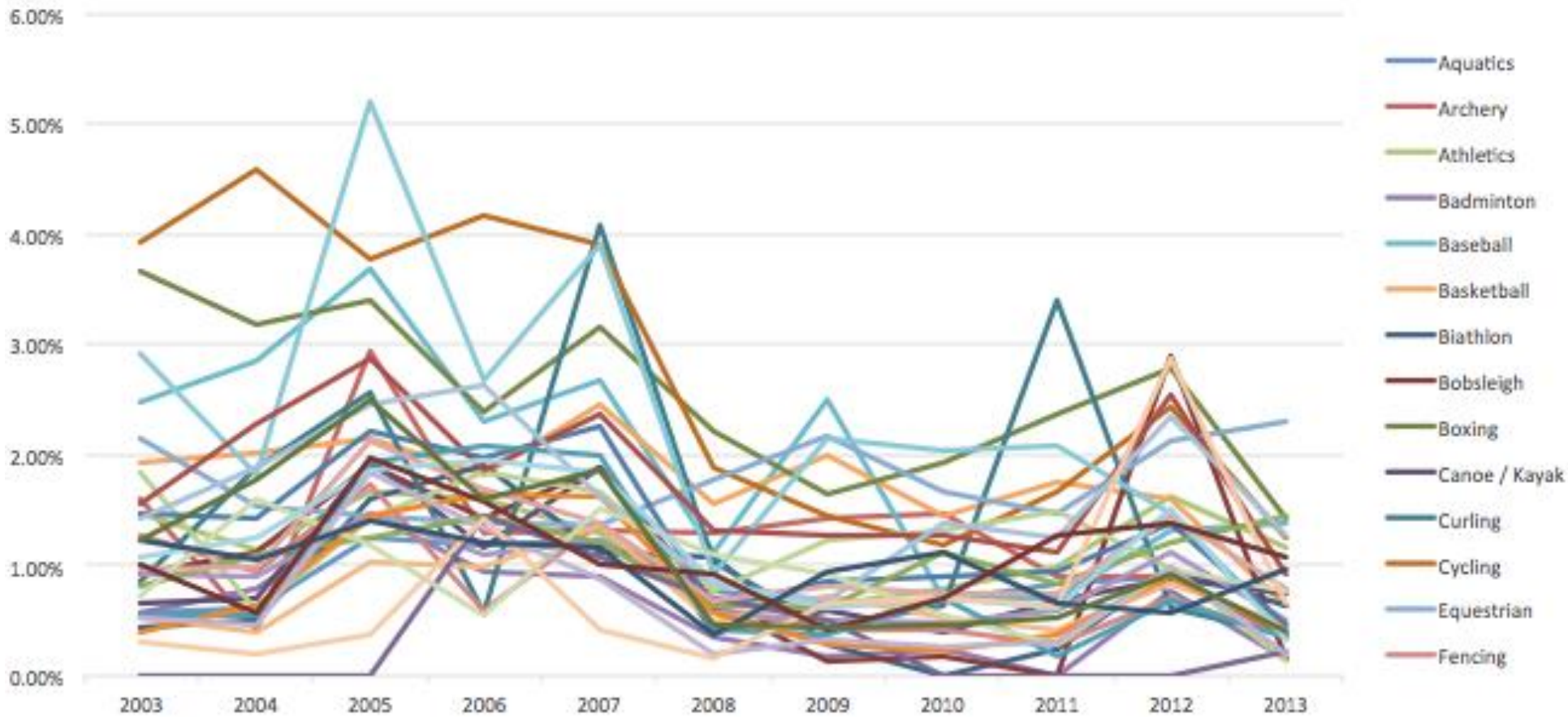


Table 3 Period prevalence of doping in various target groups using randomised response technique questionnaires

Publication	Target group	*n*	Prevalence of doping (%)
Pitsch et al. [79]	Adult elite	448	26–48 Ever; 20–39 Last year
Striegel et al. [72]	Junior elite	480	3–11 Ever
Simon et al. [81]	Fitness centre visitors	500	8–17 Ever
Stubbe et al. [80]	Fitness centre visitors	447	5–23 Last year

Table 4 Overview of estimates of the period prevalence of doping amongst elite athletes based on different analysis techniques

Analysis techniques	Estimated prevalence	Remarks
Doping control test results	1–2 % Last year [15]	Stable figure for the last 25 years. Not likely to reflect true intentional doping (see Sect. 2.1)
Population estimates based on biological value parameters	14 % Over 10 years [36]	Blood manipulations in elite athletes in athletics; data on other sorts of doping or sports modalities as yet unavailable (see Sect. 2.2)
Standard questionnaires	1–15 % [4, 45–59]	Mostly performed on adolescents and/or students; little research in elite sports (see Sect. 3.1)
Randomised response questionnaires	20–39 % Last year (adult) [79] 3–11 % Lifetime (junior) [72]	German athletes; data on other nationalities or sports modalities as yet unavailable (see Sect. 3.2)
Inferences from athletic performances	–	Popular input for doping-related discussions but impossible to reflect prevalence of doping (see Sects. 4.1, 4.2)
Inferences from ego documents	–	Give some insight into the sociological background of doping and perceived prevalence, but not true prevalence (see Sect. 5)

de Hon, O., et al. (2015). "Prevalence of doping use in elite sports: a review of numbers and methods." Sports Med **45**(1): 57-69.

LIST OF PROHIBITED SUBSTANCES AND METHODS

WADA – http://www.wada-ama.org **SLOADO – http://www.sloado.si**

How does a substance become prohibited?

What are the criteria for adding a substance to the List?

Must meet any 2 of the following 3 criteria:

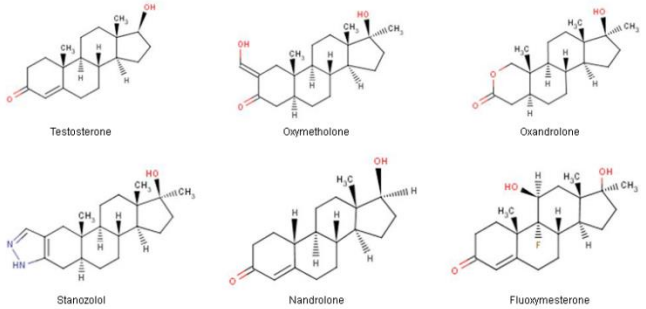
- It has the potential to enhance or enhances sport performance;
- It represents an actual or potential health risk to the athlete;
- It violates the Spirit of Sport.

One example: AAS

Most widely abused doping substances

S1. ANABOLIC AGENTS

Anabolic agents are prohibited.

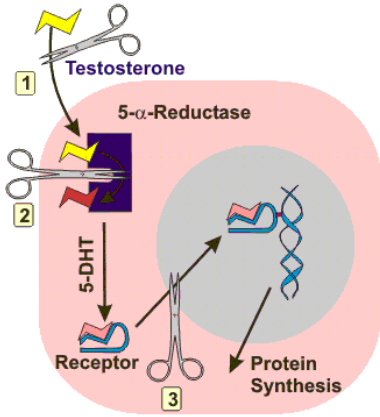


1. Anabolic Androgenic Steroids (AAS)

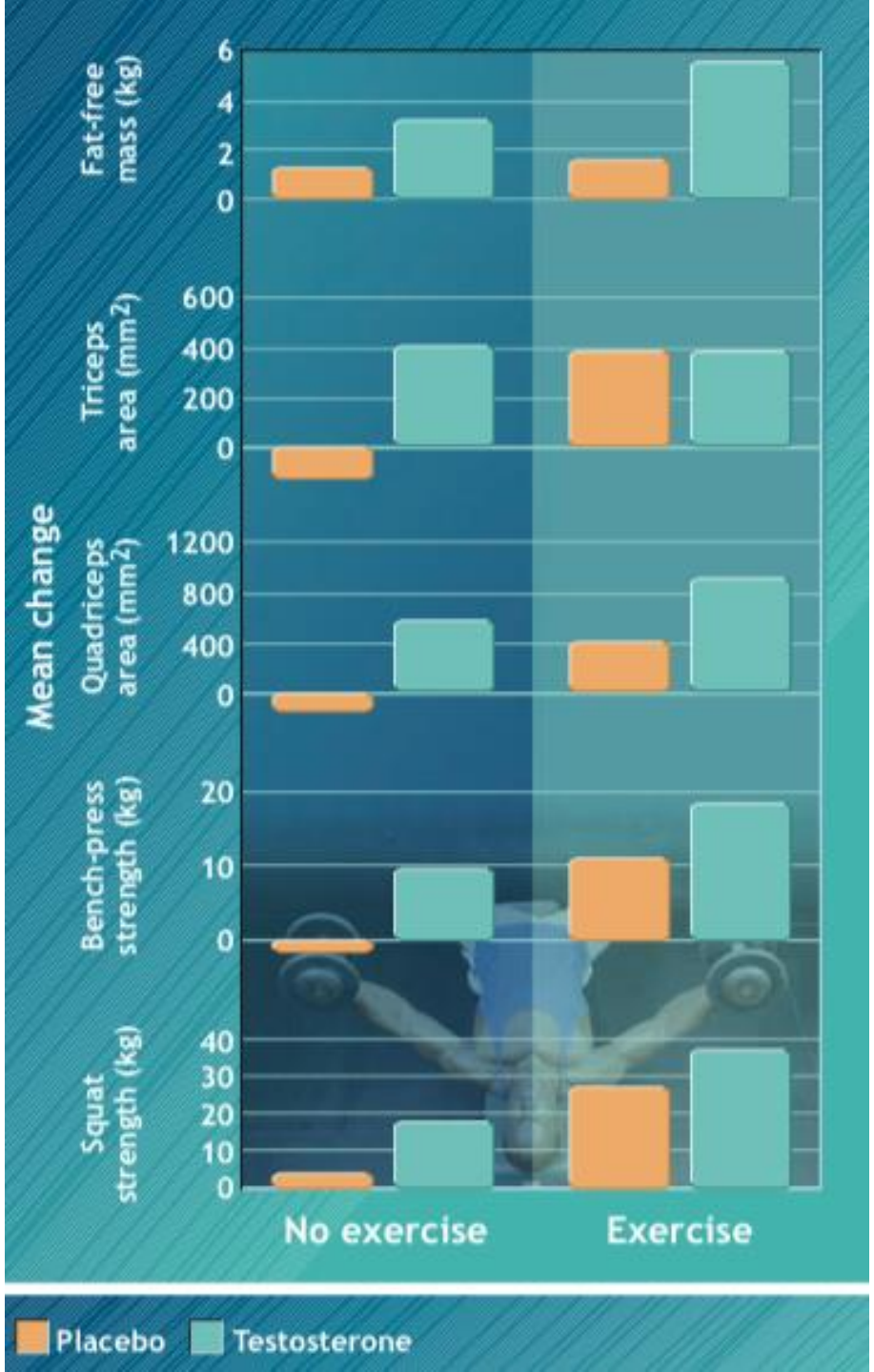
a. **Exogenous*** **AAS**, including:

1-androstenediol (5α-androst-1-ene-3β,17β-diol); **1-androstenedione** (5α-androst-1-ene-3,17-dione); **bolandiol** (estr-4-ene-3β,17β-diol); **bolasterone**; **boldenone**; **boldione** (androsta-1,4-diene-3,17-dione); **calusterone**; **clostebol**; **danazol** ([1,2]oxazolo[4',5':2,3]pregna-4-en-20-yn-17α-ol); **dehydrochlormethyltestosterone** (4-chloro-17β-hydroxy-17α-methylandrosta-1,4-dien-3-one); **desoxymethyltestosterone** (17α-methyl-5α-androst-2-en-17β-ol); **drostanolone**; **ethylestrenol** (19-norpregna-4-en-17α-ol); **fluoxymesterone**; **formebolone**; **furazabol** (17α-methyl [1,2,5]oxadiazolo[3',4':2,3]-5α-androstan-17β-ol); **gestrinone**; **4-hydroxytestosterone** (4,17β-dihydroxyandrost-4-en-3-one); **mestanolone**; **mesterolone**; **metandienone** (17β-hydroxy-17α-methylandrosta-1,4-dien-3-one); **metenolone**; **methandriol**; **methasterone** (17β-hydroxy-2α,17α-dimethyl-5α-androstan-3-one); **methyldienolone** (17β-hydroxy-17α-methylestra-4,9-dien-3-one); **methyl-1-testosterone** (17β-hydroxy-17α-methyl-5α-androst-1-en-3-one); **methylnortestosterone** (17β-hydroxy-17α-methylestr-4-en-3-one); **methyltestosterone**; **metribolone** (methyltrienolone, 17β-hydroxy-17α-methylestra-4,9,11-trien-3-one); **mibolerone**; **nandrolone**; **19-norandrostenedione** (estr-4-ene-3,17-dione); **norboletone**; **norclostebol**; **norethandrolone**; **oxabolone**; **oxandrolone**; **oxymesterone**; **oxymetholone**; **prostanozol** (17β-[(tetrahydropyran-2-yl)oxy]-1'H-pyrazolo[3,4:2,3]-5α-androstane); **quinbolone**; **stanozolol**; **stenbolone**; **1-testosterone** (17β-hydroxy-5α-androst-1-en-3-one); **tetrahydrogestrinone** (17-hydroxy-18a-homo-19-nor-17α-pregna-4,9,11-trien-3-one); **trenbolone** (17β-hydroxyestr-4,9,11-trien-3-one);

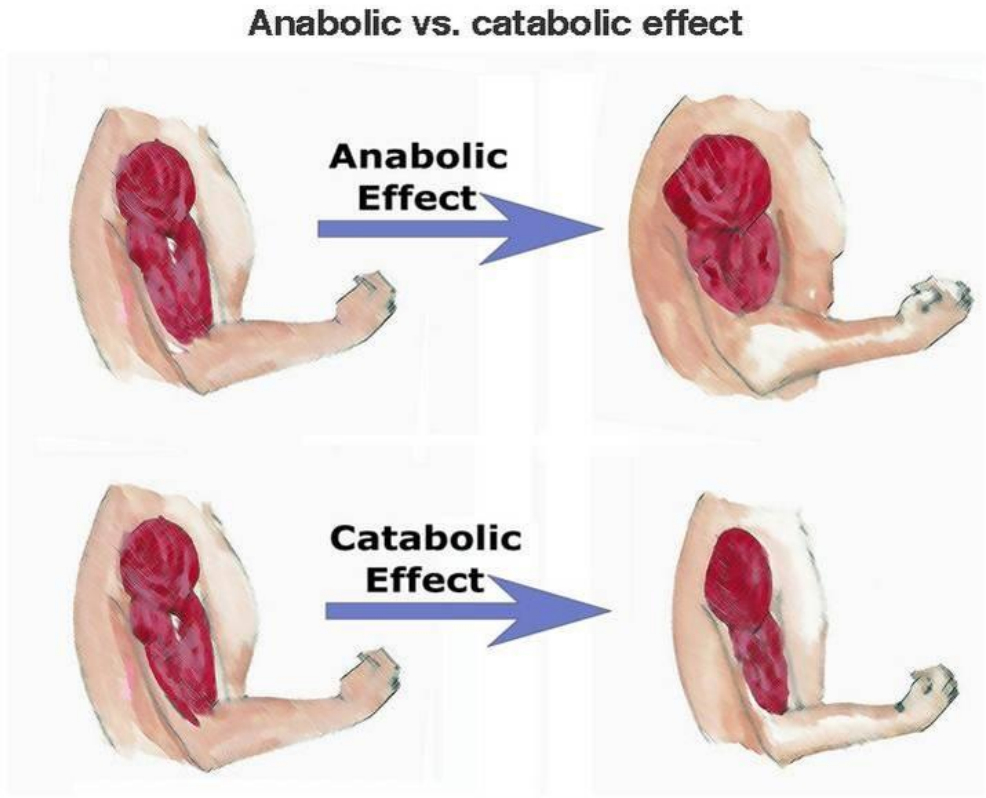
and other substances with a similar chemical structure or similar biological effect(s).



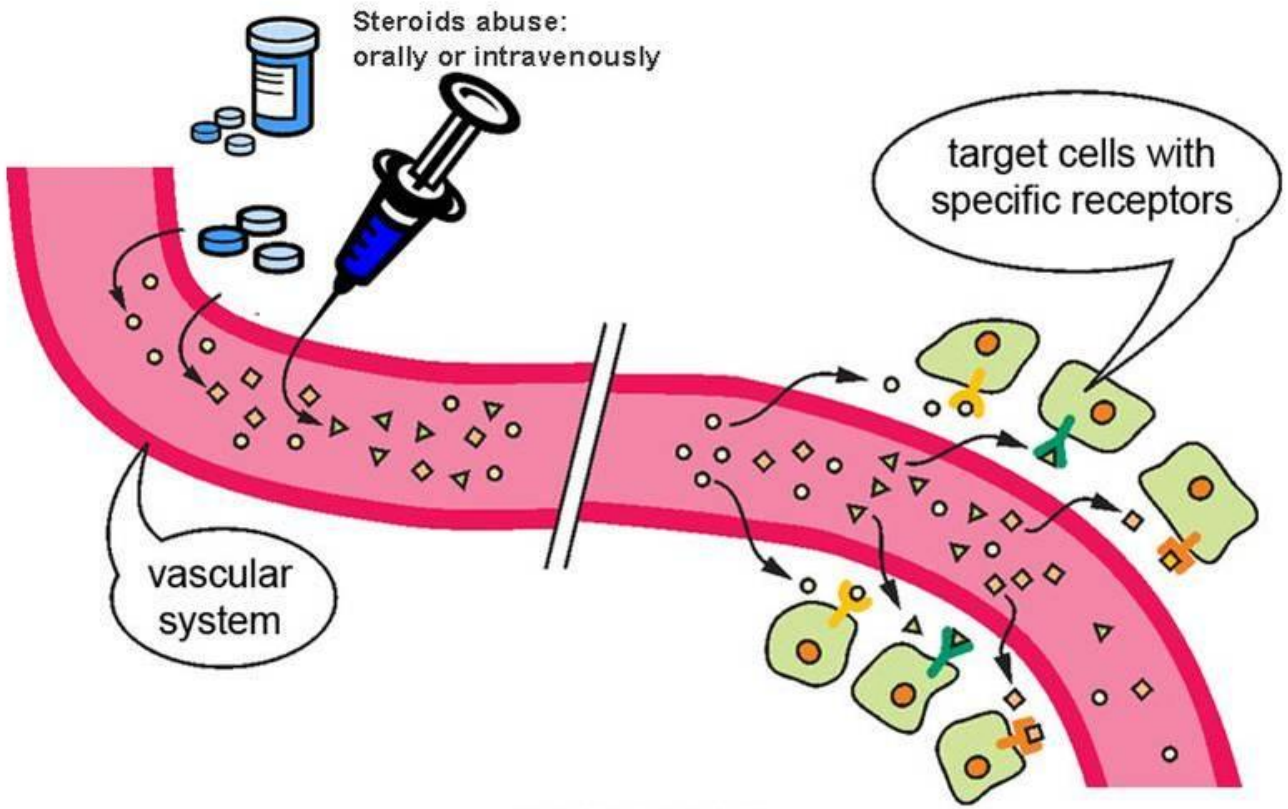
- "exogenous" refers to a substance which is not ordinarily produced by the body naturally.
- "endogenous" refers to a substance which is ordinarily produced by the body naturally.



10 weeks of testosterone use (Bhasin S, et al. N Engl J Med 1996; 335:1)

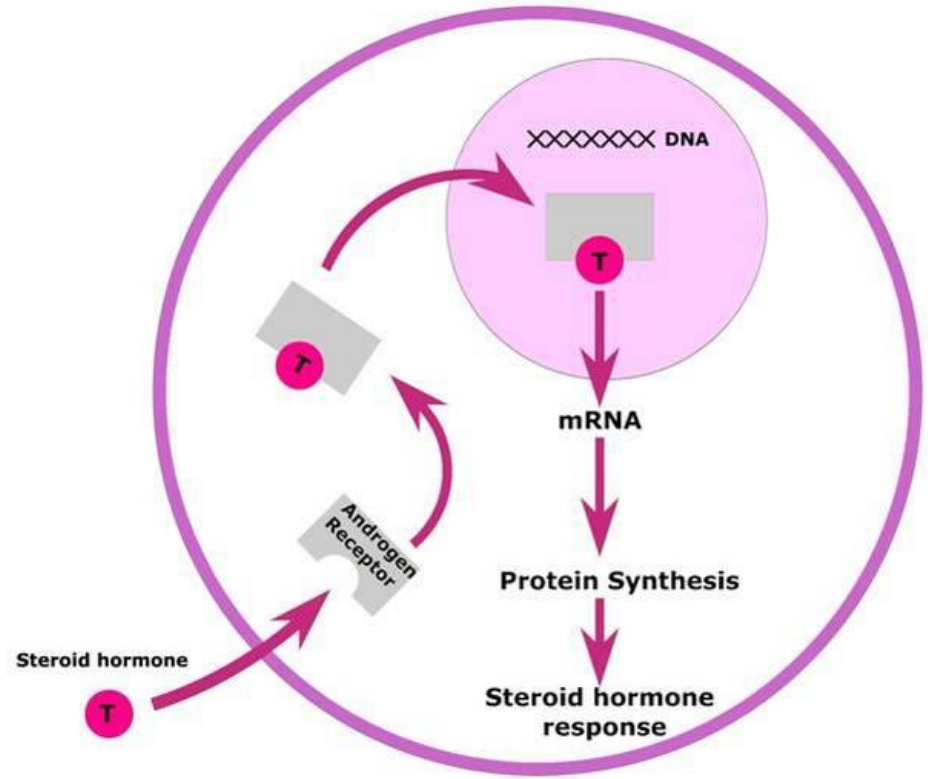


Mode of action I



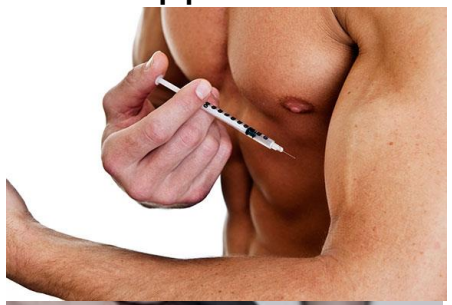
Müller-Esterl: Biochemie, 2004,
© Spektrum Akademischer Verlag, Heidelberg

Mode of action II



peroral application

intramuscular application



topical (scrotal patch) application

Biomedical side effects of anabolic androgenic steroids…

…on the skin

Anabolic androgenic steroids (AAS)

↓

Hypertrophy of sebaceous glands

↓

Sebum excretion ⇧

Skin surface lipids ⇧

Propionibacterium acnes ⇧

Acne by AAS abuse

Melnik, Jansen & Grabbe (2007): Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem. J Dtsch Dermatol Ges. 5 (2):110-117. © by courtesy of Wiley-Blackwell

Biomedical side effects of anabolic androgenic steroids…

…on the skin

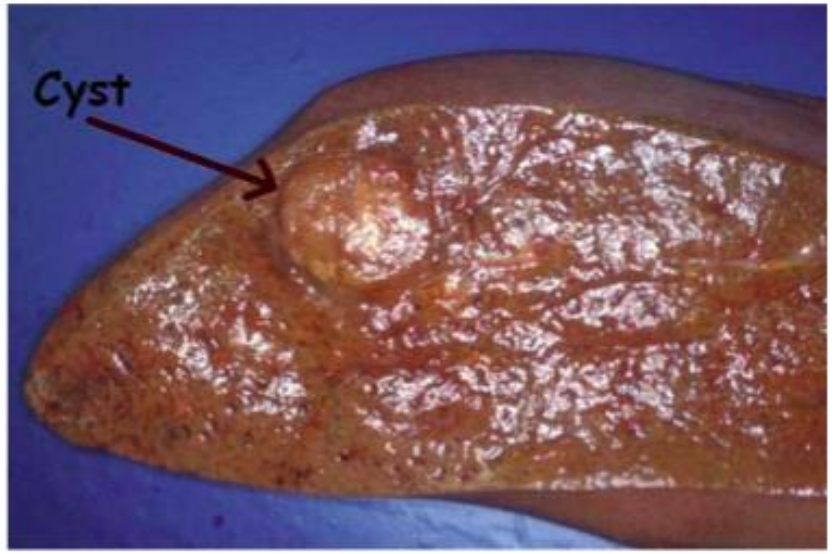
Intake of Anabolic androgenic steroids

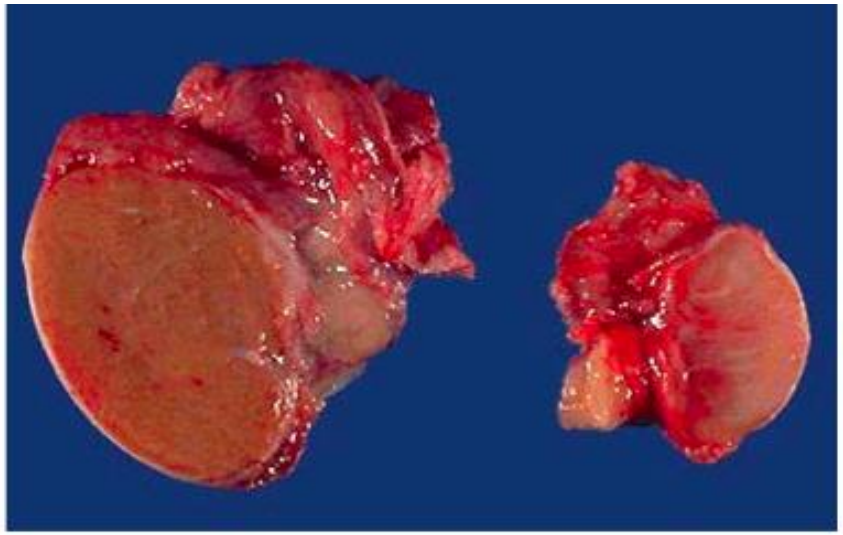
Striae distensae developing at places of strong skin stretching (e.g. shoulder, upper limb, breast or back)

*Karamfilov & Elsner (2002): Hautarzt, p98-103.
° Wollina et al. (2007): Acta Dermatoven APA, p117-122.

General side effects:

- Psychological dependence
- Increased aggression
- Mood swings
- Increased risk of liver disease
- Increased risk of cardiovascular disease
- High blood pressure



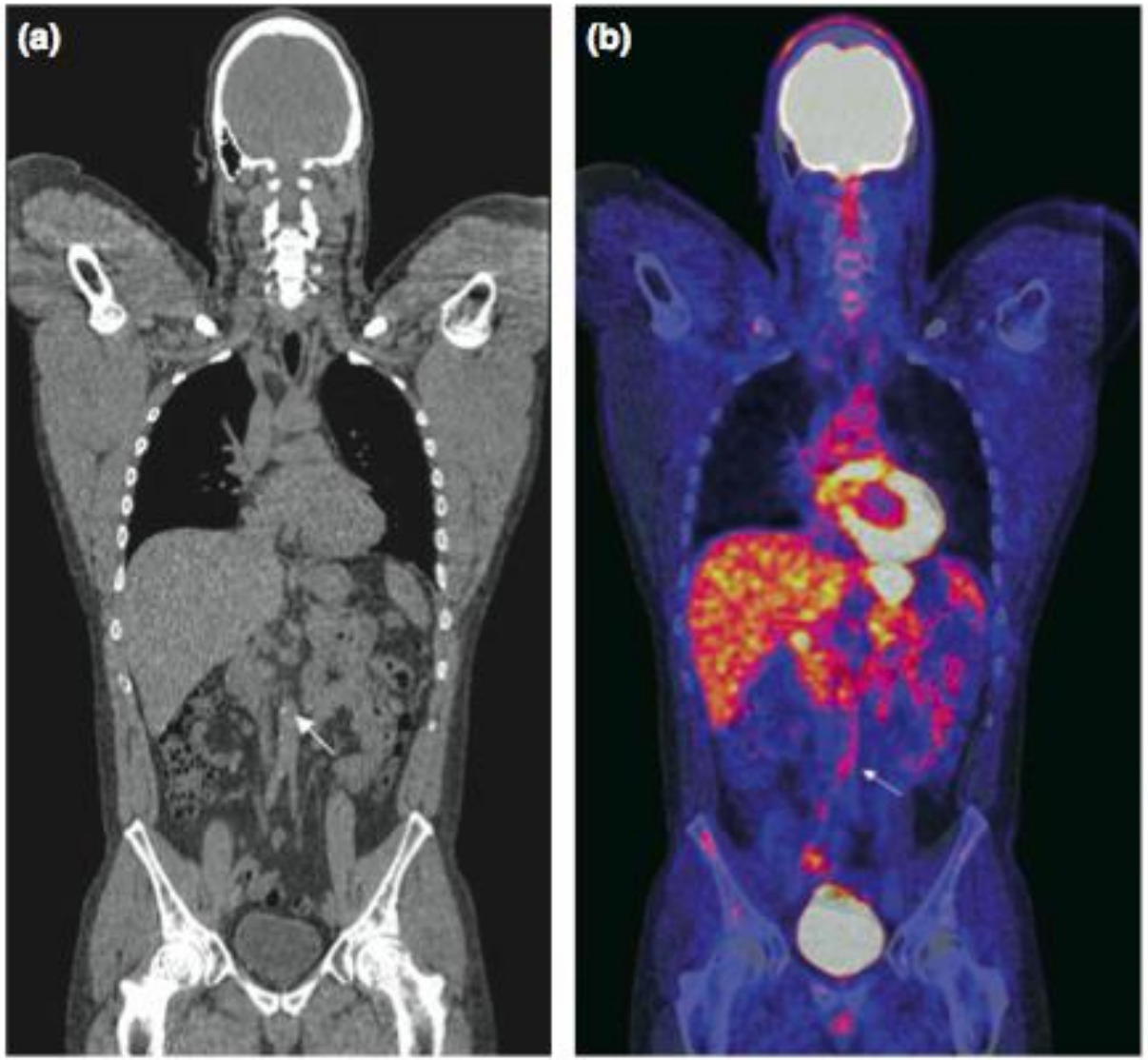


Side effects by an abuse on semen parameters

THE REVERSIBILITY OF ANDROGEN - INDUCED HYPOGONADISM IN A BODYBUILDER [Case Report]

Semen parameters	After 10 months abuse	5 months post cessation	10 months post cessation	Normal ranges
Volume (mL)	1.5	1.5	2.0	1.5 - 5.0
Sperm count (millions per mL)	0	3	20	>60
Motility (%)	0	6	30	>60
Normal morphology fraction (%)	0	13	42	>60
Testosterone ($nmol \cdot L^{-1}$)	0.54	1.25	20.58	8.7- 33

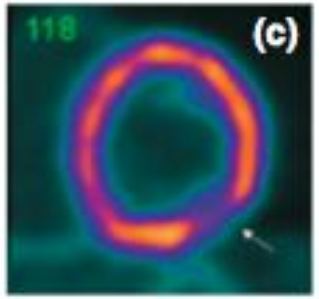
Boyadjev, Georgieva, Massaldjieva & Gueorguiev (2000): Reversible hypogonadism and azoospermia as a result of anabolic-androgenic steroid use in a bodybuilder with personality disorder. A case report. J Sports Med Phys Fitness, 40, p271-274



^{18}F-FDG PET/CT

40-years old bodybuilder with chronic application of AAS

- mild abdominal aortic atherosclerosis
- inferolateral infaction (occlusion of R coronary art.)



Golestani, R.; Slart, R. H. J. A.; Dullaart, R. P. F.; Glaudemans, A. W. J. M.; Zeebregts, C. J.; Boersma, H. H.; Tio, R. A.; Dierckx, R. A. J. O. Adverse cardiovascular effects of anabolic steroids: pathophysiology imaging. *European Journal of Clinical Investigation* **42**: 795–803; 2012.


GYNECOMASTIA

HIRSUTISM

Long-term Adverse Effects:

Cardiovascular toxicity:

- left ventricular hypertrophy, diastolic heart failure,
- arhythmias,
- hypertension,
- endotelial dysfunction, atherogenic lipid blood profile, increased development of atherosclerosis
- **higher risk of acute myocardial infarction and acute heart failure (acute heart arrest)**

Long-term Adverse Effects:

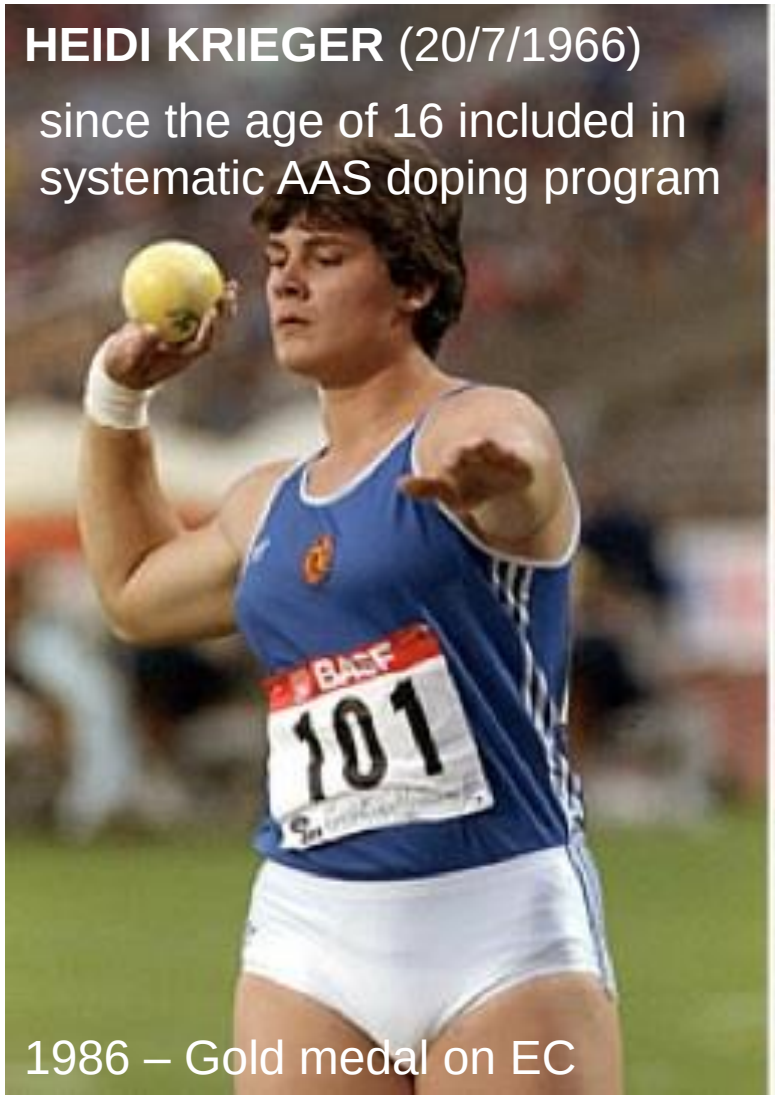
Higher incidence of cancer:

- primary liver neoplasms
- renal carcinoma
- testicular cancer
- prostate cancer.

RISK OF DEATH is for AAS users 4.6 x higher in comparison to the control group.

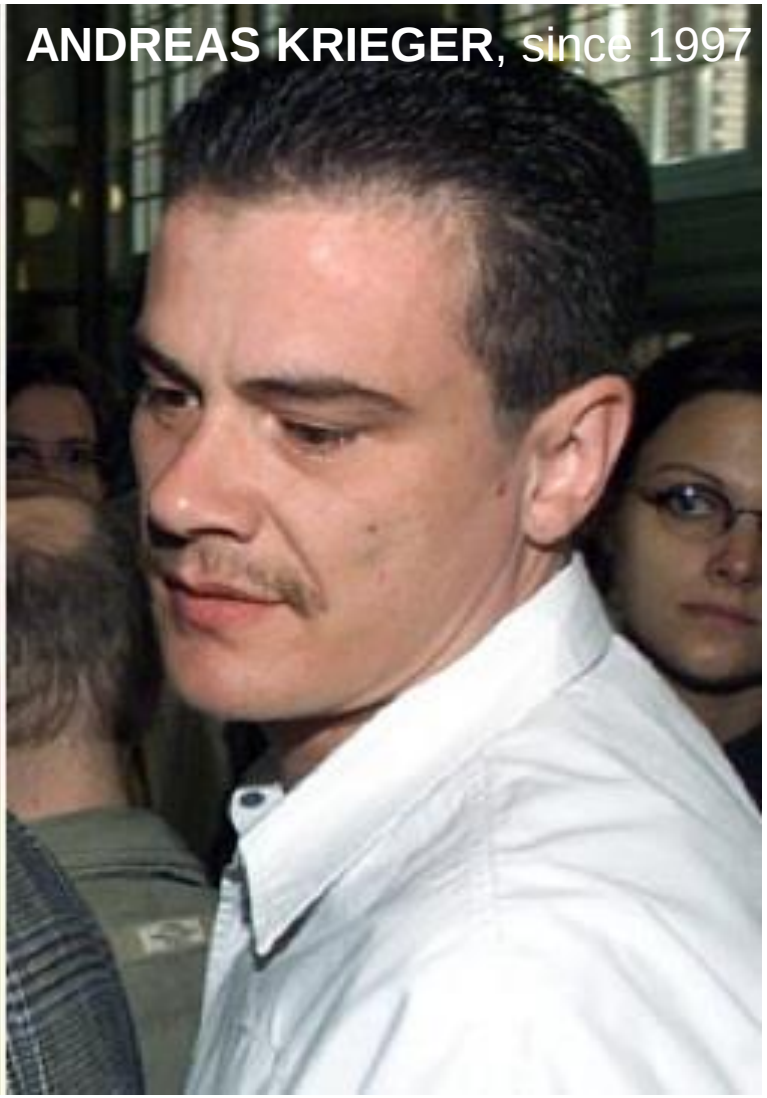
HEIDI KRIEGER (20/7/1966)

since the age of 16 included in systematic AAS doping program



1986 – Gold medal on EC

ANDREAS KRIEGER, since 1997



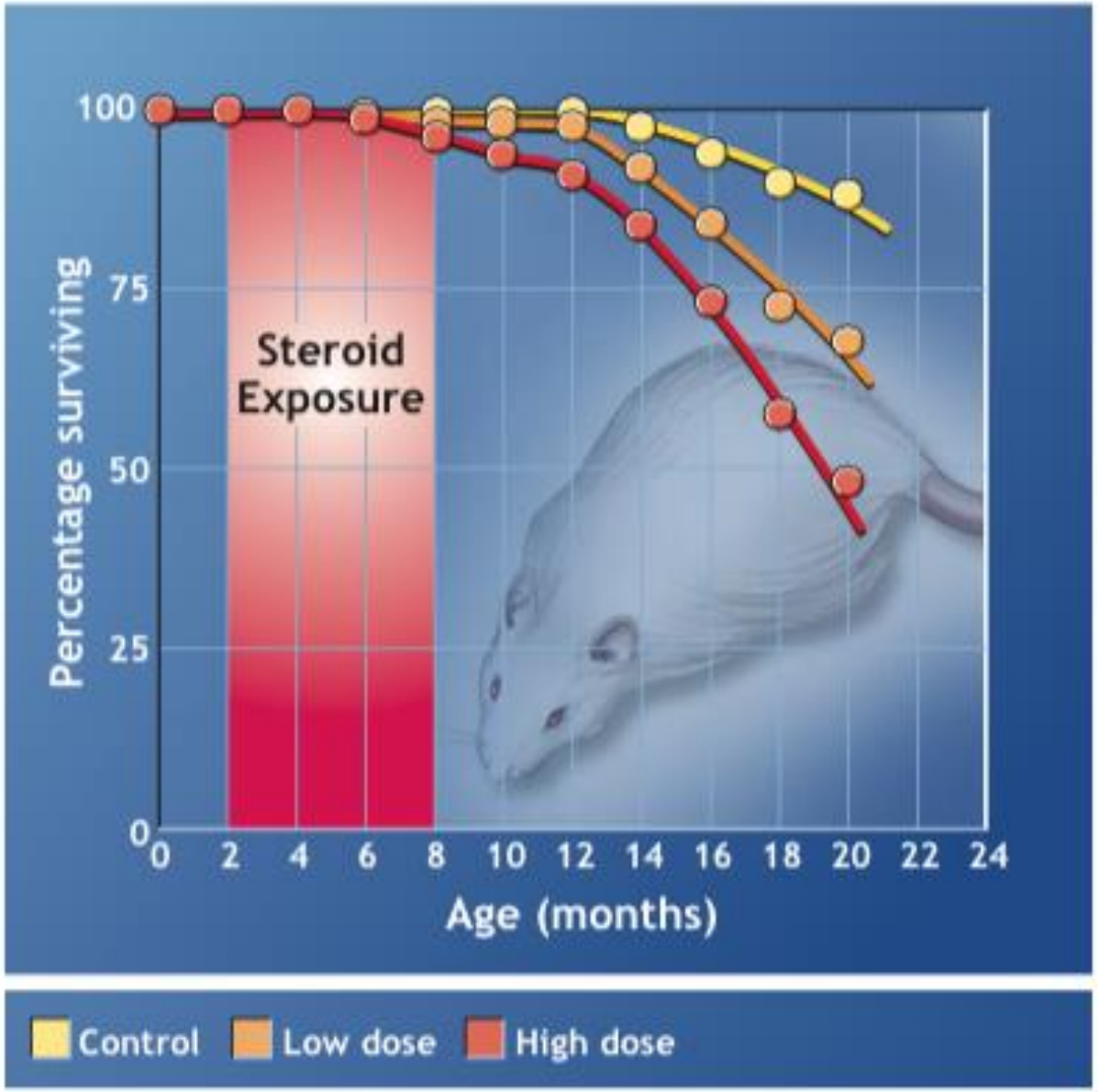


Figure 23.4 • Life-shortening effects of exogenous anabolic steroid use in mice. (Modified from Bronson FH, Matherne CM. Exposure to anabolic–androgenic steroids shortens life span of male mice. Med Sci Sports Exerc 1997;29:615.)

- shorter life span
- long-term consequences due to AAS use when ”young“
- 6-months of AAS use on mice - cca 20% of average mouse life span

Non-intentional / Accidental / Mistake vs. On Purpose?

INADVERTENT DOPING


KICKER VENCILL


CREDIT
LYONNAIS
le Tour de France
2005
LANCE ARMSTRONG

TESTED POSITIVE ON DOPING

- in 2003 tested positive due to the contamined nutriotional supplement: **multivitamins contained traces of 19-norandrosterone.**
- He lost his spot at US national team for **Olympic Games in 2004 in Athens**
- in 2005 he won $578,635 suit against the nutritional supplement producer: Ultimate Nutrition of Farmington, Conn.

NEVER TESTED POSITIVE ON DOPING

7 – times winner of Tour de France, world champion, Olympic medal winner

EPO, testosteron, cortikosteroids, hGH, blood doping

Assessment 20 m$/year -> 83.333 $/day
Source: http://www.best-reviewer.com

Scand J Med Sci Sports 2013: 23: 244–252
doi: 10.1111/j.1600-0838.2011.01374.x

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Gateway to doping? Supplement use in the context of preferred competitive situations, doping attitude, beliefs, and norms

S. H. Backhouse[1], L. Whitaker[1], A. Petróczi[2,3]

[1]Carnegie Research Institute, Leeds Metropolitan University, Leeds, United Kingdom, [2]Faculty of Life Sciences, Kingston University, Kingston, UK, [3]Sheffield University, Sheffield, UK
Corresponding author: Susan H. Backhouse, PhD, Carnegie Research Institute, Leeds Metropolitan University, Headingley Campus, Leeds, LS6 3QS, UK. Tel: +44 (0)113 812 4684, E-mail: s.backhouse@leedsmet.ac.uk

Accepted for publication 20 June 2011

Nutritional supplement (NS) use is widespread in sport. This study applied an integrated social cognitive approach to examine doping attitudes, beliefs, and self-reported doping use behavior across NS users ($n = 96$) and nonusers ($n = 116$). Following ethical approval, 212 competitive athletes (age mean = 21.4, s = 4.5; 137 males) completed self-reported measures of doping-related social cognitions and behaviors, presented in an online format where completion implied consent. Significantly more NS users (22.9%) reported doping compared with nonusers (6.0%; $U = 4628.0$, $P < 0.05$). NS users presented significantly more positive attitudes toward doping ($U = 3152.0$, $P < 0.05$) and expressed a significantly greater belief that doping is effective ($U = 3152.0$, $P < 0.05$). When presented with the scenario that performance-enhancing substances are effective and increase the possibility of winning, NS users were significantly more in favor of competing in situations that allow doping ($U = 3504.5$, $P < 0.05$). In sum, doping use is three-and-a-half times more prevalent in NS users compared with nonusers. This finding is accompanied by significant differences in doping attitudes, norms, and beliefs. Thus, this article offers support for the gateway hypothesis; athletes who engage in legal performance enhancement practices appear to embody an "at-risk" group for transition toward doping. Education should be appropriately targeted.

MULTI-SUPPLEMENT USERS ?

Table 2: Prevalence of multiple supplements use in the full sample (n = 874) and among supplement users (n = 520)

Number of supplements reported	% of all athletes	% of all supplement users
None	40.2	
1 supplement	10.4	17.4
2 supplements	14.2	23.7
3 supplements	12.9	21.6
4 supplements	9.8	16.4
5 supplements	5.6	9.4
6 supplements	3.2	5.4
7 supplements	1.8	3.1
8 supplements	1.0	1.7
9 supplements	0.8	1.3

around 60% of athletes are using NS

Somerville SJ, Lewis M, Kuipers H. Accidental breaches of the doping regulations in sport: is there a need to improve the education of sportspeople? Br J Sports Med. 2005Aug.;39(8):512–516.

RISK FOR INADVERTENT DOPING

- strict-liability of the athlets in accordance with WADA (World Anti-Doping Agency) code:

"athletes remain responsible for substances detected in their biofluids, irrespective of their origin"

REGULATIVE CHALLENGES

- A **dietary supplement** **is not reviewed pre-market** and does not have to be proven safe in order to be sold on the shelves of a store.”

- In USA: in 2004 – 2012 FDA removed 237 nutritional supplements from the market

Nutritional supplement can come to the market without being tested for SAFETY or EFFICACY.

Recall -- Firm Press Release

FDA posts press releases and other notices of recalls and market withdrawals from the firms involved as a service to consumers, the media, and other interested parties. FDA does not endorse either the product or the company.

SmartLipo365 Issues Voluntary Nationwide Recall of Smart Lipo Due to Undeclared Sibutramine, Desmethylsibutramine, and Phenolphthalein

Contact:
Consumer:
1-(800)-547-6365

FOR IMMEDIATE RELEASE — June 3, 2015 — Dallas, TX, SmartLipo365 is voluntarily recalling 122 lots of Smart Lipo (800, 900, 950 mg) capsules, to the consumer level. FDA received samples of 800 and 900mg capsules of Smart Lipo and the lab

Problems of contaminated NS

1. producers **don‘t specify ingredients properly**

2. **cross-contamination** with prohibited substances (company working with other substances using same equipment)

3. **Intentional addition of pharmacologically-effective substances** to get better results

Table 1. Nutritional supplements cross-contaminated with anabolic-androgenic steroids (prohormones) in different countries in 2001/2002[23,24]

Country	No. of analyzed products	No. of cross-contaminated products	Percentage of cross-contaminated products
Netherlands	31	8	25.8
Austria	22	5	22.7
UK	37	7	18.9
USA	240	45	18.8
Italy	35	5	14.3
Spain	29	4	13.8
Germany	129	15	11.6
Belgium	30	2	6.7
France	30	2	6.7
Norway	30	1	3.3
Switzerland	13	–	–
Sweden	6	–	–
Hungary	2	–	–

WHICH PROHIBITED SUBSTANCES?

- stimulants
- precursors of anabolic steroid hormones
- anabolic-androgenic steroids
- β2-agonists

Case study: NS product CREATINE

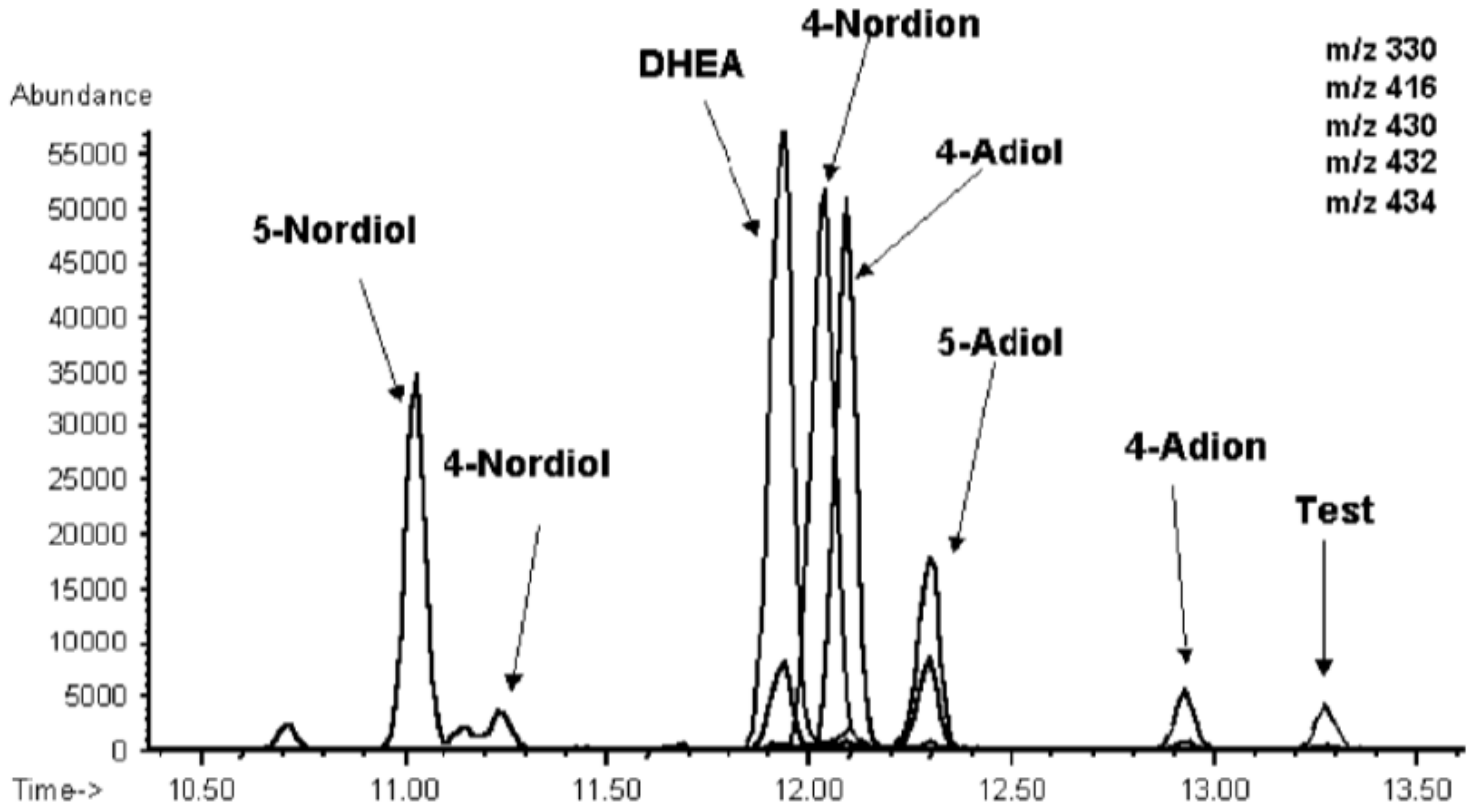


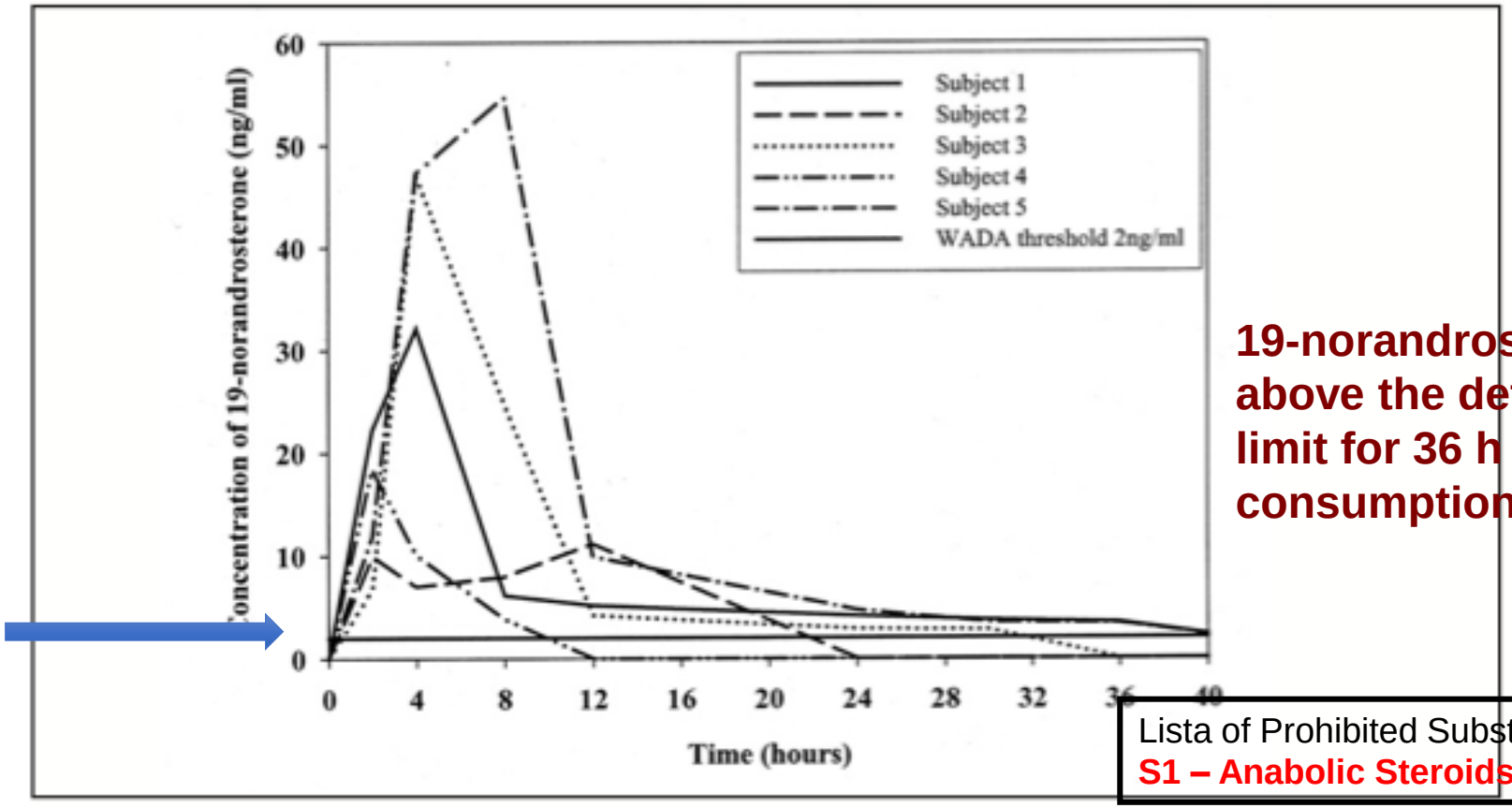
Figure 2. SIM-chromatograms of a creatine product with seven prohormones and testosterone not declared on the label (all steroids are pertrimethylsilylated)[22] 5-nordiol: 19-nor-5-androstene-3β,17β-diol, 4-nordiol: 19-nor-4-androstene-3β,17β-diol, DHEA: dehydroepiandrosterone, 4-nordion: 19-nor-4-androstene-3,17-dione, 4-adiol: 4-androstene-3β,17β-diol, 5-adiol: 5-androstene-3β,17β-diol, 4-adion: 4-androstene-3,17-dione, test: testosterone.

Contamined creatine product contained **7 steroid precursors and testosterone**

Geyer H, Parr MK, Koehler K, Mareck U, Schänzer W, Thevis M. Nutritional supplements cross-contaminated and faked with doping substances. J Mass Spectrom. 2008Jul.;43(7):892–902.

CAN ATHLETE TEST POSITIVE?

WADA detection limit for adverse analytical finding



19-norandrosterone above the detection limit for 36 h after consumption

Lista of Prohibited Substances:
S1 – Anabolic Steroids

Fig. 1. Urinary concentrations of 19-norandrosterone in 5 male volunteers after administration of a contaminated nutritional supplement.

van der Merwe PJ, Grobbelaar E. Unintentional doping through the use of contaminated nutritional supplements. S. Afr. Med. J. 2005Jul.;95(7):510–1.

CAN ATHLETE TEST POSITIVE?

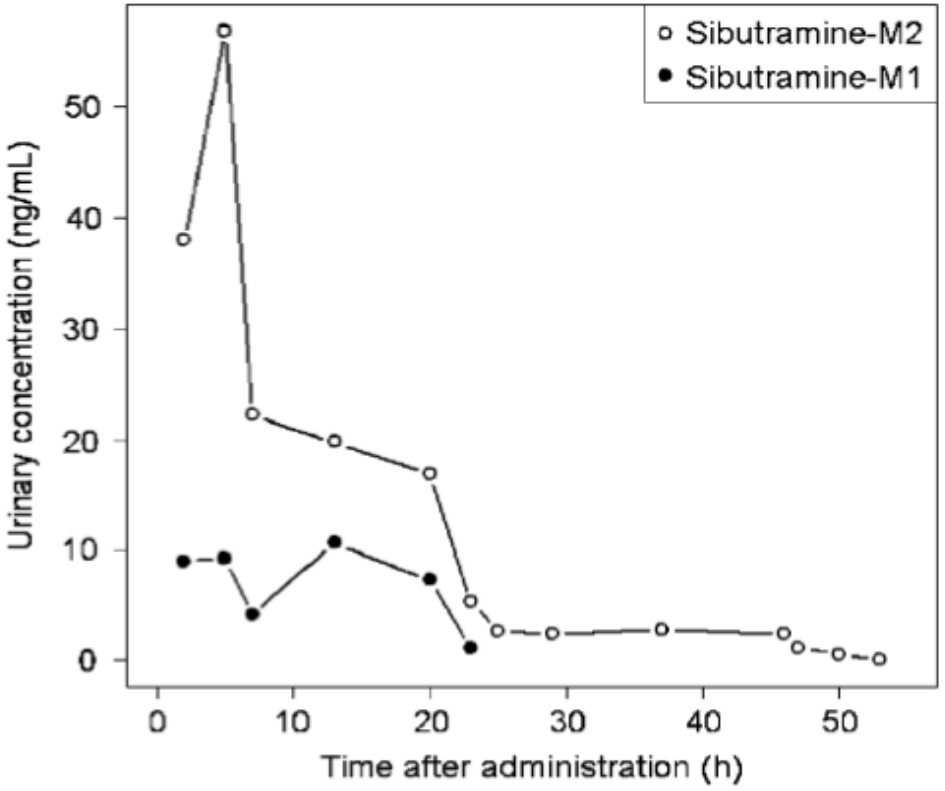


Figure 1. Urinary excretion of sibutramine metabolites following the consumption of faked Chinese slimming tea[19] sibutramine-M1: desmethyl sibutramine, sibutramine-M2: bisdesmethyl sibutramine.

Chinese herabl tea for weight loss contaminated with sibutramine

Lista of prohibited substances:
S6 - STIMULANTS

Geyer H, Parr MK, Koehler K, Mareck U, Schänzer W, Thevis M. Nutritional supplements cross-contaminated and faked with doping substances. J Mass Spectrom. 2008Jul.;43(7):892–902.

Supplement 411

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Supplement Dilemma | Challenge The Reasons | Why Risk Exists | Reduce The Risk

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Supplements

Understand the issues

Learn to reduce risk

Make an informed decision

Start Tutorial Here

NEWS

10/4/2012
Dozens of dietary supplements are illegally labeled
Associated Press

10/2/2012
Questioning the Superpowers of Omega-3 in Diets
Wall Street Journal

10/1/2012
To supplement or not, that is the question
Macon Telegraph

ADDITIONAL RESOURCES

Supplement Bottle

In this section, viewers will get an in-depth look at a hypothetical dietary supplement bottle and explore the real-life issues associated with dietary supplement packaging.

High Risk Dietary Supplement List

By submitting this form the user agrees to receive the USADA high risk dietary supplement list as well as follow-up correspondence regarding the list.

Updated August 17, 2012 - Not a Complete List

Products that have been tested and shown to contain prohibited substances.

Brand Name	Company	What the label says:	Prohibited List Classification	Test Results show:
11-OXO (Lot EL40)	ErgoPharm		S1. Anabolic Agents	Contains 4-androstendione and turinabol
3 Test OXO (Lot # PB0079712)	Complete Nutrition	Label lists a variety of herbals including tribulus terrestris, maca extract, saw palmetto berry, and others.	S1. Anabolic Agents and S6. Stimulants	Contains dehydroepiandrosterone, progesterone, cathine, epehdrine, methylhexaneamine, octopamine, psuedoephedrine
Andro-XS (Lot not specified)	Sports One Nutrition	4-chloro-17α-methyl-andro-4-ene-3β,17β-diol	S1. Anabolic Agents	Contains turinabol
Craze (Lot 1202487)	Driven Sports	N,N-Dimethyl-B-Phenylethylamine	S6. Stimulants	Contains amphetamine; N-methylphenethylamine, beta-methylphenethylamine, ethylamphetamine
Decabolen (Lot 0906162)	CTD Labs	4-chloro-17α-methyl-andro-4-ene-3β,17β-diol ; 2α17α-dimethyl-5 α-androstan-3-one	S1. Anabolic Agents	Contains 4-chloro-17α-methyl-andro-4-ene-3β,17β-diol was not detected in the product but methasterone (2α17α-dimethyl-5 α-androstan-3-one) and its isomer
DR1 (Lot# PB0079412)	Complete Nutrition		S1. Anabolic Agents and S6. Stimulants	Contains 4-Androsten-3,6,17-trione, formestane, 4-Androstenedione, drostanolone, 4-Androsten-3ß,17a-diol, 4-Androsten-3a,17ß-diol, cathine, ephedrine, methylephedrine, N-methylphenethylamine, psuedoephedrine.
Dual Action Grow Tabs (Lot CW-68)	IDS		S1. Anabolic Agents	Contains 1- androstenedione, 4-androstenedione, methandione, turinabol.
E-911 (Lot #9164)	LG Sciences		S6. Stimulants	contains methylsynephrine, octopamine

Cologne List

The Cologne List supports the assessment of a certain nutritional supplement by athletes, coaches and sport medicine specialists. The Cologne List and respectively the Olympic Centre Rhineland do not take on any responsibility using a product published on the Cologne List. The ultimate responsibility remains with each athlete.

Please note:
Neither the fact that a product is published on the Cologne List nor a negative laboratory analysis is a warranty that the product does not contain any prohormones, anabolic substances, or stimulants. The Cologne List only ascertains that listed products are associated with a minimized risk of doping.

Search in list ▸

Kölner Liste – Serviceplattform des OSP Rheinland

Product »	Product category »	Company »	Last analysis Prohormones »	Last Analysis Stimulants »
Vitalis Langzeitvitamintablette A-Z Balance	Other (miscellaneous) products	PHARCONA GmbH	20.08.2012	20.08.2012
Vitalis Langzeitvitamintablette A-Z Generation 50+	Other (miscellaneous) products	PHARCONA GmbH	20.08.2012	20.08.2012
Vitalis Magnesium-Liquide Orangengeschmack	Other (miscellaneous) products	PHARCONA GmbH	14.02.2012	14.02.2012
Vitalis Magnesium 250 mg + Vitamin E-Sticks	Mineral nutrients and trace elements	ALDI Einkauf GmbH & Co. OHG	29.08.2012	29.08.2012
Vitalis Magnesium 350mg + Vitamin C Brausetablette	Other (miscellaneous) products	ALDI Einkauf GmbH & Co. OHG	20.03.2012	20.03.2012
Vitalis Magnesium Tabletten	Other (miscellaneous) products	PHARCONA GmbH	20.08.2012	20.08.2012
Vitalis Multivitamin Brausetablette	Other (miscellaneous) products	ALDI Einkauf GmbH & Co. OHG	20.03.2012	20.03.2012

Overview | Formula Comparison | Frequently Asked Questions | Reviews | Supplement Facts

Super-Concentrated Pre-Workout Stimulant

Introducing the 2nd generation NeuroCore™ super-concentrated formula with new powerful ingredients and a new and improved great taste. Engineered to redefine extreme energy, intense focus, enhanced muscle strength and powerful muscle pumps, NeuroCore helps you shatter your limits and push past your plateaus. It's packed with precise doses of scientifically studied, fully disclosed key ingredients, including a newly added energy and focus complex to bring an added edge to any hardcore training session.

Compare us to the competition **right now**.

Neurocore MuscleTech Geranium Extract (Geranium robertianum, aerial parts)
Methylhexaneamine, **S6. Stimulants**

MUSCLE

NeuroCore contains 3200mg of beta-alanine – the exact dose scientifically shown to help enhance the muscle- and strength-building process.

STRENGTH

A highly potent and unique creatine known as creatine HCl has been infused into the formula. Creatine is clinically validated to amplify gains in size and strength.

PUMP

NeuroCore™ is formulated with a research-tested dose of pure L-citrulline instead of L-arginine or L-arginine AKG for intense, long-lasting muscle pumps. L-citrulline has actually been shown in research on nitric oxide metabolism to reach superior peak plasma arginine levels compared to a larger dose of L-arginine.

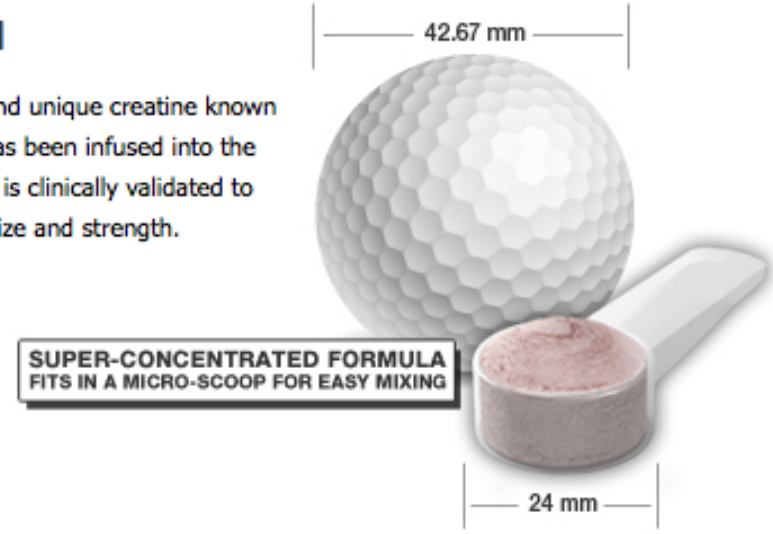

IMAGE NOT ACTUAL SIZE

ENHANCED SENSORY EXPERIENCE

A potent yohimbe bark extract has been added to NeuroCore™. This extract supplies rauwolscine and yohimbine, which are categorized as selective alpha-2 receptor antagonists. Human research indicates that blocking alpha-2 receptors may play a significant role in supporting blood flow.

The Facts Don't Lie

Many pre-workout concentrates do not disclose the ingredient amounts in their formulas, so we tested their formulas and discovered that they're underdosed when it comes to the latest scientific research – and we have the third-party lab tests to back it up.

NeuroCore		Competitor #1	Competitor #2	What You Should Know
Ingredient Amounts Fully Disclosed	**YES**	NO	NO	Unlike the competitors who do not disclose the ingredient amounts in their formulas, NeuroCore is different. The doses of its clinically validated and scientifically tested ingredients are fully disclosed so you know exactly what you are getting.

1 Schwedhelm et al., 2007. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. *Br J Clin Pharmacol.* 65(1):51-59.

2 Campbell et al., 2006. Pharmacokinetics, safety and effects on exercise performance of L-arginine alpha-ketoglutarate in trained adult men. *Nutrition.* Sep;22(9):872-81.

3 Greer et al., 2011. Acute arginine supplementation fails to improve muscle endurance or affect blood pressure response to resistance training. *J Strength Cond Res.* July;25(7):1789-94.

4 Hoffman et al., 2006. Effect of creatine and beta-alanine supplementation on performance and endocrine responses in strength/power athletes. *Int J Sport Nutr Exerc Metabol.* 16:430-46.

5 Goldstein et al., 2010. International society of sports nutrition position stand: caffeine and performance. *J Int Soc Sports Nutr.* 7(1):5.

6 Owen et al., 2008. The combined effects of L-theanine and caffeine on cognitive performance and mood. *Nutr Neurosci.* 11(4):193-198.

7 Spasov et al., 2000. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-5 extract on the fatigue of students caused by stress during an examination period with repeated low-dose regimen. *Phytomedicine.* 7(2):85-89.

8 Panossian et al, 2005. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. *Phytother Res.* 19(10):819-38.

Frequently Asked Questions

What can I expect to feel on NeuroCore?

NeuroCore is a super-concentrated pre-workout performance-enhancing stimulant formulated to deliver intense energy, mental focus, increased muscle and strength and awesome muscle pumps for an outstanding training experience.

CARDIOTOXICITY – ACUTE MYOCARDIAL INFARCTION

News › UK news

DMAA supplement linked to marathon runner's death is still on sale online

Stimulant taken by Claire Squires before she died during marathon is legally available in UK through overseas websites

CASE REPORT

Cardiac Arrest in a 21-Year-Old Man After Ingestion of 1,3-DMAA–Containing Workout Supplement

Lioudmila V. Karnatovskaia, MD, Juan C. Leoni, MD,† and Michelle L. Freeman, MD**

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Case Reports

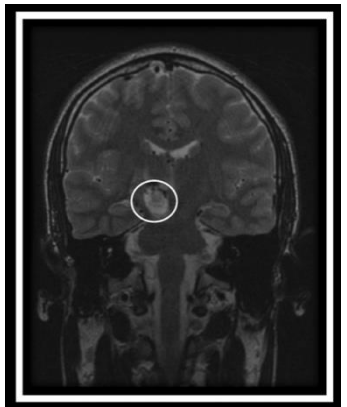
Acute Myocardial Infarction Associated with Dietary Supplements

Containing 1,3-Dimethylamylamine and *Citrus aurantium*

Triston B. Smith, MD
Brian A. Staub, MD
Gayathri M. Natarajan, MD
David M. Lasorda, DO
Indu G. Poornima, MBBS

We describe the case of a previously healthy 22-year-old man who presented with anginal chest pain and was diagnosed with a non-ST-elevation myocardial infarction. For 3 weeks, he had been ingesting the dietary supplements Jack3d® (principal ingredient, 1,3-dimethylamylamine) and Phenorex™ (principal ingredient, Citrus aurantium*) daily, before undertaking physical activity. Coronary angiograms revealed a proximal left anterior descending coronary artery thrombus with distal embolization. A combined medical regimen led to resolution of the thrombus. Three months later, the patient was asymptomatic with no evidence of ischemia.*

The primary ingredients in the sympathomimetic supplements taken by our patient are controversial in the medical community and have been individually associated with adverse cardiac events. There are no safety data on their simultaneous use. We discuss other reports of adverse effects associated with these supplements and recommend that the relevant safety guidelines be revised. ***(Tex Heart Inst J 2014;41(1):70-2)***



contaminant **1,3-dimetilamilamin (DMAA) – sympaticomimetic activity**

MILITARY MEDICINE, 177, 12:1450, 2012

Hemorrhagic Stroke in Young Healthy Male Following Use of Sports Supplement Jack3d

LT Colin Young, MC USN; LT Olamide Oladipo, MC USN†; ENS Samuel Frasier, MC USN‡; ENS Robert Putko, MC USN‡; LT Stacy Chronister, MC USN§; Mary Marovich, MD, DTMH, FACP‖*

HEPATOTOXICITY – ACUTE LIVER FAILURE

- Hawaii Department of Health (HDOH) in period May – October 2013 evaluated **29 acute hepatitis (acute liver failures)** related to the use of OxyElitePro
- **1 athlete died**
- **2 athletes needed liver transplantation**
- **2 athletes with long hospital stay**
- **aegelin, DMAA**

Notes from the Field: Acute Hepatitis and Liver Failure Following the Use of a Dietary Supplement Intended for Weight Loss or Muscle Building — May-October 2013

Weekly
October 11, 2013 / 62(40);817-819

Guidelines: “Clinicians evaluating patients with acute hepatitis should ask about consumption of dietary supplements as part of a comprehensive evaluation. “

Nutrition
Volume 47, March 2018, Pages 110-114

Case report

Fat burner–induced acute liver injury: Case series of four patients

Aleksandar Gavrić M.D. [a], Marija Ribnikar M.D. [a], Lojze Šmid M.D., Ph.D. [a], Boštjan Luzar M.D., Ph.D. [b], Borut Štabuc M.D., Ph.D. [a]

Show more

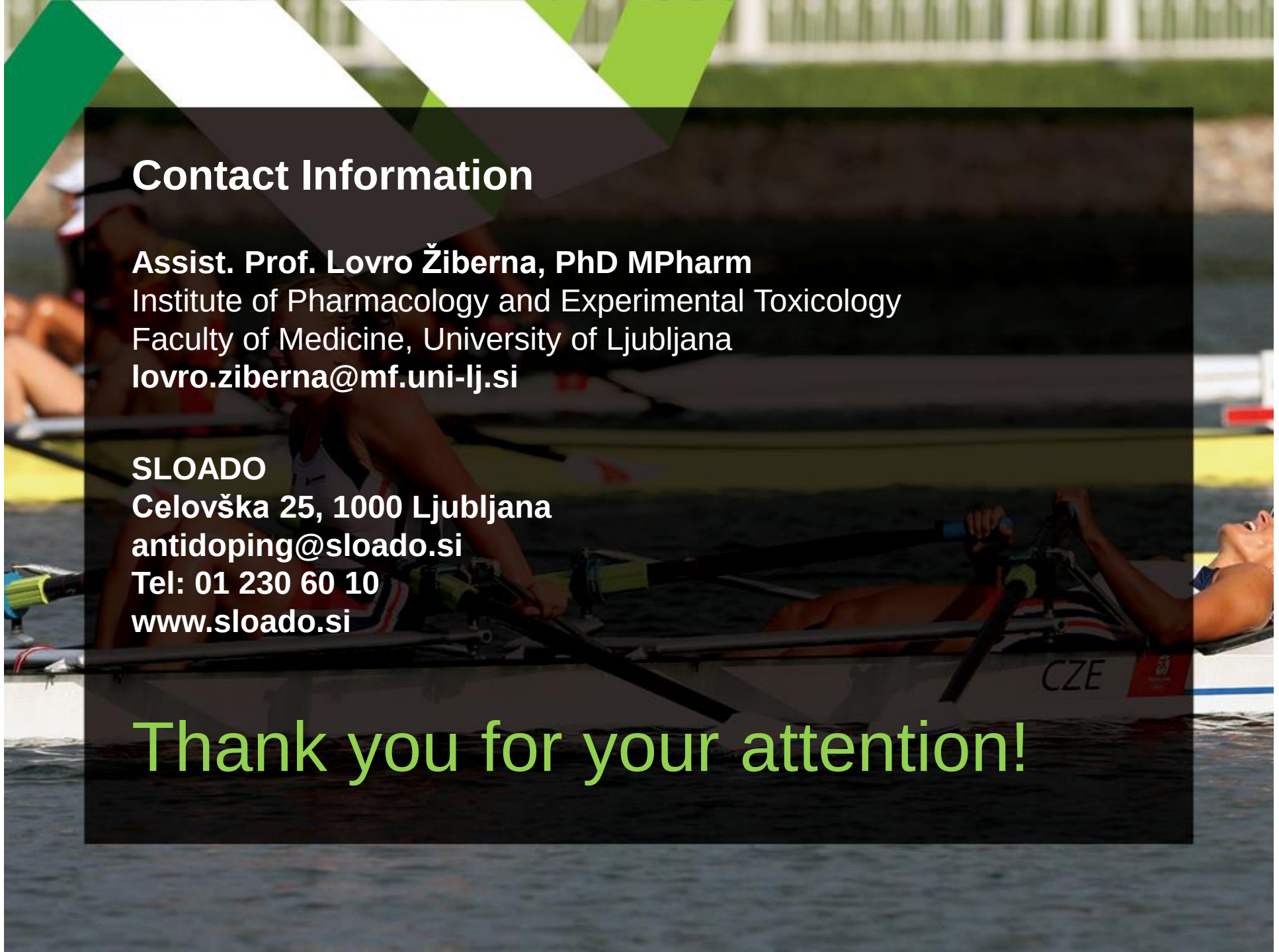
https://doi.org/10.1016/j.nut.2017.10.002

University Medical Center Ljubljana, in Slovenia, from May 2010 to July 2015

Healthy women using "fat-burners"

TABLE 2. Patient information, main ingredient of fat burner product, commercial name (if available) and the extent of the liver injury.

	Patient	Product	Histological type of liver injury
Case 1	57-y white female patient	Contains green-blue algae spirulina.	Fulminant hepatitis. Patient underwent liver transplantation.
Case 2	52-y white female	Contains green tea extract.	Hepatitic and cholestatic idiosyncrastic liver injury.
Case 3	45-y white female	Contains green coffee bean extract.	Cholestatic idiosyncrastic liver injury.
Case 4	57-y white female 1st admission / 62-y 2nd admission	**Chili Burn™** (green tea leaves 486 mg / dill 150 mg / ginger root 50 mg / chili pepper 12 mg / peppermint 4.50 mg) **SlimCut** (Garcinia cambogia (60% HCA), Guarana (22% Caffeine), Citrus aurantium,	Hepatitic idiosyncrastic liver injury.



Contact Information

Assist. Prof. Lovro Žiberna, PhD MPharm
Institute of Pharmacology and Experimental Toxicology
Faculty of Medicine, University of Ljubljana
lovro.ziberna@mf.uni-lj.si

SLOADO
Celovška 25, 1000 Ljubljana
antidoping@sloado.si
Tel: 01 230 60 10
www.sloado.si

Thank you for your attention!