



FIRST STEPS IN DOPING PREVENTION! BASIC LEVEL

SLIDE 2:

There are various theories about the origin of the term “doping”. The Kaffir tribe in Africa named a primitive alcoholic drink which was used in religious ceremonies as a stimulant with the phrase “dop”. Other reports describe Zulu warriors using “dop”, an alcoholic drink made of grape skins and cola beverage. Later, the Dutch colonists (Boers) used the term “dop” to describe any stimulant beverage and hence the term was spread worldwide. Eventually, the term was adapted to a wider range of substances and in sports, using those substances was further on described as “doping”, first appearing in an English dictionary in 1889.

- Doping means the **usage of forbidden substances or forbidden methods** leading to an enhancement of performance.
- Doping is an **unfair act and holds health risks**.
- According to the **World Anti-Doping Code 2003** doping is defined as the occurrence of one or more of the anti-doping rule violations set forth in Article 2.1 through Article 2.8 of the Code.

The World Anti-Doping Agency defines the World Anti-Doping Code as follows:

“One of the most important achievements to date in the fight against doping in sport has been the drafting, acceptance, and implementation of a uniform *set of anti-doping rules*, the World Anti-Doping Code (Code). The Code is the core document that provides the *framework for harmonized anti-doping policies, rules, and regulations within sport organizations and among public authorities*. It works in conjunction with four International Standards aimed at bringing harmonization among anti-doping organizations in various areas: testing, laboratories, therapeutic use exemptions (TUEs) and the List of Prohibited Substances and Methods. ...”

(The complete and official version of the Code is available at www.wada-ama.org)

The Prohibited List

The Prohibited List is an International Standard identifying Substances and Methods prohibited in-competition, out-of-competition, and in particular sports. It was first published in 1963 under the leadership of the International Olympic Committee. Since 2004, WADA is responsible for the preparation and publication of the List. The

list is updated and published annually. The currently available Prohibited List can be downloaded under www.wada-ama.org/en/dynamic.ch2?pageCategory.id=370.

SLIDE 3:

In the Greek Olympic Games of the Antique, specialists were described offering athletes nutritional ingredients in order to enhance their physical performance. This was considered absolutely necessary and the providers may be compared with current sports medicine specialists. Furthermore, athletes were reported trying to increase their physical strength by eating different kinds of meat or bloody bread prior to the games. The reports about the use of **herbs, fungi and testis of the bull** to enhance performance can be retraced to the ancient times, Roman Empire and Middle Ages.

- 1896: The first reported death caused by doping occurred in this year. The English cyclist **Arthur Linton** died due to strychnine intake after the race Paris-Bordeaux.
- 1904: At the Olympics St. Louis marathon, **Thomas Hicks** who had just won the race, collapsed and the Doctors proved strychnine (stimulant) and cognac (alcohol) intake before the race: He almost died of a combination of alcohol and stimulant.
- 1939-1945: It is commonly known that during the World War II the **Aviators** took stimulants to stay alert/awake

SLIDE 4:

- 1960: A dramatic increase in using **anabolics** as doping substances started in the 1960s. The society believed those days that there were drugs capable of achieving everything. Stimulants were widely used and were implicated in at least two deaths in cyclists.
- 1980s: With ongoing pharmaceutical developments, in particular, complex substances intrinsic to the body came to be available on the market as effective agents tending to enhance performance, strength and endurance. Among these the hormone **erythropoietin (EPO)**, which stimulates the formation of the red blood cells, became popular in **endurance sports**.
- 2003: discovery of the **designer-steroid** THG (Tetrahydrogestrinone), an anabolic steroid. The drug was made public when the United States Anti-Doping Agency (USADA) was contacted by an anonymous athletics coach, who provided the USADA with a syringe containing THG

2007: diverse scandals and speculations related to doping (blood doping, EPO etc.) at the **Tour de France**

SLIDE 5:

The first big step in the fight against doping was committed in 1960, when the council of Europe, presented a resolution against the use of doping substances in sports. It seems that the first deaths were necessary in order to sensitize the authorities for this phenomenon. The 1st anti-doping legislation appeared in France in 1963, while Belgium followed in 1965. In 1967, the International Olympic Committee (IOC) established the relative medical commission of the IOC.

1968: Drug tests were first introduced at the Summer **Olympic Games** in Mexico in 1968 and at the Winter Olympic Games in Grenoble. A list of banned substances and methods (Prohibited List) was set up by the IOC, although the technical equipment and the testing procedures were still inadequate.

1988: First introducing of **out-of-competition testing** (OOC) in Germany. Definition of OOC according to the '*Guideline for out-of-competition testing*' of WADA: Any Doping Control which is not In-Competition. <http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=463>

1999: Due to another big scandal during the Tour de France in 1998, the IOC convened the World Conference on Doping in Sport in Lausanne in February 1999. The main result of that conference was the establishment of the **World Anti-Doping Agency (WADA)** on November 10th 1999.

2004: **The Code** is the core document that provides the framework for harmonized anti-doping policies, rules, and regulations within sport organizations and among public authorities. It works in conjunction with four **International Standards** aimed at bringing harmonization among anti-doping organizations in various areas: testing, laboratories, therapeutic use exemptions (TUEs) and the List of Prohibited Substances and Methods.

2007: The Convention represents the first time that governments around the world have agreed to apply the force of international law to anti-doping. This is important because there are specific areas where only governments possess the means to take the fight against doping forward. Accordingly, the Convention helps to formalize global anti-doping rules, policies and guidelines in order to provide an honest and equitable playing environment for all athletes. But not all governments have fully implemented this.

SLIDE 6:

While performance enhancing drug abuse in sport is clearly defined as doping and thus by the list of prohibited substances and methods, the drug abuse in leisure sports is mostly neglected. In our highly competitive society, performance enhancing drug abuse can be observed in a large number of persons, not solely among those participating in professional sport activities. Because of their effectiveness, different substances which are prohibited in the field of **competitive sport** are also used in **leisure sports**.

The larger group of so-called "sportsmen" consists of individuals doing lower-level **leisure sports**, who have other reasons for using drugs, mostly to improve their physical appearance. Results from scientific surveys confirm a high amount of drug abuse in competition as well as in recreational and fitness sports.

Furthermore, performance enhancing drug abuse is not just a problem in sports; **lifestyle** drug abuse among pupils, teenager etc. makes this matter a new public health problem worldwide. By now it is also known that specific occupational groups take specific drugs to cope their **work load**.

⇒ Drug abuse = doping is not only a problem in sport but also in society!

SLIDE 7:

Summary and keywords to know!

SLIDE 8:

Most doping substances are originally pharmaceutical drugs. These drugs are used for the medical treatment of a range of medical conditions. According to this aspect, these drugs have on the one hand their desired effects on the illness but on the other hand their undesirable side effects. These biomedical side effects are controlled and tested within several special trials and are proved to be acceptable in reference to the problems arising from the original illness.

The problem of the use of medical drugs as performance-enhancing substances is the fact that healthy athletes take drugs without an adequate necessity. And furthermore most substances abused are taken in so called suprapharmacological doses or in different combinations ("stacking") without prior medical investigation leading to biomedical side effects which no one can really predict.

Picture shows: The relationship between drugs used for **medical purpose** and drugs abused in sports. The medically used drugs show therapeutic effects within **pharmacological** doses, whereas performance-enhancing drugs could show

hazardous effects cause of the usage in **suprapharmacological** doses. As a consequence the side effects can be **short-term, reversible, irreversible or result in delayed adverse effects**.

SLIDE 9:

Anabolic steroids or **anabolic-androgenic steroids (AAS)** are **hormones**. Like most hormones they travel in the blood to **regulate specific body functions**. AAS for example may enhance the metabolism of proteins leading to an increased muscle mass.

Anabolic means “**to build up**”

Andro + genic means “**male**” + “**to produce**”

Steroids are a kind of **lipid molecules**

For example, **testosterone** is an anabolic steroid, in particular a male sex hormone which is endogenously produced in the testis, ovary, and adrenal cortex and in the liver. An example of the medical use of an application of anabolic steroids is muscle dystrophy (muscle diseases that cause progressive muscle weakness).

Picture shows: The hormone is produced by specific cells in the respective organs and afterwards secreted into the blood (**vascular system**). In the vascular system the hormone can be transported to any place within the body. Target cells have specific receptors which recognize the steroid hormone and respond accordingly.

SLIDE 10:

The desired effects of an AAS-abuse in sports derive from the anabolic part of the substance (cell growth). Athletes sometimes want to “**build up**” muscles by misusing steroids, which enhance the protein synthesis leading to an increased muscle tissue growth. Because of the increased protein synthesis, steroid abuse may also help to regenerate faster. AAS can have an effect on the musculature in particular when training is carried out under the influence of these agents.

Nevertheless, the athletes have to stay active, because anabolic **steroids do not lead to a muscle growth for itself**. Furthermore, muscles (in fact the whole human body) are **physiologically not prepared for such an extreme and fast growth**, so that damages on the muscles can appear resulting from the abuse of anabolic steroids during training.

Picture shows: AAS may be taken in the form of tablets, or else given as an intramuscular injection, leading to additional indirect health risks, like infections (e.g. hi-virus or hepatitis caused by sharing needles).

SLIDE 11:

The misuse of AAS results in an enhancement of the motivation to train and along with this an increased risk of over-training, with all the detrimental effects that this has on the motor apparatus.

There is a widely held view, too, that the misuse of AAS in great quantity will produce considerable effects, while the organic side-effects will often be rendered harmless or denied. In actual fact, however, side-effects that appear harmless make an appearance at an early stage, and these are the precursors of the much more dangerous side-effects to the internal organs.

The health hazards of anabolic-androgenic steroids are largely based on the androgenic part. **Male abusers** could show an enlargement of breast growth, the so-called gynaecomastia (**getting more female**) and in contrast **female abusers** show an increased development of male sexual characteristics (**getting more male**).

Further side effects are:

- Steroid-related **acne** is less dangerous but an aesthetically unpleasant side-effect (*Picture a*)
- Inflammations of the liver; fatty degeneration of the tissue and the formation of **liver cysts** are examples of the direct damage to tissue that may occur (*Picture b*)
- **Shrinking of the testis** (*Picture c*)
- **Gynaecomastia** (*Enlargement of breast in males; Picture d*)
- **Degeneration on skeletal system**
- **Cardiovascular disturbances** appear on the heart as an inadequate supply with oxygen because of the heart muscles growth without adaptation of the blood vessels, further disturbances are seen on the circulatory system with a reduction of High Density Lipids (HDL), which protect the walls of the blood vessels and an increase of Low Density Lipids (LDL), which damage the walls of the blood vessels
- **Deepening of the voice** (*women*)
- **Beard growth** (*women*) / **go bald** (*men*)
- **Increased aggressiveness** (*roid-rage*)

SLIDE 12:

Summary and keywords to know!

SLIDE 13:

Stimulants, like amphetamine, ephedrine or caffeine were the first group of effective agents which were placed on the doping list that was drawn up in 1967. However, caffeine is no longer considered as a doping agent and thus not on the "Prohibited List". This group of substances includes very different agents, both natural agents and their derivatives and those that are artificially produced. Stimulants are exogenous substances (like ephedrines) **affecting the central nervous system** by stimulating the release of several transmitters (e.g. Acetylcholine). These substances **increase the heart rate, breathing rate and brain function** and may lead to euphoria.

Their counterparts in the human body are adrenaline or noradrenaline. These endogenous substances increase the energy metabolism, too.

Stimulants or amphetamines are used for medical purpose mainly for local administration like **relaxing bronchi** or to decongest the nasopharynx mucosa (**cold medicine**). Furthermore, stimulants are also widely abused as drugs, e.g. XTC.

Picture shows: A neurone – the functional cell of the brain – with its input structures (dendrites) and its output structure (axon) communicating with other cells by synapses. The synapse is a cell junction for the communication between cells - stimulants affect here! Stimulants lead to an increased release of transmitters.

SLIDE 14:

Stimulants increase the excitation of the brain and the body. The abuse by the athletes is based on the attaining of **increased alertness, reduced tiredness** and an **increased competitiveness and aggression with less sensitivity to pain**. **Stimulants do not directly increase physical performance.**

The most commonly used stimulants in sport are amphetamines, cocaine, ephedrine and caffeine.

Graphic shows: The state of "total exhaustion" is under normal circumstances (e.g. in sports) not achievable. It is something like an autonomously protected resource and can only be activated under specific circumstances. But with stimulants it is possible to take the last resources of the body!

SLIDE 15:

Stimulants lead to the suppression of fear or exhaustion. Their effect is so powerful that an athlete will not realise how exhausted he is, and there have been cases of overexertion leading to death, especially in top-level competitive sports. Associated with these effects, dehydration may also occur as a result of prolonged effort, and generally hyperthermia as well.

Biomedical side effects of stimulants are on the one hand the development of **psychological disturbances like an addiction or depression** or on the other hand **physiological effects** like:

- **dysregulation of the body temperature**
- **loss of appetite and sleep**
- **hallucinations**
- **body trembling, restlessness, agitation, tension**
- **cardiac arrhythmia**

Due to their euphoric effect, stimulants are abused in the field of sports and out of sports!

SLIDE 16:

Summary and keywords to know!

SLIDE 17:

The abbreviation EPO stands for the **hormone erythropoietin** which is a growth factor formed especially in the kidney and **stimulates synthesis of the red blood cells**. **Red blood cells** or erythrocytes **carry oxygen to the tissues**.

The cycle of the formation of red blood corpuscles is controlled by the oxygen content in the blood, which is “measured” by receptors on an ongoing basis as a control variable. If the oxygen content is reduced and the body reaches a state of hypoxia, the production of EPO will be triggered, and following from this red blood corpuscles will be formed in the bone marrow. The important organ in connection with this cycle is the kidney, the tissue of which EPO is very probably formed.

It is possible to intervene in this control loop by introducing EPO externally, bringing about an increase in the red blood corpuscle count even without training.

Erythropoietin is used for **medical treatment** of anaemia.

Picture shows: **Erythropoietin** is produced by the **renal cells** and secreted into the blood (**vascular system**). It stimulates the red blood cell production in the bone marrow.

SLIDE 18:

Erythropoietin stimulates the production of **red blood cells** or erythrocytes in the bone marrow, which are responsible for the carriage of oxygen. This oxygen is essential for the physiological functions of the human body. In addition to the brain, the muscles need most of the oxygen to **secure endurance performance**. As a consequence, some cyclists, long-distance runners or cross-country skiers are tempted to abuse EPO to **increase their tissue oxygenation**.

A **legal and much more secure option** to increase endurance performance or more precisely oxygen binding capacity is **high altitude training**. The reduced availability of oxygen in the mountain air leads to a stimulation of the synthesis of red blood cells: this is a perfectly legal way to increase the number of red blood cells.

Picture shows: The Finnish Nordic skier Eero Mäntyranta has a mutation in the gene of his erythropoietin receptor. This led to an increased capacity to transport oxygen in the blood, giving him a legal advantage and leading him to several Olympic gold medals.

SLIDE 19:

Erythropoietin (EPO), whether in the form natural to the body (human [h] EPO) or that produced by gene technology (recombinant human [rh] EPO), has minor side-effects based on its structure like allergic (seldom) or immunological reactions. All its effects that are hazardous to health are linked to the formation of red blood corpuscles leading to an **increased blood viscosity**. Accordingly, EPO-abuse **increases the risk of arterial hypertension** (high blood pressure) **or of thromboembolic events** (blood clots) in the lung, brain or heart, that can result in an infarct or stroke.

EPO-abuse can be strongly life-threatening!

Picture shows: On the left side of the picture you see the right heart ventricle; and on the right side you see the left heart ventricle of a pathologically enlarged heart, and the infarction is marked with the blue circle.

SLIDE 20:

Summary and keywords to know!

SLIDE 21:

Blood doping belongs to the illegal methods of manipulation and is a **direct form of enhancing the oxygen transfer** with an immediate effect by enhancing the amount of red blood cells. In contrast, EPO only induces an increased synthesis of red blood cells.

There are two different methods athletes could manipulate:

- **collecting their own blood and reinject later**
- **taking the blood of a donor and reinject if required**

The physiological effects are the same as for EPO-abuse:

- increased red blood cells
- increased capacity of oxygen delivery

Blood bottles are **used in medicine to treat enormous blood losses**.

SLIDE 22:

More red blood cells, more oxygen carrying, **more endurance-performance!** The effects are the same as those of EPO-abuse, but with an immediate consequence.

Graphic shows: The impressive effect of blood transfusion on physical performance is expressed in the following trial, showing the effect on **time to run a 10 km race with reinfusion or with placebo**.

Group 1: No effects can be seen after infusion of the placebo solution, but a significant effect results after blood reinfusion ⇒ the time to run decreases.

Group 2: The time to run 10 km decreases immediately after blood reinfusion. This improvement of time was sustained for 13 days after reinfusion of red blood cells and therefore was still present at the time of placebo infusion.

SLIDE 23:

Most of the biomedical side effects are similar to those of EPO-abuse.

Blood doping places an increased stress on the cardiovascular system leading to a **high blood pressure and an increased risk of thrombosis**. Furthermore, blood transfusions hold the **risk of a transfusion accident by allergies or incompatibilities** (ABO-system) and the **risk of severe infections like hepatitis or HIV**.

SLIDE 24:

Summary and keywords to know!

SLIDE 25:

Nutritional supplements are **substances that** are normally present in the body and are consumed in addition to normal daily nutrition, like **glucose, minerals, vitamins or trace elements**. Some of these substances are **essential for the growth and development** of a multicellular organism, like the human body, but others have no effect or may even be harmful. The nutritional supplements contain the respective substances in a concentrated form and mostly consist of several substances. The **medical purpose** for the use of nutritional supplements **is a deficiency in the body** due to malnutrition or illnesses.

The main reason for the public to use nutritional supplements is the belief that they promote health, reduce risk of getting sick and at least control body weight. Most of the supplements are not prohibited within the "List".

SLIDE 26:

Nevertheless, a well-balanced nutrition is much better than any nutritional supplementation and of course intake levels have to be taken into account to avoid the effect of an 'overdosage'.

Nutritional supplements might help **some competitive athletes to perform the intensity and duration of their sports**. They have an **extremely high calorie usage level that cannot be covered by normal daily nutrition** (like Tour de France etc.).

Critical substances are some vitamins of the B group in vegetarian athletes.

SLIDE 27:

Nutritional supplements themselves are not prohibited, unless they contain a prohibited substance, albeit this is mentioned or not mentioned on the label.

One of the main risk factors of nutritional supplements can be positive doping testing by contaminated supplements. These **unlabelled** ingredients can lead in the extreme case even to positive doping testing. As a consequence the **biomedical side effects depend on the kind of the "unlabelled" substance**. **Most detected substances are various anabolic-androgenic steroids or stimulants**.

It is a matter of fact that a lot of sportsmen are using supplements without the knowledge of side effects and recommended intake levels. In the face of the great

market of nutritional supplements (about 12 billion US\$ in the USA in the year 2001) and the tremendous selling worldwide, the edge between a recommended use and misuse is floating.

Furthermore, the assumption that the use of nutritional supplements can be used to prevent possible nutritional deficiencies may lead to less attention concerning a healthy, well-balanced diet.

Table shows: An International Olympic Committee analysis of 600 over-the-counter nutritional supplements found that one-quarter of the investigated supplements contained banned substances such as anabolic steroids.

SLIDE 28:

Summary and keywords to know!

SLIDE 29:

Genes are single sections of the DNA including the hereditary information. These **genes contain the information** for the composition of the body and therefore **for the single proteins**, too, e.g. muscle proteins. One aspect of **gene therapy is the attempt to change the information on the selective genes**.

The 2008 Prohibited List defines gene doping as *“the non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to enhance athletic performance”*.

Picture shows: The idea of gene therapy is to implement the modified genes into the cell by the help of specific transporters. After the implementation the corrected/new functional proteins can be synthesized by the cell and the disease can be healed or at least lowered.

The medical purpose of gene therapy is to correct defective genes that are responsible for the disease development, like hereditary diseases. But the problem is the abuse of the therapeutic idea for sport purposes.

SLIDE 30:

If the correction of defective genes is possible, it wouldn't be far to the modification of muscle genes. Possible aims of abuse could be:

- an **increased erythropoietin production** (remember Eero Mäntyranta, the Nordic skier), to **enhance the endurance performance**
- the **stimulation of specific** muscle growth factors to **enhance power and speed**

Left picture shows: A male child at the ages of seven months. He appeared extraordinarily muscular, with protruding muscles in his thighs and upper arms. At 4.5 years of age the male baby showed increased muscle mass and strength due to a genetic myostatin mutation leading to an increased muscle mass. He could hold two 3-kg dumb-bells in horizontal suspension with extended arms.

(The original data could be found by Schuelke et al. (2004) N Engl J Med. 350: 2682-2688)

Right picture shows: A so-called “Belgian Blue” cow with a mutation in the myostatin gene. The increased muscle mass is a distinctive visual sign.

Nevertheless, an **abuse** of gene therapy or the idea of the known gene mutations **in sports is currently not known**.

SLIDE 31:

The lack of control of the artificial gene is the major concern in gene therapy. Neither desired effects nor unwanted side effects can be predicted according to the widespread mechanisms of gene regulation.

Results from clinical trials for gene therapy methods reported that the following problems can appear:

- **cancer,**
- **multiple organ failure and**
- **other strongly life-threatening events**

Further risks are totally unknown, due to the sparse studies and publications and thus the biomedical side effects of gene therapy are uncontrollable!

SLIDE 32:

Summary and keywords to know!