STRIKING THE RIGHT BALANCE

Effectiveness of Anti-Doping Policies

OLIVIER DE HON

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Effectiveness of Anti-Doping Policies

ZOEKEN NAAR HET JUISTE EVENWICHT

Effectiviteit van het anti-dopingbeleid

(met een samenvatting in het Nederlands)

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In mooie herinnering aan Julie, die altijd overal bij zal zijn

In loving memory of Julie, who will always be present at all occasions

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TABLE OF CONTENTS

SUMMARY

Introduction

The first official anti-doping measures in human sport were adopted by the governing body of the sport of athletics at a meeting in Amsterdam, the Netherlands, in 1928. These were a result of already long existing debates on 'natural athleticism' and what could be perceived as 'normal' in sport. These debates have remained ever since, and the word 'doping' continues to spark controversies in the world of sports. There have been continuous efforts and investments to try to curb or even eradicate the use of doping in elite sports, but doping cases continue to surface and controversies remain. This begs the question: How effective are current anti-doping policies?

There are various ways to look at this question. Traditionally, discussions on doping are fed by ethical, juridical, physiological, and psychological arguments. An in-depth discussion on the effectiveness of existing anti-doping regulations has been missing for too long. In this thesis, the search for answers to this main research question is guided by (i) the extent of doping use, (ii) the effectiveness of doping substances (and methods) to influence athletic performances, and (iii) the consequences of existing policies for athletes. Specific attention is paid to the historical backgrounds and scientific foundations that have shaped current anti-doping policies, to the intended and unintended consequences of these policies, and to the dilemmas and complexities that can be encountered in this field. This broad approach can be expected to help to identify what constitutes an effective approach to deal with the issue of doping in sport and, equally important, what aspects in its current form are less effective.

Methods

For all analyses both primary sources and secondary data analyses have been used, as well as quantitative and qualitative analyses. All studies are based on real-life controversies that surfaced in the daily work of a National Anti-Doping Organisation.

Two reviews have been written on the extent of doping use: one on the available evidence about the prevalence of intentional doping use in elite sports, and one based on an as yet undisclosed dataset of the World Anti-Doping Agency (WADA)

to try to gain information on the prevalence of unintentional doping use in elite athletes who have been confronted with an anti-doping rule violation. In addition, six case studies from the recent past are presented and discussed anew. These include three case studies on the effectiveness of doping substances (and methods), and another three on the consequences of anti-doping policies. This mixed form of data collection was intended to lead to both specific and general conclusions.

Definition of effectiveness
The word 'effective' is used numerous times in the World Anti-Doping Code and there seems to be an increased interest in this subject over the last few years. But a clear definition of this word is very seldom given. In this thesis it is proposed that the best possible definition within the existing anti-doping framework is 'the degree in which current policies succeed in eradicating doping in sport'. If one fights against a certain behaviour, one aims to eradicate this behaviour regardless of the question whether it is actually feasible to achieve this.

Prevalence of doping use
Currently available data on the prevalence of doping use point to a prevalence of 4-39% of intentional doping use in various groups of competitive elite athletes. This percentage is far higher than what is traditionally found through chemical analyses of athletes' biological samples. The prevalence of doping is considerably different between types of sport, levels and nationalities. There is a great need for more data on the prevalence of doping use applying reliable measures.

An analysis of WADA's juridical database revealed that there are indications that a large minority of all athletes who are caught by an adverse analytical finding may have done this (partly) unintentionally. Based on the sanctions that athletes receive, it can be concluded that in approximately 40% of all cases juridical panels are not convinced that the athletes concerned were completely at fault, that mitigating circumstances were applicable, or that full responsibility of the suspected violation should not be held against them. This is mainly true for regular medicines (e.g. beta-2 agonists and narcotics) and/or so-called 'social drugs' (e.g. cannabinoids and various stimulants). Anabolic agents, peptide hormones, and hormone modulators lead to higher sanctions, as do combinations of several anti-doping rule violations.

Case studies on effectiveness of doping substances and methods

The first case study, into the subject of mind sports and doping, showed that it is obvious that not all substances on the prohibited list are equally relevant for all sports. This is an area where the traditional aim for global harmonisation cannot be considered to be effective; on the contrary. A flexible prohibited list of doping substances and methods that is more focussed on the sport disciplines that can be expected to be impacted by their use will improve both effectiveness and logic of the anti-doping framework.

The second case study indicated that commonly used medications (in this case glucocorticoids and beta-2 agonists) can be expected to have very different effects on athletic performances when administered in different ways. As such, blanket bans on all possible ways of administration of a group of substances can be considered ineffective. A coordinated research agenda would be able to guide discussions on the need to balance practical solutions and effective anti-doping measures. This process would be helped if WADA would publish its determination on the three criteria that guide the prohibited list with respect to all (groups of) substances and methods that are on that list (potential performance enhancement, potential health risks, violation of the 'spirit of sport'). The controversies around asthma-medicines and anti-doping regulations led to an attempt by anti-doping rule makers to influence general medical guidelines to diagnose asthma. Such extra-curricular attention cannot be considered effective.

The third case study, on the subject of gene doping, showed that the best responses to an unknown phenomenon are clear and transparent communications between all relevant stakeholders and the building of a research agenda. Even though the effectiveness of this approach cannot yet be determined, it seems to provide a good model to tackle specific (potential) problems related to doping. There is an inherent problem with studying the effects of substances or methods on elite athletic performances, and certainly when this involves newly emerging products, because it is practically impossible to study these effects in this specific group of subjects. Anti-doping policy decisions often need to be made under sub-optimal conditions.

Case studies on the consequences of anti-doping policies

The current whereabouts regulations are stretching the willingness of athletes to comply with all anti-doping regulations. Most athletes support the whereabouts

rules and understand their need, but the gradually increasing impact of anti-doping regulations on the lives of athletes over the past few decades seems to have reached a critical level. It is a clear illustration of the necessity to engage athletes more in drafting the rules. It is an uncomfortable situation that it is not really known what the impact of whereabouts information has been on the attempts to eradicate doping use in sport. There is a great need of additional proof that the whereabouts rule changes have led to a noticeable effect on doping use habits.

A second issue, that of the consumption of nutritional supplements, touches on many different aspects of the anti-doping framework. Currently, elite athletes cannot simply consume regularly and legally available nutritional supplements due to the risk of presence of unknown substances in these products. This is a clear example of an unintentional consequence of anti-doping policies. A solid solution in this area is not easy, but the least that anti-doping organisations can do is to guide athletes (and their support personnel) through this problematic issue, since it was the anti-doping community that unearthed it. Especially since supplements have the potential to act as an alternative to doping use. It is quite possible that similar problems will be encountered in the regular food industry if the constant progress in analytical possibilities will continue.

The last case study of this section focussed on the use of substances that are considered as doping in competitive sport, but are not prohibited in the predominantly non-competitive environment of fitness centres. Anti-doping policies may potentially gain in effectiveness, and will certainly increase in credibility, if they do not focus solely on competitive sports. This is not a call for more regulation in the world of fitness, but another example that more data on the impact of policies and engaging directly with athletes can be expected to lead to improvements. In this case this is particularly true for the efforts in targeting the supply lines of doping products and the effectiveness and health risks of (potential) doping substances.

Conclusions and recommendations for more effective anti-doping policies

Anti-doping policies involve many dilemmas that create huge challenges to make these policies effective. As such, drafting rules and prohibitions is a highly complex task. How effective the anti-doping framework is cannot rightfully be identified on the basis of currently available information. But the fact that this is difficult to assess, does not mean that it should not be attempted. A thorough evaluation of the effectiveness of anti-doping policies has been neglected for too long while

being an essential piece of information for explaining and improving these policies. The anti-doping framework has a great impact on athletes, the people around them, and the general public. As such, the need for this framework must not only be based on its good intentions, but needs to justify itself based on evidence related to its effectiveness as well.

The primary conclusion of this thesis is that the best possible measure to quantify the effectiveness of anti-doping policies is the percentage of athletes that use doping, intentionally or unintentionally. But since doping is a secretive act, it will never be possible to give a 100% reliable figure for this purpose. Reliable estimates can be given, however. The prime methodological candidates to gain better insight in intentional doping are randomised response questionnaires and biomarker-based modelling. Analyses of juridical outcomes of anti-doping rule violations can provide information on the likelihood of unintentional doping. It is encouraging that WADA has shown more transparency in this regard in the last two years.

Alternative methods to assess effectiveness can be expected to add pieces to this puzzle. Examples are the perception of the athletes themselves regarding the influence of doping use on the outcomes of their competitions, mathematical analyses of changes in elite athlete performances over time, and outcomes of re-analysis of stored samples. Each of these measures has its pros and cons, but taken together they can be expected to provide valuable insight in the level in which doping use has been eradicated, or not. The scientific methods to do this are readily available; they just need to be applied more often. The exact parameters of measuring effectiveness should be globally agreed upon in order to allow for comparisons over time, and as such to allow for policy evaluations.

In order to feed these necessary evaluations, and to explain the necessity of anti-doping regulations and their impact, it is important to be as transparent as possible. More specifically, the anti-doping framework should aim to retrieve more information about and explain more of the backgrounds regarding the effects of doping substances and methods, the contents of the prohibited list, the backgrounds and specifics of doping analyses, the variability in doping sanctions, and the impact of anti-doping measures on the daily lives of athletes. In the long run more is gained than lost with transparency, as long as this does not jeopardise the effectiveness itself.

Scientific input is essential in this process. When implementing scientific knowledge it is important to have an umbrella view on the entire anti-doping framework as every decision to change one specific part will inevitably lead to (profound) changes in other parts. This means that it should not be left to experts in one specific field to decide on changing a rule or implementing a new one, although exactly these experts are needed to draft rules that are accurate and relevant. Here, also, balance is needed: between the specific knowledge of experts and the practical consequences on the entire anti-doping system in order to avoid undesirable unintentional consequences. Over time, the field of anti-doping has become a profession in itself. Effective anti-doping policies require a true multidisciplinary effort and continuous evaluations. This can be a fruitful terrain for collaborations where both researchers and the subjects of such studies may benefit enormously from such a cooperation.

A fundamental improvement of the anti-doping framework would be to acknowledge that the rather vague but ethically valuable concept of 'spirit of sport' is the core of all anti-doping regulations. The decision to ban certain substances and methods is an ethical decision in itself. This state of affairs may be debated by anyone who takes issue with it, but it would be more clear, and as such more favourable, to accept this concept as a central theme in all anti-doping regulations and consequently not as an optional criterion to the practical definition of doping, i.e. the Prohibited List International Standard published by WADA. Discussions on the content of the prohibited list are better focussed when they deal solely with the issues of performance enhancement and health risks.

Based on the outcomes of this thesis, there are multifold specific areas where anti-doping policies can be improved. These include: less rigorous harmonisation of the prohibited list; focussing the prohibited list criteria more to the core of performance enhancement and health risks; studying the possibility and potential consequences of a two-tiered case management system when low concentrations of prohibited substances are found; evaluating the effectiveness of whereabouts-information and out-of-competition doping controls; aiding athletes in their quest for legitimate performance enhancement (e.g. by nutritional supplements use); and more attention for non-competitive fitness next to competitive elite sports. This is by no means a complete overview of possible measures to improve anti-doping policies. But when this broad list of potential improvements is implemented - supplemented with the traditional and current efforts in education, doping control

and juridical processes - it can be expected that anti-doping policies become more optimally effective.

The subject of effectiveness of anti-doping policies has enjoyed more and more interest over the last few years. But this is an area that has just been treaded upon. This thesis is a first broad attempt to tackle the problem. It gives examples and directions through which the issue of effectiveness can be addressed in a concerted effort. The common principles of all specific conclusions and suggestions in this thesis can be summarised as a call for acquiring more relevant data, engaging a multidisciplinary scientific approach, showing more transparency from anti-doping professionals, and holding more focussed discussions on what the core of anti-doping policies should be. Following these principles it can be expected that a better balance can be provided between the main task of anti-doping (the eradication of doping use) and the burdens placed on all athletes (who, as far as current data show, are in majority non-users). The voice of the athletes themselves is essential in this balancing act, as they are the key persons of all doping policies. With such a concerted effort it can be expected that meaningful policy evaluations, and consequently policy improvements, can be made. This is necessary as a system that fails too many athletes will ultimately implode, no matter how many good intentions have formed its basis. The issue of doping in sports is just too important to let that happen.

NEDERLANDSTALIGE SAMENVATTING (SUMMARY IN DUTCH)

Inleiding

De eerste anti-dopingmaatregelen gericht op menselijke sporters zijn vastgesteld door de internationale atletiekbond tijdens een vergadering in Amsterdam in 1928. Deze maatregelen kwamen voort uit toen al lang bestaande discussies over 'natuurlijke sportvaardigheid' en wat als 'normaal' beschouwd kan worden in de sport. Deze discussies zijn nooit meer weggegaan en het woord 'doping' staat nog steeds garant voor allerlei controverses. Er zijn in de loop der jaren vele pogingen en investeringen gedaan om doping in de sport tegen te gaan of om het zelfs volledig uit te bannen. Maar er komen steeds weer dopinggevallen bovendrijven en de controverses over dit onderwerp blijven bestaan. Dit roept de vraag op: Hoe effectief is het huidige anti-dopingbeleid?

Er zijn verschillende manieren waarop naar deze vraag gekeken kan worden. Traditioneel gezien gaan discussies over doping meestal over ethische, juridische, fysiologische en psychologische zaken. Een diepgaande discussie over de effectiviteit van bestaande anti-dopingmaatregelen wordt al langere tijd gemist. In dit proefschrift wordt de zoektocht naar antwoorden op deze centrale onderzoeksvraag geleid door (i) de mate van dopinggebruik, (ii) de effectiviteit van dopingmiddelen en -methoden om sportprestaties te beïnvloeden en (iii) de gevolgen van het bestaande beleid voor sporters. Er wordt speciale aandacht geschonken aan de historische achtergronden en de wetenschappelijke basis van het beleid, aan de bedoelde en onbedoelde gevolgen van het beleid, en aan de dilemma's en complexiteit die gekoppeld zijn aan dit onderwerp. Van een dusdanig brede aanpak kan verwacht worden dat deze het mogelijk maakt om een effectieve aanpak van het onderwerp 'doping' in de sport te identificeren en, wat net zo belangrijk is, om vast te stellen welke aspecten op dit moment minder effectief zijn.

Methoden

Zowel primaire als secundaire bronnen zijn geraadpleegd, en zowel kwantitatieve als kwalitatieve analyses zijn uitgevoerd. Alle onderzoeken zijn gebaseerd op

daadwerkelijke controverses die zijn komen bovendrijven tijdens het dagelijkse werk van een nationale anti-dopingorganisatie.

Er zijn twee overzichtsartikelen geschreven over de mate van dopinggebruik: één over de beschikbare gegevens over de prevalentie van intentioneel dopinggebruik in de topsport en één gebaseerd op tot nu toe niet beschikbare gegevens van het Wereld Anti-Doping Agentschap (WADA), waarmee gepoogd is informatie te verzamelen over de prevalentie van niet-intentioneel dopinggebruik bij topsporters die geconfronteerd zijn met een dopingovertreding. Daarnaast worden zes casestudies uit het recente verleden beschreven en opnieuw bediscussieerd. Dit zijn drie casestudies die gericht zijn op de effectiviteit van dopingmiddelen en -methoden en drie casestudies naar de praktische gevolgen van het anti-dopingbeleid. Deze keuze voor een gemengde vorm van gegevensverzameling is gemaakt om zowel specifieke als algemene conclusies te kunnen trekken.

Definitie van effectiviteit
Het woord 'effectief' wordt verschillende malen gebruikt in de Wereld Anti-Doping Code en gedurende de afgelopen jaren lijkt het onderwerp meer en meer aandacht te krijgen. Maar een duidelijke definitie van het woord wordt slechts zeer zelden gegeven. In dit proefschrift wordt voorgesteld dat de best mogelijke definitie binnen het huidige anti-dopingraamwerk luidt "de mate waarin het huidige beleid succesvol is in het uitbannen van doping in de sport". Want als men strijdt tegen een bepaald gedrag, is het doel om dat gedrag uit te bannen, ook als dit in de praktijk wellicht niet (volledig) haalbaar is.

Prevalentie van dopinggebruik
Momenteel beschikbare gegevens wijzen op een prevalentie van 4-39% wat betreft intentioneel dopinggebruik binnen verschillende groepen competitieve topsporters. Dit percentage is aanzienlijk hoger dan wat traditioneel wordt gevonden door middel van chemische analyses op de biologische monsters van sporters. Dopingprevalentie varieert aanzienlijk tussen verschillende sporten, niveaus en nationaliteiten. Het is hoognodig dat meer gegevens over de prevalentie van doping worden verzameld door middel van betrouwbare onderzoeksmethoden.

Een analyse van juridische gegevens van het WADA toonde aan dat er aanwijzingen zijn dat een grote minderheid van alle sporters die worden geconfronteerd met een 'positieve' bevinding dit (deels) niet-intentioneel hebben gedaan. Op basis van de

sancties die zijn uitgesproken kan geconcludeerd worden dat in ongeveer 40% van de gevallen het tuchtcollege niet overtuigd was van de volledige schuld van de betrokken sporter, dat verzachtende omstandigheden op hun plaats waren, of dat de verantwoordelijkheid voor de beschuldiging de betrokken sporter niet volledig is aan te rekenen. Dit geldt vooral voor overtredingen waarbij reguliere medicijnen betrokken zijn (zoals bèta-2 agonisten en pijnstillende middelen) en/of voor zogenoemde 'sociale drugs' (zoals cannabis en verschillende stimulantia). Anabole middelen, peptide hormonen en hormoonmodulatoren leiden tot hogere sancties, net als combinaties van verschillende dopingovertredingen.

Casestudies gericht op de effectiviteit van dopingmiddelen en -methoden
De eerste casestudie onderzocht het onderwerp denksporten en doping. Deze toonde duidelijk aan dat niet alle stoffen op de dopinglijst even relevant zijn voor alle sporten. Op dit gebied kan het wereldwijde streven naar harmonisatie niet effectief worden genoemd; integendeel. Een flexibele dopinglijst die beter afgestemd is op de sportdisciplines waarvan verwacht kan worden dat ze beïnvloed worden door de gebruikte doping, zal zowel de effectiviteit als de logica van het anti-dopingraamwerk verbeteren.

De tweede casestudie gaf aan dat van veelgebruikte medicijnen (in dit geval glucocorticoïden en bèta-2 agonisten) verwacht kan worden dat ze zeer verschillende effecten hebben op sportprestaties als ze op verschillende manieren worden toegediend. Dit betekent dat een volledig verbod van alle mogelijke toedieningswijzen van een bepaalde medicijngroep als ineffectief kan worden beschouwd. Een gecoördineerde onderzoeksagenda kan discussies voeden over de noodzakelijke balans tussen praktische oplossingen en effectieve dopingmaatregelen. Dit proces kan versterkt worden als het WADA voor alle stoffen en methoden op de dopinglijst het officiële oordeel zou publiceren over de drie criteria die bepalen of een stof of methode op die lijst wordt opgenomen (mogelijke prestatiebevordering, mogelijke gezondheidsrisico's, schending van de elementaire waarden en normen van de sport). De controverses rondom astmamedicijnen en dopingregelgeving hebben in het verleden geleid tot een poging van anti-dopingbeleidsmakers om de algemene medische richtlijnen om astma te diagnosticeren te beïnvloeden. Dit soort extra-curriculaire activiteiten kunnen niet als effectief worden gezien.

De derde casestudie, inzake genetische doping, toonde aan dat het beste antwoord op een onbekend fenomeen wordt gevormd door duidelijke en transparante

communicatie tussen alle betrokkenen en het opzetten van een onderzoeksagenda. De effectiviteit van deze aanpak kan in dit voorbeeld nog niet worden bepaald, maar het lijkt een goed model om specifieke (potentiële) dopingproblemen aan te pakken. Er bestaat een inherent probleem bij het bestuderen van de effecten van stoffen en methoden op topsportprestaties, vooral als dit nieuw ontwikkelde producten betreft. Het is namelijk praktisch onmogelijk om dit soort effecten bij topsporters te onderzoeken. Anti-dopingbeleid moet vaak geformuleerd worden onder suboptimale omstandigheden.

Casestudies gericht op de gevolgen van het anti-dopingbeleid
De huidige whereaboutsregelgeving omtrent de verblijfsgegevens van sporters test de bereidheid van sporters om aan anti-dopingregelgeving te voldoen. De meeste sporters steunen de whereaboutsregels en begrijpen de noodzaak, maar de in de afgelopen decennia langzaamaan groter wordende invloed van anti-dopingregelgeving op het leven van sporters lijkt een kritisch niveau te hebben bereikt. Dit is een duidelijk voorbeeld van de noodzaak om sporters meer te betrekken bij het opstellen van de regels. Het is een ongemakkelijke situatie dat het onduidelijk is wat de invloed is geweest van de verzamelde whereaboutsinformatie op de inspanningen om dopinggebruik in de sport uit te bannen. Er is een grote noodzaak om aanvullend bewijs te verzamelen of de veranderingen in whereaboutsregels hebben geleid tot een merkbaar effect op dopinggedrag.

Een tweede onderwerp, over het gebruik van voedingssupplementen, raakt vele verschillende aspecten van het anti-dopingraamwerk. De huidige situatie is dat topsporters niet zomaar supplementen kunnen gebruiken die legaal en breed verkrijgbaar zijn omdat er een risico is dat deze producten onbekende stoffen bevatten. Dit is een duidelijk voorbeeld van een onbedoeld gevolg van het anti-dopingbeleid. Een goede oplossing op dit gebied is niet gemakkelijk, maar anti-dopingorganisaties moeten op zijn minst de sporters (en hun begeleiders) door dit probleem heen gidsen omdat het de anti-dopinggemeenschap is geweest die dit probleem heeft ontdekt. Dit is vooral belangrijk omdat supplementen een mogelijk legaal alternatief vormen voor dopinggebruik. Als de constante vooruitgang op het gebied van de analytische mogelijkheden blijft doorgaan, is het goed mogelijk dat vergelijkbare problemen zullen ontstaan met betrekking tot de reguliere voedingsindustrie.

De laatste casestudie van deze sectie richtte zich op het gebruik van stoffen die als doping worden beschouwd in de competitieve sport, maar die niet verboden zijn in de voornamelijk niet-competitieve omgeving van fitnesscentra. Anti-dopingbeleid kan in potentie effectiever worden, en zal zeker geloofwaardiger worden, als het zich niet alleen richt op competitieve sport. Dit is geen oproep tot meer regulering in de fitnesswereld, maar een nieuw voorbeeld dat meer gegevens over de impact van beleid en het direct betrekken van sporters bij het beleid naar verwachting tot verbeteringen zal leiden. In dit geval draait dit vooral om de inspanningen om de aanvoerlijnen van dopingproducten tegen te gaan en informatie over de effectiviteit en gezondheidsrisico's van (potentiële) dopingmiddelen.

Conclusies en aanbevelingen voor een effectiever anti-dopingbeleid

Anti-dopingbeleid heeft vele dilemma's in zich, die ervoor zorgen dat er grote uitdagingen bestaan om dit beleid effectief te laten zijn. Dit betekent dat het opstellen van regels en verbodsbepalingen een uiterst complexe taak is. Hoe effectief het huidige beleid is, kan niet worden vastgesteld op basis van de huidig beschikbare informatie. Maar het feit dat dit lastig is om te bepalen, betekent niet dat er geen pogingen gedaan moeten worden. Een grondige evaluatie van de effectiviteit van het anti-dopingbeleid is te lang achterwege gebleven terwijl het essentiële informatie vormt om dit beleid toe te lichten en te verbeteren. Het anti-dopingraamwerk heeft een grote impact op sporters, op de mensen om hen heen, en op het algemene publiek. Dit betekent dat de noodzaak van dit raamwerk niet uitsluitend verantwoord moet worden op basis van goede bedoelingen, maar ook op basis van bewijzen over zijn effectiviteit.

De belangrijkste conclusie van dit proefschrift is dat de beste manier om de effectiviteit van anti-dopingbeleid te kwantificeren, neerkomt op het bepalen van het percentage sporters dat doping gebruikt, intentioneel of niet-intentioneel. Aangezien doping in het geheim plaatsvindt, zal het nooit mogelijk zijn om een 100% betrouwbaar getal te genereren voor dit doel. Maar betrouwbare schattingen kunnen wel worden gegeven. De belangrijkste methodologische kandidaten om meer inzicht te verkrijgen in intentioneel dopinggebruik, zijn 'Randomised Response'-vragenlijsten en -modellen gebaseerd op biologische parameters. Analyses van de juridische eindconclusies van dopingovertredingen kunnen informatie verschaffen over de waarschijnlijkheid van de mate van niet-intentionele doping. Het is bemoedigend dat het WADA op dit vlak in de afgelopen twee jaar meer transparantie heeft getoond.

Alternatieve methoden om de effectiviteit te bepalen, kunnen stukjes aan deze puzzel toevoegen. Voorbeelden hiervan zijn de perceptie van sporters over de invloed van dopinggebruik op de resultaten van wedstrijden waarin ze zijn uitgekomen, statistische analyses van veranderingen in sportprestaties in de tijd en de resultaten van heranalyses van opgeslagen dopingcontrolemonsters. Elke parameter heeft zijn eigen specifieke voor- en nadelen maar verwacht kan worden dat zij in samenhang met elkaar een waardevol beeld kunnen geven van de mate waarin dopinggebruik is uitgebannen, of niet. De wetenschappelijke methoden om dit te doen zijn al beschikbaar; ze hoeven alleen maar vaker toegepast te worden. Met welke parameters effectiviteit het best gemeten kan worden, zou internationaal afgesproken moeten worden om veranderingen in de tijd zichtbaar te maken en zo beleidsevaluaties mogelijk te maken.

Het is belangrijk om zo transparant mogelijk te zijn om deze noodzakelijke evaluaties uit te kunnen voeren en om de noodzaak en impact van anti-dopingmaatregelen uit te kunnen leggen. Het anti-dopingraamwerk zou zich meer moeten richten op het verzamelen van informatie over en het uitleggen van de achtergronden van de effecten van dopingstoffen en -methoden, de samenstelling van de dopinglijst, de achtergronden en uitgangspunten van dopinganalyses, de variatie in dopingsancties en de impact van anti-dopingmaatregelen op het dagelijks leven van sporters. Uiteindelijk wordt er meer gewonnen dan verloren door transparantie, zolang deze de effectiviteit van het beleid zelf niet in gevaar brengt.

Wetenschappelijke inbreng is essentieel in dit proces. Op het moment dat wetenschappelijke kennis wordt toegepast is het belangrijk dat een paraplublik wordt gehanteerd op het gehele anti-dopingraamwerk omdat elke beslissing om één specifiek onderdeel te veranderen, onvermijdelijk zal leiden tot (grote) veranderingen op andere onderdelen. Dit betekent dat het niet aan experts op één specifiek wetenschapsgebied moet worden overgelaten om bepaalde regelgeving aan te passen of om nieuwe regels in te voeren. Tegelijkertijd zijn juist deze experts nodig om goede en relevante regels op te stellen. Ook hier is evenwicht belangrijk: evenwicht tussen de specifieke kennis van experts en kennis over de praktische gevolgen voor het gehele anti-dopingsysteem, om zo onwenselijke niet-intentionele gevolgen te voorkomen. In de afgelopen decennia is anti-doping een beroep op zichzelf geworden. Effectieve anti-dopingmaatregelen vereisen een uitgebreide multidisciplinaire aanpak en continue evaluaties. Dit kan een vruchtbaar terrein zijn

voor samenwerking waar zowel wetenschappers als de onderzochte proefpersonen enorm van elkaar kunnen profiteren.

Het zou een fundamentele verbetering van het anti-dopingraamwerk betekenen als algemeen geaccepteerd zou worden dat het enigszins vage maar ethisch gezien belangrijke begrip 'spirit of sport' (wat in het Nederlands het beste omschreven kan worden als de elementaire waarden en normen van de sport) de kern vormt van alle anti-dopingmaatregelen. De beslissing om bepaalde stoffen en methoden te verbieden is op zichzelf al een ethische beslissing. Dat dit zo is, kan bediscussieerd worden door iedereen die er aanstoot aan neemt, maar het zou duidelijker zijn, en dus beter, om te accepteren dat dit begrip een centrale plaats inneemt in alle anti-dopingregels en dat het dus geen optioneel criterium zou moeten zijn als onderdeel van de praktische definitie van doping, namelijk de dopinglijst zoals vastgesteld door het WADA. Discussies over de inhoud van de dopinglijst kunnen beter gehouden worden over de twee andere criteria, te weten prestatiebevordering en gezondheidsrisico's.

Op basis van de resultaten van dit proefschrift zijn er veel verschillende specifieke deelgebieden waar het anti-dopingbeleid verbeterd kan worden. Dit zijn onder andere: minder rigoureuze harmonisatie van de dopinglijst, meer focus op de kerncriteria van de dopinglijst te weten prestatiebevordering en gezondheidsrisico's, nadere bestudering van de mogelijkheid om (en de gevolgen van) een getrapte beoordeling in twee lagen toe te passen bij lage concentraties van dopingstoffen, evaluatie van de effectiviteit van whereaboutsinformatie en dopingcontroles buiten wedstrijdverband, ondersteuning van sporters in hun zoektocht naar toegestane prestatieverbetering (zoals bijvoorbeeld het gebruik van voedingssupplementen), en meer aandacht voor niet-competitieve fitnesssporters naast de competitieve topsporters. Dit is zeker geen volledig overzicht van mogelijke verbetermaatregelen binnen het anti-dopingbeleid. Maar als deze brede lijst van mogelijke verbeterpunten wordt geïmplementeerd – en toegevoegd aan de bestaande huidige inspanningen op het gebied van voorlichting, dopingcontroles en juridische procedures – kan verwacht worden dat het huidige anti-dopingbeleid effectiever zal worden.

Het onderwerp 'effectiviteit binnen het anti-dopingbeleid' heeft de afgelopen jaren meer en meer aandacht gekregen. Maar het is een onderwerp dat pas in de kinderschoenen staat. Dit proefschrift vormt een eerste algemene poging het onderwerp aan te pakken. Het geeft voorbeelden en aanwijzingen op welke manier

het onderwerp 'effectiviteit' kan worden aangepakt als een gezamenlijke inspanning. In algemene zin komen de conclusies en aanbevelingen van dit proefschrift neer op een oproep om meer relevante gegevens te verzamelen, om een multidisciplinaire wetenschappelijke aanpak in te zetten, om anti-dopingprofessionals transparanter te laten werken en om meer gerichte discussies te voeren over wat de kern van het anti-dopingbeleid zou moeten zijn. Door het volgen van deze principes kan verwacht worden dat een beter evenwicht kan ontstaan tussen de hoofdtaak van anti-doping (het uitbannen van dopinggebruik) en de belasting die wordt opgelegd aan alle sporters (die, voor zover wij nu weten, in meerderheid geen dopinggebruikers zijn). De stem van de sporters zelf is van essentieel belang bij dit zoeken naar het juiste evenwicht aangezien zij de sleutelfiguren zijn van alle maatregelen op het gebied van doping. Met een dusdanige gezamenlijke inspanning kan verwacht worden dat betekenisvolle beleidsevaluaties, en daarmee beleidsverbeteringen, uitgevoerd en doorgevoerd kunnen worden. Dit is noodzakelijk omdat een systeem dat te veel sporters in de kou laat staan uiteindelijk aan zijn eigen gewicht ten onder zal gaan. Het maakt dan niet meer uit hoeveel goede bedoelingen aan de basis hebben gestaan van dit beleid. Het onderwerp 'doping in de sport' is simpelweg te belangrijk om dat te laten gebeuren.

1.
INTRODUCTION & METHODS

1.1 A short history of anti-doping

The first known anti-doping policies for humans by a sports organisation were laid down by the International Amateur Athletics Federation (IAAF) at a meeting in Amsterdam, the Netherlands, in 1928. The current anti-doping framework is based on the set of rules first introduced by the Medical Commission of the International Olympic Committee (IOC) in 1967, after several International Federations (IFs) and governments started to implement anti-doping rules on their own. This framework has been globally harmonised by the World Anti-Doping Agency (WADA), founded in 1999. With the introduction of the World Anti-Doping Program (WADP) in 2004, this harmonised set of rules is followed by most (inter-) national sport organisations.

With its core dating back to the 1960s, the current framework of rules is based on the publication of a list of prohibited substances and methods, analytical testing for indications of use of these substances and methods, and sanctioning athletes for violations of these prohibitions. These acts are encircled by education and research to support and strengthen the existing framework. During a period of almost 50 years, this basic set of rules has continuously been complemented and broadened, often as a reaction to new medical or juridical progress. As a result, the current anti-doping framework in sports is a complex set of rules and measures, where specific, and sometimes profound, historical knowledge seems to be a prerequisite for being able to understand the logic of all paragraphs and sub-paragraphs of the regulatory texts.

In the last few years, the existing anti-doping measures have been the topic of much debate. On the one hand, sport organisations are implementing new rules in order to catch more 'doping cheats', as it is often acknowledged that many doping users are currently not (yet) being apprehended by the anti-doping rules in place. Several governments are increasing their efforts to root out supply lines of doping substances and methods, and in more and more countries specific anti-doping

laws are introduced. At the same time, some journalists, lawyers, and philosophers question the fortitude with which these measures are implemented, wondering whether basic privacy laws or even human rights are challenged in the name of 'true sport'. In addition, in several individual doping cases the authority of officially accredited laboratories has been challenged by athletes and their juridical defence teams. Specific countries and sport organisations, including the individuals working for them, have been targeted as well. This situation becomes increasingly problematic with sporadic but ongoing accounts of athletes who explain how they have used doping without getting caught. This raises questions on the success-rate of anti-doping policies.

Even though the anti-doping framework is firmly incorporated in organisational and governmental structures in the world of sports, the current critiques need to be taken seriously since doubts about the validity of anti-doping measures and about their implementation will hinder general acceptance of the, sometimes burdensome, anti-doping rules. There are many stakeholders in the world of sport, and as with all rules there needs to be a certain level of agreement and understanding about the existing rules, or else they must be changed. Doubts and insecurity about the anti-doping system will first and foremost hinder those who matter most in this area: the athletes. A critical re-appraisal of the effectiveness of anti-doping policies is necessary.

1.2 Research questions

The main research question of this thesis is:

▶ How effective are current anti-doping policies?

Both an overall and an in-depth analysis of the various aspects of the anti-doping framework will be made and their effectiveness will be judged on their contribution to reach the overall goal. Special attention is paid to the coherence of these different aspects. In doing so, the main research question is guided by the following questions:

- What are the historical backgrounds and scientific foundations that have shaped current anti-doping policies?
- What are the intended and unintended consequences of these policies?
- What dilemmas and complexities are encountered in the field of anti-doping?
- What aspects of current anti-doping policies are likely to have the most impact, and what aspects are likely to have the least impact on effectiveness?

These questions are addressed, explored, and discussed in various ways, ultimately formulating an answer to the broader main research question. A summarising overall analysis will gauge what the influences of different factors are on the effectiveness of anti-doping policies. Their relative influence will be addressed, and specifically how they cooperate and contribute and as such build the anti-doping framework. Following the identified research questions, possible gaps or overlaps that may exist will be addressed and it will be determined in which way scientific knowledge (either currently available or not yet existent) may contribute to current anti-doping efforts.

Discussions on the issue of doping, including analyses of doping trends, often result in historical descriptions of definition-issues and accounts of individual cases. When in-depth analyses are performed, they generally focus on either analytical, socio-cultural, medical or juridical aspects of doping. Very seldom it is tried to analyse the entire system of anti-doping regulations and efforts as a whole, which is exactly the goal of this work. It is unavoidable that this should involve a multidisciplinary approach. The anti-doping framework has been built by many experts and many different aspects are important to fully appreciate the roles and intentions of all the components of this framework.

It is envisaged that this thesis will help to identify what constitutes an effective approach to deal with the issue of doping use in sport and, equally important, what aspects in its current form are less effective.

1.3 The current anti-doping framework

In order to discuss the effectiveness of current anti-doping policies, it is necessary to understand the basic structure of the anti-doping framework. Although the organisations and persons who are involved are many in number, in its essence it is rather straightforward. This paragraph serves as an outline of the current situation. A glossary of anti-doping abbreviations is included in appendix 1.

WADA, already mentioned in the previous paragraph, is responsible for drafting the World Anti-Doping Code (WADC), which currently contains 25 articles that outline the general rules in anti-doping regarding doping control, education, research, roles and responsibilities of various stakeholders, and regulations regarding acceptance, compliance, modification, and interpretation of the WADC (WADA 2015c). The WADC is complemented by five international standards describing the prohibited

list of doping substances and methods, the process of applying for therapeutic use exemptions for such prohibited substances and methods, the process of testing and performing investigations, analytical requirements for accredited laboratories, and general requirements to protect the privacy and personal information of individuals. Both the WADC and the five international standards are mandatory general rules that should be followed by all persons and organisations active in sports, or at least by all who have included a reference to the WADC in their rules. Together with a set of non-mandatory models of best practices and guidelines on various subjects they shape the WADP.

A specific task of WADA is the responsibility to monitor whether the organisations that have signed the WADC, the signatories, actually comply with these general rules. The consequences of non-compliance may be severe, with the possibility for international sports organisations to bar entire sports or countries from participation in major sport events, such as the Olympic Games. This possibility exists since the first WADC in 2004, but was not applied until late 2015, when several signatories to the WADC were declared 'non-compliant' by WADA. Since this happened in the late stages of this thesis, these developments will not be analysed here.

The main signatories to the WADC are the IFs that govern a specific sport (currently more than 60 in total, ranging from swimming and athletics to billiards and bridge), National Anti-Doping Organisations (NADOs; currently more than 130 in total, being either independent bodies or entities within a sports network, sometimes in an international cooperation), National Olympic Committees (currently more than 200 in total), National Paralympic Committees (currently more than 150 in total), and major event organisers such as the IOC and the Commonwealth Games Federation. All these signatories have implemented the WADC into a set of rules within their own jurisdiction.

Generally speaking, the anti-doping framework is shaped in such a way that athletes who are competing at the highest international level resort under the IFs and athletes who do not reach this level (yet) resort under the NADOs. In this sense, 'resort' means that they can expect to receive educational materials from that organisation, can expect to be submitted to doping controls by that organisation, could face a hearing and possibly a sanction from or on behalf of that organisation,

and have to apply for a therapeutic use exemption for medically prescribed substances or methods that are on the prohibited list at that organisation.

In addition to these organisations that are involved, there are currently more than 30 officially accredited laboratories that have the exclusive right by WADA to perform doping analyses in biological samples (mainly urine and blood) and there are numerous other organisations that play a specific role in the world of sports (for example athlete representatives and cross-national organisations such as the Council of Europe or the European Union). All these organisations keep each other informed and have specific interests. And although these interests in general terms may be the same when anti-doping matters are concerned (the WADC specifically outlines why doping should be banned, and they have all subscribed to this wording), it is also obvious that these interests may conflict with other interests at times. A prime example of this is an IF that starts an anti-doping case against one of their top performers while they also wish to promote their sport and as such benefit from these top performances.

An extra factor are the national governments worldwide. WADA is financed by both the IOC (being an 'overall sport representative') and national governments on a 50/50 basis, and currently its Foundation Board consists of 38 representatives, equally distributed between sports and governments. Governments are no signatories to the WADC, but have pledged to follow the principles of the Code by signing the UNESCO convention against doping in sport (currently more than 180 in total).

This situation shows that drafting and implementing anti-doping policies is a specific balancing act in itself. It means trying to find rules and wordings that are supported, or at least backed, by all organisations, from all over the world. Yet, these rules need to be clear and as unambiguous as possible. It also means that each and every organisation needs to be trusted to play their part in this intricate web of rules. Yet, the system needs to include checks to ensure that they actually do this since the issue of trust in this regard is also linked to commercialism and world politics. Literally in the last few days of writing this thesis, this became painfully clear when a state-controlled system was revealed in Russia, undermining the principles of the WADC (McLaren 2016).

This enumeration of participating organisations also shows the tremendous task that WADA needs to fulfil: working together with various stakeholders from around the world, with obvious various beliefs, convictions and wishes. WADA has introduced methods to collect feedback from these stakeholders, but keeps the ultimate decisions on the wording of regulations and drafting policies within their own realm of advisory panels, working groups, and their own staff. Ultimately, major decisions are made by its Executive Committee and Foundation Board.

Although many sport organisations adhere to the WADC, there are some influential non-stakeholders to the WADC. Professional North-American leagues in sports such as baseball, basketball, ice hockey, and American Football do possess anti-doping regulations, but have set up their own anti-doping framework. Studying the overlaps and differences between these frameworks and the WADP, and their consequences, could be an interesting study in itself, but this will not be performed in this thesis.

Finally, all these controls, education materials, panels and meetings cost money. The exact amount of the costs of the anti-doping framework is difficult to quantify. The costs of testing and analysing alone can be estimated to total at least 125 million euros per year (based on a minimum of 250,000 annual global doping controls which cost approximately 500 euros each to perform and analyse). An estimate of 300-400 million American dollars per year has been put forward in the past (Møller et al. 2015) and the president of the IOC, Thomas Bach, has mentioned an estimate of $500 million (Maennig 2014). This is obviously a large amount of money, but at the same time it is just a fraction of the global sports economy, which is estimated to be $150,000 million to $620,000 million by two different consultancy firms (Collignon et al. 2011, PwC 2011). Apparently, anti-doping should not cost more than 0.33% of the total amount of sport-related revenues and may in fact cost a much lower percentage of available funds. No matter what the exact figures are, this also brings the limits of anti-doping policies into the limelight: no matter what the exact costs are, the total budget will always be limited which calls for an optimal efficiency in spending the budget.

1.4 Backgrounds of the current study

In the field of anti-doping, self-reflection is very much present. Several Anti-Doping Organisations (ADOs) perform evaluation checks of their own efforts, for example through athlete questionnaires. As stated above, WADA has developed a system

of continuous feed-back and collecting official responses and opinions on several key-issues such as the International Standards, their Technical Documents, and the WADC itself that together form the WADP. These efforts themselves consume a large proportion of the available resources of the organisations involved. It is safe to assume that large amounts of data are present in ADO's files, without someone taking the time and/or financial resources to unearth these data and analyse them. As such, the issue of effectiveness may be talked about often, but is very seldom, if ever, translated into an instrumentalisation of effective anti-doping efforts.

This thesis will focus on performing a scientific analysis on several aspects of the anti-doping framework with a specific interest in trying to determine the effectiveness of current anti-doping policies. Ideally, 'effectiveness' in this sense refers to the degree in which anti-doping efforts contribute to the ultimate goal of anti-doping policies: the eradication of the use of doping in sport (see theoretical framework below). Even though it can be safely assumed that this ultimate goal will never be achieved, as there will always be someone who tries to bend or break the rules to gain an advantage, a doping-free sport is what anti-doping measures try to accomplish.

In setting up the structure of this thesis, it was envisaged to study the main pillars of anti-doping policies. But the operationalisation of this approach ran into ever-increasing troubles: when is a specific aspect important enough to be called a 'pillar'? Education, doping controls, and sanctions are clearly important subjects, but so are international cooperation, finances, and general policy measures. And all of these aspects are interlinked to each other, leaving blurry demarcation lines between them. It also became rapidly clear that it would be untenable to discuss all aspects of anti-doping policies in sufficient detail in one single thesis (this will be discussed more profoundly in the next two paragraphs). This resulted in a first focus on the meaning of the word 'effectiveness' itself in the context of anti-doping. A critical evaluation of the effectiveness of anti-doping policies showed that this major question currently hinges on one predominant aspect: are these policies doing what they intend to do? The intent of anti-doping policies is to refrain athletes from doping use and as such to provide non-using athletes a competitive environment that is not influenced by such use. Thus, a main focus should also be the prevalence of doping use, intentional or non-intentional. Closely related to these questions are the potential influence of doping substances on athletic performances and the impact of anti-doping measures on athletes.

As a consequence of these structural aspects, this thesis will first generally address the issue of effectiveness within the anti-doping framework. The focus turns then to the extent of doping use in the world of sports, both intentional and non-intentional, after which the effectiveness of available doping substances and methods will be discussed in three case studies. The degree in which substances are able to influence athletic performances is an essential piece of information when determining whether they should be banned or not. An additional three case studies will explore three, probably unintentional, consequences of the chosen path of anti-doping. These six case studies will be analysed both in general and in specialist terms. They have not been chosen by pure chance: they all find their origins in real-life discussions on actual problems encountered in executing anti-doping policies and as such they explore various dilemmas and boundaries of the anti-doping framework.

Theoretically, the aim of this study (a scientific analysis on several aspects of the anti-doping framework with a specific interest in trying to determine the effectiveness of current anti-doping policies) could be achieved in various ways, for example by writing policy documents, organising conferences, or even by publishing press releases. These actions are undertaken continuously, and have been undertaken by the author of this thesis as well in his past 18 years of working in the field of anti-doping as a researcher. The current format, as a scientific endeavour in the form of a PhD thesis and the collation of various scientific articles, maximises the possibility to gather results and present discussions and conclusions in an environment that is as unbiased as a human possibly can achieve. Virtually all findings are published in peer-reviewed journals and as such are independently checked, judged and reviewed in order to maximise their contribution to the existing scientific body of knowledge about this subject.

Another specific aim of this research is to transcend all specific expertises in the specific areas of anti-doping work, and to analyse the entire anti-doping framework from an overall perspective. All parts of the anti-doping framework are developed, and often executed, by experts in their specific fields (chemistry, law, psychology, medicine, etcetera). To determine the strength of the framework, it is necessary to appreciate all specificities of these specialistic subjects, but also to analyse their coherence and to identify possible gaps or overlaps in the way they are intertwined. This study will look at the anti-doping framework from above, like an umpire during a tennis match, and in order to be able to appreciate fully what one can see

from such an elevated position, one also has to take into account the specific details of the elements that build the framework.

As such, this thesis will provide a general overview of the body of knowledge that has been built in the field of anti-doping in the past, with specific emphasis on the last fifteen years, and with a focus on the work that currently is being performed and as such is shaping the future. At times it will be necessary to dig deep into the specificities of a certain subject as well. It will focus on the issue of effectiveness, and this will be done by studying various aspects of the WADP.

1.5 Epistemological position

The first and foremost aim of this thesis is to study an as yet underrecognised aspect of anti-doping policies: effectiveness. It is not intending to test hypotheses and verify or reject certain theories, but is predominantly descriptive and policy-oriented in nature. Subsequently, and based on the as such encountered current state of affairs, conclusions will be drawn and possible future improvements will be described. Obviously, one cannot describe situations and data, leading to discussions and conclusions, without following a personal framework of beliefs and values. This paragraph serves as an explanation to this theoretical framework and the epistemological position that I take.

Regarding the subject of this work, anti-doping in sport, it can be concluded that the aim of anti-doping policies is often worded in idealistic terms (protect integrity; preserve true sport; etc). But ideals are socio-culturally plastic terms – they change from one environment to the other, and from one timeframe to another. It is important to bear in mind that current anti-doping policies are not just a reflection of current socio-cultural values, but they are also a product of the way in which the issue of doping has been dealt with in the past, and it will feed the way in which doping will be handled in the future. Rules may change, and potentially they could change dramatically.

Good scientific studies are at best small catalysts of this progress, or what is currently seen as progress by a majority of the people and organisations that are involved. Such studies may in fact speed up progress, but they will never be able to change current paradigms against the wheels of time. The eventual outcome of the current process, set in motion by the foundation of WADA in 1999, is insecure. But it will largely be based on the quality of the work that is being performed right

now, on many fronts and in many countries. This thesis ambitions to contribute to this process of progress and serve as a small sprocket in the global machinery of improving current practices in the field of anti-doping.

General scientific reasoning focuses on analysing and presenting data in an objective way, or as objective as humanly possible, after which theorising and drawing implications may begin. And where the correct data are not available, perhaps efforts should be increased to collect them. This way, the current state of anti-doping policies can be described, studied, and discussed. And, eventually, decision makers may use such analyses and their results to draw up future policies.

This study follows the principles of organisation science as described by Deetz (Deetz 1996). It is not possible to simply state that a study is performed in an objective or more subjective manner; general and open research should be judged in its entireness. Likewise, it can be misleading to make a distinction between qualitative and quantitative research, as proper scientific research includes both aspects and should focus on reaching the core of a specific subject, regardless of the point of entry. As Deetz states, "More important than data collection techniques are the questions asked and the intent of analysis" (Deetz 1996).

The intent of this study is to critically look at what is currently known about the effectiveness of anti-doping policies, to describe several empirical studies that touch upon this subject, and to start up discussions on what should be known to allow for better evaluations in this area. As Deetz warns, an attempt to analyse an entire system as a whole (in this case anti-doping regulations and efforts, what I will call 'the anti-doping framework') runs the risk of shallow research findings unless profound specialist analyses are being performed. But as profound specialist analyses can only be performed when basic data are agreed upon, it seemed valuable to start discussions on effectiveness on a broad level. This is by no means an attempt to keep specialists in certain scientific fields away from studies regarding anti-doping policies. On the contrary: specialists are necessary to provide in-depth knowledge and state-of-the-art approaches, which will increase the strength of the anti-doping framework.

The current study is set up as a verifiable collection of data interpretations, and general conclusions are drawn very cautiously and rather hesitantly. As such, this scientific study strives for objectivity. However, this does not mean that my analysis

is 'value-free'. An identical dataset on the prevalence of doping and the effectiveness of anti-doping policy can be interpreted by one person as clear evidence that the anti-doping battle should be waged with even more intensity, whereas another person may conclude that this stalking of athletes has lasted long enough. Such diverse opinions are commonplace, especially in relation to an ethical issue such as anti-doping policies. I do not take a 'neutral' position in this debate. I have worked for 18 years in an organisation which mission is to create doping-free sports in the Netherlands. My responsibility in this organisation has been to collect and disseminate scientific knowledge about all sorts of doping related issues. In this function, weighing all evidence that I have encountered and personal experiences I have witnessed, I have developed the following position in the discussion whether performance enhancing substances and methods that are labelled today as doping should be allowed or not: given the effects of several existing pharmacological substances (Hartgens & Kuipers 2004, Sjoqvist et al. 2008, Heuberger et al. 2012, Van Breda et al. 2014) it is unavoidable to place certain restrictions to the use of such substances, as athletic competitions will change dramatically if there are no restrictions in place. This means that the fight against doping as such will not be questioned in this thesis. Its existence will be regarded as a normative postulate, which is the current practical situation in the world of sports, even though fundamental questions on its legitimacy can and should be asked now and in the future.

As an extra background of the author, I should say beforehand that I received my MSc-title in human movement sciences at the Vrije Universiteit (VU University) in Amsterdam. This study is particularly multidisciplinary, studying human movement from all angles (anatomical, physiological, psychological, sociological, etcetera). This training will be reflected in this thesis as well in an attempt to combine all relevant expertises. This also means that this thesis does not follow one single theoretical framework. It draws from various scientific reasonings with an aim to be as practical as possible.

Anti-doping policies have been described and studied by a variety of scholars (Houlihan 1997, 1999, Savulescu et al. 2004, Kayser et al. 2005, 2007, Miah 2007, Bowers 2009b, Mazanov & Connor 2010, McNamee & Tarasti 2010, Møller 2010, McNamee & Møller 2011, Wiesing 2011, Hunt et al. 2012, Hoberman 2014, Møller & Dimeo 2014, Møller et al. 2015). In essence, they all discussed the issue of effectiveness as well, although they did not always mention it specifically. The aim of the current thesis is to bring this specific subject into the limelight. It

will use several case studies as an exploration into various aspects of the issue of effectiveness. Based on these findings, it will try to paint a picture of the current status, and desirable future developments.

Before any description or interpretation can be shared, it can be stated that anti-doping rules are patronising by default since they lay down restrictive rules for the sake of common health protection. This does not mean that they will not be seen as necessary by many, for example in a situation where an overzealous parent pushes, and effectively changes, the physical and medical condition of an immature child by means of the illegal administration of medicines – and this is a real-life example that happened more than once in the history of modern sport. The exact circumstances of the context in which anti-doping policies will be judged to be logical, necessary, desirable, obsessive, superfluous, or tragic will never be agreed upon globally. In that sense, WADA has a goal that can only be reached on an institutional level. It can be stated beforehand that harmonising the opinions of a world with kaleidoscopically different opinions, interests and objectives on one identical topic, namely the use of doping in elite sport, is logically impossible. But this does not mean that scientific reviews of the current situation are impossible.

1.6 Methodology

As described above, this thesis is built on describing the current situation in the anti-doping framework based on specific case studies and the conclusions will evolve from there. Data have been gathered in the past eighteen years working as a scientist in the field of anti-doping. These data were mainly intended to evaluate current or foreseen policy measures as well as to assist in specific scientific subjects stemming from individual doping-related cases. This has always been coupled to a keen interest into the history and backgrounds of the current situation. In retrospect these specialistic case studies proved to have more in common than originally thought: they are all focussing on areas of anti-doping that were perceived as problematic at that time, and although progress has been achieved they may still continue to be debated by the stakeholders in anti-doping. That is why it was deemed useful to bring them together, to discuss them anew on the basis of general research questions, and to discuss and analyse them in their coherence. The reason behind this approach is that it is exactly on the borders of existing policies, in the areas where basic foundations scratch against the surfaces of reality up to a point where it may start to hurt, it is there where these basic foundations are tested to the core. This is also why these case studies are still topical. Whenever texts have been

published before, either as a scientific article or as a report, this is clearly marked. All texts have been reviewed and subsequently they are newly discussed to reflect the situation in 2016.

This first chapter has introduced the issue of 'doping in sports', hopefully sufficiently to make clear that this is indeed a peculiar and specific aspect of the current sport environment. But even though the issue of 'doping' is specific, the practical realisation and instrumentalisation of this topic is highly multidisciplinary. An athlete who contemplates doping (which involves the scientific disciplines of psychology and sociology) will need to get access of prohibited substances (law, criminology, economics) to gain an athletic advantage (physiology), mostly at the risk of certain health effects (medicine, toxicology). They will very seldom act alone (sociology, anthropology). These athletes are bound by a set of rules (governance) that are overseen by a system of analytical controls (chemistry) and that in its essence will always be arbitrary (philosophy, ethics). From its onset it can be asserted that none of these scientific specialties can be fully appreciated and discussed in one thesis. Yet, in order to study and discuss the issue of doping, they all need to play a role. That is the main challenge of this thesis in the specialty 'doping'.

Having said that, it is necessary to instrumentalise the effectiveness of anti-doping policies. This issue will be discussed in more depth in the next chapter, but generally speaking an evaluation of effectiveness needs to take into account an overall goal. For this thesis it is postulated that the goal of anti-doping policies is to eradicate doping in sport. Regardless of one's philosophical convictions on autonomy rights for every individual, the goal of anti-doping policies is to fight doping in sport. And if one fights against a certain behaviour, one aims to eradicate this behaviour regardless of the question whether it is actually feasible to achieve this.

Another aspect of effectiveness is that any effort will always come with certain costs. These costs can be financial (in currency), but also social-psychological (in freedoms). Either way, the costs can be expected to be maximised within a framework of rules and regulations that is predominantly guided by ideological ideas. Different groups with different interests are bound to judge the maximum costs differently, but certain limits will always exist.

Once the concepts of effectiveness and doping have been discussed, the attention will be focussed on the extent of doping use, and the effectiveness of possible

doping substances and methods. The latter will not be a complete physiological discussion on all physiological properties of prohibited substances and methods, as these are discussed in detail elsewhere (Bahrke & Yesalis 2002, Congeni & Miller 2002, Hartgens & Kuipers 2004, Kuipers & Ruijsch van Dugteren 2006, Orchard et al. 2006, Petrou 2006, Sjoqvist et al. 2008, Heuberger et al. 2012, Momaya et al. 2015). Instead, three separate case studies will explore the extent in which sport performance can be altered by prohibited substances and methods and how anti-doping policy makers have been dealing with these characteristics. When the extent of doping use is considered together with the potential impact of doping on athletic performances, it can be discussed what the influence of doping is, or at least can be, on modern sports. Following these paragraphs three different case studies will describe specific consequences of anti-doping policies on the lives of (elite) athletes. This information will be taken together to describe potential amendments to current anti-doping policies, and overall conclusions will be drawn along the lines of the research questions as formulated above, ending with an epilogue containing some thoughts on an often proposed potential new approach to anti-doping: permitting the use of substances and methods that are currently prohibited, either completely or up to a certain degree, under strict medical supervision.

2.
RESULTS & DISCUSSION

2.1 Conceptualising effectiveness

When trying to achieve something with a limited amount of resources, one has to set priorities. And when one tries to evaluate retrospectively whether this could have been done in a better, or more efficient, way, there are various ways to tackle such an evaluation. The dictionary provides the following definitions of words originating from the Latin verb efficere which translates into 'to bring about':

- efficacy - the power to produce a desired result or effect;
- efficiency - the ability to do something or produce something without wasting materials, time, or energy;
- effectiveness - producing a decided, decisive, or desired effect (Merriam-Webster 2015).

As one of the aims of this thesis is to be practical, it will not be discussed elaborately what the specific differences are or could be between these words. Obviously, there are limited resources in anti-doping and nobody who is involved intends to waste resources. The word 'effectiveness' was chosen as the core concept as anti-doping is an obvious area of pursuing a desired effect. In an optimal situation a maximum effect is reached with a certain amount of resources, or a certain effect with a minimum amount of resources, whatever the point of departure is. The ratio of this equation may be seen as an index of effectiveness. But since the units of the denominator and the numerator will very seldom be the same, the quantification of this word is very seldom of any true meaning. The economic way of solving this problem, using currency as both denominator and numerator, is highly relevant and should be discussed as well, but is a totally different issue. Besides, this becomes only relevant when some degree of consensus has been reached on what should be in the numerator when anti-doping is discussed.

There are obvious practical problems when assessing and comparing effectiveness in anti-doping. Within the current harmonised setting it is practically impossible

to set up a comparative study with distinctly different dependent variables. It would also be ethically unacceptable to separately feed two groups of athletes with differing anti-doping regulations yet to have them compete against each other. One could try to reveal performance determinants of ADOs and rank these in a performance index as has been done in different areas of organisational science, thus trying to identify best practices in the work of ADOs. No research in this area has been published before, but it is currently being done in a WADA-sponsored study (Jann In progess). Still, such an endeavour will only provide part of an answer as it is solely targeted at the organisational structures of the framework, and not at other aspects nor at the framework in its entireness.

2.2 Effectiveness and anti-doping policy

In this paragraph, first the current materialisation of the word 'effectiveness' in the anti-doping framework will be discussed, after which the concept of 'doping' will be defined.

The three versions of the WADC that have been in place since 2004 have used the word 'effective' many times. In the (current) 2015 Code it is also mentioned in the paragraph describing the 'purpose, scope and organization of the world anti-doping program and the code':

'The purposes of the World Anti-Doping Code and the World Anti-Doping Program which supports it are:

- to protect the Athletes' fundamental right to participate in doping-free sport and thus promote health, fairness and equality for Athletes worldwide; and
- to ensure harmonized, coordinated and effective anti-doping programs at the international and national level with regard to detection, deterrence and prevention of doping.' (WADA 2015c)

The word 'effective' is used numerous times in other sections of the WADC 2015 as well, referring to effective testing, harmonisation and education. No specific definition is given, but both the purpose of the Code and the context of these statements give sufficient clues on how to understand effectiveness, best illustrated by article 18.4: 'All Signatories and Athletes and other Persons shall cooperate with each other and governments to coordinate their efforts in anti-doping information and education in order to share experience and ensure the effectiveness of these

programs in preventing doping in sport.' Hence, it is all about battling the presence of doping itself, being a noun or a verb.

WADA has addressed the issue of effectiveness several times in the last few years. This happened most obviously in a report by a working group chaired by Dick Pound, titled 'Report to WADA executive committee on lack of effectiveness of testing programs' (Ayotte et al. 2013). Focussing predominantly, but not exclusively, on the issue of doping controls, this report concludes that "To date, testing has not proven to be particularly effective in detecting dopers/cheats." The report does not provide a definition or interpretation of the word 'effective'. It is mainly a set of recommendations, based on a series of observations mentioned in the appendix, but did not include a comprehensive review of the number of 'dopers/cheats' that are supposed to be out there. It calls upon WADA to be more strict against non-compliant stakeholders, implicitly centering the issue of effectiveness on an issue of compliance to the WADC. This is also what WADA-management predominantly is talking about when discussing effectiveness: the degree in which stakeholders do what they are supposed to do according to the WADC, although current WADA-president Craig Reedie seemed to address all possible meanings of increased effectiveness in a recent interview, such as compliance, better testing, and better analytical methods (Owen 2015). But again, there has been no official definition of 'effectiveness'.

The definition of doping has long been debated (Houlihan 1999, Gomez 2005, McNamee & Møller 2011, Gleaves 2015, Møller et al. 2015, Schneider 2015). Many historical accounts start with explaining the allegedly performance enhancing substances that were used in ancient Greece during those Olympic, and other, Games (Birchard 2000, Yesalis & Bahrke 2002, Papagelopoulos et al. 2004, De Rose 2008, Müller 2010). But this is misleading, as the word 'doping' did not exist in those times, and as far as we know it the use of concoctions such as human breast milk (which contains IGF-1) or animal testicles (which contain testosterone) was not prohibited. As a side note, it is interesting to realise that the use of clothing was prohibited during the ancient Olympic Games, a rule that in its essence is equally arbitrary as current anti-doping regulations (Yalouris 1982). Fast forward to the 1800s, when organised sports started to grow, and the use of performance enhancing substances grew along as well. In those times, the word 'doping' came into use, but it was by no means prohibited yet. The first known prohibition was agreed upon in 1928, by the IAAF, in the lead-up towards the modern Olympic

Games in Amsterdam, the Netherlands (IAAF 1928). With the issue debated more and more in the 1950s and 1960s, the IOC brought harmonisation for at least the Winter and Summer Olympics starting in 1968. But not until the formation of WADA in 1999 the process of harmonisation across all sports during all competitive seasons started. WADA also settled the debate around the definition of doping, since the WADC provides this in a juridical sense as the occurrence of one or more of the anti-doping rule violations set forth in the WADC itself, currently being:

- presence of a prohibited substance or its metabolites or markers in an athlete's sample;
- use or attempted use by an athlete of a prohibited substance or a prohibited method;
- evading, refusing or failing to submit to sample collection;
- whereabouts violations;
- tampering or attempted tampering with any part of doping control;
- possession of a prohibited substance or a prohibited method;
- trafficking or attempted trafficking in any prohibited substance or prohibited method;
- administration or attempted administration to any athlete in-competition of any prohibited substance or prohibited method, or administration or attempted administration to any athlete out-of-competition of any prohibited substance or any prohibited method that is prohibited out-of-competition;
- complicity;
- prohibited association (WADA 2015c).

In practice, doping is materialised by the Prohibited List International Standard, which is routinely renewed on (at least) an annual basis in order to follow new experiences and scientific findings. This is a list of more than 200 substances and a few methods, arranged in fifteen groups, that are considered prohibited in sport. It was one of the first hallmarks of WADA to clearly write down what sort of substances and methods may be considered for this prohibited list: besides substances and methods that can mask the use of prohibited substances, these are any substance (or method) that is deemed to meet at least two of the following criteria: potentially performance enhancing, potentially representing a health risk, or WADA's determination that it violates 'the spirit of sport' (McNamee 2012, WADA 2015c). This concept shall be discussed in more depth later, but at this

point it is worth mentioning that this list is an 'open list' in the sense that most groups of substances include descriptive words like 'including, but not limited to' or 'and other substances with a similar chemical structure or similar biological effect(s)'. This immediately showcases the reality of anti-doping measures: the core may be clear, but at the edges of its realms it comes down to an interpretation of general rules. For practical purposes this often needs an interpretation by WADA, which sometimes will be challenged by the appropriate juridical panels such as, for example, in the case of cyclist Maria Calle Williams (ADKC 2005).

Having defined 'doping', even though it may raise a few question marks on the edges of the definition, it is possible to define what will be regarded as 'effectiveness of anti-doping policies' in this thesis: the degree in which current policies succeed in eradicating doping in sport. The word 'policies' is interpreted in the broadest sense of the word, meaning all measures that have an impact on the stakeholders in this area (political, juridical, economical) but most focus will be on the practical consequences of the policy decisions that are being made.

The concept of effectiveness of anti-doping policies can be discussed in various ways, but all ways encircle the central issue whether the efforts that are undertaken weigh in in the eradication of doping use. This key topic of all doping-related discussions is a surprisingly barren field, although some scientific work is available. Therefore, this chapter will first discuss the available data on the extent of doping use itself (paragraph 2.3). As a second layer around this central question, several case studies on the effectiveness of doping substances and methods will be discussed. The Prohibited List International Standard has been generating discussions on its content since its inception and the expected impact of these substances and methods on athletic competitions will contribute to discussions on effectiveness of policies as well (2.4). Finally, as a third layer around the core issue of actual doping use, it is important to discuss the impact of anti-doping policies on all athletes. Measures against certain unwanted behaviour should always be balanced between the group of people that show this behaviour, and those who do not (2.5). The borders of these three layers may be porous at times, yet this approach is expected to provide a general framework of discussing various effectiveness-issues leading to both specific (3) and general (4) conclusions on this subject.

2.3 The extent of doping use

How many athletes are indeed doping? The answer to this question may be regarded as the Holy Grail of doping research. A review has been written in order to study all aspects of this difficult question, and also to provide the best possible answer in competitive elite sports based on currently available data. This review has been published in the journal *Sports Medicine* (De Hon et al. 2015). It mainly focuses on intentional users of doping, also labelled 'deliberate cheats', since the main focus when trying to eradicate doping use in sports is on this group of athletes. It is recognised that the word 'cheats' is a highly flammable denomination but it is only fair to use this term in the current anti-doping context (Schermer 2008, Vorstenbosch 2010). The subject of unintentional doping use will be discussed more extensively in paragraph 2.3.2, partly based on an article that has been written on the basis of data that had been provided by WADA (De Hon & Van Bottenburg 2016).

2.3.1 The prevalence of intentional doping use in elite sports

The following text is the full text of an article published in the journal *Sports Medicine* in 2015.

PREVALENCE OF DOPING USE IN ELITE SPORTS — A REVIEW OF NUMBERS AND METHODS

O de Hon, H Kuipers & M van Bottenburg

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Abstract

The prevalence of doping in elite sports is relevant for all those involved in sports, particularly for evaluating anti-doping policy measures. Remarkably, few scientific articles have addressed this subject so far, and the last review dates back to 1997. As a consequence, the true prevalence of doping in elite sports is unknown. Even though it is virtually impossible to uncover the exact prevalence of a prohibited activity such as doping, various methods are available to uncover parts of this particular problem, which enables the circumvention (to a certain degree) of the issues of truthfulness, definition problems and the limits of pharmacological evidence. This review outlines the various methods that exist and presents the scarce data available in this area. It is concluded that a combination of questionnaires using the Randomised Response Technique and models of biological parameters is able to provide the statistical possibilities to reveal accurate estimates of this often undisclosed practice. Data gathered in this way yield an estimation of 14-39% of current adult elite athletes who intentionally used doping. These period prevalences have been found in specific subgroups of elite athletes, and the available data suggest that the prevalence of doping is considerably different between sub-groups with varying types of sport, levels and nationalities. The above-mentioned figure of 14-39% is likely to be a more accurate reflection of the prevalence of intentional doping in elite sports than that provided by doping control test results (estimate of doping: 1-2% annually) or questionnaire-based research (estimations between 1 and 70% depending on sport, level and exact definitions of intent and doping). In the future, analytical science may play a more important role in this topic if it may become feasible to detect very low concentrations of prohibited substances in sewage systems downstream of major sporting events. However, it is clear that

current doping control test results show a distinct underestimation of true doping prevalence. It does not seem feasible to distil better estimates of the prevalence of doping based on performance indicators or ego documents because of the various existing effects that influence athletic performance. Such information can only be used as extra information to augment the accuracy of prevalence rates that have been found by using other techniques. True doping prevalence studies have been scarce in elite sports so far. With the correct application of the available scientific methods, preferably using harmonised definitions of the terms 'doping' and 'elite sports', more information on this topic may be gathered in a relatively short time. This would assist anti-doping professionals in the future in order to evaluate the effects of possible anti-doping measures, and better anti-doping policies would serve athletes who compete without doping. The existing anti-doping measures seriously impact the lives of elite athletes and their immediate entourage, which imposes a moral burden to evaluate these measures in the best possible way.

Key Points

- The prevalence of doping in elite sports is likely to be between 14 and 39%, although this figure can differ widely in various sub-groups of athletes.
- The prevalence of doping can be best measured using a combination of questionnaires using the Randomised Response Technique and available models of biological parameters.
- Measuring the prevalence of doping in elite sports is important for both anti-doping policy discussions and for the athletes themselves. Trustworthy prevalence figures provide a tool for evaluating the effectiveness of anti-doping policies.

Introduction

The true prevalence of doping in elite sports is often discussed. Various methods exist to study doping prevalence, but recent revelations by various elite cyclists underlined a discrepancy between true prevalence figures and positive doping tests.[1,2] This discrepancy is probably not limited to cycling,[3] and casts serious doubts on the effectiveness of current anti-doping policies.

The main aim of this article is to discuss the advantages and disadvantages of available methods to gather information on the prevalence of doping in elite sports: (1) laboratory-based chemical analyses; (2) questionnaires; (3) inferences from performances; and (4) inferences from ego documents. A secondary goal is to discuss the currently available scientific data on the prevalence of doping use in

elite sports in order to estimate actual doping use. The last review on this subject was published in 1997.[4]

Practical Limitations of Studying Doping

Three inherent limitations are associated with trying to reveal prevalence figures for doping in elite sports. First, chemical analyses cannot detect all the doping substances or methods available to an athlete. The pharmacokinetics of doping substances are such that performance-enhancing effects often outlast the time window for detecting traces of a substance in an athlete's bodily specimen.[5] Over the last few years there has been an increasing number of anti-doping rule violations (ADRVs) based on indirect (non-analytical) evidence of the use of prohibited substances. Such efforts can be expected to narrow the gap between actual doping and analytical results. However, as yet, these cases are limited in number.[3]

A second limitation is that of any study design that relies on personal input from athletes; they cannot be expected to be completely truthful, as doping is prohibited. Particularly when athletes are still active, there is an obvious barrier to discussing doping in detail. This limits the accuracy of data gathered using personal contacts.

Third, there is a definition issue. Some prohibited substances, such as cocaine, marihuana and alcohol, are also used in so-called 'social' settings without any intention to enhance athletic performance. Some athletes may not regard this as doping, while the anti-doping rules will flag this as an ADRV when traces of these substances are found in an athlete's urine during the competition, even when the actual use occurred several days before. When asked about their 'doping' such athletes may not provide full and correct information, even if they intend to cooperate truthfully with the researcher.[6] The opposite is also a confounder: an athlete may be convinced that he is breaking the rules even when the substance is in fact not prohibited. Such misunderstandings regarding the legal definition of 'doping' limit the interpretation of available data on this issue.

The Need for Reliable Data

Despite these inherent limitations, it is important to try and determine a reliable, clearly defined prevalence of doping in elite sports. For anti-doping professionals, such information allows for an evaluation of the effectiveness of their policies (preventive measures, education, tests, sanctioning regime, focus on drug trafficking, etc.). Such evaluations are currently essentially lacking in the field

of anti-doping, which begs the question from some critics whether anti-doping policies are legitimised at all.[7-11] The various efforts aimed at informing athletes of the existing anti-doping rules (education, tests, sanctioning) require considerable resources. All these efforts are legitimised by the perception of as yet non-disclosed violations. But the true extent of the problem is seldom addressed, and so estimations on doping prevalence tend to vary to a large degree, starting from 'few' to 'all' athletes.[12,13] This also leads to popular but unfounded statements such as 'it is impossible to cycle a Tour de France without doping' or 'every finalist in an Olympic 100 m track final must have used doping'. Reliable scientific data would enable such general statements to be verified. In addition, factual information about doping prevalence would perhaps give more support to true clean champions.

Definitions

Definitions of the most essential terms in this review are outlined in table 1. In this article, the term 'substances' should be read as 'substances and/or methods' so as to include all prohibited substances and methods that are mentioned on the official Prohibited List International Standard.[14]

Table 1 Definition of terms

Prevalence	True point prevalence refers to a total number of identified cases in a specific population at a given point in time. When studying the available data on doping, many data actually refer to period prevalences, signalling the occurrence of a condition within a specified period of time (true incidences are absent altogether in this area). In this review, the word 'prevalence' will refer to all cases identified within a specified population, in this case doping amongst elite athletes. The exact backgrounds of the available data are mentioned where appropriate.
Doping	The term 'doping' refers to the set of prohibited substances and/or methods as identified by the ruling body of the particular sport. Globally speaking, almost all sport federations follow the Prohibited List International Standard of the World Anti-Doping Agency,[14] which is reviewed and updated at least once a year. This means that the term 'doping' in this review does not reflect other doping violations mentioned in the World Anti-Doping Code, such as whereabouts failures or trafficking.
Sports	The term 'sports' is reserved for all activities that fit the broad definition as defined by SportAccord.[110] SportAccord currently has 91 international sports federations as members, including both Olympic and non-Olympic sports. Generally speaking anti-doping rules are only present in competitive sports, and non-competitive activities such as walking and fitness therefore receive little interest in this review.

Elite sports	Without defining a strict lower boundary for this term, we consider all athletes who compete at the level of international championships and highest national championships as 'elite'. This includes juniors and adults in their respective age groups. So-called 'masters athletes', being athletes who compete against similarly aged opponents once their athletic prime has passed, are not considered 'elite' in the context of this review. The inclusion of the highest national championships makes this term broader than solely those athletes who represent their countries at major sport events such as the Olympic Games, Commonwealth Games, World Championships or continental championships but fits the current practice where Anti-Doping Organisations focus their attention primarily on these levels.

Search Methods

Data were extracted from personal files, as well as from a comprehensive literature search in the PubMed database without limits in search period. Key words were 'prevalence' or 'incidence', combined with 'doping' or 'performance', followed by individual inspection of titles and, if necessary, abstracts. Reviews and original articles focusing on elite athletes were always included; prevalence studies in other groups of athletes were only included if their content or methodology added something new to the previously collected studies.

Laboratory-Based Chemical Analyses

Doping Control Test Results

An obvious source of information for the prevalence of doping use is the result of doping tests, based on either urine or blood analyses. Since 2003, the World Anti-Doping Agency (WADA) annually publishes an overview of Adverse Analytical Findings (AAFs) reported by official WADA-accredited laboratories;[15] the International Olympic Committee (IOC) did this in the years before (personal communications). These data encompass more than 50 different sports, including all Olympic and Paralympic sports. Table 2 lists these data, which are generally difficult to access publicly. WADA has improved the transparency of these data during the last few years, but detailed information on the exact substances found in which sports or laboratories is not provided. These are anonymous data by default, since a doping control laboratory does not know the identity of the athlete who produced the sample.

These data have various limitations. First, they only show what substances have been found at the time of sample collection. Detection windows of the various prohibited substances are highly variable, ranging from hours to months after last

use.[5,16,17] Some effective doping substances have a very short detection window, especially when used in low doses, and thus cannot be traced days or even hours after administration. Intentional users of doping are known to employ such techniques, knowing that they will not be tested every day.[1,18,19] This means that doping tests, even when performed at irregular intervals at unexpected times, will never catch all athletes who dope.

A second limiting factor for detecting doping is the analytical capability of doping laboratories at the time of analysis. According to current anti-doping rules, re-analysis of older samples may be done up to 8 years after sample collection to benefit from improved analytical techniques. The cases where this was deployed, such as for methoxy polyethylene glycol-epoetin beta and methandienone, yielded some new doping cases, but these were only small in number, yet very high profile at times.[20,21] In 2005, the French newspaper L'Équipe published the results of re-analysis for recombinant human erythropoietin (rhEPO) in samples from the 1999 Tour de France. These retrospective analyses, which at the time were judged to be legally inadmissible according to the anti-doping rules that were in place in 1999, but which later proved to be correct at least in the case of 1999 first-finisher Lance Armstrong, revealed that 20 samples showed signs of rhEPO out of a total of 67 extra analyses shown by the newspaper (point prevalence of 30%).[22]

Third, the official laboratory data simply refer to the substances that have been found in an athlete's specimen, even when an athlete had a genuine therapeutic need for a particular substance. In such a case, the athlete may have a valid 'Therapeutic Use Exemption' (TUE) to use this substance. For example, an asthmatic using formoterol and budesonide will show up twice in the overview of AAFs, but this cannot be regarded as doping as long as therapeutic guidelines given by the doctor are followed. This means that the anonymous overviews of laboratory findings also possess an inherent overestimation, particularly of intentional doping.

An extra problem for assessing accurate prevalence data of doping is that most AAFs in the category 'anabolic steroids' refer to atypical steroid profiles, which do not constitute an ADRV. In such cases, additional testing is needed before such 'atypical' findings can be regarded as proof for doping. As shown in table 2, WADA has reported the difference between AAFs and ATFs since 2008, but this distinction was not made in the years before. A large proportion of the reported AAFs are in fact not linked to ADRVs. This example also shows the difficulty in

using these data in longitudinal analyses. The data that are published annually are based on the rules at that time.[15,23] Since these rules may change, it is difficult, if not impossible, to compare these data over the years. The percentage of 'findings' in doping test results have fluctuated between 0.96 and 2.45% over the years. Analyses per country yield similar period prevalences, although the fluctuations may be somewhat larger.[24-27]

Table 2 Laboratory findings in doping tests 1987-2013[15]

Year	Doping tests (n)	AAFs (n)#	ATFs (n)#	Total findings (AAFs + ATFs)	Findings (%)§
1987	37,882			854	2.25
1988	47,069			1,153	2.45
1989	52,371			1,206	2.30
1990	71,341			932	1.31
1991	84,088			805	0.96
1992	87,808			993	1.13
1993	89,166			1,222	1.37
1994	93,680			1,278	1.36
1995	93,938			1,516	1.61
1996	96,454			1,569	1.63
1997	106,561			1,779	1.67
1998	105,250			1,926	1.83
1999	118,259			2,341	1.98
2000	117,314			2,229	1.90
2001	125,701			2,075	1.65
2002	131,369			2,371	1.80
2003	151,210			2,447	1.62
2004	169,187			2,909	1.72
2005	183,337			3,909	2.13
2006	198,143			3,887	1.96
2007	223,898			4,402	1.97
2008	274,615	2,956	2,105	5,061	1.84
2009	277,928	3,091	2,519	5,610	2.02
2010	258,267	2,790	2,027	4,817	1.87
2011	243,193	2,885	1,971	4,856	2.00
2012	267,645	3,190	1,533	4,723	1.76
2013	269,878	3,529	2,433	5,962	2.21

AAFs = adverse analytical findings, ATFs = atypical findings
# Available since 2008
§ Percentage of findings (AAFs + ATFs) as a proportion of the total number of doping tests. Further explanations of the terms AAFs and ATFs can be found in WADA's laboratory testing figures.[15]

A final major problem for obtaining accurate prevalence data is that it is impossible to derive the level of intentionality of doping use on the basis of AAFs or ADRVs alone. Preliminary analyses in the sport of tennis showed that a majority of ADRVs are most likely to be unintentional.[28,29] The legal description of ADRVs in WADA's World Anti-Doping Code does not address the issue of whether the rules have been broken knowingly or inadvertently, although this can play a role in the determination of the exact sanction once a violation has been established. This strict focus on violations per se has led some individuals to conclude that there is no such thing as 'unintentional doping'. Yet, fundamentally speaking, there is a big difference between intentional and unintentional violations. Also, when evaluating the effectiveness of the existing policies, it is important to make a distinction between deliberately violating the existing rules and so-called 'accidents'. The backgrounds of ADRVs may require completely different educational efforts.

Population Estimates Based on Biological Parameters

An indirect way of estimating the prevalence of doping in a group of athletes is to look at the distribution of certain biological parameters. Some work has been performed in this area regarding blood parameters, which gives information on the prevalence of blood-related doping methods, such as erythropoietin-use and other haematological manipulations. In elite cycling, the percentage of 'extreme' (and therefore suspect) haematological values has dropped between 2001 and 2009 from 11 to 2%,[30] which can be regarded as an indication that haematological doping (or at least 'extreme' doping methods) has decreased during these years. In other sports, similar attempts have been made to link possible doping use to individual blood parameters.[31,32] A more sophisticated method has been introduced into the area of anti-doping by Sottas et al.[33] It is based on a Bayesian model that includes relevant parameters and empirically validated data analysis of both users and non-users of doping. Given a certain population-wide dataset, the model identifies what percentage of the data can be expected to be 'unnatural'. The final result is an estimate of blood manipulation.[34,35]

A disadvantage of thus obtained prevalences is that the model uses certain assumptions, especially regarding as to what constitutes 'normal' and 'supra-physiological' values. Subsequently, it is able to produce different outcomes based on the same input. As an example, Sottas et al.[36] present two columns of possible prevalences of blood manipulations in track and field, dependent on the possible use of 'microdosing' doping. This difference in pre-calculation hypotheses leads to

sometimes considerable differences in prevalences (up to 30% in %points) but, generally speaking, this method provides good insight into doping practices in certain (sub)populations. The most likely estimate is that, in the period between 2000 and 2010, 14% of all elite athletes in track and field have engaged in some sort of illegal blood manipulation.[36] WADA's AAF reporting has shown much lower period percentages in this sport: 1.0% in 2011 and 0.8% in 2010.[15] Weighing all circumstances, the estimate of 14% seems far more accurate, noting that this estimate only relates to blood-related doping practices. It is also interesting to note that this study showed a large variation in likely doping between countries, even in the same events, suggesting that doping is not per se a sports-wide problem, but has selective origins and is limited by socio-economical structures.

Other sports, such as cycling, football, cross-country skiing, speed skating, and biathlon, possess similar data.[30,32,37-39] and it would be relevant to see similar analyses in these sports, including distributions per country, per team or per performance level. This is interesting since in cross-country skiing it has been shown previously that those athletes with the highest haemoglobin values are more likely to finish in the top places in elite competitions,[38] whereas such a relationship is absent in speed skating.[39,40] Such differences may occur as a result of differences in physiological and biomechanical determinants of performance in the specific sport and/or sociological differences in doping/permissiveness, but such discussions should be based on clear and unambiguous data on the prevalence of doping.

The same principle can also be applied to testosterone-related analyses,[41] but this method has not yet been fully implemented. This means that the Sottas et al. models of doping prevalence currently reveal only part of the picture: they only describe 'haematological doping'. However, they do, in all likelihood, refer solely to intentional doping practices. Although haematological values are known to vary because of various permitted behaviours (such as altitude training) or clinical factors (such as dehydration, sickness), the strength of analysing blood distributions is that the models account for all such factors. The main setbacks of this source of information are the inability to link the available data to individual doping, and the currently very limited availability of actual data from the world of elite sports.[42]

A different approach to looking at doping at a population level could be the chemical analysis of waste water downstream of the sewage system of a selected population.

An example of this approach has been published by Schroder et al.[43] near fitness centres. It is an atypical approach that is able to yield general information on the quantities of doping. Unfortunately, current analytical capabilities make it impossible to deploy this for all doping substances, and obviously it will never be possible to link these results to individual doping use. However, it is an interesting option to test the water downstream of athlete villages at major events, such as the Olympic Games, as it is a relatively easy and cheap way of gathering information on a large group of people and to see whether these results reflect similar levels of prohibited substances as found in official doping tests. This principle has been used in prevalence studies on social drugs before, but, as yet, has still to prove its practical usefulness.[44]

Conclusion from Laboratory-Based Chemical Analyses

Doping control test results yield reproducible data and an anonymous, yet individual, account of the presence of doping substances in an athlete's body. However, in practice, these data have limited statistical value, since they include an unreported percentage of legitimate therapeutic use of medications and an unknown percentage of unintentional doping infractions. These data are also much dependent on changes in the regulations of reporting AAFs at the moment of sample collection. However, the most important drawback, is the dependence on underlying testing procedures and on the availability of approved analytical methods, which sometimes lag behind doping. In conclusion, the annual percentage of AAFs cannot be expected to reflect the actual prevalence of doping.

Population-based models based on physiological parameters can be expected to yield a far better estimate of actual doping period prevalences. The major drawback of this approach is not the inherent uncertainty of modelling, but that this approach has only been reported in a subset of athletes in track and field, and only in relation to haematological doping. That particular prevalence figure (14%) is an extra indication that the percentage of AAFs in many sports modalities is an underestimate of true doping prevalence. More information is available to various anti-doping organisations, but so far these have not been made public.

Questionnaires

Standard Questionnaires

Straightforward questioning about possible doping is very rarely used in scientific studies involving elite athletes. Many studies have been conducted with North-

American high school athletes or European students, yielding percentages of 1-12%.[45-59] These studies have focused primarily on anabolic androgenic steroids. Whenever subgroups of non-competitive athletes who train in fitness centres are included, period prevalences rise up to 70%.[60-69] But these are not the target groups for this review. Petroczi et al.[70] claim a self-reported doping prevalence in Olympic sports of between 1 and 30%, but fail to back up this statement with references.

Elite athletes' doping habits were reviewed in 1997 by Laure,[4] who estimated self-reported doping amongst adult athletes at 5-15% (presumably period prevalence). This sort of research has received little attention since. This is likely because self-response questionnaires have limited value, especially on controversial issues such as doping, since they have the inherent risk of drawing socially accepted answers in a possibly biased response group.[71,72]. Thevis et al.[59] effectively showed, by means of chemical analyses, that elite sport students do not report all use of prohibited substances in questionnaires. However, self-assessment questionnaires have been shown to have some validity in studies focusing on non-athletic drug abuse.[73,74]

A strategy to navigate around these pitfalls is to present the issue as a hypothetical question. The standard example that is often (mis)used in discussions about doping in elite sports is the infamous question 'if you would be offered a magic drug that would guarantee that you would win all important competitions in the next 5 years, but you will die from it shortly afterwards—would you take it?' This question was first asked by author Bob Goldman to 198 of his acquaintances, who all participated in strength sports.[75] The results of this 'study' (a staggering 52% said 'yes') are very often extrapolated to all sorts of populations of elite athletes, whereas an attempt to interpret these data as being applicable to all strength athletes seems already too much extrapolation. This quintessential urban legend obviously lacks any scientific merit. Recent research has shown that, in a more representative field of elite athletes in the sport of athletics, this percentage does not reach 2%.[76]

Randomised Response Technique

The two biggest confounders in regular questionnaire-based research, a biased response group and amongst responders the tendency to give socially desirable answers, can be effectively tackled by an alternative questionnaire approach: the 'randomised response technique' (RRT).[77] This is a technique where the anonymity of the answers is increased by a deliberate mathematical confounder. Respondents first engage in an activity with a known stochastic distribution (e.g. rolling a dice)

and depending on this outcome, they either are obliged to answer 'yes', 'no', or the truth. The researcher does not know the outcome of the first activity, and thus does not know whether the given answer is based on the forced-response or the truth. After the dataset has been collected, it can be mathematically calculated how many of the answered 'yes' and 'no' must originate from the introduced element of chance, and (thus) how much of 'yes' and 'no' answers must have been truthful. The idea is to enlarge the confidence of the subjects because of the introduced anonymity. The element of play may also play a role in the respondents' willingness to cooperate. The downside is that a certain level of uncertainty must be accepted, as the outcome will not be a single percentage, but a confidence interval. It also means that there are no individual data points; this method will only yield population averages.

The RRT has been used and tested in a variety of socially 'undesirable' behaviour situations since the 1960s, such as social welfare fraud, law-abiding behaviour and sexual habits. Each and every time, the prevalences arising from this study design are higher than those that result from traditional questionnaires, and research has shown that these higher prevalences are closer to the truth.[77-79]

In doping-related research, only one study has been published that used RRT to investigate intentional doping amongst elite adult athletes.[79] They found that between 26 and 48% of a group of 448 German Olympic-level athletes admitted to having used doping at some point in their career. The last-year period prevalence was estimated at 20-39%. The exact reliability of the statistical calculations is not reported. In Germany, RRT has also been applied for doping-related research in two other groups of athletes and in the Netherlands it has been applied once (table 3).[72,80,81] All these studies have yielded higher prevalences than previously found in regular questionnaire research. For the purpose of doping research, one anticipated aspect cannot be tackled by RRT: a respondent might still be inclined to lie because of the possible consequences on the image of his or her sport, since the athlete is informed that the outcomes will be used for that purpose. Current methods are unable to take this aspect into account.

Conclusions from Questionnaires

Questionnaire-based research indicates that somewhere between 1 and 70% of all athletes have used doping at some point in their career, depending on their sport and level.[45-69] It is difficult to compare the studies that have been performed because of varying definitions of 'sport', 'elite level' and 'use of doping'. Traditional

questionnaires have a large caveat because their outcomes are prone to socially desirable answers, and as such are likely to underestimate true doping prevalence. The sole study involving adult elite athletes that tried to control for this confounder found a lifetime prevalence of 26-48% and a last-year prevalence of 20-39%.[79] This figure needs to be confirmed in different groups of athletes from different nationalities. These sorts of studies currently give the most accurate estimations of doping use in sports. An extra benefit of using RRT questionnaires is that the level of intentionality can be added into the study design.

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

Inferences from Performances

Athletic Performance and Non-Peer-Reviewed Literature

It is tempting to attribute outstanding performances to the alleged use of doping.[82,83] The main problem with such a line of thinking is that the athlete will always lose in any such discussion: no matter how much he trains without the use of any prohibited substance, as soon as he excels he is, by default, a doping suspect. The essence of sport is to excel, and if excelling becomes synonymous with suspicions of cheating, each and every sport performance turns into an attack on the essence of sport itself. If such reasoning persists, this will seriously jeopardise the credibility of sport.

Especially in cycling, there are a number of (semi)scientific websites that try to link performances in time trials or standardised circuits or climbs (expressed in time or in power outputs) to doping confessions or allegations.[84-86] These efforts have not yet reached the scientific, peer-reviewed literature. They conclude unequivocally that current champions do not reach the performance levels of the best riders of the 1990s or early 2000s. However, it is difficult to make a direct link to doping. In addition, it is possible that performances drop because the amount of doping has decreased, even though the number of individuals who dope may not have decreased.

Athletic Performance and Peer-Reviewed Literature

For the purposes of this review, the more scientific explorations of the relationship between athletic performances and doping-related issues bear some significance. The previously mentioned finding that, in the 1990s, most top finishers in cross-country skiing have the highest haematological values suggests that haematological doping in that specific culture was performance determining.[38] In such a homogenous group of elite athletes, one would not expect a linear relationship between oxygen transport capability and performance as, in elite sports, it is often not as much the physiological training status but small details such as 'form on the day' or psychological focus that determine who wins and who fails to make the podium. Athletic capabilities are a prerequisite to reach the top, but not necessarily a ticket to win.[87] Unfortunately, this approach does not enable the calculation of a prevalence of doping and may serve only as a hint.

Another aspect of performances and doping use was studied by Seiler et al.[88] They looked at the relative performances between men and women in various power events (running, swimming, speed skating) and noticed that these two groups grew closer to each other up until approximately 1990, after which the gender gap increased again. Discussing various possible reasons for this trend, they conclude that the most likely reason is the advent of out-of-competition testing in the late 1980s, making it more difficult for athletes to use anabolic steroids during training periods. Anabolic steroids, all derived from testosterone, can be expected to have more performance enhancing properties in females than in males.[89] These findings have been confirmed in later, more extensive, statistical calculations.[90–92]

An innate problem with trying to link performances to possible doping infractions is that athletic performances are influenced by many factors, such as talent, improvements in training techniques, nutrition, psychological support, and changes in equipment and environment. Over time, athletic achievements tend to improve in every sport, but this does not mean that a failure to progress or even a slight drop in top performances mean that these can be related to doping patterns; they may just as well relate to one or more of the other factors that influence performance. Pure statistical studies into the times of elite cyclists in various races failed to reach a clear conclusion,[93,94] and this variability in factors that influence the final outcome of a race are most probably the reason to explain this ambiguity. Ernst and Simon speculated that recent improvements in sprinting performance in athletics could be indicative of a novel, very effective doping procedure (with

insulin-like growth factor-1 being the primary candidate), but they also could not prove such assumptions.[95]

The most basic disadvantage of inferences from performances is that even though these examples (haematological values, gender gap, or other) yield information on the trends of suspected doping, they will never give detailed information on a true doping prevalence percentage, let alone in individual cases. In theory, one could do a similar exercise with performances as for the haematological values as discussed in the section labelled 'Population Estimates Based on Biological Parameters': modelling what is 'normal' and estimating what is not. This has not yet been performed in practice. A serious limitation to this approach is that one would need to choose a standardised performance measurement and study this extensively. It is not likely that such data will be available.

Conclusions from Performance Inferences

Analyses of performance data may suggest general trends in doping patterns, but such information can only be used to confirm findings that are collected by other methods. For example, the relative performance gap between male and female athletes has given some information in sport events that are highly dependent on muscular strength and power. These data give an indication that anti-doping efforts influence performances, and that, on a group level, doping patterns have changed in the last 30 years in various sports. However, such data cannot be linked to the prevalence of doping. It can be concluded that, on the basis of performances alone, an individual assessment on possible doping is simply not possible, and, in addition, any attempt to try to do this will violate the essence of sport. Linking extraordinary athletic performances to doping use is highly insulting to clean champions. Both scientifically and morally it is not recommended to try and link performance levels to doping use; at best performances can be used to identify general influences of anti-doping measures on the entire population of elite athletes.

Inferences from Ego Documents

Published accounts of personal experiences, either in autobiographical books or press interviews, give insight into the environment in which an athlete performs or performed. Especially in cycling, various autobiographies have been published that included self-admitted doping.[19,87,96–99] Other sports have also been put under the spotlight.[12,100,101] Such information is never neutral, but a collection of individual

accounts may serve as a socio-cultural description of perceived doping use amongst fellow competitors. These ego documents are the practical equivalents of case reports in the medical scientific literature. As such, they may serve as a particular data source for the subject of doping use in elite sports, but they will never produce reliable prevalences. As they are also partly commercially induced, the information on the individual level is doubtful. Their value is in pinpointing certain sociological constructs, and the perceptions of doping use by other competitors. These can also be studied by more scientific methodologies such as face-to-face interviews or participant observations, which have already been used in doping studies although not very often.[18,102,103] It should be taken into account that humans have a tendency to legitimise their own behaviours by their perception that many others do the same, even if this perception may be inaccurate.[104]

Conclusions from Ego Documents

In theory, a study could be conducted to make an inventory of perceived doping use by elite athletes amongst their direct competition and possibly in other sports. Social networking studies or other sociological approaches may yield interesting qualitative results on the expected degree of doping use. In the end, such figures will mainly reflect the aura of doping, not doping itself. Ego documents from elite athletes will be able to give a hint of doping prevalence in the past, and may confirm data that have been collected by other methods. However, they are not likely to give credible factual information.

Discussion

WADA's Director General, David Howman, has stated that he expects that true doping amongst elite athletes is likely to be 'a double-digit figure'.[105] It is striking that the person who may be the best informed person in the world on this subject can do no better than an educated guess when asked about the prevalence of doping use. It is an area in which scientists may be of help to diminish the level of uncertainty.

Methodological Aspects of Studying the Prevalence of Doping

A combination of questionnaires using the RRT and models of biological parameters provide statistical possibilities to reveal accurate estimates of this often undisclosed practice. Unfortunately, these techniques have rarely been applied in elite sports.

It should be kept in mind that these methodologies will only be able to provide an estimate, with confidence intervals on either side of the point estimation; they yield population-based averages without the possibility to draw conclusions on the individual level. However, this uncertainty is much more preferable than the flawed exact numbers that chemical-based analyses show. This does not mean that doping tests have no value for anti-doping purposes; it merely shows that these data should not be used to claim knowledge on the accurate prevalence of doping use, especially in the format in which WADA is currently publishing these figures. The value of doing tests is in providing the strongest possible juridical proof that someone used doping. However, the robustness on the individual level cannot be extrapolated to the group level.

Based on the available evidence, it can be concluded that the prevalence of doping can be very different between sports, countries, and training groups. This has been shown extensively in gyms, and the limited data available in elite sports show a similar picture. Doping tends to concentrate in particular athletic groups who share a coach, trainer, doctor, manager, or other person with a permissive attitude towards doping. The International Association of Athletics Federations (IAAF) study, being the single available scientific description of doping prevalence in world-class sports, shows that, at least in athletics, this number is largely dependent on the country for which one is competing, presumably because doping is not so much an individual decision, but rather a final outcome of a social environment that is rather permissive towards doping.[18,106,107]

Doping prevalence is also likely to vary between levels of play. The analysis by Maquirriain[28] of tennis-related ADRVs indicated that the prevalence of doping in this sport was in fact lower at the highest levels of the sport. It can be imagined that, at lower levels, the occurrence of 'accidents' (i.e. non-intentional ADRVs) is higher because of less than optimal doping education, although this assumption cannot yet be substantiated by any available data.

Estimating the Prevalence of Doping in Elite Sports

With so much attention given to doping in elite sports, and after almost a decade of intensified anti-doping research since the involvement of WADA in global anti-doping efforts, it is disappointing to see that only two studies have given a good insight into the prevalence of doping in a certain subpopulation of elite athletes: Pitsch et al.[79] in Germany and Sottas et al.[36] in athletics. These approaches should

be used more extensively in many more subpopulations in order to reveal the effects of anti-doping measures and to gain as much insight as possible into the central question of anti-doping initiatives: how many athletes are resorting to doping substances or methods? Based on the currently available data, the most likely general period prevalence amongst adult elite athletes is the estimate originating from Germany based on RRT questionnaires: 20-39% in the last year.[79] This estimate can be supplemented with the population estimates based on biological value parameters in track and field: 14% of 'haematological' doping between 2000 and 2010 (table 4).[36] This fits rather well with the scarcely available results of re-analysis of older samples when new analytical techniques have been developed, as discussed in the section called 'Doping Control Test Results'. These figures obviously need further substantiation in different groups before we can use doping prevalence estimates in policy evaluations.

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
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
Standard questionnaires	1-15%[4, 45-59]	Mostly performed on adolescents and/or students; little research in elite sports
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
Inferences from athletic performances	-	Popular input for doping-related discussions but impossible to reflect prevalence of doping
Inferences from ego documents	-	Give some insight into the sociological background of doping and perceived prevalence, but not true prevalence

In the annual reports of doping tests results, WADA limits itself to the publication of all AAFs and has not yet established an overview of ADRVs. Without such information, it is extremely difficult to evaluate the effectiveness of doping tests.

Even without this essential information, it can be concluded that doping tests in their current form will show only a small percentage of intentional doping users. One might argue that, if the average length of a career in elite sports is 10 years, an approximate 1% of AAFs each year will result in 'catching' 10% of the entire elite athlete population. But this figure is still lower than the currently available best estimate of the prevalence of doping.

It is striking to see that a study into the use of a permitted substance that might be performance enhancing (nicotine) showed a prevalence of use of 19-56%, dependent on the sports modality.[108] If the entire doping test system is indeed unable to keep the use of prohibited substances at a lower level than a permitted substance, it adds to the idea that current anti-doping testing is far from effective in curbing doping. It is also disconcerting that calls for more clarity in this area that were made more than 25 years ago have not yet yielded much progress.[109] There has been very little progress since the review by Laure[4] in 1997.

Future Guidelines and Research Agenda

Ideally, the prevalence of doping in all sports and at different levels should be monitored regularly. The most promising tools are questionnaire-like studies using the RRT and population estimates based on physiological variables. These two approaches offer the most accurate objective data on the prevalence of doping and can thus be expected to approximate the truth as closely as possible. One should accept that it is impossible to generate true prevalence figures of any prohibited activity, but modern science provides several possibilities to come close to reality. Anti-doping professionals have not yet taken full advantage of these techniques—or if they have, they have not published them in order to be scrutinised by peer scientists. When analytical science continues to progress, it may become possible in the future to collect data from sewage systems downstream of major sport events.

Reliable information on the prevalence of doping is necessary to perform policy evaluations. However, this is a far cry from current practice. We propose that, first, a harmonised approach to collecting data on prevalence of doping is agreed upon. WADA could be a leading organisation to draft guidelines on how to perform such actions. We propose that the definitions of 'doping' and 'elite sports' are used as they are in this article, and that 'prevalence of doping' will be operationalised as both the last-year and lifetime incidence of intentional use of one or more prohibited substances with the intention to enhance performance in the sport of the athlete

involved. Point prevalences or incidence figures may have additional value, but, given the current state of affairs in this field, it is proposed to focus predominantly on period prevalences in order to optimise comparability.

Conclusion

The most accurate way of estimating the prevalence of doping in elite sports is by using a combination of questionnaires using the RRT and models of biological parameters. So far, these evaluations have not been performed very often, or at least they have not been published. All doping-related discussions and decisions would be strengthened if this vital piece of information, i.e. scientifically reliable information on the prevalence of doping, becomes more readily available.

Current data suggest that 14-39% of elite athletes are doping, but this figure needs further confirmation in different groups of athletes with varying levels and backgrounds. Doping prevalence can be expected to fluctuate substantially between different groups. However, the prevalence figure can be expected to be far higher than the average of 1-2% of athletes who are caught with doping substances, or their metabolites, in their system. There are many efforts underway to close this gap, but this process is by no means complete.

Evaluations of the prevalence of doping use are not only interesting for sports fans and journalists. They are necessary for anti-doping professionals to enable true evaluation of the effectiveness of their policies. If the non-dopers are cheated by the dopers too often, and when doping tests are insufficient to control doping use in a meaningful manner, anti-doping efforts are doomed to fail. This is not a problem for the anti-doping professionals, but first and foremost for the athletes they have vowed to protect. Tools to evaluate the prevalence of doping use in sports are readily available; they only need to be used more often.

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Extended discussion on prevalence of intentional doping use

In this review, we have been critical on the value of doping controls as a measure of determining the prevalence of intentional doping use. Obviously, this does not mean that doping controls have no value at all. Any prohibition needs some form of control, and the current control system which is built on 50 years of practical experience and legal challenges and subsequent improvements plays an important role in many aspects of the World Anti-Doping Program. Any control is an important reminder to athletes and their support personnel of the existing doping regulations and as such has an innate educational value as well. In addition, to many young athletes the first doping control is considered as a 'rite of passage' that the elite level has been reached. Finally, it is still the most common cause for determining anti-doping rule violations, despite its limitations. A closer look at the relationship between doping controls and prevalence of doping use is warranted.

All controls culminate in biochemical analyses in one of the WADA-accredited laboratories. As such, debates on the prevalence of doping use in elite sports, and certainly to the prevalence of intentional doping use, are closely linked to frequently resurfacing discussions on the reliability of biochemical analyses. This means that an extended discussion on the analytical characteristics of doping controls is necessary in this study into the effectiveness of anti-doping policies.

It can be stated beforehand that constant progress has been made in this area over the years (Hemmersbach 2008, Shackleton 2009, Sonksen & Holt 2009, Müller 2010, Ivanova et al. 2012). But, obviously, the chemistry-side of anti-doping has also been under close scrutiny during legal procedures between athletes and ADOs. The rules and regulations of these analyses are described in the International Standard for Laboratories (ISL), one of five obligatory standards that are connected to the WADC, and which together with non-obligatory model rules and guidelines form the WADP. The ISL is supplemented with several Technical Documents that contain (obligatory) descriptions of specific technical aspects regarding analyses and reporting.

A full discussion of all aspects of the ISL would stretch too far for this thesis, but several aspects will be discussed in light of the main research question and as a discussion of the main issues that have been identified in the literature and in juridical cases.

The fundamental question of identification by means of analyses is: when is one confident that the presence of a prohibited substance has been proven? The anti-doping framework follows the classical reasoning in traditional chemical analysis that mass spectrometry coupled to either gas or liquid chromatography provides satisfactory proof that a certain substance is present in a sample if three different m/z-values (indicative of the fragments of molecules as identified in the analysers) and their (relative) retention times are found in accordance with known standards (Baldwin et al. 1997, Rivier 2003, Van Eenoo & Delbeke 2004, Milman 2005, Stein & Heller 2006, Catlin et al. 2008). Albeit this assumption is challenged at times (De Zeeuw 2004), it is internationally acknowledged that this trait proofs presence above a certain threshold value known as the 'Limit of Detection'. In analyses where different analysing techniques are used, such as affinity binding assays, it is always necessary to perform a two-way confirmation. To the best of my knowledge these latter techniques have never led to any controversies in anti-doping, but it must be said that the substances to which this applies have not often been part of high-profile doping cases.

The story of doping analysis is a story of successes and critiques. Part of the successes are the slow but steady advances in analytical potential and the introduction of new, long-lasting, metabolites for well-known anabolic steroids. Examples include the use of new metabolites for the anabolic steroids metandienone in 2006 and stanozolol and dehydrochlormethyltestosterone in 2013, which produced dozens of extra Adverse Analytical Findings (AAFs) (Schänzer et al. 2006, Sobolevsky & Rodchenkov 2012, Schänzer et al. 2013). Regarding stanozolol, it is encouraging to see that an article with a similar message was published ten years earlier, showing the continuous progress in analysing techniques (Schänzer et al. 1996).

Retrospective analyses have also yielded several new anti-doping rule violations (ADRVs), including gold-medal winners at Olympic Games and World Championships. This may challenge the faith of spectators, who nowadays do not know whether the first finisher in a particular sports event will indeed be the true champion, but from a biochemical/analytical point of view these are clear successes which show continuous progress. Future advances can be expected from an increased interest in proteomics (Pitsiladis et al. 2014) and possible introductions of Dried Blood Spot Analysis (Thomas et al. 2012) and/or saliva analyses (Anizan & Huestis 2014). If saliva analyses would become possible and viable for all doping

substances, this would mean a far lesser burden for both athletes and doping control officers. So far this is a theoretical option only.

The advent of so-called biological passports (where longitudinally collected biological data are stored and compared to check for possible 'unnatural' shifts) is also seen as a new success by many. It marks a shift from direct evidence towards indirect proof that, taken together with all circumstances, might be judged as being sufficient evidence for an ADRV (Sottas et al. 2011, Van Renterghem et al. 2011). Where some may judge this shift as a sign of weakness or a judgment of inadequacy towards traditional laboratory analyses, others point to the fact that it is primarily an additional tool in order to search and find intentional users of doping. Indeed, the increased importance of indirect evidence may also serve a purpose in directing doping controls and other resources towards those athletes that can be regarded as 'suspicious' even though as yet there is insufficient proof for an ADRV. The individual cases that have led to doping-related sanctions may indicate individual successes in the field of anti-doping, but a reliable quantification of its effectiveness cannot be given at this point, also because it is unclear to what extent this sort of information has contributed to 'traditional ADRVs'.

Critiques regarding doping analysis have primarily been focussed on laboratory performance (Berry 2008, Blackledge 2009), transportation circumstances (Kuenen & Konings 2010), and sub-optimal sensitivity, particularly in erythropoietin-testing (Lundby et al. 2008), or downright accusations of a lack of specificity or even false positives (Delanghe et al. 2008, Faber 2009). Such publications are met with numerous comments and reactions, as in any good scientific debate. Most of these discussions focus on the fact that in anti-doping testing it is not clear what the chances are of false-positive results. When new analyses are explored and whenever an AAF is being communicated, anti-doping laboratories will always seek the 'safe' side, which means they will rather let an athlete with suspected doping-traces off the hook than risking to damnify a non-using athlete. This is an area where a call for transparency collides with the purpose of anti-doping policies themselves. Sharing all details of analytical tests with the general public will undoubtedly also mean that ill-intending experts use this sort of information in an attempt to circumvent current testing. These two issues need to be balanced. Generally speaking, this balance is currently present since discussions about more transparency in the field of chemical analyses are predominantly held in the periphery of the scientific debate. But the discussions

are important, and they have forced anti-doping professionals to counteract such claims and to explain into more detail how the anti-doping framework has come about and what principles are followed (Lasne 2006, Ljungqvist et al. 2008, Sottas et al. 2008, Bowers 2009b, Flenker & Schänzer 2009). In the past, such critiques have undoubtedly led to improvements in anti-doping analyses, for example in the introduction of measures of uncertainty in quantifications in the late 1990s, even though long scientific discussions prevailed for many years (Van der Veen 2003, Van Eenoo & Delbeke 2003, King 2004). In its essence these are scientific discussions that are appropriately held in scientific journals and according to the theories of Karl Popper and Imre Lakatos such discussions will only help to bring science to a higher level. But because of its great practical consequences it is also an area where more involvement of those who matter most in this area is warranted: the athletes.

Obviously, the analytical challenges in anti-doping are great. It is an aspect where there is an inherent confrontation between transparency (one of the core traits of scientific endeavours) and effectiveness (in the sense that the analytical procedures should be able to 'catch' the users of doping unexpectedly). The anti-doping framework has chosen to provide security about the robustness of this work through strict regulations and to stress the issue of reproducibility of results. The rules that are in force are in some ways arbitrary (for example: any athlete may ask for a B-analysis, but this will always need to be performed in the same laboratory as the A-analysis) but they are clear and whenever they are compromised the Court of Arbitration for Sport (the highest body to settle disputes related to sport) will not hesitate to acquit an athlete (ADKC 2009). All in all it can be concluded that the analytical framework does indeed catch many 'cheats', which is also shown by the fact that numerous athletes admit their guilt after having proclaimed their innocence for extended periods of time (Floyd Landis and Tyler Hamilton, among others). In that sense, the system shows signs of effectiveness but how many is 'many' and how do these numbers relate to the overall amount of doping 'cheats'? A quantitative analyses cannot be performed unless the actual prevalence of doping use is known (Lentillon-Kaestner & Ohl 2011, De Hon et al. 2015). Which brings the discussion back to the issue of prevalence.

The review on prevalence of doping use as presented in this paragraph showed that the prevalence of doping use in elite sports can be estimated, and our conclusion was that it can be estimated with sufficient reliability. A recent report describing a

randomised response protocol in Dutch elite athletes showed a reliable estimate of 4.2% (95% confidence interval: 1.8-8.5%) in a sample size of approximately 300 athletes, participating in 40 sport modalities (Duiven & De Hon 2015). If the estimate can be expected to be higher, this method can even be used in smaller sample sizes. A current estimate of intentional doping in elite sports would consequently be between 4 and 39%, but the conclusion that much more work in this area needs to be done is still very valid. Together with the biomarker-based prevalence estimates these prevalence studies will also open the door to conclusions about the effectiveness of the current doping control system. Laboratory analyses play a major role in this system, but in order to evaluate the effectiveness of doping controls it is necessary to include the whole chain of this process, which also encompasses selecting athletes, finding them, performing the control procedure, performing analyses, and finally the juridical consequences that can be coupled to possible analytical findings. The latter issue will be discussed in the following paragraph.

2.3.2 True dopers or negligent athletes?

The general public mainly thinks about deliberate use when the subject of doping is discussed, or encountered in the media. But those who work in the field know that a mistake can be easily made, either by athletes or by the people directly around them, in the WADC called 'athlete support personnel'. There are various ways of studying this issue, but all are principally difficult to perform as intentional dopers usually have a first reaction to go long ways to explain how it was not their fault that they have been suspected of an ADRV. It was decided to study this outcome based on the juridical outcome of doping cases, and for this purpose a cooperation with WADA was sought, and found. The following text was submitted to the journal 'Substance Use and Misuse' early 2016 but was considered too long to be published. At the invitation of the editor, the core content is currently under review to be published as a 'brief research note', but what follows here is the full text.

TRUE DOPERS OR NEGLIGENT ATHLETES - AN ANALYSIS OF ANTI-DOPING RULE VIOLATIONS REPORTED TO THE WORLD ANTI-DOPING AGENCY 2010-2012

O de Hon & M van Bottenburg

The core content of this paper is currently under review as a 'brief research note' by the journal Substance Use and Misuse, after a first review process and at the invitation of the editor. The brief research note will include an offer to provide the full text to those who are interested. This full text is re-printed with permission from Taylor & Francis.

Abstract

Background: The sanction that an athlete receives when an anti-doping rule violation has been committed depends on the specific circumstances of the case. Hearing panels decide on the final sanction, following the rules of the World Anti-Doping Code.

Objectives: To assess the athletes' degree of fault based on the length of sanctions imposed on them.

Methods: Analysing data from the results management database of the World Anti-Doping Agency for anonymous information of anti-doping rule violations in eight selected sports covering the years 2010-2012.

Results: The database provided 1,831 adverse analytical findings and 363 other anti-doping rule violations. Four out of ten athletes who committed an anti-doping rule violation received a suspension that was lower than the two year period of ineligibility that used to be standard pursuant to the 2009 World Anti-Doping Code. This is an indication that juridical panels in many instances are not convinced that the athletes concerned were completely at fault, that mitigating circumstances were applicable, or that full responsibility of the suspected violation should not be held against them. Anabolic agents, peptide hormones, and hormone modulators lead to higher sanctions, as do combinations of several anti-doping rule violations. Non-analytical findings lead to higher sanctions than those based on laboratory analyses.

Conclusions: In the authors' view, this first analysis of information from WADA's results management database indicates that a large proportion of the athletes who commit anti-doping rule violations may have done this unintentionally. Anti-doping professionals should strive to improve this situation in various ways.

Introduction

The World Anti-Doping Code (WADC; an overview of all abbreviations used in this article can be found in table 9, preceding the discussion) states that anti-doping programs seek to preserve what is intrinsically valuable about sport (WADA 2009, 2015c). Athletes who test positive after submitting to a doping control commit an Anti-Doping Rule Violation (ADRV). Many of these athletes deny that they consciously breached the existing anti-doping regulations. Some excuses have become legendary in the folklore of anti-doping, such as 'these medicines were intended for my dog' or 'it must have been an ingredient of my tooth paste'. Some athletes change their story during the course of the legal proceedings, and some keep with their stories for years and years. But this may also be because their particular story might be true…

If a good-willing athlete who follows all anti-doping regulations to the best of his/her abilities is caught by the anti-doping system unexpectedly, this may be regarded as a double mistake: the good-willing athlete will be sanctioned, whereas a potential intentional cheat may escape punishment because he/she was not in the focus of the anti-doping authorities at that particular moment as the available resources were spent elsewhere. Some people would argue that there are no 'innocent athletes' in this regard. If one is found in breach of the existing anti-doping regulations, there is always a certain degree of guilt, if only because of diligent negligence. But it is disconcerting that a preliminary study into the ADRVs within the sport of tennis concluded that up to two thirds of ADRVs in this sport may in fact have been unintentional in the years 2003-2007 (Pluim 2008). Various possibilities for unintentional ADRVs have been described in scientific literature (Yonamine et al. 2004, Anderson 2011). As an aside, the psychology of doping use as a conscious decision has been excellently reviewed rather recently (Ntoumanis et al. 2014).

This paper intends to explore this issue more elaborately: to what degree can the athletes that are sanctioned be regarded as true dopers, i.e. deliberate cheats? And how many of the sanctioned athletes can be considered to be, at least partially, casualties of the anti-doping system in the sense that they might not have realised

what rule they broke at the time they were notified of a possible ADRV? In this article, a 'true doper' is defined as someone who intentionally breaks the anti-doping rules of his/her chosen sport.

In this study, we will look into this issue on the basis of the length of the sanctions that have been laid upon the athlete. The premise is that hearing panels or tribunals can and will use the possibility rendered in the WADC to lower anti-doping sanctions when this is deemed appropriate. Reasons to lower sanctions are almost always related to a lower degree of perceived intent to break the anti-doping rules. This premise has become increasingly difficult to uphold with the newly revised WADC in place since January 2015, as this version takes a different approach to establish standard sanctions (dependent, among other things, on the substance involved) and describes in more detail the possibility of 'substantial assistance' to suspend the execution of a part of the athlete's period of ineligibility depending on the seriousness of the anti-doping rule violation committed by the athlete and the significance of the substantial assistance provided by the athlete to the general effort to eliminate doping in sport (WADA 2015c). This is why this particular study focuses on the years before 2015. It intends to explore the possibility to use a database containing the lengths of sanctions to feed policy-related conclusions.

Beforehand it can be said that the exact juridical implications of the words 'guilt', 'fault', 'negligence' and 'intent' can by no means be extracted from the length of a sanction alone. It is also accurate to say that the true backgrounds of any ADRV will only be known to the concerned athlete, if it can be known at all. But we will argue that on the basis of the length of sanctions that are laid upon athletes by the acting anti-doping tribunals, information on this issue can be gathered and presented since each tribunal weighs the specific backgrounds of each ADRV diligently, and is embedded in an anti-doping system that consists of many checks and balances.

Methods

At the request of the authors, WADA provided all ADRVs in eight selected sports within their results management database from the years 2010, 2011, and 2012. This means that the applicable WADC in this study is the 2009 version. WADA agreed to provide the data, but the analysis of these data and the conclusions and views expressed in this article are those of the authors alone and are not necessarily shared or endorsed by WADA.

We aimed to include a reasonable volume of ADRVs in order to be able to make a meaningful analysis, and to include both team sports and (more or less) individual sports, with various degrees of 'doping sensitivity'. In this study 'doping sensitivity' was solely based on the percentage of Adverse Analytical Findings (AAFs, being the chemical-analytical results of doping controls) in relation to the total number of doping controls in the years of study in order to avoid subjective decisions. The following sports were chosen: Aquatics, Athletics, Cycling, Field hockey, Football, Skating, Skiing, and Weightlifting. These are all Olympic sports. This was chosen as non-Olympic sports tend to perform less doping controls and (consequently) have less ADRVs, which may lead to less-experienced tribunals and an insufficient volume of data to allow for general conclusions. Sports with strong professional competitions in North America were excluded, as most controls will originate from these professional competitions, but these do not follow the full World Anti-Doping Program (WADP). Three different years were included in order to provide information on possible annual differences.

The available information per case consisted of: sport, nation, type of ADRV, the substance(s) involved (if applicable), timing of test (in-competition or IC and out-of-competition or OoC), and the length of the sanction. The athlete's name was unknown to the researches as was any other personal information. Whilst the length of the sanction is the primary parameter of this study, the other characteristics are used to provide more background on both the variability of sanctions and the reliability of the database.

Results

Contents of WADA's results management database

WADA's database yielded 1,831 ADRVs based on AAFs in the years 2010-2012, meaning the irrefutable presence of a banned substance in an athlete's specimen that has led to a sanction, according to article 2.1 of the WADC (AAF-sanctions). According to the principle of 'strict liability' an athlete is held liable for all substances found in a bodily specimen. In addition, the database contained 363 ADRVs based on other violations that are listed in the WADC (non-AAF-sanctions). These ADRVs can be found in WADC-articles 2.2 through 2.8 (WADA 2009) and relate to cases of use or attempted use of doping substances, refusing sample collection, violation of applicable requirements regarding availability for out-of-competition testing (whereabouts violations), tampering with doping control procedures, and the possession, trafficking, or administration of doping substances. It is also prohibited

for athletes to assist, encourage, aid, abet, or cover up any (attempted) anti-doping rule violation. Finally, there were some violations of the prohibition of participation during a period of (anti-doping related) ineligibility (article 10.10.2). Several combinations also occurred. It was not possible to include specific information on the possible application of sanction-shortening or sanction-lengthening articles in the WADC such as specific circumstances (10.4), no fault (10.5.1), no significant fault (10.5.2), substantial assistance (10.5.3), admission (10.5.4), aggravating circumstances (10.6), or multiple violations (10.7) as this information was not available in WADA's results management database in the years under study.

Table 1. Number of AAFs in WADA's juridical database and in WADA's reports of the findings in accredited anti-doping laboratories in the years 2010-2012.

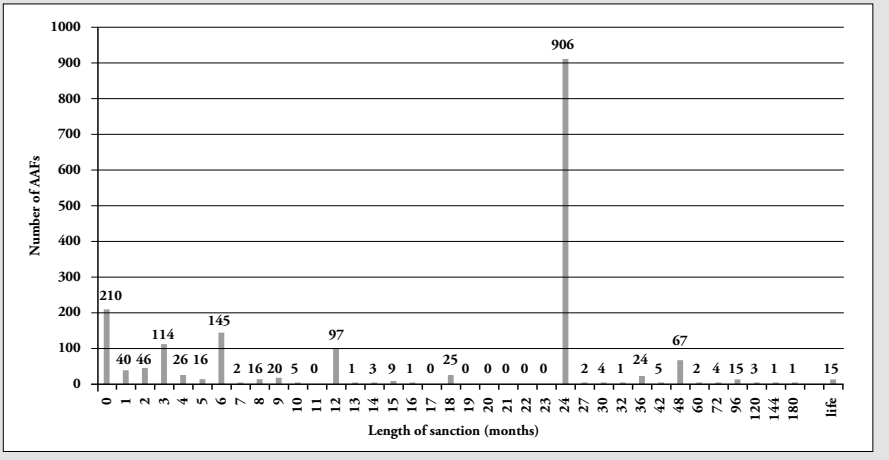
Sport	Juridical database	Total AAFs of 3 years	2010		2011		2012	
			#tests	#AAFs	#tests	#AAFs	#tests	#AAFs
Aquatics	114	264	13,138	90	11,953	100	13,069	74
Athletics	525	740	25,013	196	23,799	234	27,836	310
Cycling	477	845	21,427	254	19,139	321	20,624	270
Field hockey	41	71	2,275	30	1,679	25	2,165	16
Football	310	477	30,398	146	28,578	172	28,008	159
Skating	23	37	3,660	10	3,818	12	3,882	15
Skiing	31	95	5,332	38	5,334	33	5,114	24
Weightlifting	310	696	8,316	201	7,693	243	8,659	252
Total of 8 selected sports	1,831	3,225	109,559	965	101,993	1,140	109,357	1,120
Total of all Olympic Sports	-	5,217	180,584	1,624	167,820	1,762	184,955	1,831

Backgrounds of AAF-sanctions

The distribution between sports can be seen in table 1. This table also lists the annual number of doping controls and AAFs based on the reports of WADA-accredited laboratories in the selected eight sports (personal archives; the current WADA website does not list these documents anymore). This allows for a comparison between all Olympic sports and the information in the results management database. The eight selected sports represent 320,909 controls (60% of all 533,359 that were performed on behalf of all 35 Olympic sports) and 3,225 AAFs as reported by the laboratories (62% of all 5,217 AAFs reported on behalf of all 35 Olympic sports). A total of 38 cases were still open for possible appeal at the time of data collection (December 2013).

The length of sanctions for the AAFs varied between 0 months ineligibility and a lifetime sanction, with obvious peaks at rounded numbers of months (3, 6, 12, 18, 24; see figure 1). Five sanctions were unknown. Fourteen AAF-cases occurred simultaneously with non-AAF violations. These 14 cases resulted in bans ranging from 6 months to 4 years. Approximately half of the sanctioned athletes received the rather fixed sanction of 2 years ineligibility (being the standard sanction for first time offenders in the 2009 WADC) and an additional 8% gets periods of longer than that. One in nine gets no period of ineligibility, and an additional 29% gets a sanction of one year or less.

Figure 1. Distribution of the length of sanctions in months for 1,826 AAFs. On the horizontal axis all sanctions longer than 24 months are only shown if they actually occur within the dataset.



Relationship between sanctions and substances

WADA's Prohibited List consists of 15 groups of prohibited substances and methods (see table 2). Most AAF-sanctions involve the groups S1 (anabolic agents; 36%), S6 (stimulants; 21%), and S8 (cannabinoids; 13%). In 7% of all cases a combination of more than one substance out of different groups was found. There were no AAFs in the groups of S0, M2, M3, P1, or P2 and just one for the group of M1. The length of sanctions varies considerably between different groups. For the groups S3 and S5 through S9 the majority of sanctions are less than two years of ineligibility. Table 3 shows an overview of the length of sanctions between the various groups of substances of the Prohibited List.

Table 2. Groups of substances and methods on the anti-doping Prohibited List.

Group	Name of group of substances or methods, including examples	
S0	Non-approved substances	Repoxygen, TB-500
S1	Anabolic agents	Testosterone, stanozolol, clenbuterol
S2	Peptide hormones, growth factors and related substances	Erythropoietin, chorionic gonadotrophin, growth hormone
S3	Beta-2 agonists	Salbutamol, salmeterol, terbutaline
S4	Hormone and metabolic modulator	Clomiphene, formestane, tamoxifen
S5	Diuretics and other masking agents	Furosemide, canrenone, hydrochlorothiazide
S6	Stimulants	Amphetamine, methylhexaneamine, cocaine
S7	Narcotics	Methadone, morphine, oxycodone
S8	Cannabinoids	Marijuana, synthetic delta 9-tetrahydrocannabinol
S9	Glucocorticosteroids	Betamethasone, budesonide, prednisone
M1	Enhancement of oxygen transfer / Blood manipulation	Blood doping, efaproxiral (RSR13)
M2	Chemical and physical manipulation	Intravenous infusions, tampering
M3	Gene doping	Transfer of nucleic acid sequences
P1	Alcohol	Ethanol
P2	Beta-blockers	Atenolol, metoprolol, propranolol

Table 3. Length of AAF-sanctions per group of substances (absolute and relative distributions). The total amount of sanctions in this figure is 1,828; from two sanctions in the database it is not known with which group of substances they are associated, and one involved a 24 month sanction for an M1-infraction.

		Sanction (months)							
		0-23.9		24		24.1-life		Unknown	Total
		n	%	n	%	n	%	n	N
Group on prohibited list	S1	55	8.3	530	79.9	76	11.5	2	663
	S2	10	8.8	89	78.1	15	13.2	0	114
	S3	30	81.1	6	16.2	0	0.0	1	37
	S4	4	28.6	9	64.3	1	7.1	0	14
	S5	78	73.6	24	22.6	3	2.8	1	106
	S6	231	59.2	141	36.2	18	4.6	0	390
	S7	8	88.9	1	11.1	0	0.0	0	9
	S8	209	87.1	26	10.8	4	1.7	1	240
	S9	111	88.8	13	10.4	1	0.8	0	125
	Combination of groups	39	30.0	65	50.0	26	20.0	0	130
	Total per sanction period	775	42.4	904	49.5	144	7.9	5	1,828

Relationship between sanctions and timing of tests

Of all sanctions, 1,476 or 81% originate from AAFs established after IC-controls. This high percentage is related to the fact that only groups S0 through S5 and M1 through M3 are prohibited during both IC and OoC-controls; the remaining groups of the Prohibited List are prohibited during IC-controls only. The distribution of AAFs between IC and OoC-controls for those groups on the Prohibited List where both types of controls are actually relevant can be found in table 4. The overall lengths of sanctions in relation to IC and OoC-controls are listed in table 5.

Table 4. Number of AAFs in WADA's juridical database; time of test versus group on the Prohibited List (absolute and relative distributions). Only AAFs that relate to those groups of substances that are prohibited both IC and OoC are listed.

		Time of test				
		IC		OoC		Total
		n	%	n	%	n
Group on prohibited list	S1	453	68.3	210	31.7	663
	S2	69	60.5	45	39.5	114
	S3	31	83.8	6	16.2	37
	S4	9	64.3	5	35.7	14
	S5	85	80.2	21	19.8	106
	M1	1	100.0	0	0.0	1
	Combination of groups	93	86.9	14	13.1	107
	Total per timing of doping control	741	71.1	301	28.9	1,042

Table 5. Length of AAF-sanctions originating from IC or OoC-controls in those groups of substances that are prohibited both IC and OoC (absolute and relative distributions).

		Sanction (months)							
		0-23.9		24		24.1-life		Unknown	Total
		n	%	n	%	n	%	n	n
Time of test	IC	158	21.4	502	68.1	77	10.4	4	741
	OoC	48	15.9	211	70.1	42	14.0	0	301
	Total per sanction period	206	19.8	713	68.4	119	11.4	4	1,042

Non-AAF sanctions

WADA's results management database contained 363 ADRVs that are not connected to AAFs in the selected years. The sport of cycling yields by far most of these 'non-analytical ADRVs': 185. In decreasing order the other sports yield 66 (athletics), 36 (weightlifting), 32 (football), 27 (aquatics), 14 (skiing), 3 (skating), and 0 (field hockey). ADRVs include the full range of possible WADC-violations and often involved combinations of two or more violations (table 6). The database separates the violations of WADC-article 2.8 by clustering administration and attempted administration on the one hand and the acts of assisting, encouraging, aiding, abetting, and covering up on the other. In ten cases a combination of a non-AAF-ADRV and an AAF ('presence') occurred, which cases are listed in this section. Eight non-AAF cases were still open for possible appeal at the time of data collection.

Table 6. Distribution of non-AAF ADRVs in WADA's juridical database in the years 2010-2012 according to WADC-articles (WADA 2009b). Both the number of individual cases and the number of total violations are presented.

ADRV	WADC article	n (case)	n (total)
(Attempted) Use	2.2	73	104
Refusal	2.3	59	63
Evading sample collection	2.3	25	28
Whereabouts violations	2.4	37	37
(Attempted) Tampering	2.5	10	16
Possession	2.6	18	60
(Attempted) Trafficking	2.7	10	46
(Attempted) Administration	2.8	31	61
Assisting, encouraging, aiding, abetting, covering up	2.8	14	19
Violation of the prohibition of participation during ineligibility	10.10.2	3	11
Combinations of non-AAF ADRVs	-	73	-
Unknown	-	10	10
Presence of a prohibited substance in an athlete's sample	2.1	-	10
Total		363	465

Figure 2. Distribution of the length of sanctions in months for 362 non-AAF violations. On the horizontal axis all sanctions longer than 24 months are only shown if they actually occur within the dataset.

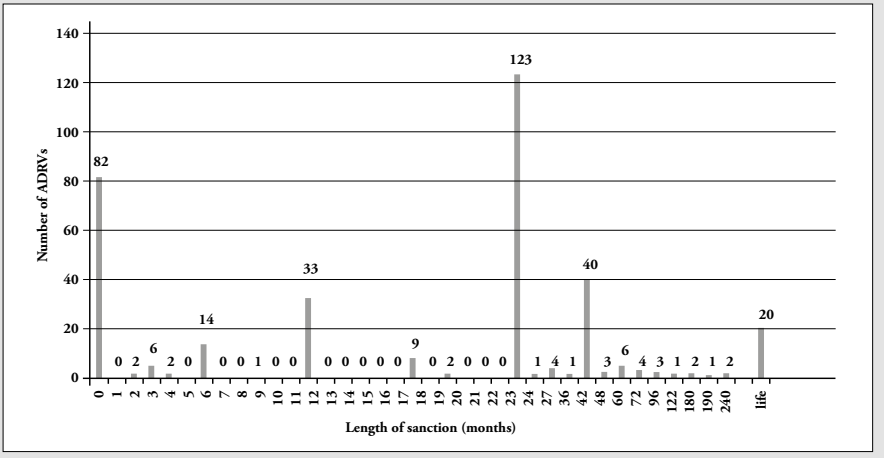


Figure 2 shows the variation in sanctions of 362 non-AAF-ADRVs (one sanction was unknown). The standard sanction is slightly diffuse for various of these ADRVs (four years of ineligibility for trafficking and administration, for example, while whereabouts violations can only be sanctioned with a period of ineligibility between one and two years (WADA 2009)), but it is obvious that many sanctions are lower than the most common standard of two years ineligibility. 82 Sanctions (23%) yield no period of ineligibility. Table 7 shows that in comparison to the AAF-ADRVs heavier sanctions are more frequently occurring in non-AAF-ADRVs, which indicates that the latter form of ADRV is generally seen as more severe than a 'traditional' AAF-case.

Table 7. Length of non-AAF-sanctions per ADRV (absolute and relative distributions).

		Sanction (months)							
		0-23.9		24		24.1-life		Unknown	Total
		n	%	n	%	n	%	n	n
ADRV	(Attempted) Use	32	43.8	35	47.9	6	8.2	0	73
	Refusal	14	23.7	37	62.7	7	11.9	1	59
	Evading sample collection	17	68.0	7	28.0	1	4.0	0	25
	Whereabouts violations	33	89.2	4	10.8	-	-	0	37
	(Attempted) Tampering	4	40.0	5	50.0	1	10.0	0	10
	Possession	10	55.6	7	38.9	1	5.6	0	18
	(Attempted) Trafficking	3	30.0	0	0.0	7	70.0	0	10
	(Attempted) Administration	9	29.0	4	12.9	18	58.1	0	31
	Assisting, encouraging etc.	4	28.6	5	35.7	5	35.7	0	14
	Violation of prohibition etc.	1	33.3	2	66.7	0	0.0	0	3
	Combinations	14	19.2	17	23.3	42	57.5	0	73
	Unknown	10	43.8	0	0.0	0	0.0	0	10
	Total	151	41.6	123	33.9	88	24.2	1	363

Regional distribution

The 1,831 AAFs originate from 115 different countries, reflecting the international distribution of elite sport. The 363 non-AAF-ADRVs originate from 43 countries (table 8). Countries from Africa and Oceania are underrepresented and Europe is overrepresented when the distribution of countries with at least one case is compared to the distribution of countries per continent that have signed the ‹Copenhagen declaration›, pledging their intent to comply with all the principles and the content of the WADC (WADA 2015b). This skewed distribution is even more profound when one looks at the total number of AAFs. With the non-AAF-ADRVs this distribution is even more skewed, with also Asia being underrepresented. The total number of AAFs is better comparable with the total number of participants in the 2010 Winter and 2012 Summer Olympic Games (Wikipedia 2010, 2012).

Table 8. Regional distribution of countries with at least one ADRV. For comparison, information is given on the number of countries that have signed the Copenhagen Declaration (see text) and the number of participants of the 2010 and 2012 Olympic Games.

Continent	#countries	#AAFs	#non-AAF ADRVs	Copenhagen declaration	#participants Olympic Games
Africa	19 (17%)	120 (7%)	7 (2%)	47 (24%)	932 (7%)
America's	24 (21%)	295 (16%)	39 (11%)	42 (22%)	2,485 (19%)
Asia	30 (26%)	393 (21%)	23 (6%)	41 (21%)	2,256 (17%)
Europe	40 (35%)	1,003 (55%)	291 (80%)	48 (25%)	6,987 (52%)
Oceania	2 (2%)	20 (1%)	3 (1%)	15 (8%)	723 (5%)
Total	115 (100%)	1,831 (100%)	363 (100%)	193 (100%)	13,383 (100%)

Table 9. Doping nomenclature.

Abbreviation	Full meaning
AAF	Adverse Analytical Finding (in a bodily specimen)
ADO	Anti-Doping Organisation (like WADA, a NADO, an IF)
ADRV	Anti-Doping Rule Violation
IC	In-Competition
IF	International Federation (responsible for a specific sport)
NADO	National Anti-Doping Organisation (responsible for a specific country)
OoC	Out-of-Competition
WADA	World Anti-Doping Agency
WADC	World Anti-Doping Code (core document in anti-doping regulations)
WADP	World Anti-Doping Program (entire set of anti-doping regulations)

Discussion

Backgrounds of the data

This is the first report of an analysis of information that has come from WADA's results management database of ADRVs. This database can be regarded to be the most complete database available on this subject as all Anti-Doping Organisations (ADOs) are obliged to report the ADRVs within their results management responsibility to WADA according to article 14.1.2 of the (at the time of the studied violations applicable) 2009 WADC (WADA 2009). There is also an extra check through the findings of the accredited anti-doping laboratories: all

laboratory sample numbers (laboratory analyses within the anti-doping system are anonymous by default) and their concomitant findings are relayed to WADA on a continuous basis by the WADA-accredited laboratories, and WADA will monitor the outcome of these findings with the ADO that is responsible for test result management in this particular case. This is a closed system; only WADA-accredited laboratories may analyse official doping controls.

At the closing stages of finalising this paper, it became known that the WADA-accredited laboratory in Moscow, Russia, may not always have followed the official WADA protocols, and did not report all AAFs the way it should have (McLaren 2016). Such actions, completely unknown at the time of analysis, may have had an impact on the conclusions but this impact is as yet completely unknown. The Moscow-lab accounted for the analysis of 6.8% of all samples world-wide in the years under study (personal archives).

In the three years that are the focus of this study the eight selected sports were confronted with 3,225 AAFs, of which 57% (1,831) reached the status of an official ADRV in WADA's results management database. The other 43% are a reflection of the fact that many AAFs do not imply a violation. The most common reasons for this are either the presence of an official Therapeutic Use Exemption (such as for asthma or diabetes medicines) or the AAF is an atypical finding provoking extra studies and/or controls but which by itself is not a violation (De Hon et al. 2015). This also means that several AAFs may be coming from one individual athlete.

All available background characteristics suggest that the cases under study are indeed a trustworthy representation of global anti-doping sanctioning, although there is no possibility to verify this suggestion without perusing all relevant annual reports of National Anti-Doping Organisations (NADOs), which would involve three separate reports for 115 different countries, an effort that was beyond the scope of this study.

The reliability of the data in WADA's results management database can be expected to be high. Firstly, the source is the international agency that leads a collaborative worldwide movement for doping-free sport, WADA. WADA's legal department oversees doping-related tribunal decisions on a global scale and has the right to appeal in many scenarios (see article 13 of the 2009 WADC). All omissions or unknowns are reported in the results-section of this article and overall these

are rare. The validity of the data, and especially the inferences we try to make on the basis of the length of the sanctions, is a more complicated issue. Exploring relationships between juridical outcomes and previous (health related) acts and circumstances is notoriously difficult (see e.g. (Slobogin 2007)). In addition, the relationship between an infraction of rules or laws and the appropriate sanction or penalty has been a matter of debate for a long time (Tsebelis 1990, 1993). Tribunals are expected to weigh all aspects of an individual case, and according to the WADC these lead to a certain sanction within a specific range of a period of ineligibility in sports. Extrapolating this information to an estimation of the level of intent to break the rules has been done once before in the sport of tennis (Pluim 2008). After reading all juridical awards of the 40 doping cases before the tribunal of the International Tennis Federation in the period 2003-2007, she concluded that only 13 of these cases (33%) were related to the intention to enhance performance.

The strength of our current study is in the source of the data (WADA's results management database) and the number of cases involved (2,194 in total). These two factors provide a dataset that can be expected to reflect, on average, the impact of the WADP on sanctioned athletes as closely as practically possible. This means that in this study an overall picture could be painted of global anti-doping sanctioning, giving an indication on the frequency in which hearing panels exercise their right to decrease or increase the standard sanction of two years ineligibility in sport.

As mentioned above, there are numerous reasons why a sanction can be altered by a panel (WADA 2009). In most ADRVs tribunals may decide within a certain range of a period of ineligibility. Lengthening a sanction can be based on aggravating circumstances, which is reflected in the current dataset. For example, finding a combination of several doping substances can be an aggravating circumstance in itself, as explained in a comment by WADA to WADC article 10.6 (WADA 2009). This is shown by the fact that the 'combination' category in table 3 yields the highest percentage of aggravated sanctions (more than 2 years of ineligibility). Shortening a sanction can be based on various mitigating circumstances (articles 10.4 and 10.5) and all of these can be seen as an interpretation by the hearing panel that the athlete involved had either a lower degree of guilt, was less at fault, or can be regarded as partially negligent and as such should not bear the full consequences of a standard sanction. In all instances, the athlete is deemed to be no 'clear cheat' (in the traditional interpretation of this word) by the hearing panel that rendered the final decision. A notorious example of a 'no fault' judgment is the consumption

of regular food contaminated with the anabolic agent clenbuterol which under certain circumstances may lead to no period of ineligibility (Shao et al. 2009, Guddat et al. 2012, Thevis et al. 2013). This dataset contains 20 of such clenbuterol cases, which represents more than one third of the mitigated sanctions in the S1-category. Another possibility to receive an alleviated sanction is to assist anti-doping organisations in discovering other ADRVs. This article has been applied very seldom before it was used in the extensive cycling investigations by the United States Anti-Doping Agency released in October 2012 (USADA 2012) and as such will be of limited influence on the dataset of this study.

It is of course possible that on the basis of the actual circumstances an athlete could be entitled to a particular adaptation in the standard sanction, but is unable to come up with the required proof. In those cases, the length of the sanction will not reflect the true circumstances. But the final outcome of a case is a blueprint of the legal circumstances that have been presented to the disciplinary panel and were judged admissible or inadmissible. This final outcome also automatically turns into 'the truth' for the athlete involved, as it states what the length of the sanction is that should be borne. In the current study just 38 AAF-cases (2%) and 8 non-AAF-ADRVs (also 2%) were still open to appeal by either party at the time of data collection.

The eight selected sports, both Winter and Summer Olympic sports and both team- and individual sports, provide more than half of all AAFs stemming from Olympic sports and are responsible for more than half of all doping controls in Olympic sports. Thus, they represent a large proportion of 'doping sensitive' sports in general.

We conclude that the 2194 cases presented in this study provide a crude yet credible description of the overall situation. The length of the sanctions can be regarded as a rather noisy outcome of various parameters, but can generally be expected to reflect the level of intent to break the existing anti-doping rules.

Principal findings

A majority of the sanctioned athletes received a penalty of two years ineligibility or more, which means that the hearing panels judging the case found the athlete to be at fault. But a large minority received lesser sanctions. More than 11% of the athletes who tested 'positive' after doping control received a sanction of zero

months ineligibility, which means that these athletes were either regarded to be of no fault or negligence for the AAF because of the circumstances of the case, or the available evidence was insufficient to justify a ban. In retrospect, these cases can be regarded to be AAFs for which doping sanctions were not intended to apply. An additional 31% of sanctioned athletes received an AAF-related sanction of less than two years, indicating a decreased degree of fault. As discussed above, other mitigating circumstances may have played a role, following the rules in the WADC. But generally speaking this decision is most likely to have been based on the level of intent to enhance performance or the degree of fault of the person involved, since admission of an ADRV or the possibility to assist anti-doping organisations in discovering other ADRVs are far less likely to occur, especially in the years under study. A similar picture can be seen in the outcomes of non-AAF-ADRVs, even though these ADRVs are generally sanctioned with longer periods of ineligibility than 'traditional' AAFs. It can thus be assumed that up to 40% of all ADRVs did not 'catch' intentional doping cheats in the eyes of the juridical panels.

The dataset shows that juridical panels use the latitude granted by the WADC to aggravate sanctions when combinations of several doping violations occur. Future studies should show whether the revised WADC that gained jurisdiction in 2015 (WADA 2013, 2015c) will affect the severity of sanctions.

Backgrounds of anti-doping sanctions

More than half of all ADRVs originate from European countries. It is not known how many of the doping controls are performed within Europe. The number of controls by NADOs are public knowledge, but the controls by IFs may be performed all over the world, and this distribution is unknown. Thus, it may be assumed but it cannot be proven that most anti-doping testing, at least in the eight selected sports, is being performed on the European continent. This assumption is backed by the fact that the regional distribution of Olympic participants in the same time period (an estimate of active athletes at the highest international level) is rather comparable with the regional distribution of AAFs in WADA's database.

From these data it can also be concluded that 60% of all doping controls in the 35 Olympic sports were performed in just 8 sports, and that a similar percentage (62%) of AAFs originate from these controls. This indicates that in the field of practice there are large differences between sports in the number of doping controls performed, but this does not lead to relatively more ADRVs. The percentage of

'hits' in the field of doping controls seems to be independent from the number of controls that are performed. WADA has improved its reporting on doping controls and concomitant AAFs in recent years and this will definitely be an interesting topic of future studies.

The Prohibited List specifically mentions which groups of substances and methods are prohibited during doping controls that are performed outside event periods (OoC-controls) in addition to the IC controls right after a match, race or competition. Currently, the substances listed in groups S0 through S5 and M1 through M3 are prohibited at all times. It is striking to see that of the 1042 AAFs that are found in those groups where this is relevant (57% of all AAFs in this dataset) just 29% of all AAFs originate from OoC-controls (301 versus 741). The chances of finding an AAF with IC-controls seems to be much larger. Most ADOs strive for a 50/50 distribution between IC and OoC-controls but this is not always accomplished. This is also sport-dependent. Since 2012 WADA publicly reports how many of the controls per sport are actually performed IC or OoC and since 2013 more in-depth statistics are available (WADA 2014, 2015a). However, these statistics do not give a distribution per class of substances which means that a fair comparison is not yet possible. This issue goes hand-in-hand with discussions on the effectiveness of out of competition doping controls which has been addressed before in reports, but not yet in a scientific study (Palmer et al. 2011). This is also certainly an area that deserves more attention in future studies.

Limitations of the study

The data on the length of the sanctions are based on the ruling of the disciplinary body. As such, these data are not objectively quantifiable. Each case is an individual doping case. Each sanction is the result of individually weighted circumstances and are not intercomparable. This analysis is not trying to re-weigh all possible aspects of a particular case, nor is this ever possible in a secretive act such as doping use. This means it is impossible to judge each and every individual case on all merits of the case. On the other hand: such a 're-trial' has limited value since the true backgrounds of an ADRV, especially regarding the level of intentionality, is likely to remain known solely to the athlete involved. Even in criminal law, which is profoundly different than sport-related regulations, proof of the level of intentionality is extremely difficult to give (Kahmen 2013). Nowadays, with the WADC firmly in place, anti-doping panels are generally formed by knowledgeable people who can be expected to reach a fair decision in the context of the WADC.

The selection of sports in this study was made to maximise the experience of the anti-doping panels involved.

Since it is highly work intensive to extract these data from the available databases it was not possible to include all sports or to re-analyse all individual cases based on legal documents. As a consequence, a selection was made which means that the available data are merely indicative of all ADRVs in the years under study. Due to time constraints it was decided to target the current study predominantly on quantitative data and not on qualitative sources. The strength of the data lies in the unique source and the fact that three calendar years were included, without great differences between years. This allowed for a sufficient volume of cases to draw general conclusions and for sufficient confidence to see the included cases as being crudely representative for the situation under the 2009 WADC.

European countries, and cases, are overrepresented in the results management database in comparison to the countries that have signed the Copenhagen Declaration. This may be due to the fact that the majority of anti-doping testing is being performed on this continent, at least in the selected sports, but this cannot be verified. Since most Olympic participants originate from Europe a certain tendency towards this continent is unavoidable and this opens the door for potential bias in the data based on culture or wealth.

Implications for anti-doping policy

Being the first study into this subject, using an unavailable database so far, the study is predominantly descriptive in nature although some preliminary policy conclusions may be formulated. Besides providing a first view of the intricate relationships between doping controls, timing of these controls, ADRVs, substances involved, their regional distribution and the length of sanctions, a 'practicality plot' can be drawn for both AAFs and non-analytical ADRVs (tables 10 and 11). Demarcation points for the occurrence frequency are drawn arbitrary, and intended to provide a practical threefold separation in the three-year period that is included in this analysis.

Table 10. Practical overview of AAFs; relationship between the most often occurring sanction period and occurrence frequency per group of substances on the Prohibited List (see table 3).

		Relative sanction length		
		Low sanction (0-23.9 months)	**Standard sanction (24 months)**	**High sanction (24.1+ months)**
Relative Occurrence	**Low occurrence (0-100x)**	Beta-2 agonists Narcotics	Hormone modulators	-
	Medium occurrence (101-300x)	Diuretics Glucocorticosteroids	Peptide hormones Combinations	-
	High occurrence (301+)	Stimulants Cannabinoids	Anabolic agents	-

Table 11. Practical overview of non-AAF ADRVs; relationship between the most often occurring sanction period and occurrence frequency per prohibited behavior (see table 7).

		Relative sanction length		
		Low sanction (0-23.9 months)	**Standard sanction (24 months)**	**High sanction (24.1+ months)**
Relative Occurrence	**Low occurrence (0-10x)**		Tampering Violation of prohibition	Trafficking
	Medium occurrence (11-40x)	Possession Evading collection Whereabouts	Assisting & encouraging	Administration
	High occurrence (41+)		Use Refusal	Combinations

These last two tables show that AAFs with substances from the S1, S2 and S4-categories yield the highest sanctions, with anabolic steroids being the most frequently encountered group of substances in practice. These groups, together with violations regarding combinations of substances, also contain the highest percentages of sanctions that last longer than 2 years of ineligibility (7.1 to 20%). For non-analytical ADRVs the most severe sanction periods are handed out for trafficking in or the administration of prohibited substances. A combination of prohibited behavior occurs most frequently, and also draws the longest periods of ineligibility (58% of all combination cases resulting in more than 2 years of ineligibility). These ADRVs can be regarded as the most severe doping infractions. It is encouraging that the juridical system in place in the field of anti-doping is able to alleviate the standard sanction of two years ineligibility in cases where this is deemed opportune, but at the same time these cases place a large burden

on the athlete during the period between the notification of the result and the final outcome of the juridical process (a process that may take several months, and sometimes years). These cases involve all possible doping substances, but a majority of these cases are related to regular medicines and/or so-called 'social drugs' (beta-2 agonists, diuretics, stimulants, glucocorticosteroids, narcotics, and cannabinoids; the 'left panel' of table 10). The same is true for the non-analytical violations labelled as possession, evading sample collection, and whereabouts violations (the 'left panel' of table 11). These findings highlight the importance of doping regulations that are able to sieve and extract the assumed cases of intentional performance enhancement, which warrant the standard penalty, or even higher. The current system seems to be able to sieve out an approximate 60% of all identified cases. It should be a matter of further debate what the exact place of the other 40% of cases should be within the anti-doping framework.

Whether the situation described above is caused by an inability for doping controls to discriminate sufficiently between intentional cheaters and unintentional 'by-catch' is difficult to say. Indeed, athletes who are guilty of (profound) negligence should be picked up by the anti-doping system as they will benefit from the potential performance enhancing capacities of the particular substance that has been found in the sample that they provided. The level of intentionality is extremely difficult to quantify in legal terms, but at the very least the results of this study give a strong indication that it is quite possible that a significant amount of up to 40% of all athletes who are caught by an AAF did not intentionally violate the anti-doping regulations. The same is true for some non-analytical doping violations. This is an important message, both to the athletes, to the general public and to the anti-doping professionals. In which ways this can be best remedied is beyond the scope of this article, but this could involve increased anti-doping education, changes in the Prohibited List, changes in the analytical capabilities of the labs, the interpretations of lab results by hearing panels or by various other means.

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Declaration of interest

The authors report no conflicts of interest, except that the first author works for the Dutch NADO. Only the authors themselves are responsible for the content and writing of the paper.

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Extended discussion on prevalence of unintentional doping use

The article discusses the possible backgrounds of anti-doping rule violations, based on the length of sanctions. This is a rather crude measure. It is, however, always important to try and look behind the one-line newspaper article that athlete x tested positive for substance y and therefore will be suspended until date z. Completely different worlds of backgrounds can be found behind this simple news fact. Many substances can be consumed inadvertently (Yonamine et al. 2004, Anderson 2011), even though the first WADA-president Dick Pound often stressed the rarity of unintentional doping by using the following analogy: 'If you're captured and held down by a squad of Nazi frogmen and injected with something' [you may qualify for a reduction or even elimination of a sanction] (Slater 2007). On the other side of the spectrum there will always be strong advocates and/or believers of an athlete's full innocence, particularly among their lawyers and hard-core fans. Such unclarities are unavoidable as a doping control is one single scan of the substances in an athlete's body at that particular time; it is impossible to derive from that single analysis what happened in the hours, days, weeks or even months before that.

If doping use is seen as disturbing true athletic achievements, and current anti-doping policies are largely based on that principle, it can be argued that it does not really matter that much if the doping substance has been used deliberately or intentionally (the same holds true for doping methods, but unintentional method application is difficult to imagine). For if an athlete has the benefit of a potent doping substance during training or competition, the performance is logically related, at least to some degree, to this particular substance. This principle is built in the WADC as even if it can be established that the athlete concerned is entirely not to blame for the presence of a prohibited substance in his or her sample (i.e. no fault or negligence can be established), the competitive results of that particular day, and possible more days surrounding the day of doping control, will be disqualified. The most (in)famous effectuation of this rule has been in the case of gymnast Andreea Raducan, who had to return an Olympic gold medal despite sufficiently proving that she ingested a prohibited substance unknowingly (ADKC 2000). It is also true that the mere existence of sanctions will act as a deterrent against doping use, although in itself it is by no means deterrent enough (Overbye et al. 2015).

The difficulty with effectuating this rule, is that a large majority of athletes confronted with an AAF do not admit intentional doping use, and explain in quite simple or

very complicated ways how this ADRV came about without them knowing anything about it. The same holds true for non-analytical ADRVs, even though many of these are, by their nature, less prone to unintentional behaviour (the exceptions being possession, evading sample collection, and whereabouts violations; see table 11 of the article above). These explanations are always difficult to evaluate. There are numerous well-documented cases where the presence of a prohibited substance can be explained by behaviour that constitutes no doping offence. To name just a few examples: the consumption of codeine which may lead to a morphine AAF (Delbeke & Debackere 1991, Thevis et al. 2003), the consumption of meat in China or Mexico that may lead to a clenbuterol AAF (Shao et al. 2009, Guddat et al. 2012, Thevis et al. 2013), or the consumption of coca-leaf tea that may lead to a cocaine positive (Jenkins et al. 1996, Mazor et al. 2006). An extra difficulty with these real-life examples, is that intentional cheats are offered an easy way out of a potential sanction when they are confronted with a codeine/clenbuterol/cocaine AAF. There is a reversed inverse relationship with the level in which these circumstances are well-known, and the possibility to use them as excuses in anti-doping cases: the better known they are, the better the athlete should have known that this particular situation needed to be avoided, and the higher the sanction will be.

In the end, it is the task of the juridical panel that looks at the case to decide on the weight that should be attached to the explanation of the athlete, and to feed this consideration into the regulations laid down in the relevant rules. The ultimate sanction is the final result of a juridical process that may include more than one decision by various panels: a national panel, a national appeal body, a body within the IF involved, and ultimately the Court of Arbitration in Sport. This process is closely watched by WADA, which will intervene if it sees necessary according to their mission to act as the guardian of the values inherent in the WADC. Each step in this juridical system is based on the principles of natural justice and the balance of powers. This system of checks and balances can be expected to produce a decision that is true to the (spirit of the) WADC. Ultimately, as in any legal matter, a civil judge may get involved as well if an athlete, or other person or organisation, wishes to exercise this basic right.

The WADC names several specific instances where special circumstances can lead to a lower sanction than 'normal'. In this sense, the sanction of an athlete, or any other person or organisation breaking the anti-doping rules, also yields information on the intentionality of the infraction, albeit indirectly. That was the

reason to ask WADA for their cooperation in providing some of the contents of their juridical database (WADA kindly provided the data, but the interpretation of the data was solely performed by the authors). This is a prime example of an ADO, in this case the primus inter pares namely WADA itself, that possesses relevant data but simply does not have the time within their current workload to share this publicly in an anonymous manner. These data, however, are potentially highly interesting in evaluating the effectiveness of anti-doping policies, not just because of the length of sanctions, but also in comparing sports, timing of sample control, and many other background statistics. The aforementioned article is just one example of how these data could be used to evaluate anti-doping policies. The length of sanctions, although a rather simple set of digits and a crude measure that includes many variables, is highly interesting information for evaluating anti-doping policies. From a practical point of view, it is even the most important measure as for an athlete (and their competitors) it is of essential importance when someone is again eligible to compete.

Since the data collection took place, WADA has made extra steps in this area and published an overview of ADRVs per sport and per testing authority (WADA 2015a). This is a laudable and work-intensive effort, which will enable evaluations of what sort of ADRVs take place. This is an important step forward in comparison to the laboratory testing statistics that have been published by WADA since 2003, especially with the extensive elaboration of AAF-data that has been made public since 2012. It would be even better if annual evaluations can take place on extra descriptive data, as has been done in the article above. But most of all it would be interesting to track possible changes in the length of eventual sanctions (or absence thereof) over the years. The revised WADC has allowed more leniency in lengthening sanctions, but shortening sanctions is still possible if certain requirements are met (WADA 2015c).

The methodology used in the article above can still be applied with the revised WADC, but the new Code does require some extra attention in certain areas. In the last couple of years, there has been an increasing number of athletes who have received lesser sanctions because of their cooperation with ADOs after committing an ADRV, which makes it more difficult to draw conclusions based solely on the length of sanctions. It is important to monitor this sort of data as it provides information about the degree in which the involved athlete has been regarded as

being 'a cheat' by the juridical system in place or whether mitigating circumstances have been taken into account.

In order to evaluate the effectiveness of anti-doping policies it is highly relevant to know what proportion of the sanctioned athletes (and support personnel) can be expected to be 'by catch' in the efforts to eradicate doping in sports. No system can be expected to be 100% perfect, but every athlete that is sanctioned on the basis of anti-doping rules but who did not do so intentionally is a scratch in the anti-doping framework, and an indication that this may be occurring in up to 40% of the cases is simply too high to ignore. Several ways in which this situation may be improved will be discussed in chapters 3 and 4.

2.4 The effectiveness of doping substances and methods

Doping in sports would not exist if there were no performance enhancing substances available, or at least when athletes (and their trainers, coaches, and advisors) would not think that performance enhancing substances would be available. The degree in which performance enhancement is indeed possible by using doping is heavily debated at times. This is an area where science may help to find answers, but finding conclusive answers is not as easy as it may sound at first.

The main problem is that research into the effects of doping on performances is highly complicated. There are not many institutions interested in these findings, and as such there are not a lot of funds available to conduct performance-related doping research. Scientific funds within the anti-doping community are generally spent on improvements in analytical science, and over the last couple of years the number of studies into psychological backgrounds of doping use are increasing. But purely physiological studies within an athletic setting continue to be rare. When performing such studies, there is also the practical problem that administering doping substances to active athletes is not allowed by doping regulations, for obvious reasons. This means that the results of such studies need to be extrapolated from sub-elite athletes. These practical issues add to the 'standard' scientific challenges in sports sciences of finding a standardised performance measurement that resembles real-life competitions as closely as possible, recruiting sufficient subjects in order to study the whole range of possible individual responses, and convincing ethical committees that these substances are indeed used in high dosages by athletes and that this fact may justify giving medical drugs at these high dosages to otherwise

healthy subjects. The result is a prohibited list of doping substances that in many ways is built on beliefs and experiences, rather than scientific studies.

In order to shed more light on the issue of performance enhancement by means of doping substances, three cases will be presented that address this issue. Because performance effects are never studied in isolation, these cases also address other aspects of the issue of effectiveness. All three cases surfaced from actual policy questions that surfaced as a result of doping policy related discussions.

2.4.1 Case 1: Mind sports and anti-doping, or the boundaries of sports

Introduction to case 1

Drawing up policy measures for sports indisputably brings up the question: what makes an activity a 'sport'? From a sport philosophy point of view, this answer is often found in Bernard Suits' classic definition of a game: a voluntary attempt to overcome unnecessary obstacles, with three necessary components: a 'prelusory goal' also known as the 'object of the game', constitutive rules which forbid the most efficient means toward the goal, and a 'lusory attitude' or the players' conscious acceptance of rules which makes the game possible (Suits 1995). Although many people would include some aspect of physical exertion to this definition when changing the concept of 'game' into 'sport', fact of the matter is that in many countries, and also by the IOC, activities like chess and bridge are considered to be full members of the 'sport family'. So from an organisational point of view all mind sports are indeed sports.

This is relevant to doping policies as well. In 1999 the Dutch government made it obligatory for all national sport federations to conduct doping controls, among other anti-doping measures, in order to be eligible for governmental funding. Up till then there had never been any doping controls in any of the mind sports and the national federations jointly argued that an exemption should be made. This led to the political-related question: should mind sports be obliged to conduct doping controls?

The following is the text of a report based on a literature review that was conducted in 1999/2000 and an expert-meeting with various scholars, athletes and policy makers (De Hon & Hartgens 2000). Since it was also intended as a policy document, a choice was made at the time to not include all relevant references throughout the

text, but to provide a list of references at the end of the report. The text of this review has not been published in a scientific journal and as such has not been subjected to a peer-review process, although it has been shared with the respective national and international federations, numerous governmental institutions, the IOC, and the fledgling WADA. It is included in this thesis as a means to explore the subject of harmonisation over all sports, and because the majority of the contents is still valid. Even though this is not a scientific article in the strict sense of the word, it is nevertheless marked as an article because of its relevance for the overall aim for this thesis, and also because of consistency reasons.

MIND SPORTS AND DOPING - AN INVESTIGATION OF PHARMACOLOGICAL SUBSTANCES THAT MAY ENHANCE PERFORMANCE IN MIND SPORTS

O de Hon & F Hartgens

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www.dopingautoriteit.nl/media/files/documenten/Mind__Sports__and__doping.pdf

Abstract

As a result of the ratification of the Anti-Doping Convention in 1995, the Dutch government has increasingly compelled the national sports federations to pursue an active anti-doping policy. As a minimum, these federations must have anti-doping regulations. However, mind sports (chess, draughts, bridge, and Go) have provisionally been exempted from this ruling because there are doubts about the relevance of this policy to these sports. In response to a request from the Dutch federations of various mind sports, the Dutch Ministry of Health, Welfare, and Sport has asked the Netherlands Centre for Doping Affairs to investigate whether pharmacological substances can be used to enhance performance in mind sports.

The foremost purpose of this investigation was to determine whether there are pharmacological substances that may enhance performance in mind sports. In addition, it was studied whether the use of such substances is detrimental to the user's health. In the context of this study, a substance that both enhances performance and is detrimental to health is considered a doping agent. The issue of whether a certain substance might harm the image of a sport was not addressed. Since there is little literature available on the direct pharmacological manipulation of performance in mind sports, it was decided to consult experts. These experts were (former) top mind sport competitors, representatives of the Dutch federations

of various mind sports, and neuroscientists. These experts were first consulted individually and then they took part in an expert meeting to bring the available expertise together.

The first conclusion that was drawn was that mind sports require completely different skills than physical sports do. The main difference lies in the major role of mental processes in determining performance in mind sports. This primary role of cognitive factors is the same for the sports of chess, draughts, bridge, and Go. This justifies a special position for these mind sports within the existing anti-doping regulations. The experts from the world of mind sports had the impression that pharmacological substances were used only sporadically to enhance performance. The general belief is that these substances are more harmful than beneficial to performance in mind sports. However, on the basis of the proven effects of such substances, it can be assumed that they could be used to improve performance in mind sports.

As far as it is known, it is not possible to enhance mind sport performance directly with pharmacological substances; however, it is probably possible to achieve this is an indirect manner. Pharmacological substances can be used to improve several cognitive functions, such as, alertness, attention, vigilance, memory, information processing, speed of thought, and the ability to perform a certain cognitive task for a long time. These cognitive functions support the performance of cognitive processes, which in turn determine the way complex tasks, such as playing mind sports, are performed. Statements about this final step can only be based on assumptions because of a lack of sufficient knowledge regarding the relationship between cognitive processes and performance in mind sports. Since the cognitive effects of pharmacological substances are generally minor, the effects on mind sport performance are expected to be minor as well.

In consultation with the experts and with reference to the scientific literature, a list was drawn up of substances that might be expected to enhance performance in mind sports. This broad approach was chosen in order not to exclude any potentially relevant substance. Because of the difference in the factors that determine performance in mind sports and physical sports, this list differs from the existing list of prohibited substances and methods prepared by the International Olympic Committee (IOC). The potential performance-enhancing substances in mind sports have been classified into three categories. The first category incorporates

substances and substance groups that can be expected to enhance performance in mind sports and whose use is accompanied by harmful effects on health. These substances are nicotine and other cholinergics, amphetamines, ephedrine, cocaine, beta blockers, and substances that increase the availability of oxygen in the brain. On the basis of the definition of doping used in this study, these substances should be regarded as doping agents. The substances caffeine, MDMA-analogues (such as ecstasy, or XTC), cannabinoids, opiates, alcohol, and benzodiazepines do not meet the definition of doping used in this study. At the moment, scientific knowledge is not clear as to whether certain substances, for example, 5- HT1A agonists, the neuropeptides, and the hormones growth hormone, oestrogens and testosterone, can improve performance in mind sports. Thus, it is currently not possible to determine whether these substances should be regarded as doping agents in the context of mind sports.

The following conclusions may be drawn:

- the factors that determine performance are substantially different between mind sports and physical sports, and this justifies separate anti-doping regulations;
- in the world of mind sports itself, the impression exists that pharmacological substances are used only sporadically to enhance performance;
- it can be expected that performance in mind sports can be enhanced by means of pharmacological substances; however, the expected effect of such substances is minor;
- some of the possible performance-enhancing substances may be harmful to health, which means that these substances should be considered as doping agents;
- it is recommended that the mind sports federations formally prohibit doping and that these federations draw up regulations that enable sanctions to be imposed when prohibited substances are used in mind sports;
- if the decision is taken to prohibit doping in mind sports, it is recommended that a specific list of prohibited substances be drawn up. The current (IOC) list of prohibited substances should not be used unadapted;
- it is important that national and international anti-doping regulations concerning the mind sports are consistent. This investigation may contribute to the harmonisation of these regulations.

Introduction

In 1995, the Dutch Government ratified the Anti-Doping Convention of the Council of Europe. As a consequence, the Government is obliged to pursue an active policy against the use of doping in sports. To this end, the Government has compelled all sports federations that are affiliated with the Dutch Olympic Committee*Dutch Sports Federation (NOC*NSF; a list of abbreviations can be found at the end of this report) to draw up, and when necessary enforce, anti-doping regulations as of 1 January 1999. As of the same year, federations that do not comply with this will receive a reduced subsidy from the Dutch Ministry of Health, Welfare, and Sport. However, it is unclear whether these regulations apply to certain sports federations, namely, the chess federation, the draughts federation, the bridge federation, and the Go federation. At the moment, these Dutch federations do not have anti-doping regulations. These federations query whether, given the specific characteristics of mind sports, the general regulations concerning physical sports are applicable to their branch of sport or whether they need to have their own anti-doping regulations. The issue is thus whether mind sports are sufficiently different from other sports that mind sports federations are justified in claiming a different status with regard to anti-doping regulations. In order to determine this, it is first necessary to ascertain whether there are substances that can be considered as doping in the context of mind sports and what these substances are. The Ministry of Health, Welfare, and Sport has asked the Netherlands Centre for Doping Affairs (NeCeDo) to carry out an investigation designed to answer these questions.

Assignment

The task assigned by the Ministry of Health, Welfare, and Sport is to determine whether there are pharmacological substances that may enhance performance in mind sports.

Interpretation of the assignment

The assignment has been broadly interpreted. The underlying question is whether or not Dutch mind sports federations should enforce current anti-doping regulations. In order to be able to draw conclusions about whether certain substances should be considered as doping agents, it was also necessary to investigate the effects of these substances on health. In addition, a small group of involved parties were consulted about the opinion of the mind sports world concerning doping and anti-doping regulations.

Definition of terms

In this section the terms "mind sport", "doping", and "pharmacological substance" are explained in order to avoid confusion.

Mind sport

The sports chess, draughts, bridge, and Go are termed mind sports. The term "mind sport" implies a contrast to physical sports. In physical sports, there is more emphasis on physical activity than in mind sports, although this distinction is not absolute. Physical activity is also necessary in mind sports and mental activity in physical sports. The difference lies in the fact that, in physical sports, the way in which physical movements are performed is a determinant of the success of the competition or match. This is not the case in mind sports, where the physical manner in which pieces are moved or cards are played is irrelevant to the result of the competition.

This distinction between mind and physical sports is used in this report. The mind sports encompass chess, draughts, bridge, and Go. The federations of these sports are temporarily exempted from the obligation to draw up anti-doping regulations by the Ministry of Health, Welfare, and Sport.

Pharmacological substances

In this report, the term "pharmacology" is used in a broad sense, which means that attention is paid not only to medicinal drugs but also to chemical substances in general. Certain pharmacological substances are referred to as being members of a group when they show very similar effects and mechanisms of action.

Doping

The use of doping goes against the spirit of fair play that should be inherent to all voluntary competition between people. This feeling is shared by many; however, before such a feeling can be incorporated in regulations it is necessary to define the term doping further. The term is defined mainly on the basis of the three arguments put forward to ban doping.

The first argument is based on unfair improvement of performance. The use of performance-enhancing substances is seen as unfair competition. The second argument concerns the health of the sports man or woman. Some sports are dangerous in themselves, but the use of certain substances or methods can be unduly harmful to the player's health. The third argument that could play a role

in whether a certain substance or method is considered to be doping is the image argument. Some instances or bodies involved in sport emphasise the "clean" character of the sport and for this reason forbid the use of substances and methods that they do not want to be associated with.

In this report, emphasis is laid on the answers to the questions related to the first two arguments, namely, whether a certain substance can improve performance in mind sports and whether it is deleterious to the health of the user. The third argument, the image argument, is not considered. The questions concerning the first two arguments will be answered on the basis of current scientific knowledge. If the two questions are answered affirmatively, then this report will recommend that these substances be considered as doping agents in the context of mind sports.

Investigation protocol

The issue of doping is new to mind sports. Although there is anecdotal information about players who have used substances to improve their performance, to date the mind sports federations have never had a reason to draw up anti-doping regulations. However, the international agreements made by the Dutch Government has confronted the Dutch mind sports federations with the issue of anti-doping regulations in their sports.

The question arose whether the mind sports chess, draughts, bridge, and Go have such an unusual position compared to other sports that the mind sports federations do not need to meet the requirements laid down for other Dutch sports federations. In order to answer this question, more knowledge is needed as to the possibility to enhance performance in mind sports by means of pharmacological manipulation.

Research questions

The following questions have been formulated in order to gain insight into whether performance in mind sports can be improved by means of pharmacological substances:

1. Are there data in the scientific literature about potential performance-enhancing substances for the sports chess, draughts, bridge, and Go?
2. Which pharmacological substances can improve human functions to such an extent that they could improve performance in the above-mentioned sports?
3. What are the harmful effects on health of these potential performance-enhancing substances?

Research strategy

This investigation makes use of the framework of existing anti-doping regulations for physical sports. This framework is based on a list of prohibited substances, groups of substances, and methods. This investigation has taken into account the specific differences, namely, the functions that determine performance, between the two types of sport.

The investigation is divided into three components: a search of the literature, consultations with experts, and documentation of the findings. The investigation took place between October 1999 and March 2000.

Literature search

As a first step, the literature was searched for relevant scientific studies of the effect of pharmacological substances on performance in mind sports. Only one relevant study was found, which investigated the effect of two substances on the chess-playing performance of six volunteers. Both substances had variable effects. Nothing was found in the literature about the other mind sports. This provided an answer to the first research question. However, it is clear that the other two research questions could not be answered on the basis of this single study.

Consultation with experts

The lack of sufficient scientific literature on the direct effect of pharmacological substances on mind sport performance made it necessary to adopt an indirect approach in order to be able to answer the second and third research questions. This indirect approach was focused on determining the factors that play a role in mind sports. Then it was investigated which pharmacological substances have a positive effect on these factors. In addition to accessing the relevant literature, it was decided to request the assistance of experts. The experts consulted were either involved in mind sports or were scientists. The experts from the mind sports were (former) top players and members of federation executive boards. The scientists mainly had a background in the neurosciences, with specialisation in neurophysiology, psychopharmacology, and related fields. An overview of the experts who were consulted is given below.

The opinions of the experts concerning the research questions were first determined in individual interviews. Then a joint meeting was held with all experts to discuss the topic and to bring the available expertise together. During this expert

meeting, the (former) top players and the members of the executive boards of the mind sports federations gave an overview of the extent to which doping plays a role in mind sports. This was followed by a discussion with the scientists about the physiological functions that are important for mind sports. The scientists then indicated to what extent it would be possible to influence these functions pharmacologically.

The discussion on the potential for pharmacological improvement of performance was based on an overview of substances that might be expected to improve mind sport performance. This broad approach was chosen so as not to exclude any potentially relevant substances. It was based on the existing list of prohibited substances and methods of the International Olympic Committee (IOC), but was adapted in consultation with the experts.

It was the aim to reach consensus during this meeting. The minutes of the meeting were sent to all participants for their approval.

Documentation of findings
On the basis of the available literature and the opinions of the experts involved, it was possible to get a good picture of the potential to improve mind sport performance by means of pharmacological substances. This information is presented in this report, which concludes with recommendations for the Dutch Ministry of Health, Welfare, and Sport.

The current situation

This section gives a brief overview of how the world of mind sports looks at doping and anti-doping regulations. A distinction is made between the Dutch and the international situations.

The Dutch situation
At the meeting of experts it became clear that the mind sports representatives do not consider doping to be a problem in their sport, either now or in the past. A few players use sedatives on doctor's prescription and others may use alcohol or marihuana for the same purpose. One chess player is known to drink the energy drink "Red Bull" during matches because he is convinced that it keeps him alert. This is not a cause of surprise or unrest in the chess world. The main ingredient of "Red Bull" is caffeine, which is also found in coffee. Chess players do not consider

caffeine as an "unnatural" way of improving performance, or players who drink coffee as being unfair.

Another argument advanced as an indication that there is no doping in mind sports is the conviction that pharmacological substances are more likely to have a negative than a positive effect on performance. Moreover, if a substance or method could improve performance, players would use it openly. There are no rules that forbid this, and the aim of every player to perform at his or her best would make the use of such a substance or method a matter of course. These arguments have led to a certain scepticism in the mind sports world about the need for anti-doping regulations. It is also feared that mention of doping in the context of mind sports may create a problem, by focusing attention on the topic. However, it is generally recognised that mind sports are now confronted with the current anti-doping regulations of other branches of sport. This is a consequence of the Dutch ratification of the Anti-Doping Convention of the Council of Europe and the inclusion of the Netherlands in the group of countries that have signed the International Anti-Doping Arrangement (IADA). This means that the Dutch government has agreed to implement an anti-doping policy for all sports. Thus, these international agreements have led to a doping problem, namely, that there are no anti-doping regulations for the mind sports.

The international situation

The unfamiliarity of the mind sports world with anti-doping regulations is not only a problem in the Netherlands. Several countries have ratified the Anti-Doping Convention of the Council of Europe, and in some of these countries the question about the extent to which mind sports federations should comply with current anti-doping regulations has also arisen. Thus, the mind sports federations of Spain, Italy, and Finland are also confronted with the issue of anti-doping regulations. The national bridge federation in Italy and the national chess federation in Finland carry out doping controls on the basis of the current IOC doping list. These countries have not attempted to adjust the list according to the specific characteristics of mind sports. The Spanish chess federation has not yet replied to a request to indicate in what way it interprets the anti-doping regulations in the context of mind sports.

The international federations are also confronted with the current anti-doping regulations for physical sports. Both chess and bridge want to be recognised as

Olympic sports and the international federations have already approached the IOC. The International Draughts Federation has joined the General Association of International Sports Federations (GAISF), which is a first step to recognition as an Olympic sport. Similar steps may be taken by Go federations in the future. Affiliation with the IOC means that federations must comply with the anti-doping regulations of the IOC. Spokesmen/women of the international federations for chess and bridge have indicated that they have pointed out the special position of their sports to the IOC. To date, it is not clear how the IOC and the international mind sports federations will deal with the matter. During the world bridge championships held early in 2000, all players were tested for all substances listed on the IOC doping list.

It is important that, in the future, the Dutch situation and the international situation be harmonised. This will be made difficult if there is a difference of opinion between Dutch and international policy makers regarding anti-doping regulations. According to international anti-doping regulations, potential performance-enhancing substances should be considered as doping agents if they improve performance or if they are harmful to health. The Dutch government considers that a substance should be considered a doping agent if it improves performance and is harmful to health. It is not desirable that, in the future, a situation could arise in which Dutch participants of international mind sports competitions would have to comply with regulations that are different from those that are valid for national competitions. As indicated before, this investigation is based on the Dutch point of view because the investigation was primarily performed for the Dutch situation.

Factors determining performance in mind sports

There are clear differences between the factors that determine performance in mind sports and physical sports. This is the main reason why mind sports federations consider that they are in an unusual position with regard to current Dutch anti-doping regulations. This section describes the factors that determine performance in chess, draughts, bridge, and Go.

Many factors determine mind sport performance. For example, the player's experience, talent, mental well-being at the time of the match, and physical fitness. The physical fitness of the player is of great importance during tournaments, when matches are held every day. However, under normal circumstances, the physical fitness of the player is not of decisive importance. The most important factor for

good performance in mind sports is the way in which a player, at the moment of the competition, knows to unite knowledge and skills to make the right move or to play the right card. This is determined by the way the brain is functioning at that moment, in other words, by the level of "cognition". If mind sport performance is to be improved, it will be necessary, more than anything else, to improve the player's cognitive functioning. The experts agreed that this was the essential difference between mind sports and physical sports.

Cognitive functions, cognitive processes, and mind sport performance

Theoretically, many cognitive functions can be expected to be important to the playing of mind sports. Examples of these functions are alertness, attention, vigilance, memory, information processing, speed of thought, and the ability to perform a certain cognitive task for a long time. The latter could be termed "cognitive stamina" or "mental condition". The scientific experts agreed that it would not be possible to make a list of all cognitive processes that are important to mind sport performance. Moreover, it is possible that functions that have not yet been identified may be important during complex cognitive processes.

There has been considerable psychological research into the cognitive functioning of players of mind sports, with emphasis on the difference between top and intermediate chess players. The Dutch scientist A.D. de Groot has done much pioneering work in this field. It has been shown that top chess players are much better than intermediate players at recognising positions and at matching patterns; their visual acuity is also much better. Interestingly, these are more cognitive processes than cognitive functions. During the expert meeting it became clear that cognitive functions do not necessarily determine cognitive performance. Several cognitive functions are addressed at the same time during thought. Although it is difficult to determine the exact interaction between these functions during the thought process, it is clear that the processes that play a role in this ultimately determine cognitive performance. It is thus better to refer to cognitive processes rather than cognitive functions when discussing cognitive enhancement. Cognitive functions do affect cognitive processes. But, while an improved cognitive function will lead to a more efficient course of the entire process, the implementation of cognitive processes ultimately determines cognitive performance.

The use of the term "cognitive processes" has another advantage over the use of the term "cognitive functions". It facilitates and clarifies the discussion of the effects

of pharmacological substances on mind sport performance. The question of which pharmacological substances can influence human functions to such an extent that they could improve mind sport performance can best be answered in terms of cognitive processes. These processes do not necessarily have to be identified. The experts agreed that it is possible to draw conclusions about the potential to affect cognitive processes without necessarily having to specify the relevant processes.

The last step that needs to be taken is to extrapolate the possibility to influence cognitive processes to the possibility to improve mind sport performance. This is difficult because there is not yet enough knowledge available on which to base an unequivocal conclusion. Statements about the potential to improve mind sport performance are always based on assumptions. The conclusions of this investigation reflect what can be expected on the basis of current scientific knowledge concerning the manipulation of cognitive processes. These conclusions are based on the general opinion of several expert neuroscientists.

Chess, draughts, bridge, and Go

Chess, draughts, bridge, and Go differ from each other, not only in the use of different objects (chess pieces, draughts, cards, and Go stones respectively) but also in the organisation, implementation, and duration of competitions. These differences justify questioning whether these sports can be grouped together with regard to doping issues.

An important difference is the distinction between individual and team sports. Bridge is a team sport in which communication between partners is essential for the results of the match. Chess, draughts, and Go are played by individual players. Another difference is how long a single game lasts. With bridge, several games are played in one day, whereas with the other sports one game may last the entire day. In fact, games are sometimes scheduled over two days. This means that the loss of one game in bridge is less serious than the loss of a game in the other sports.

Despite these differences, at the meeting of experts the representatives of the mind sports were unanimous that the four mind sports should be treated similarly with regard to doping and potential pharmacological manipulation. This is because cognitive processes are equally important to all four mind sports.

Potential performance-enhancing substances for mind sports

The aim of this investigation was to provide an overview of pharmacological substances that might enhance performance in mind sports. To this is coupled the question whether these substances should be considered as doping by mind sports federations. We start with a review of the basic principles of the investigation, which have been explained in the previous sections. A detailed overview of pharmacological substances and groups is then presented.

Basic principles

In this investigation, two criteria were used to determine whether a certain substance or group of substances should be considered as doping in the context of mind sports. These criteria are that a substance 1. improves performance, and 2. is harmful to health.

Both criteria have to be met before a substance or group of substances can be considered as doping. If there is no improvement of performance, then the substance is of no relevance to players of mind sports and thus it is not relevant to ban the substance. If a substance improves performance, but is not harmful to health, then the recommendation of this report is that the substance or group of substances should not be considered as doping.

These two criteria make it possible to identify, on the basis of scientific evidence, certain substances or groups of substances as doping agents. It is possible that, even though a substance does not meet both criteria, it may be desirable to consider that substance as a doping agent on the basis of yet another criterion. Substances can also be banned for ethical reasons, for example, to protect the image of the sport; however, this investigation has not taken this aspect into consideration. This investigation has focused on the scientific information that enables the two above-mentioned questions to be answered.

The first question is difficult to answer. There has been only one study of the direct effect of pharmacological substances on performance in mind sports, and it is difficult to extrapolate "improvement of cognitive processes" to "improvement of mind sport performance". For this reason, statements are always based on assumptions. Another difficulty in determining the effects of pharmacological substances is the inter-individual variation. Pharmacological substances influence

many systems, and the precise effects can be very different in different individuals. This makes it difficult to provide a general answer to the second question because the dangers to health can vary substantially between different individuals. It is important to be aware of these difficulties when looking for answers to the two questions. With these limitations in mind, an attempt has been made to make generalisations about the various substances.

Overview of potential performance-enhancing substances
This overview was prepared on the basis of the IOC list of substances considered as doping agents. This list was adapted and extended during the discussions with the experts. Final modifications were made after the expert meeting and subsequent evaluation. This review gives a complete picture of the pharmacological substances that, on the basis of currently available scientific knowledge, might be expected to improve mind sport performance.

Currently, there is no single substance known that can directly improve human thought or other cognitive processes; however, this does not mean that cognitive processes cannot be affected. All cognitive processes are based on cognitive functions such as, for example, alertness, concentration, vigilance, memory, information processing, speed of thought, and the ability to perform a certain cognitive task for long periods of time. Improvement of one of these cognitive functions will lead to more efficient cognitive processes. In this way, pharmacological substances may have an indirect effect on the execution of cognitive processes and as a consequence lead to better performance in mind sports.

Experience shows that pharmacological substances generally have a minor effect on cognitive functions. Research has seldom documented more than a marginal improvement. Thus, such substances are generally expected to have only a minor effect on mind sport performance.

Caffeine
Caffeine is probably the most commonly used stimulant in modern society. It is found in coffee, tea, cocoa, soft drinks, and other foods. Caffeine stimulates the central nervous system and in this way influences several bodily functions. The most frequently reported effects are increased alertness and vigilance, diminished fatigue, shorter reaction times, and increased availability of blood sugars and fatty acids.

The effects of caffeine are highly dose and task dependent. Task dependence is revealed by the diminishing favourable effect of caffeine as task complexity increases. With complex tasks, a dose of 75 to 250 mg leads to cognitive improvement after about 30 minutes. Higher doses (250–500 mg) first lead to a worsening of cognitive performance and then, after 90 minutes, to an improvement. With still higher doses the negative effects are predominant. A cup of coffee contains about 90 mg of caffeine and a cup of tea contains about 40 mg of caffeine.

The increased alertness and vigilance seen after a low dose of caffeine in particular will facilitate various cognitive processes. Thus, it can be expected that caffeine will improve mind sport performance. Players will obviously try to avoid the negative effects that high doses of caffeine (higher than 250 mg) have on complex cognitive processes.

Caffeine has numerous effects on health. In high doses, caffeine leads to nervousness, restlessness, sleeplessness, and tremor of the limbs. Headache and stomach-ache are among the side effects. Caffeine stimulates the heart and is a diuretic. It is addictive and tolerance can develop. The doses at which these effects occur and their severity depend strongly on the individual, as do all side effects of medicinal drugs.

On the basis of the daily consumption of coffee, tea, and chocolate, it can be concluded that the negative effects of "normal" caffeine usage are not that serious.

It can be concluded that caffeine in low doses (less than 250 mg) will probably improve mind sport performance. At this dose, the effects on health are negligible. Higher doses are detrimental to performance in both the short and long term. Caffeine, irrespective of the dose used, thus does not meet the criteria to be considered doping in the context of mind sports.

Nicotine and other cholinergics

Nicotine is best known for its presence in cigarettes and other tobacco products. It can also be obtained in pills and patches, from which it is taken up through the skin. The route of administration does not influence the effect of nicotine. Nicotine acts via the nicotinic acetylcholine receptors, which are distributed throughout the body. Several other substances can affect cognitive processes directly or indirectly via acetylcholine. These substances are called cholinergics, and they can be subdivided

into cholinesterase inhibitors, cholinergic precursors, and muscarinic receptor agonists. These substances have effects similar to those of nicotine, although not all their potential effects have been investigated as yet.

Nicotine is a stimulant and has several proven effects on various cognitive processes. It increases the efficiency of information processing and improves the performance of vigilance and other cognitive tasks. These effects occur within 30 minutes to an hour after nicotine administration. These substances can be expected to improve mind sport performance.

Besides its effects in the brain, nicotine also affects the endocrine system, the heart and blood vessels, and the gastrointestinal tract. Moreover, it is highly addictive. It gives rise to mental and physical dependence and tolerance. These side effects are also seen, to a greater or lesser extent, with the other cholinergics, especially with the cholinesterase inhibitors. The addictive potential of the other cholinergics is less strong.

Given the deleterious effects on health and the expected performance-enhancing effects of nicotine and the other cholinergics, these substances should be considered doping agents in the context of mind sports.

Amphetamines

Amphetamines belong to the group of psychostimulants. As such, they have several effects, some of which can be considered harmful to health. Amphetamines suppress feelings of fatigue while the body and mind use up their reserves unnoticed. They can increase blood pressure and heart rate, diminish feelings of hunger, and cause abdominal pains, acute liver failure, mood changes, headache, and dizziness. Overdose can dysregulate body temperature and cause sleeplessness, depression, cerebral infarction, and acute cardiac arrest. Amphetamines have the potential to be strongly addictive on repeated usage.

Amphetamines have two effects that are important to mind sports. The suppression of fatigue makes it possible to carry on cognitive processes at a certain level for longer. Thus, attention can be sustained for longer. This is true for both tired and rested individuals. The other effect of amphetamines is on mood. They cause euphoria in the short term, which results in the user taking risks sooner than he or she would otherwise do. The feeling for danger is gradually lost. This dual

effect makes it difficult to determine the effect of amphetamines on mind sport performance. Although the longer attention span is positive, overrating the ability to make judgements can have serious consequences if a threatening situation is not recognised as such. The potential dangers of amphetamines to health are evident.

Given that amphetamines have the potential to improve mind sport performance and are clearly deleterious to health, it is recommended that they should be considered as doping agents in the context of mind sports as a preventive measure.

MDMA-like substances
MDMA stands for methylenedioxymethamphetamine, the active agent of so-called "party drugs" such as ecstasy, or XTC. The MDMA-like substances are derived from amphetamines but the two groups of substances have different actions.

MDMA-like substances increase euphoria and give the user a feeling of energy, so that he or she is less aware of being tired. At the same time, the person is more aware of his or her surroundings and loses social inhibitions. The addictive potential of MDMA-like substances is not yet known. There is evidence that long-term use of these substances can severely affect the neurotransmitter systems of the brain. On the basis of the similarity between MDMA-like substances and amphetamines, it can be expected that MDMA-like substances will have a positive effect on cognition; however, such an effect has never been demonstrated, not even after once-only usage. The available studies mainly report negative effects, so that performance-improving effects in mind sports are not to be expected.

Given that the scientific literature describes only negative effects on cognition, the MDMA-like substances do not meet the definition of doping used in this investigation.

Ephedrine
Ephedrine, which is obtained from plants of the genus Ephedra, has been used in Chinese herbal medicine for more than 5000 years. It can be used against, for example, the common cold because it reduces oedema of the nasal mucosa. Ephedrine also has effects on the central nervous system.

Ephedrine is a weak stimulant. In certain individuals, even low doses of ephedrine can lead to shaking limbs, panic attacks, and sleeplessness. Higher doses can

cause dizziness, episodes of profuse sweating, heart rhythm disturbances, and even psychoses. Ephedrine can theoretically be addictive, but this has not yet been proven.

The effects of ephedrine on cognitive processes can be compared to those of amphetamines, but the effects of ephedrine are weaker. Its effect on mind sport performance would be expected to be marginal.

The side effects of ephedrine can be harmful to health, especially those of high doses. Given the theoretical potential of ephedrine to improve mind sport performance and its deleterious effect on health when given in high doses, ephedrine should be considered a doping agent in the context of mind sports.

Cannabinoids

Cannabinoids are derived from the Cannabis sativa plant. Depending on the manner in which the plant is harvested and processed, the end product is referred to as cannabis, marihuana, or hashish. The pharmacologically active component of cannabinoids is delta-9-tetrahydrocannabinol.

Cannabinoids can have an analgesic action, but can also cause panic attacks, delusions, fear, sleepiness, and visual problems. Their effects on cognitive functions are solely negative. Attention, concentration, and memory are diminished and the ability to make judgements declines. This makes it extremely unlikely that cannabinoids can improve mind sport performance. It is thus pointless to use these substances before or during competitions to improve performance; indeed, they may have the opposite effect on performance.

Given the lack of potential beneficial effects on mind sport performance, cannabinoids cannot be considered as doping agents in the context of mind sports.

Morphine and other opiates

Morphine is extracted from the dried milky exudate of the seed capsule of the opium poppy. It is an opiate, as are methadone, heroin, and codeine. The opiates bind to receptors that are found, among other places, in the central nervous system. Although morphine and the other opiates have many potential effects, they are not known to have beneficial effects on cognitive processes. It is thus not worthwhile to use these substances to improve mind sport performance.

Because morphine and other opiates do not improve performance, they should not be considered as doping agents in the context of mind sports.

Cocaine
Cocaine is obtained from the coca plant. It is a relatively strong stimulant and was used before the First World War as a local anaesthetic. Cocaine is a "hard drug", which means that in the Netherlands it is illegal to produce, trade, and possess it.

Cocaine is mostly used because of its short-acting euphoric effect. It stimulates the central nervous system, increases the heart rate and respiration, and increases the blood pressure. These effects are clearly harmful to health. Nervousness, restlessness, sleeplessness, shaking limbs, and headache and stomachache often result from cocaine use. The urge for euphoria can be very addictive. With repeated use, cocaine can lead to chronic fatigue, extreme weight loss, and a poorly functioning immune system.

The stimulant effect of cocaine increases alertness. Once-only usage of cocaine can be expected to improve cognitive processes and hence mind sport performance. With repeated use, as occurs with addiction, the cognitive processes are negatively affected.

The effects of cocaine on cognitive processes lead to a dual conclusion, depending on the frequency of cocaine use. According to the guidelines used in this report to determine whether a substance should be considered doping or not, once-only usage of cocaine should be considered as doping, whereas repeated use of the drug is irrelevant in this context. At doping controls it is difficult to determine whether cocaine has been used once or repeatedly. To prevent misunderstanding, it would be better to consider cocaine as a doping agent in the context of mind sports.

Alcohol
Alcohol is a well-known and much-used stimulant. It has a short-lasting stimulant effect, and thereafter generally has a relaxant effect. Alcohol also affects the ability to assess and evaluate situations. It thus has a negative effect on cognitive functioning. Cognitive processes are often affected by only one glass of alcohol, even though the user perceives this differently. It is especially the combination of diminished cognitive functioning and the lack of awareness of this that can have

dire consequences for mind sport performance. Players of these sports are strongly advised not to use alcohol.

Alcohol should not be considered as a doping agent in the context of mind sports.

Benzodiazepines
Benzodiazepines can be prescribed as anxiolytics (they repress anxiety) but also as antipsychotics (they diminish psychotic symptoms) and soporifics (they induce sleep). The sedative effect of benzodiazepines is characterised by muscle relaxation and sleepiness. This often results in loss of concentration. Because the benzodiazepines overlap with soporifics, they always have a stupefying effect. This is disadvantageous to cognitive processes and for the playing of mind sports.

Benzodiazepines should not be considered as doping agents in the context of mind sports.

Beta blockers
Although they are not true anxiolytics, beta blockers are often considered as such. The term beta blocker describes their specific action: they block the beta receptors of the adrenergic system, thus rendering adrenaline and similar substances ineffective. Beta receptors are distributed throughout the body, but especially in the heart and circulatory system and in the airways. Beta blockers are prescribed for heart problems, hypertension, and sometimes for migraine. They reduce shaking of the hands and thus are very effective against the visible consequences of fear and tension.

Although beta blockers generally do not have a direct effect on the central nervous system, a central, albeit indirect, action cannot be excluded. It is plausible that this central effect may make cognitive processes more efficient, but there is no evidence for this. Thus it is not improbable that beta blockers have a beneficial effect on mind sport performance.

As side effects, beta blockers may produce asthmatic symptoms, cold hands and feet, dizziness, and headache. The heart rate can be slowed and blood pressure can decrease.

Theoretically, beta blockers can improve cognitive processes and hence improve mind sport performance. They are also harmful to health. Thus, beta blockers should be considered as doping agents in the context of mind sports.

5-HT1A agonists

5-HT (5-hydroxytryptamine) is the chemical name of the neurotransmitter serotonin. This transmitter plays a role in many cognitive processes. Because of their serotoninergic action, 5-HT1A agonists can be expected to influence cognitive processes. Although there is some evidence for this beneficial effect of 5-HT1A agonists on cognitive processes, this evidence is relatively new and is not yet generally accepted.

5-HT1A agonists are prescribed for the short-term treatment of symptoms of panic. As side effects, they cause dizziness, headache, nervousness, increased sweat production, nausea, and gastrointestinal disorders.

The evidence that 5-HT1A agonists improve cognitive performance is not generally accepted. For this reason, it is not yet necessary to consider these substances as doping agents in the context of mind sports.

Neuropeptides

Neuropeptides are naturally occurring peptide hormones that are synthesised by neurones. They influence communication in the nervous system, among other ways by affecting various transmitter systems in the brain. The same systems mediate the effects of caffeine, amphetamines, and nicotine. Some of these neuropeptides, such as oxytocin, vasopressin, and adrenocorticotropin (ACTH), can promote cognitive processes, especially when the same task has to be performed for a long time. This is the case in mind sports. However, they have a small effect, and it is doubtful whether this effect results in a substantial effect on mind sport performance.

Relatively little is known about the dangers of neuropeptides to health. Theoretically, the administration of additional neuropeptides could disturb the hormonal balance in the body, which could lead to, among other things, dysregulation of the fluid balance and to mood disturbances. Changes in neurotransmitter levels can ultimately lead to psychoses and other psychic disorders.

It is highly questionable whether neuropeptides can really improve mind sport performance. Given the reasonable doubt about the efficacy of neuropeptides on mind sport performance, it is not yet appropriate to consider neuropeptides as doping agents.

Substances that increase the availability of oxygen in the brain

It is recognised that the brain functions better when the amount of oxygen available is higher than normal. This has been shown in studies in which volunteers took several breaths of pure oxygen. It is plausible that mind sport performance will also improve. The availability of oxygen in the brain can be increased by increasing the capacity of the blood to transport oxygen, for example, by blood transfusion or by administration of erythropoietin or perfluorocarbons.

Increasing the availability of oxygen in the brain is associated with health hazards. An increased oxygen concentration in the brain is potentially harmful because an increased concentration of oxygen radicals (oxygen can react as a free radical) may damage the structure of the brain. Use of alternatives to the existing red blood cells to transport oxygen often results in flu-like symptoms. Finally, the use of erythropoietin may increase the risk of myocardial and cerebral infarction because of the increased viscosity of the blood.

Increasing the availability of oxygen in the brain will probably improve mind sport performance. The extent to which health is adversely affected depends on the method used to achieve this increase in oxygen availability. The use of substances that increase the availability of oxygen in the brain should be considered as doping.

Growth hormone, oestrogens, and testosterone

Growth hormone, oestrogens, and testosterone are naturally occurring hormones in the body. It was suggested that these hormones be considered during the evaluation of the expert meeting, but they were not discussed at the meeting.

The scientific literature on the effects of hormone therapy on cognitive performance is limited. Recent studies indicate that these hormones may have beneficial cognitive consequences. If this is the case, then mind sport performance could also be improved with these substances. However, there is no evidence that these cognitive effects actually occur.

Given the uncertainty of the potential of growth hormone, oestrogens, and testosterone to improve performance, it is not yet appropriate to consider these substances as doping agents.

Conclusions and recommendations

In this section, the research question is answered, supplemented by conclusions that are applicable to the interpretation of the assignment. This section ends with several recommendations.

Answer to the research question

The central question of this investigation was whether it is possible to enhance mind sport performance by means of pharmacological substances. This can be answered affirmatively, even though the enhancement of performance will generally be limited. This enhancement of performance occurs in an indirect manner and is based on the assumption that mind sport performance will be enhanced if cognitive processes are improved.

Other conclusions

The factors that determine performance in mind sports are different from those in physical sports. As a consequence, pharmacological manipulation of performance occurs in a different way in the two types of sport. This means that, with regard to anti-doping regulations, the current IOC list of prohibited substances and methods cannot be applied unchanged to mind sports. For the purposes of this investigation, a separate list of potential performance-enhancing substances was drawn up for the mind sports chess, draughts, bridge, and Go. The impression was gained that the use of pharmacological substances to improve performance occurs only sporadically in mind sports. The prevalent opinion inside the mind sports world is that such substances are more likely to have a negative than a positive effect on performance.

Doping or not

For the purposes of this investigation, a substance was considered as a doping agent if it both improves performance and is deleterious to health. The argument that certain substances should be considered as doping agents in order to protect the image of the sport was not used in this investigation.

In this overview, potential performance-enhancing substances have been divided into three categories. The first category includes substances and groups of substances that should be considered as doping in the context of mind sports, in accordance with the criteria used in this report. The second category includes substances and groups of substances that should not be considered as doping in the context of mind sports. The third category includes substances for which

there is currently too little information available on which to base a decision about whether these substances can affect mind sport performance.

a) Pharmacological substances that should be considered as doping:
- nicotine and other cholinergics;
- amphetamines;
- ephedrine;
- cocaine;
- beta blockers;
- substances that increase the availability of oxygen in the brain.

b) Pharmacological substances that should not be considered as doping:
- caffeine;
- MDMA-like substances;
- cannabinoids;
- morphine and other opiates;
- alcohol;
- benzodiazepines.

c) Pharmacological substances of which the effect is not yet clear:
- 5-HT1A agonists;
- neuropeptides;
- growth hormone, oestrogens, and testosterone.

Recommendations

The following recommendations can be made, based on the findings of this investigation into the possibility of improving performance in mind sports by means of pharmacological substances:

- it is recommended that mind sports federations should formally prohibit the use of doping and that they draw up regulations that enable sanctions to be taken against those that use such prohibited substances in the mind sports;
- it is recommended that, should doping be prohibited in the mind sports, a specific list of substances to be banned should be drawn up and that the current IOC list of prohibited substances should not be used unadapted;
- it is important to harmonise national and international regulations for mind sports. This document may contribute to this harmonisation of anti-doping regulations.

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Appendix – Experts consulted

The following people were consulted during this investigation. They are thanked for their input and time.

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- Mr H. Wiersma* Top draughts player; trainer/coach KNDB.
- Mr G. van der Scheer* President, Dutch Bridge Federation (NBB).
- Mr F.J. Vergoed* Former top bridge player.
- Mr J. van Rongen* Chairman Dutch Go Federation (NGoB).
- Mr F. Janssen* Top Go player.
- Mr W. van Beek, PhD* Chairman Fédération Mondiale du Jeu de Dames (FMJD; international draughts federation).

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- Mr B.G.J. Bohus, PhD* University of Groningen, professor of animal physiology and neurobiology.
- Mr J.K. Buitelaar, PhD University of Utrecht, professor of biopsychosocial determinants of behaviour.
- Mr A.R. Cools, PhD* Catholic University of Nijmegen, professor of psychoneuropharmacology.
- Mr R. Hijman, PhD* University of Utrecht, lecturer and neuropsychologist.
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- Mr F.H. Lopes da Silva, PhD University of Amsterdam, professor of animal physiology.
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- Mr J. Snel, PhD University of Amsterdam, senior lecturer in psychonomics.
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- Mr M.P. Witter, PhD Free University, professor of anatomy and embryology.

Representatives from the Netherlands Centre for Doping Affairs
- Mr F. Hartgens* Head, scientific department; doctor specialised in sports medicine.
- Mr O. de Hon* Staff member, scientific department.
- Mr R. van Kleij* Head, communications department.
- Mr P. van der Kruk* Director.
- Mr F. Stoele Staff member, information and documentation.
- Mr S. Teitler Staff member, legal affairs.

Representative from the Ministry of Health, Welfare, and Sport
- Mr M. Koornneef* Senior staff member; doctor specialised in sports medicine.

* Present at the expert meeting.
** Chairman of the expert meeting.

Abbreviations

- ACTH Adrenocorticotropin
- FMJD Fédération Mondiale du Jeu de Dames
- GAISF General Association of International Sports Federations
- HT Hydroxytryptamine
- IADA International Anti-Doping Arrangement
- IOC International Olympic Committee
- KNDB Koninklijke Nederlandse Dam Bond [Royal Dutch Draughts Federation]
- KNSB Koninklijke Nederlandse Schaak Bond [Royal Dutch Chess Federation]
- MDMA Methylenedioxymethamphetamine
- NBB Nederlandse Bridge Bond [Dutch Bridge Federation]
- NeCeDo Nederlands Centrum voor Dopingvraagstukken [Netherlands Centre for Doping Affairs]
- NGoB Nederlandse Go Bond [Dutch Go Federation]
- NOC*NSF Nederlands Olympisch Comité * Nederlandse Sport Federatie [Dutch Olympic Committee*Dutch Sport Federation]

Extended discussion on case 1 (mind sports)

Following the study described above, for a few years it was national policy in the Netherlands to analyse 'mind sport doping samples' for the restricted list of prohibited substances only. But despite international lobbying the respective IFs chose to test for the full list. And when the WADC entered into force in 2004, with the main goal to globally harmonise anti-doping policies, the battle was over: all mind sports followed the same general rules as all other sports, such as weight lifting and athletics. At this moment in all mind sports doping controls are being performed, juridical panels are set up, and cases are heard. All mind sports still follow the full list of Prohibited Substances, even though it is generally acknowledged that many of those substances are extremely unlikely to influence the performance in this particular set of sports. In addition, it is safe to assume that the substances that might be relevant as 'doping substances' in these sports all fall in the category of substances that are solely prohibited during 'in competition' periods, rendering out of competition doping controls superfluous. Yet, these controls do happen (WADA 2015b).

All this is even more remarkable since the prohibited list possesses two separate groups of substances that are only prohibited in explicitly mentioned sports, thus providing a precedent on how to handle the matter of substances that are performance enhancing in some sports only. The reasons why this precedent is only limited to alcohol and beta-blockers is not officially communicated by WADA, but it is likely to be based on the heritage of the IOC-prohibited list from 2003 and earlier. This leaves an awkward and unsatisfying situation, but at least it seems that there is a practical answer to the old philosophical question on 'what is sports'? A modern-day practical answer to this question is: 'an activity in which doping controls are being performed'. But this is certainly no proof of effective application of a rather expensive tool in the anti-doping framework, namely doping controls. As a side-step, the gaming industry (also known as eSports) is currently talking about introducing some sort of anti-doping regulations as well (Kamen 2015, Parkin 2015). It will be interesting to see if they follow the example of mind sports or choose a path of their own when introducing restrictions to the use of certain substances.

The fact that pharmacological substances exist that may have a potential to increase cognitive performance continues to draw attention from both the scientific community and mainstream press (Greely et al. 2008, Maher 2008, Cakic 2009).

And it is not just substances: transcranial direct current stimulation is a method that possesses the potential to stimulate the brain as well (Reardon 2016). This is a technique that may be more effective than any available drug, and as such is likely to challenge anti-doping regulations in the future.

The study described above was a first attempt to tackle the issue of sports that due to their intrinsic characteristics might not fit into the general realm of harmonised anti-doping regulations. The result was a proof of principle that 16 years later may still very well work as a guide to improve effectiveness in this area. It is likely that the panel of relevant doping substances in mind sports should be changed in comparison with the study described above, as science has progressed since that time and a more international approach and consensus of opinion is favourable. But it is an example how a thorough investigation of a very specific area, in this case the boundaries of the concept of 'sport', may lead to insights that have the potential to improve the entire system.

Case 1 showed that in anti-doping regulations harmonisation trumps logic in at least the practical definition of doping, i.e. what substances and methods are on the prohibited list for a particular sport. Mind sports serve as an example in this thesis, but this is not a new issue (Mottram 1999, Kuipers & Ruijsch van Dugteren 2006), and still highly relevant. The example of mind sports may be extreme, but the same holds true for banning erythropoietin in archery, or anabolic steroids in curling. It may be plain and easy to communicate a harmonised approach, both to athletes and to the general public, but it can hardly be called effective to spend funds on the analysis of substances in sports, or to be more precise sport disciplines, where they have no impact whatsoever on the result of competitions. Let alone the agony and uncomfortableness for everyone involved when AAFs are reported and athletes need to be summoned to a disciplinary panel. One might even question the legality of possible sanctions in these cases, but such a juridical analysis falls outside the scope of this thesis.

This conclusion is not necessarily a call for prioritising the impact of effectiveness above all other relevant (policy) aspects. It may be true that harmonisation as a general theme can be regarded to be more important than specificity and effectiveness on the level of a certain sport. But at the very least such choices should be shared in a transparent manner. Fact of the matter is that all mind sports governing bodies, in particular the IFs of chess, bridge, and draughts, have

easily accepted their inauguration into the world of anti-doping, including doping controls, Therapeutic Use Exemption applications, testing pools and everything. From an effectiveness point of view it is understandable to possess some sort of anti-doping measures in these sports, as in eSports, since there is a potential of abuse of substances, and even methods, that might possess the characteristics of 'doping'. But it cannot be called effective to test for all substances in these sports when performing doping controls and it defies logic as well. The current rigid harmonised approach heavily tests the support of anti-doping measures amongst athletes and the general public. I would like to argue that the current status of the anti-doping framework, with WADA holding a firm position after four Olympiads of service, is more than firm enough to lift the focus on general harmonisation to a certain degree and to introduce a flexible prohibited list of doping substances and methods that is more focussed on the sport disciplines that can be expected to be impacted by their use.

2.4.2 Case 2: Commonly used medications, or the impact of anti-doping policies on one's medical care

Introduction to case 2

Most substances on the prohibited list are registered medications. From the inception of anti-doping policies it has been deemed unfair to deny patients who happen to be elite athletes a medication regimen that would be considered 'normal' in non-athlete populations. As with many other aspects in anti-doping, this issue has been harmonised and explicitly regulated with the arrival of WADA. Since the launch of the WADP the International Standard for Therapeutic Use Exemptions has been available to lay down the rules of this procedure with the main aim to allow medication use to bring 'patient athletes' back to the 'normal' level of performance, but not above it. The principle of egalitarianism is of course one of the core principles in anti-doping, with WADA using the tagline of 'creating a level playing field' on many occasions.

This is a prime example of one of the grey areas in anti-doping. There is an obvious fundamental unknown in the pursuit of allowing patient athletes to compete while using medication: what is 'normal' in this sense? The International Standard specifies the general principles of granting a Therapeutic Use Exemption (TUE) but ultimately an individual decision has to be made in every case. Then, there is the practical reality that some athletes, or their advisors, are clearly interested in using medication that is mentioned on the prohibited list, because 'if it is on

there, it must be doing something'. Another belief that is often shared informally is 'if two puffs may be improving my performance, why don't I use four or eight puffs of the same substance'. There is clear anecdotal information that this line of reasoning is present in sports, and partly fed by these stories hard-line anti-doping advocates often criticise the TUE-rule stating that athletes who need medication to perform optimally may not be elite athletes in the first place since they evidently lack the 'naturally given' physiology to perform at the elite level. The fact that the TUE system is known to have been abused in the past by confessed doping-users does not help either (Hamilton & Coyle 2012, USADA 2012).

Another issue is that many TUEs have been granted for medications that are controversial on the prohibited list to begin with. In the year 2005 nasal administration of glucocorticoids needed an administrative action by the athlete, known as 'abbreviated TUE', and in 2009 the use of salbutamol per inhalation required a full TUE, including an elaborate medical declaration with the results of pulmonary function tests (up till then a simple declaration by any doctor sufficed). These two measures prompted separate studies to review and discuss the necessity of these measures for two quite regular medications, that could be doubted to have any effect on athletic performance (Kuipers et al. 2008, Pluim et al. 2011). Both had their impact on anti-doping regulations as they filled a void in scientific knowledge at that time, although the exact effects of such studies, and publications, is impossible to quantify. The following texts are the full texts of those two articles.

FOUR WEEKS OF CORTICOSTEROID INHALATION DOES NOT AUGMENT MAXIMAL POWER OUTPUT IN ENDURANCE ATHLETES

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Abstract

Objective: To assess possible ergogenic properties of corticosteroid administration.
Design: A balanced, double-blind, placebo-controlled design was used.
Participants: 28 well-trained cyclists and rowers.
Intervention: 4 weeks' daily inhalation of 800 mg budesonide or placebo.
Main outcome measurements: The subjects performed three incremental cycle ergometer tests until exhaustion, before and after 2 and 4 weeks of placebo or budesonide administration, to measure maximal power output (Wmax). Once a week they filled in a profile of mood state (POMS) questionnaire.
Results: There was no significant difference in Wmax between the placebo (376 (SD 25) W) and the corticosteroid group (375 (36) W) during the preintervention test, and there were no significant changes in either group after 2 and 4 weeks of intervention. No effect of the intervention on mood state was found.
Conclusion: 4 weeks of corticosteroid or placebo inhalation in healthy, well-trained athletes did not affect maximal power output or mood state. Hence no ergogenic properties of 4 weeks' corticosteroid administration could be demonstrated, which corroborates previous studies of short-term corticosteroid administration.

Introduction

Glucocorticosteroids are used for the treatment of a large variety of common medical conditions where an inflammatory response is involved, such as skin rash, topical allergy, or inflammatory airway disease, and are therefore also widely

used by athletes. Corticosteroids are included on the list of prohibited substances issued by the World Anti-Doping Agency (WADA; http://www.wada-ama.org). Although inclusion on the doping list does not require performance-enhancing properties, for athletes possible ergogenic properties are relevant. Except for one recent study,[1] all available data on the effects of corticosteroids in healthy athletes do not suggest any performance enhancement.[2-4] Concerning possible ergogenic effects, it has been suggested that the use of glucocorticosteroids may increase carbohydrate availability during exercise by elevating plasma glucose concentration, which might indirectly enhance performance. In addition, it has also been suggested that the performance enhancement could be mediated by corticosteroidinduced euphoria. Informal reports from athletes and support personnel suggest that there may be some abuse of corticosteroids for performance enhancement, although it is impossible to quantify the efficacy of these individual actions. Only a few controlled studies of corticosteroid administration on physical performance capacity have been conducted.[1-4] The first published double-blind, placebo-controlled study in professional cyclists was conducted by Soetens et al.,[2] who administered adrenocorticotropic hormone (ACTH) by injection, to enhance endogenous cortisol production. No evidence was found for an enhancement or reduction of cycling performance under standard laboratory conditions.[2] Marquet et al[3] studied the effects of 4 to 5 days of oral dexamethasone administration on ventilatory threshold, lactate parameters, maximal oxygen uptake and exhaustion during exercise. There was no effect on any of these performance parameters. A remarkable finding, however, was that, compared with placebo, the administration of both low and high doses of dexamethasone produced decreased plasma glucose levels during exercise.[3] A third, double-blind, placebo-controlled study by Arlettaz et al.[4] showed that the administration of a single oral dose of 20 mg prednisolone, alone or in combination with salbutamol, did not enhance endurance performance in healthy, moderately trained men. Arlettaz et al1 studied the effect of short-term prednisolone intake (60 mg/day) in recreational athletes also, and found an increase in endurance time at 70-75% of peak VO2. However, the effects of short-term glucocorticoid administration may differ from daily administration over a longer period of time.

Therefore, the aim of this study was to add to previous data on short-term administration and to investigate the effect of 4 weeks of corticosteroid (budesonide) inhalation in therapeutic dosage, on maximal power output in well-trained athletes,

measured on a cycle ergometer under standard laboratory conditions. In addition, the effect of corticosteroid inhalation on mood state was assessed.

Materials and methods

Subjects and experimental design

Twenty-eight well-trained, male endurance athletes involved in cycling and rowing were recruited via advertisements. Subjects could only enroll when they met the following criteria: a) they had trained at a constant level during the 3 months prior to the study, b) they had trained regularly on a bicycle at least three to four times per week, including exercise at maximal intensity, c) they did not use corticosteroids and were not in possession of an (abbreviated) therapeutic use exemption (TUE or an aTUE) for corticosteroids, and d) to avoid possible doping violations, at the time of the intervention they did not compete in events where doping control tests might be involved.

Before entering the study, all subjects received oral and written information about the study; the design, purpose, possible risks and inconveniences (such as light throat irritation because of the forced inhalation). In addition, instructions about inhalation of the drug were provided. Before participation the subjects signed an informed consent form and were informed that they could withdraw their participation at any time. The local medical ethics committee approved the study. A double-blind, placebo-controlled design was used with parallel groups without cross-over.

Procedure

Subjects visited the lab on three occasions. During the first visit they received more detailed information about the study and underwent a baseline graded exercise test. After the first exercise test they received the medication for the next 4 weeks and were instructed how to use the inhaler properly. Using a placebo inhaler, the subjects practised inhalation in the presence of the researcher until a proper inhalation technique had been acquired. Before subjects mounted the cycle ergometer the saddle height and position of handle bar were adjusted.

Because maximal power output is a valid and easy measurable parameter for aerobic exercise performance in cyclists,[5-7] and is strongly related to time trial performance,[8-10] in the present study maximal power output (Wmax) was the outcome parameter for exercise performance. Therefore all subjects performed three graded exercise tests on a cycle ergometer (Lode Excalibur, Lode, The Netherlands).

The first exercise test was done before the start of the intervention, whereas the two consecutive tests were done after 2 and 4 weeks of intervention, respectively. Heart rate was measured with a heart rate monitor (Sport Tester PE3000, Polar, Kempele, Finland).

The cycle ergometer tests started with a 5 minute warm-up at 150 W, after which the power output was increased by 50 W every 2.5 minutes. From a heart rate between 155 and 160 beats/min onwards the load was increased by 25 W every 2.5 minutes, until the subject was unable to continue exercise. The subjects did not receive any feedback about the workload and were encouraged to push as far as possible.

Maximal power output (Wmax) was calculated with the following equation: Wmax=Wprevious+t/150*25 W. Wprevious is the workload that could be completed for the full 2.5 minutes before the last, not fully completed workload, and t the number of seconds that the last workload could be sustained.[11]

To avoid diurnal variations in exercise performance all three measurements in each subject were done at approximately the same time of the day. Consequently also the time between the last inhalation and the exercise test were constant in every subject, and varied between subjects from 2 to 8 h. In every subject the protocol and increments in the second and third tests were identical to the first test.

To study possible effects on mood the participants filled out a questionnaire once a week, in which the profile of mood state (POMS) was scored. For this purpose the shortened, adjusted version translated into Dutch was used, as described by Albani et al.[12]

Drug intervention

Medication and placebo were manufactured by the hospital pharmacy, while the responsible pharmacist kept the key of the blinding protocol until the study was completed. The inhalers (Turbuhaler, AstraZeneca) filled with placebo or budesonide were identical, apart from the number written on the package (from 1 to 28). The testers and subjects could not tell the difference between the actual and the placebo inhalers.

During the 28 days the subjects took two puffs twice daily (in the morning and evening) of either budesonide (Pulmicort; each puff contained 200 mg budesonide) or placebo. The subjects were advised to rinse their mouths after each

drug administration to prevent possible local side effects. At every laboratory visit the subjects were asked about any health problems and/or potential side effects.

Data collection and data handling

The obtained data were stored in a database (Excel) and analysed with ANOVA using the SPSS package. Analyses for sequence and treatment effects were conducted. In the case of any significant effect, a Tukey post hoc test was used for locating any differences. Statistical significance was set at $p<0.05$.

Results

Subjects' characteristics are presented in table 1. All subjects were able to complete the study and all reported full compliance.

Table 1 Subjects' characteristics

	Corticosteroid group (n=14)	Placebo group (n=14)
Age (years)	24 (6) (19–40)	24 (8) (18–50)
Height (m)	1.86 (0.13) (1.74–2.03)	1.88 (0.10) (1.76–1.98)
Weight (kg)	76.9 (9.3) (65.1–103.3)	78.6 (10.1) (97.9–65.0)
BMI (kg/m)	22.3 (1.8) (19.2–25.5)	22.1 (1.8) (18.7–25.6)
Max HR (beats/min)	189 (10) (168–206)	194 (7) (182–205)

BMI, body mass index; max HR, maximal heart rate.
Data presented as mean (SD) (range). There are no statistically significant differences between the groups.

Ten subjects reported during the first weeks of the study mild throat irritation and/or a strange aftertaste after inhalation (seven subjects in the steroid group and three in the placebo group). No other side effects were reported. Blinding was successful, and 46% from the placebo group and 54% from the corticosteroid group guessed correctly about the intervention.

Table 2 presents the data from the three graded exercise tests. The mean maximal power output in the baseline graded cycle ergometer test was 376 (SD 25) W in the placebo group and 375 (36) W in the corticosteroid group. Maximal heart rate between the two groups was not significantly different, and within each group no differences in maximal heart rate were found between the three tests.

Table 2 Maximal power output (Wmax) in the placebo and corticosteroid groups during the three consecutive incremental cycle ergometer tests

Test	Corticosteroid group Wmax (W)	Placebo group Wmax (W)	p Value
Baseline	375 (36) (313–462)	376 (25) (321–414)	0.981
2 weeks	377 (40) (317–463)	374 (22) (333–417)	0.757
4 weeks	378 (37) (315–470)	374 (26) (317–425)	0.766

Results expressed as mean (SD) (range).

No significant differences in maximal power output were found between the budesonide and the placebo groups, in any of the three exercise tests. When the maximal power output of the three tests was compared within each group, no differences were found at any time.

During the 4 weeks of intervention no changes were found in body weight in either of the two groups.

The questionnaire reflecting the profile of mood state (POMS) did not show any consistent pattern. Especially, the items that might reflect euphoria did not change in either of the two groups.

Discussion

The aim of the present study was to assess the effects of 4 weeks of therapeutic corticosteroid inhalation on physical performance capacity and mood state in well-trained endurance athletes. No effect on performance capacity or profile of mood state was found. In the present study maximal power output was used as a performance measure because it has been shown that maximal power output is a good indicator of performance in cyclists[6-7] and is also strongly related to time trial performance.[8-10]

Three previous studies where possible ergogenic effects of short-term corticosteroid administration were investigated also failed to demonstrate ergogenic benefits of corticosteroid administration.[2-4] Arlettaz et al.[4] showed that addition of salbutamol to prednisolone failed to enhance performance in healthy humans. One study in racehorses also failed to observe an ergogenic effect of dexamethasone administration.[13] The only study showing an increase in endurance time[1] may be explained by the exercise intensity. Arlettaz et al[1] used endurance time at 70-75% of

peak VO2, while other studies used a higher, or maximal, exercise intensity, which is more related to sport performance.[5]

A novel and significant aspect of the present study is that, in addition to acute corticosteroid administration, also after 2 and 4 weeks' inhalation of a corticosteroid no positive effect on exercise performance could be demonstrated.

Although all the performed studies were unable to find any direct performance enhancement, it has been suggested that corticosteroid administration may indirectly affect sport performance by stimulating gluconeogenesis or changes in mood state. Concerning the suggested possible (corticosteroidinduced) stimulatory effect on gluconeogenesis, the administration of corticosteroids could theoretically increase gluconeogenesis to its maximal capacity of 0.1 g per minute, which can maintain normal blood glucose levels in the resting state during periods of inadequate glucose intake such as starvation.[14] However, the maximal capacity of gluconeogenesis is far below the carbohydrate requirement during exercise, which may vary from 1 to 3 g per minute.[15] Although it can be argued that even small contributions to carbohydrate availability may help sport performance, Marquet et al.[3] failed to show any increase in carbohydrate availability during exercise. In fact they observed that, after administration of high and low doses of dexamethasone, plasma glucose levels decreased during exercise. Therefore the contribution of gluconeogenesis to meeting carbohydrate requirements during strenuous exercise is negligible. It has also been shown that corticosteroid administration decreases insulin sensitivity[16] and glycogen synthesis,[17-18] both of which are crucial factors for optimal, high-intensity endurance performance. Therefore, it appears that administration of corticosteroids to athletes may have negative rather than positive effects on high-intensity endurance performance.

Another suggested mechanism of performance enhancement is the euphoria-inducing effect of corticosteroids. For that reason the profile of mood state was measured. The data failed to reveal any change in mood state during the study in either group. It is possible that higher dosages are required to obtain a significant effect on mood state, or that the period of euphoria is transient and is not measured by a weekly assessment of the profile of mood state. However, it has also to be realised that, although corticosteroid administration may induce euphoria, in some individuals depression and psychosis may occur,[19] which may also have a negative impact on sport performance.

While no positive effects on sports performance could be detected in any of the studies performed, it is quite possible that corticosteroids may exert a negative impact on sport performance, and jeopardise the athlete's health. Löfberg et al[20] showed that 3 days of oral administration of a therapeutic dosage of 60 mg of prednisolone does have a catabolic effect on muscle protein synthesis, which is likely to have a negative effect on physiological training and exercise adaptations.[21] It has to be emphasised that even low doses of inhaled corticosteroids like budesonide, as used in the present study, may have an adrenal-suppressive effect, as shown by Kaliner.[22] Also a single periarticular injection of corticosteroids may induce adrenal insufficiency.[23] Adrenal insufficiency may affect both physiological training adaptations and physiological responses to various types of stress.[21] Another potential negative effect of long-term corticosteroid administration, in particular with higher doses, is a decrease of bone mineral density.[24] Therefore, corticosteroids should only be prescribed based upon a sound medical indication.

Considering the requirements for including a substance on the list of banned substances, the presence of corticosteroids and ACTH on the WADA list of prohibited substances in sport can be questioned as far as performance enhancement is concerned. An often ignored aspect of a list of prohibited substances and methods, as used in the international sporting arena, is that many people, including those involved in sport, assume that everything on the list is ergogenic. The mere fact that corticosteroids and ACTH are on the doping list strengthens this belief, which in turn may stimulate their use and misuse.[25] The fact that such a widely prescribed medication is included on the list of banned substances also carries a great risk for unintentional doping violation, when no valid TUE is available at the time of testing, because of administrative procedures.

In conclusion, 4 weeks of corticosteroid or placebo inhalation in healthy, well-trained athletes did not affect maximal power output or mood state. Hence no ergogenic properties of corticosteroid administration with high-intensity exercise could be demonstrated, which corroborates previous studies of shortterm corticosteroid administration.

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Competing interests

None.

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β2-AGONISTS AND PHYSICAL PERFORMANCE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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Abstract

Inhaled β2-agonists are commonly used as bronchodilators in the treatment of asthma. Their use in athletes, however, is restricted by anti-doping regulations. Controversies remain as to whether healthy elite athletes who use bronchodilators may gain a competitive advantage.

The aim of this systematic review and meta-analysis is to assess the effects of inhaled and systemic β2-agonists on physical performance in healthy, nonasthmatic subjects. To this end, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to August 2009. Reference lists were searched for additional relevant studies. The search criteria were for randomized controlled trials examining the effect of inhaled or systemic β2-agonists on physical performance in healthy, nonasthmatic subjects. Two authors independently performed the selection of studies, data extraction and risk of bias assessment. Parallel-group and crossover trials were analysed separately. Mean difference (MD) and 95% confidence intervals were calculated for continuous data and, where possible, data were pooled using a fixed effects model.

Twenty-six studies involving 403 participants (age range 7-30 years) compared inhaled β2-agonists with placebo. No significant effect could be detected for inhaled β2-agonists on maximal oxygen consumption (VO2max) [MD -0.14mL•kg-1•min-1; 95% CI -1.07, 0.78; 16 studies], endurance time to exhaustion at 105-110% VO2max (MD -1.5 s; 95% CI -15.6, 12.6; four studies), 20-km time trial duration (MD -4.4 s; 95% CI -23.5, 14.7; two studies), peak power (MD -0.14 W•kg-1; 95% CI -0.54, 0.27; four studies) and total work during a 30-second Wingate test (MD 0.80

J•kg-1; 95% CI -2.44, 4.05; five studies). Thirteen studies involving 172 participants (age range 7-22 years) compared systemic β2-agonists with placebo, with 12 studies involving oral and one study involving intravenous salbutamol. A significant effect was detected for systemic β2-agonists on endurance time to exhaustion at 80-85% VO2max (MD 402 s; 95%CI 34, 770; two studies), but not for VO2max (placebo 42.5– 1.7mL•kg-1•min-1, salbutamol 42.1– 2.9mL•kg-1•min-1, one study), endurance time to exhaustion at 70% VO2max (MD 400 s; 95%CI -408, 1208; one study) or power output at 90% VO2max (placebo 234.9– 16 W, salbutamol 235.5 – 18.1 W, one study). A significant effect was shown for systemic β2-agonists on peak power (MD 0.91 W•kg-1; 95% CI 0.25, 1.57; four studies), but not on total work (MD 7.8 J•kg-1; 95% CI -3.3, 18.9; four studies) during a 30-second Wingate test. There were no randomized controlled trials assessing the effects of systemic formoterol, salmeterol or terbutaline on physical performance.

In conclusion, no significant effects were detected for inhaled β2-agonists on endurance, strength or sprint performance in healthy athletes. There is some evidence indicating that systemic β2-agonists may have a positive effect on physical performance in healthy subjects, but the evidence base is weak.

Introduction

Inhaled β2-agonists are commonly used bronchodilators and are essential as reliever therapy in the management of asthma.[1] Elite athletes have an increased risk of asthma and exercise-induced bronchoconstriction compared with the general population.[2-11] In sports, the use of inhaled β2-agonists in the treatment of asthmatic athletes is restricted by anti-doping regulations. This is based on the assumption that β2-agonists have the potential to improve physical performance, resulting in an unfair competitive advantage when taken by healthy athletes.

The origins of these rules can be traced back to 1972, when inhaled salbutamol was prohibited for the first time at the Olympic Games in Munich, Germany.[12] Since then, inhaled β2-agonists have alternately been allowed and prohibited at the Olympic Games. Their status has switched from prohibited (1972-5) to permitted with notification before the event (1976-83; 1993-2000), permitted with retrospective notification (1984-5), fully permitted (1986-92), and prohibited without a therapeutic use exemption (2001-9).[12]

In January 2010, the rules of the World Anti-Doping Agency (WADA) changed again and the use of all β2-agonists was prohibited in athletes (both in and out of competition), except for salbutamol and salmeterol by inhalation, which required a declaration of use.[13] In January 2011, the requirement to submit a declaration

of use was lifted for salbutamol and salmeterol and these are now permitted by inhalation.[14] Urinary salbutamol concentration is not allowed to exceed 1000 ng•mL-1.[14]

However, the performance enhancing effects of β2-agonists have been questioned. Kindermann[15] reviewed 19 randomized, placebo-controlled trials, and concluded that the performance enhancing effect of inhaled formoterol, salbutamol, salmeterol and terbutaline could not be proven, whereas, oral administration of salbutamol seemed to improve muscle strength and endurance performance. Backer et al.[16] argued that it was debatable whether or not β2-agonists enhance performance and that they should therefore not be permitted for use by athletes without objective signs of asthma. The authors suggested that systemic use would probably enhance performance. In the International Olympic Committee (IOC) consensus statement of January 2008, it was suggested that inhaled β2-agonists are not considered to enhance performance, but that oral salbutamol increases strength.[17] Finally, in a review by the Joint Task Force of the European Respiratory Society and the European Academy of Allergy and Clinical Immunology, it was concluded that neither inhaled nor systemic β2-agonists improve physical performance in healthy athletes.[1]

To resolve this issue, we conducted a systematic review and meta-analysis of randomized controlled trials with the aim of assessing the effect of inhaled and systemic β2-agonists on physical performance in healthy, non-asthmatic athletes.

Literature Search Methodology
Criteria for Considering Studies for this Review

Types of Studies

We considered all the randomized controlled studies that addressed the effect of β2-agonists on physical performance.

Types of Participants

We included studies with healthy subjects (all ages, male and female). We looked for studies on elite athletes, recreational athletes and non-athletic participants. We sought to document the level and intensity of sports participation, the training level (maximal oxygen consumption [VO2max]) and the type of sport at inclusion. Athletes were considered to be highly trained if they had a VO2max above 55mL•kg-1•min-1 (females) or 60mL•kg-1•min-1 (males).

Studies that included some or all participants with diseases such as asthma, chronic obstructive pulmonary disease and cardiovascular disease, were excluded,

as were studies in which participants used other medications (except for oral contraceptives in women), unless the results of healthy subjects were presented separately.

Types of Interventions
For any short- or long-acting inhaled or systemic (oral or intravenous) β2-agonist, the use could be single (once) or administered at multiple occasions (1 or more days to weeks). Studies with clenbuterol were excluded, as this drug has been defined as an anabolic agent and not a β2-agonist by the WADA.[14]

Types of Outcome Measures
The types of outcome measures in the studies were as follows:

1. VO2max in L•min-1 or mmol•L•kg-1•min-1 determined with a maximal exercise test on a treadmill or cycle ergometer. If information was provided on peak power output only, VO2max was estimated using the equation according to Arts and Kuipers;[18]
2. endurance time(s) to exhaustion during an exercise test at a predetermined percentage of VO2max;
3. duration time(s) of a time trial, in which a certain distance has to be covered or a certain amount of work has to be delivered;
4. peak power (W or W•kg-1), average power (W or W•kg-1), or total work (J or J•kg-1) during a Wingate test;
5. the one-repetition maximum(1RM, kg) or concentric peak torque (Nm•s-1 or Nm•kg-1•s-1) during an isokinetic strength test of any muscle group;

Studies that did not provide quantitative results for at least one of these physical performance variables were excluded.

Search Methods for Identification of Studies
One of the authors (JL), a medical librarian with experience in conducting searches for systematic reviews, undertook a systematic search of the electronic databases MEDLINE (1950 to August 2009), EMBASE (1980 to August 2009) and Cochrane Central Register of Controlled Trials (CENTRAL) (to August 2009) to identify controlled clinical trials on β2-agonists in healthy individuals. No language or any other restrictions were applied. The search included an iterative process to refine the search strategy through adding search terms as new relevant

citations were identified. We downloaded all references identified into Reference Manager® software (version 11.0). The search strategy consisted of free-text words and subject headings (MeSH, SH) related to the intervention (β-agonists, including individual agents) and the population (i.e. athlete*, sport*), the outcome (i.e. doping, endurance, muscle strength, wingate*) or sport-specific journals (i.e. sport*.jw.). In MEDLINE and EMBASE, the search was combined with broad RCT filters, developed for Cochrane Systematic Reviews of interventions. We searched reference lists of identified randomized controlled trials for additional studies or relevant reviews.

Data Collection and Analysis

Selection of Studies

Two authors independently evaluated studies for inclusion (BMP and OdH). In case of disagreement, further discussion was undertaken to achieve consensus.

Data Extraction and Management

The same two authors (BMP and OdH) independently extracted data. Information was extracted from each study for the following characteristics: design, participants (sample size, sex, age [mean –SD and/or median – range]), type and level of sports participation, training level (VO2max), intervention (brand, type, dose, study duration) and outcome (type of outcome analysis, outcomes analysed). Data were extracted for each of the outcomes considered by the review. Data were entered by one reviewer (BMP) and double checked on a separate occasion by a second person (OdH).

Assessment of Risk of Bias in Included Studies

The risk of bias was independently assessed and scored by the two reviewers (BMP and OdH) using the methodological criteria listed in table I.[19] In addition to the specific domains recommended for Cochrane reviews, we added whether participants were adequately tested for asthma.[13] An inclusion of asthmatic participants could lead to an overestimation of the effect of the intervention. The items were scored as either yes, no or unclear. A consensus method was used to resolve disagreements and a third author was consulted if disagreements persisted (JBS).

Table I Assessment of risk of bias[19]

Criteria/definition	Comment
Method of randomization adequate	A random (unpredictable) assignment sequence. Examples of adequate methods are the use of computer-generated random number tables and the use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers or alternation were not regarded as appropriate
Concealment of treatment allocation	Assignment generated by an independent person not responsible for determining the eligibility of the participants. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the participant. The use of coded canisters was also considered adequate
Blinding of subjects, researchers and outcome assessors	If there was enough information about the blinding of the various persons, a 'yes' was scored
Follow-up	Withdrawal rate described and acceptable: the number of participants who were included in the study but did not complete the observation period or were not included in the analysis, must be described and reasons given. If the percentage of withdrawals did not exceed 20% for short-term follow-up (1-6 weeks) and 30% for long-term follow-up (>6 weeks), and appeared not to lead to substantial bias, a 'yes' was scored
Intent-to-treat analysis	All randomized participants should have been reported/analysed in the group to which they were allocated by randomization for the most important moments of effect measurement (minus missing values), irrespective of non-compliance and co-interventions
Participants adequately tested for the absence of asthma[13]	In order to receive a 'yes', an objective measurement of airflow obstruction must have been used, such as a bronchodilator reversibility test (12% increase in FEV1) or a bronchial provocation test (test-specific decrease in FEV1). Both direct stimuli (metacholine, histamine) and indirect stimuli (exercise, eucapnic voluntary hyperventilation, mannitol, hypertonic saline) can be used. Peak flow measurements, lung function at rest and questionnaires on medical history or bronchial complaints are not considered adequate testing (FEV1 = forced expiratory volume in 1 second)

Data Analysis

Analyses were performed for inhaled and systemic β2-agonists separately. For all outcomes, we used the mean difference (MD) with a 95% confidence interval as a measure of effect. Where data were suitable for combining, pooled results were

calculated. Caution was used in deciding whether the results could be meaningfully combined. If the studies were sufficiently similar with respect to the participants, interventions and (timing of the) outcomes, a weighted MD was calculated by the use of a generic inverse variance method. For crossover studies, we extracted from each study, the paired MD and standard error. However, if the results were presented as if the trial had been a parallel-group trial, with standard deviations for each intervention separately, we estimated the standard error of the MD using these intervention-specific standard deviations and an imputed correlation coefficient of 0; in general, this will increase the variance and down weigh the importance of these studies. We assessed statistical heterogeneity by visual inspection of the forest plots and Cochran's Chi-square test for heterogeneity. We quantified heterogeneity by the use of the I-squared (I^2) statistic.[19] For all analyses, we used RevMan 5 software.[20] A fixed effect model was used, but in case of statistical heterogeneity in the absence of clinical heterogeneity, a random effects model was applied.

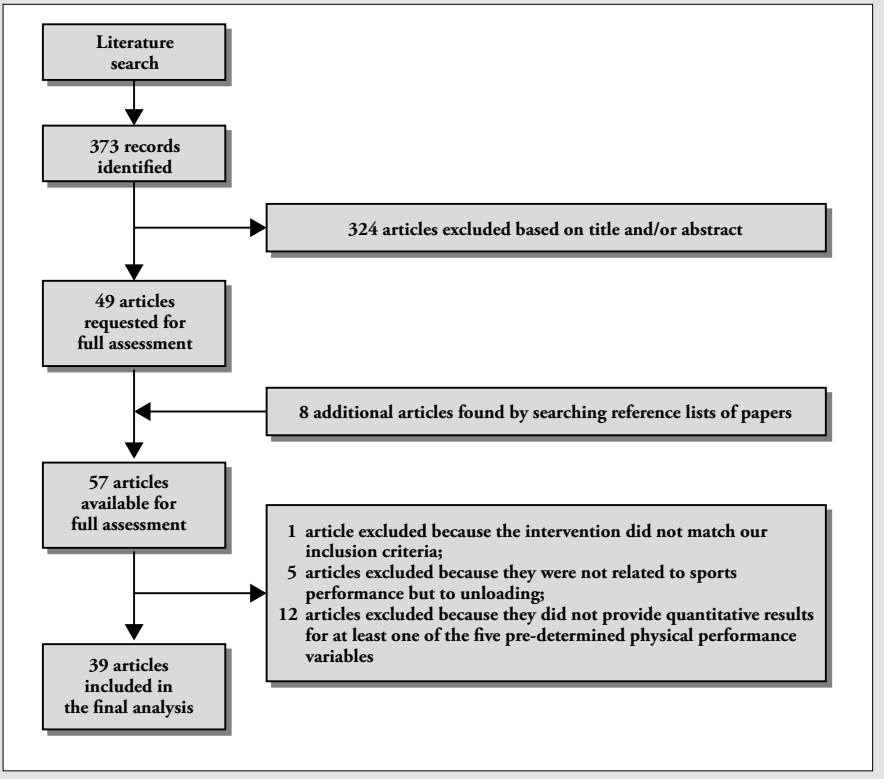
Subgroup Analysis

We planned a priori the following subgroup analyses: adults versus children, type of β2-agonist, and duration of the intervention – single (once) versus short term (1 week to ≤6 weeks) or long term (>6 weeks).

Sensitivity Analysis

To investigate how sensitive the results of the meta-analyses were for changes of the size of the imputed correlation coefficients, we repeated those meta-analyses by imputing a correlation coefficient of 0.5 (instead of 0) into the crossover studies that did not provide sufficient information to determine the correlation of the paired measurements. The value of 0.5 was the average correlation coefficient between the paired responses in crossover studies that did provide sufficient information regarding the correlation.

Figure 1 Flow chart for search results



Findings

Search Results

The search was carried out in August 2009 and 373 records were identified (figure 1). Forty-nine papers were requested for full assessment by both reviewers. All were graded independently by both reviewers and the bibliographies searched for additional studies or relevant reviews, identifying eight further papers for full assessment. We excluded 18 studies, because the intervention consisted of a β2-agonist in combination with a corticosteroid[21] or unloading,[22-26] or the authors did not report on any of the primary outcome measures.[27-38]

Finally, 39 studies involving 575 people were included.

Description of Studies

The characteristics of the included studies are presented in table II.

Twenty-six studies involving 403 participants (age range 7-30 years) compared placebo with inhaled β2-agonists.[39-64] Twenty-five of 26 studies were single treatment; one study lasted 1 week[64] and one study involved children.[56]

Thirteen studies involving 172 participants (age range 7-22 years) compared placebo with systemic β2-agonists.[65-77] Twelve studies investigated the effect of the use of oral salbutamol.[65-76] Five studies were single treatment and seven studies were short-term treatment (3-6 weeks).

One study with seven subjects compared placebo with intravenous β2-agonists.[77]

Assessment of Risk of Bias in Included Studies

The results of the risk of bias assessment in the individual studies are shown in table III.

Twelve of 26 studies using inhaled β2-agonists had adequate allocation concealment, whereas sequence generation was described in only four of 26 studies. However, this is unlikely to have been a source of bias in view of the fact that most studies (24/26) were double blind and 25 of 26 studies were single use with a crossover design. In the majority of the studies, the participants were adequately tested for asthma (21/26). The training level of the subjects in most studies was high (20/26).

Only one of 13 studies on systemic β2-agonists described allocation concealment, and none of the studies reported the randomization procedure. This may have led to selection bias in the three parallel-designed studies. Although all studies were double blind, masking of treatment characteristics was incomplete in at least four of the studies (taste differences in one study and side effects of salbutamol were reported in three studies). Information on patient withdrawal was missing in all seven longitudinal studies. In only three of 13 studies were participants adequately tested for asthma. Eight of 13 studies on systemic β2-agonists were performed in the same institution. The training level of the subjects varied from untrained to moderate; no studies included highly-trained athletes.

Table II Characteristics of included inhaled (26 studies) and systemic (13 studies) β2-agonists studies

Study, year	Design	Study population no. of subjects; sex; age [y] ± SD	Study population activity and performance level	Intervention#	Primary outcome measures
Inhaled studies					
Decorte et al.,[39] 2008	3-way crossover	10; M; 23.3±3.2	Physically active, 5.9±2.0 h•wk-1	Salbutamol 200 µg, 800 µg	Quadriceps muscle strength during maximal voluntary contraction and femoral nerve magnetic stimulation before and after (i) a maximal incremental cycling test; and (ii) 50 maximal isometric one-leg extensions
Sporer et al.,[40] 2008	4-way crossover	30; M; 29±6	State level cyclists and triathletes, VO2max 67.1±4.3 mkm	Salbutamol 200 µg, 400 µg, 800 µg	Mean power (W) and duration of 20-km time trial
Tjorhom et al.,[41] 2007	Crossover	23; M; 29.2±4.5	Endurance athletes, VO2max 60.6±3.8 mkm	Formoterol 18 µg	Running time to exhaustion at -20°C at 107% VO2max
Riiser et al.,[42] 2006	Crossover	20; M; 29.2±4.4	Endurance athletes, VO2max 61.1 mkm	Formoterol 18 µg	VO2max, running time to exhaustion in hypobaric conditions at 107% VO2max
Van Baak et al.,[43] 2004	Crossover	16; M; 23±3	Regional cyclists and triathletes, VO2max 69.9±6.8 mkm	Salbutamol 800 µg	Cycling time to exhaustion at 75% Wmax
Stewart et al.,[44] 2002	3-way crossover	10; M; 26.2±2.8	Highly trained athletes, VO2max 65.6±2.4 mkm	Formoterol 12 µg, salbutamol 400 µg	VO2max, 30-s Wingate test
Goubault et al.,[45] 2001	3-way crossover	12; M; 23±2	Trained athletes, VO2max 57.9±5.1 mkm	Salbutamol 200 µg, 800 µg	Cycling time to exhaustion at 85% VO2max
Carlsen et al.,[46] 2001	Crossover	24; M; 25.0±2.8	Competitive athletes, VO2max 67.4±5.0 mkm	Formoterol 9 µg	VO2max, running time to exhaustion at 105% VO2max

Sue-Chu et al.,[47] 1999	Crossover	8; M; 23±4	Highly trained cross-country skiers, VO2max >70 mkm	Salmeterol 50 µg	VO2max, running time at 90–80% VO2max and then incremental to exhaustion at -15°C
Sandsund et al.,[48] 1998	Crossover	8; M; 25.1±3.6	Highly trained cross-country skiers, VO2max 75.3±5.0 mkm	Salbutamol 400 µg	VO2max, running time at 50–95% VO2max and then incremental to exhaustion at -15°C and 23°C
Larsson et al.,[49] 1997	Single-blind crossover	20; M; 24±6	Elite cyclists, skiers, runners, VO2max 70.8 (68.2–73.3) mkm	Terbutaline 3 mg	VO2max, running time to exhaustion during maximal exercise test at -10°C
Carlsen et al.,[50] 1997	3-way crossover	18; M; 22.9±6.3	Runners, VO2max >63.1 mkm	Salbutamol 800 µg, salmeterol 50 µg	VO2max, running time to exhaustion during maximal exercise test
McDowell et al.,[51] 1997	Crossover	11; M; 24.6±3.7	Elite cyclists, US Cycling Federation category I and II	Salmeterol 42 µg	30-s Wingate test
Norris et al.,[52] 1996	Crossover	15; M; 25±4	Well trained cyclists, VO2max 62.8±7.0 mkm	Salbutamol 400 µg	VO2max, 60-s Wingate test, 20-km time trial duration
Morton et al.,[53] 1996	Crossover	16; M; 23.3±3.5	High performance cyclists, triathletes, cycling Australia grade A or B	Salmeterol 50 µg	10-s and 30-s Wingate test; isokinetic strength knee flexion and extension
Lemmer et al.,[54] 1995	Crossover	14; M; 22.6±3.7	Elite cyclists, US Cycling Federation category I and II	Albuterol 360 µg	30-s Wingate test
Heir & Stemshaug,[55] 1995	Crossover	17; M; range 18-30	Highly trained skiers, runners, orienteers, VO2max >70 mkm	Salbutamol 50 µg·kg-1	VO2max, running time to exhaustion at 110% VO2max
Unnithan et al.,[56] 1994	Single-blind crossover	10; M; 10.4±0.5	School boys, VO2max 55.3±5.8 mkm	Terbutaline 500 µg	VO2peak, total running time, submaximal running economy

Fleck et al.,[57] 1993	Crossover	21; M; 23.8±5.0	Elite cyclists, US Cycling Federation category I and II	Albuterol 360 μg	Wmax
Morton et al.,[58] 1993	Crossover	17; M; 22±4	Athletes (power events)	Salbutamol 200 μg	10-s Wingate test; isokinetic strength knee flexors and extensors
Signorile et al.,[59] 1992	Crossover	15; 8 M, 7 F; range 18–33	Healthy subjects	Albuterol 360 μg	Four 15-s Wingate tests
Meeuwisse et al.,[60] 1992	Crossover	7; M; 23.6±4	Highly trained cyclists, VO2max >60 mkm	Salbutamol 200 μg	VO2max, 30-s Wingate test, timed sprint to exhaustion after 45min exercise at 70% VO2max
Morton et al.,[61] 1992	Crossover	17; 16 M, 1 F; 21.6±4	High performance runners, VO2max 75.3±6.8 mkm	Salmeterol 50 μg	VO2max, running time to exhaustion during maximal exercise test, 10-s and 30-s Wingate test
Gong et al.,[62] 1988	Crossover	15; 14 M, 1 F; 23±5	Endurance cyclists, triathletes, VO2max 61 ±4 mkm	Albuterol 180 μg	VO2max after 60-min submaximal exercise and exhaustive final sprint; exposure to ozone or filtered air
Booth et al.,[63] 1988	Crossover	10; F; 21.6±7.25	Trained cyclists, VO2max 50.1±4.9 mkm	Salbutamol 100 μg	Wmax
McKenzie et al.,[64] 1983	Parallel design	4; M; 25.0±7.7 5; M; 27.0±9.6 5; F; 24.4±8.6 5; F; 26.0±13.4	Highly trained track and field athletes 64.0±2.2 mkm 64.7±4.4 mkm 59.4±12.1 mkm 61.9±8.7 mkm	Salbutamol 800 μg Placebo Salbutamol 800 μg Placebo	VO2max

Systemic studies					
Le Panse et al.,[65] 2007	Crossover	12; F; 22.3±3.1	Athletics, weight-lifting, cycling, 1–3 times per wk	Salbutamol 4mg	30-s Wingate test
Le Panse et al.,[66] 2006a	Crossover	14; F; 20.9±1.1 (recreational athletes), 23±2.4 (sedentary subjects)	7 recreational athletes, 2–3 times per wk, 7 sedentary subjects	Salbutamol 12mg•day-1 for 4 wk	30-s Wingate test
Le Panse et al.,[67] 2006b	Crossover	14; F; 22 ±1.7	7 recreational athletes, 7 sedentary subjects	Salbutamol 12mg•day-1 for 4 wk	VO2max
Le Panse et al.,[68] 2005	Crossover	15; M; 29.1±6.2 (strength-trained athletes), 30.5±6.9 (sedentary subjects)	8 strength-trained athletes, 7 sedentary subjects	Salbutamol 12mg•day-1 for 3 wk	30-s Wingate test
Collomp et al.,[69] 2005	Crossover	13; M; 31.2±5.8	Sedentary subjects and recreational weight-lifters, 1–3 times per wk	Salbutamol 4mg	30-s Wingate test
Caruso et al.,[70] 2005	Parallel design	22; M; 18–22	Healthy men	Salbutamol 16mg•day-1 for 3 wk	Isokinetic strength elbow and knee flexors and extensors
Collomp et al.,[71] 2002	Crossover	8; M; 26±5.9	Normally active, VO2max 54.4 ± 2.2mLkg-1min-1	Salbutamol 6mg	Cycling time to exhaustion at 90% VO2max

Collomp et al.,[72] 2000a	Crossover	9; M; 24.6±3.9	Moderately trained: cycling, running, ball games	Salbutamol 6mg	Cycling time to exhaustion at 80–85% VO2max
Collomp et al.,[73] 2000b	Crossover	8; M; 23.4±2.3	Recreational runners and cyclists, 3-5 times per wk	Salbutamol 12mg•day-1 for 3 wk	Cycling time to exhaustion at 80–85% VO2max
Van Baak et al.,[74] 2000	Crossover	16; M; 23.3±2.1	Healthy volunteers, twice per wk: track and field, fitness, hockey, soccer, cycling	Salbutamol 4mg	Cycling time to exhaustion during at 70% VO2max, isokinetic leg strength
Caruso et al.,[75] 1995	Parallel design	22; 13 M, 21.4±3.3 9 F, 21.4±1.8	Sedentary subjects and recreational athletes, fitness <1 per wk, aerobic training <3 times per wk	Albuterol 16mg•day-1 for 6 wk	Isokinetic strength knee extensors
Martineau et al.,[76] 1992	Parallel design	12; 6 M; 29±2: 6 F; 25±2	Healthy men	Salbutamol 16mg•day-1 for 3 wk	Isometric strength knee flexors and extensors; grip strength
Violante et al.,[77] 1989	Crossover	7; M; 33.7±7.8	Healthy men	Salbutamol 4 µg•kg-1 in 20 min, then 3 µg•kg-1•min-1	12-min walking distance, VO2max

A European label claim of formoterol 12 mg is equivalent to a US label claim of formoterol 9 mg; a European label claim of salbutamol 100 mg is equivalent to a US label claim of albuterol 90 mg.

F = female; M= male; mkm = mL•kg-1•min-1; wk = week; VO2max = maximal oxygen consumption; VO2peak = peak oxygen consumption; Wmax = maximal Watts.

Table III Risk of bias assessment

Study, year	Adequate sequence generation	Allocation concealment	Blinding of participants	Blinding of researchers	Blinding of outcome assessors	Compliance acceptable	Incomplete outcome data addressed (withdrawals)	Were the participants adequately tested for asthma?	Total number of fulfilled anti-bias criteria
Inhaled									
Decorte et al.,[39] 2008	?	Y	Y	Y	Y	Y	N	N	5
Sporer et al.,[40] 2008	?	Y	Y	Y	?	Y	Y	Y	6
Tjorhom et al.,[41] 2007	Y	Y	Y	Y	Y	Y	Y	Y	8
Riiser et al.,[42] 2006	Y	Y	Y	Y	Y	Y	Y	Y	8
Baak et al.,[43] 2004	?	?	Y	Y	?	Y	Y	N	4
Stewart et al.,[44] 2002	?	Y	Y	Y	?	Y	Y	Y	6
Goubault et al.,[45] 2001	?	Y	Y	Y	?	Y	Y	Y	6
Carlsen et al.,[46] 2001	Y	Y	Y	Y	?	Y	Y	Y	7
Sue- Chu et al.,[47] 1999	?	?	Y	Y	?	Y	Y	Y	5
Sandsund et al.,[48] 1998	?	?	Y	Y	?	Y	Y	Y	5
Larsson et al.,[49] 1997	?	N	Y	N	N	Y	Y	Y	4
Carlsen et al.,[50] 1997	?	?	Y	Y	?	Y	Y	Y	5
McDowell et al.,[51] 1997	?	?	Y	Y	?	Y	Y	Y	5
Norris et al.,[52] 1996	Y	Y	Y	Y	?	Y	Y	Y	7
Morton et al.,[53] 1996	?	?	Y	Y	?	Y	Y	Y	5
Lemmer et al.,[54] 1995	?	?	Y	Y	?	Y	Y	Y	5
Heir & Stemshaug,[55] 1995	?	?	Y	Y	?	Y	Y	Y	5
Unnithan et al.,[56] 1994	?	N	Y	N	N	Y	Y	Y	4
Fleck et al.,[57] 1993	?	?	Y	Y	?	Y	Y	Y	5

Morton et al.,[58] 1993	?	?	Y	Y	?	Y	Y	N	4
Signorile et al.,[59] 1992	?	Y	Y	Y	?	Y	Y	N	5
Meeuwisse et al.,[60] 1992	?	Y	Y	Y	?	Y	Y	Y	6
Morton et al.,[61] 1992	?	?	Y	Y	?	Y	Y	Y	5
Gong et al.,[62] 1988	?	Y	Y	Y	?	Y	Y	Y	6
Booth et al.,[63] 1988	?	?	Y	Y	?	Y	Y	N	4
McKenzie et al.,[64] 1983	?	Y	Y	Y	?	Y	Y	Y	6
Oral									
Le Panse et al.,[65] 2007	?	?	Y	Y	?	Y	?	?	3
Le Panse et al.,[66] 2006a	?	?	Y	Y	?	?	Y	N	3
Le Panse et al.,[67] 2006b	?	?	Y	Y	?	?	N	N	2
Le Panse et al.,[68] 2005	?	?	Y	Y	?	?	N	?	2
Collomp et al.,[69] 2005	?	?	Y	Y	?	?	N	?	2
Caruso et al.,[70] 2005	?	Y	Y	Y	?	?	N	N	3
Collomp et al.,[71] 2002	?	?	Y	Y	?	Y	Y	Y	5
Collomp et al.,[72] 2000a	?	?	Y	Y	?	Y	N	Y	4
Collomp et al.,[73] 2000b	?	?	Y	Y	?	Y	Y	Y	5
Van Baak et al.,[74] 2000	?	?	Y	Y	?	Y	Y	N	4
Caruso et al.,[75] 1995	?	?	Y	Y	?	?	N	N	2
Martineau et al.,[76] 1992	?	?	?	?	?	?	N	N	0
Intravenous									
Violante et al.,[77] 1989	?	?	Y	Y	?	Y	Y	N	4

N= no; Y = yes; ? indicates unclear.

Effect of Interventions

Inhaled β2-Agonists

Twenty-six studies involving 403 participants (age range 7-30 years) addressed the effects of inhaled β2-agonists. The summary results are presented in table IV and in figure 2.

The effect estimates for VO2max, endurance time at 105-110% VO2max, peak power and total work during a 30-second Wingate test were all negative for β2-agonists; none of the effects were statistically significant. Eight studies could not be included in the pooling for the following reasons: (i) VO2max could not be indexed;[47] (ii) the study provided insufficient data for the VO2max (no standard deviations, 95% confidence intervals for subgroups only);[64] (iii) the time trials were performed at submaximal levels (70% and 90% VO2max)[43,45] instead of (supra-) maximal levels (105-110%); and (iv) the Wingate tests lasted 10 seconds,[53,58] 15 seconds[59] or 60 seconds,[52] instead of 30 seconds. The results of these studies are shown in table V.

Subgroup Analysis of Inhaled β2-Agonists

There was only one trial with children showing no effect of inhaled β2-agonists on VO2max[56] and pooled results were not affected by removing this study from the meta-analysis (figure 2). Subgroup analysis into the type of β2-agonist did not influence the results either.

Systemic β2-Agonists

Thirteen studies involving 172 participants (age range 7-22 years) addressed the effects of systemic β2-agonists. The summary results are presented in table IV and figures 3 and 4. Two studies could be pooled to determine the effect of oral β2-agonists on endurance time at 80-85% VO2max; a statistically significant effect was found. Four studies were pooled to determine the effect of oral β2-agonists on peak power and total work indexed for weight during a 30-second Wingate test. A statistically significant effect was detected for peak power (figure 3), but not for total work (figure 4).

Seven studies could not be included in the pooling because the outcome was examined in only one study,[67,71,77] or outcomes could not be meaningfully combined.[70,74-76] The results of these studies are presented in table V.

Subgroup Analysis of Systemic β2-Agonists

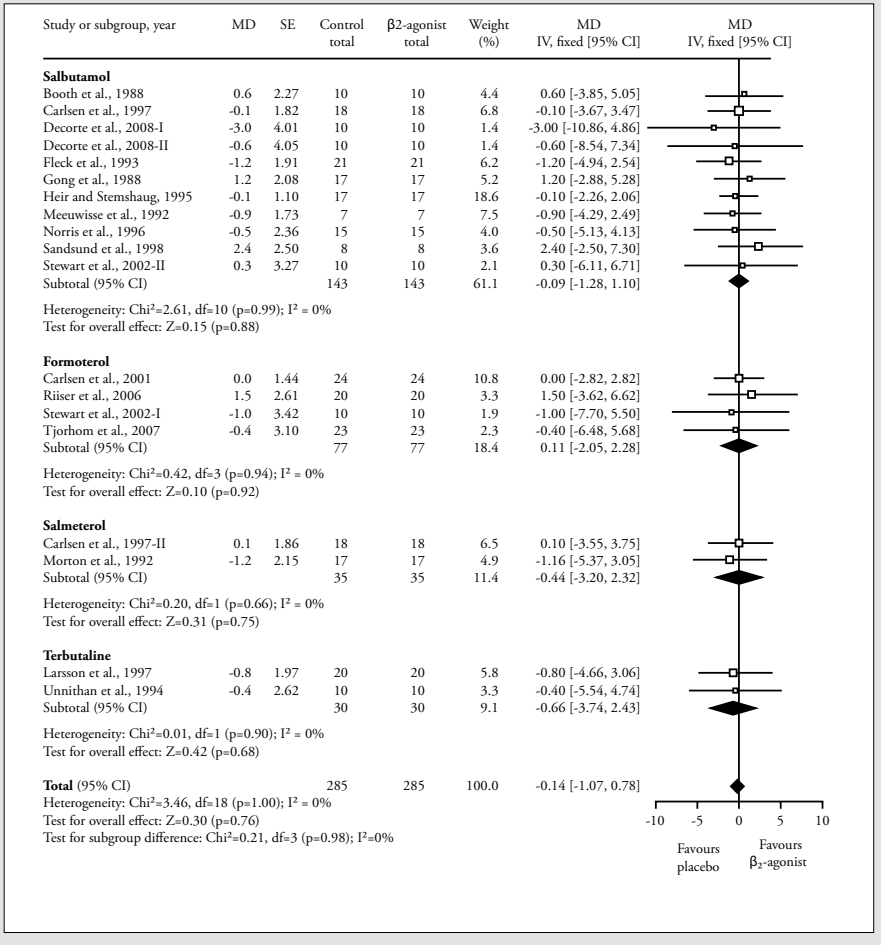
Subgroup analysis into duration of intervention (single or short-term use) diluted the effect of single use on peak power, resulting in no significant effect (figure 3).

Table IV Meta-analysis of effect of inhaled and systemic β2-agonists on performance

Outcome	No. of participants (age range [y])	Type of β2-agonists (no. of studies)	Summary result: MD (95% CI)	p-value	References
Inhaled					
VO2max	247 (7-23)	Salbutamol (10), formoterol (4), salmeterol (2), terbutaline (2)	-0.14 mkm (-1.07, 0.78)	0.76	39,41,42,44,46, 48-50,52,55-57,60-63
Endurance time at 105-110% VO2max	69 (17-24)	Salbutamol (1), formoterol (3)	-1.5 s (-15.6, 12.6)	0.83	41,42,46,55
20-km time trial duration	42 (15-27)	Salbutamol (2)	-4.4 s (-23.5, 14.7)	0.65	40,52
Indexed peak power; 30-s Wingate test	42 (7-14)	Salbutamol (3), formoterol (1), salmeterol (1)	-0.14 W•kg-1 (-0.54, 0.27)	0.51	44,51,54,60
Indexed total work; 30-s Wingate test	59 (7-17)	Salbutamol (4), formoterol (1), salmeterol (1)	0.80 J•kg-1 (-2.44, 4.05)	0.63	44,51,53,54,60
Peak concentric strength; KE at 120°•s-1	31 (15-16)	Salbutamol (1), salmeterol (1)	-1.13 Nm (-17.8, 15.6)	0.89	53,58
Peak concentric strength; KF at 120°•s-1	31 (15–16)	Salbutamol (1), salmeterol (1)	-0.37 Nm (-11.2, 10.5)	0.95	53,58
Systemic					
Endurance time at 80-85% VO2max	17 (8–9)	Salbutamol (2)	402 s (34, 770)	0.03	72,73
Indexed peak power; 30-s Wingate test	25 (12–13)	Salbutamol (4)	0.91 W•kg-1 (0.25, 1.57)	0.007	65,66,68,69
Indexed total work; 30-s Wingate test	25 (12–13)	Salbutamol (4)	7.8 J•kg-1 (-3.3, 18.9)	0.17	65,66,68,69

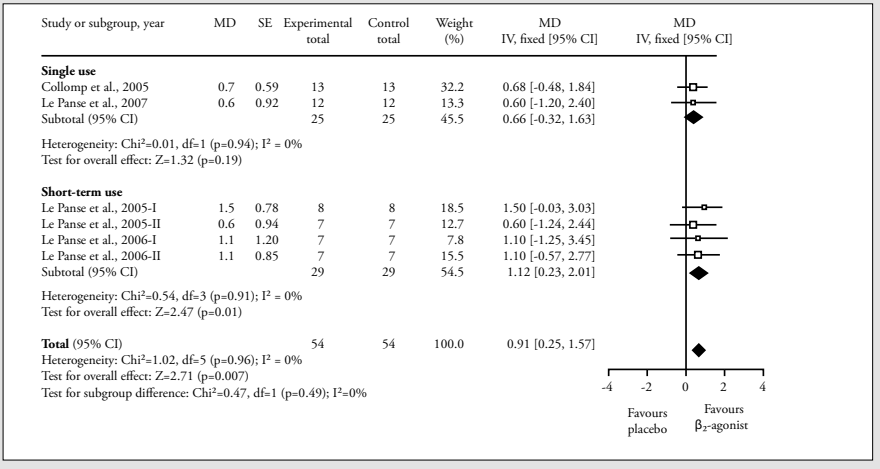
KE= knee extensors; KF = knee flexors; MD= mean difference; mkm = mL•kg-1•min-1; VO2max = maximal oxygen consumption.

Figure 2 Forest plot comparison of inhaled β2-agonists vs placebo; outcome maximal oxygen consumption in mL•kg-1•min-1. Study weights are calculated by taking the inverse of the variance of the estimate of the study-specific mean differences (MD). The size of each square is proportional to the size of the weight that the study contributes to the overall weighted summary MD.[38,39,41,42,44,46,48-50,52,55-57,60-63]



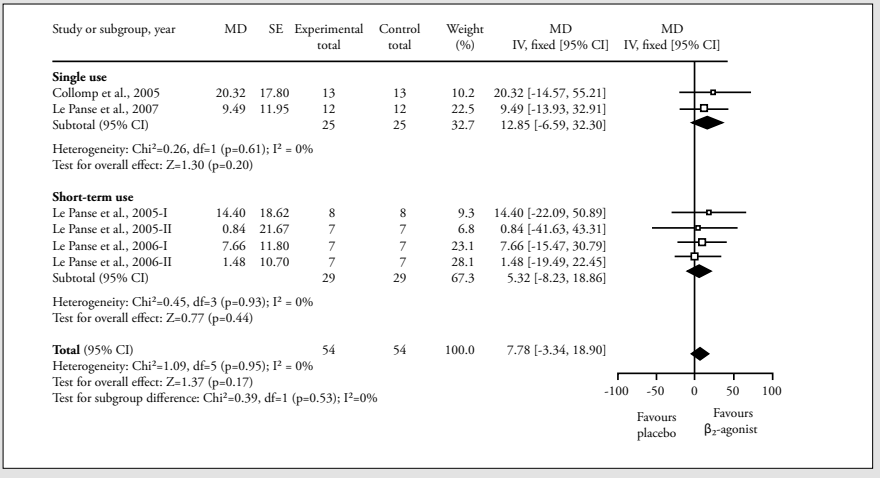
Chi² = Chi-square test; df = degrees of freedom; I^2 = I-squared statistic; IV = inverse variance; SE = standard error; Z = Z-test.

Figure 3 Forest plot comparison of systemic β2-agonists vs placebo; outcome indexed peak power in W•kg-1. Study weights are calculated by taking the inverse of the variance of the estimate of the study-specific mean differences (MD). The size of each square is proportional to the size of the weight that the study contributes to the overall weighted summary MD.[65,66,68,69]



Chi² = Chi-square test; df = degrees of freedom; I² = I-squared statistic; IV = inverse variance; SE = standard error; Z = Z-test.

Figure 4 Forest plot comparison of systemic β2-agonists vs placebo; outcome indexed total work in J•kg-1. Study weights are calculated by taking the inverse of the variance of the estimate of the study-specific mean differences (MD). The size of each square is proportional to the size of the weight that the study contributes to the overall weighted summary MD.[65,66,68,69]



Chi² = Chi-square test; df = degrees of freedom; I² = I-squared statistic; IV = inverse variance; SE= standard error; Z = Z-test.

Table V Effect of inhaled and systemic β2-agonists: results of individual studies

Outcome	No. of participants	Type, dose and duration of β2-agonists	Results (β2-agonists vs placebo)	Reference
Inhaled				
VO2max	8	Salmeterol 50 mg	5.7±0.6 vs 5.7±0.3 L•min-1, NS	47
VO2max	19	Salbutamol 800 mg•d-1 for 1 wk	F 59.1 ▶ 57.1 vs 61.9 ▶ 58.5mL•kg-1•min-1, NS M 66.7 ▶ 62.6 vs 64.8 ▶ 64.0mL•kg-1•min-1, NS	64
Endurance time 90% VO2max	12	Salbutamol 200 mg, salbutamol 800 mg	1411±296 (200 mg) vs 1260±225 (800 mg) vs 1398±308 (placebo) s, NS	45
Endurance time 70% Wmax	16	Salbutamol 800 mg	3927.6±231.3 vs 4010.2±327.7 s, p < 0.05	43
60-s Wingate test; peak power and mean power	17	Salbutamol 200 mg	PP: 803±70 vs 798±79 W, NS MP: 529±40 vs 534±41 W, NS	52
10-s Wingate test; peak power and total work	16	Salmeterol 50 mg	PP 1208.9±142.7 vs 1219.8±157.9 W, NS TW 10.381±1.277 vs 10.412±1.366 kJ, NS	53
10-s Wingate test; peak power and total work	17	Salbutamol 200 mg	PP 18.63 vs 18.51 W•kg-1, NS TW 151.99 vs 150.05 J•kg-1, NS	58
15-s Wingate test; peak power and total work	15	Albuterol 360 mg	PP 886.5±218.8 vs 858.2±219.6 W, p = 0.01 TW 11.1±2.7 vs 10.9±2.7 kJ, NS	59
Systemic				
VO2max	14	Salbutamol 12mg•d-1 for 4wk	Trained F 42.1±2.9 vs 42.5±1.7 mL•kg-1•min-1, NS Sedentary F 37.4±2.9 vs 36.8±2.8 mL•kg-1•min-1, NS	67
Mean power at 90% VO2max	8	Salbutamol 6mg once	235.5±18.1 vs 234.9±16 W, NS	71
Endurance time at 70%Wmax % change in peak isokinetic strength KE and KF	16	Salbutamol 4mg once	MD 400±1160 s, NS % increase KE 4.4 % increase KF 4.9, p < 0.05	74

% change in peak concentric strength of the EE, EF, KE, KF at 90°•s-1, 180°•s-1 and 270°•s-1	11 salbutamol 11 placebo	Salbutamol 16mg•d-1 for 3wk	% change in EE and EF strength, NS; % change KE at 90°•s-1, NS; % change KE at 180°•s-1 and 270°•s-1: p< 0.05 % change KF at 90°•s-1, NS; % change KF at 180°•s-1 and 270°•s-1, p< 0.05	70
Concentric isokinetic strength of KE at 45°•s-1, peak torque and total work	13 salbutamol 9 placebo	Salbutamol 16mg•d-1 for 6 wk	PT: 269.3±59.9 ▶ 353.2±71.4 vs 246.3±39.0 ▶ 306.2±57.9 Nm•kg-1, NS TW: 296.8±71.4 ▶ 385.1±62.7 vs 287.5±65.1 ▶ 311.7±76.8 Nm•kg-1, p < 0.05	75
Change in isometric strength of KE, KF and grip strength	6 salbutamol 6 placebo	Salbutamol 16mg•d-1 for 3wk	% increase in KE strength both legs 12 ± 7; % increase D KF strength 22 ± 15; % change in ND KF strength, NS % change in grip strength, NS	76
12-min walking distance; Wmax	7	Intravenous salbutamol 4 µg•kg-1 for 20 minutes, then 3 µg•kg-1	1492±66.0 vs 1489±57.5 m, NS 254.5±28.1 vs 261.4±29.3 W, NS	77

D= dominant; EE = elbow extensor; EF = elbow flexor; F = female; KE = knee extensor; KF = knee flexor; M= male; MD= mean difference; MP= mean power; ND= non-dominant; NS= non-significant; PP = peak power; PT = peak torque; TW= total work; VO2max = maximal oxygen consumption; Wmax = maximal Watts; ▶ indicates change from pre- to post-treatment.

Discussion

Principal Findings

This systematic review shows that there is no evidence that inhaled β2-agonists improve aerobic or anaerobic capacity. Results were consistent and heterogeneity in the studies was low, whether the outcome was VO2max, 20-km time trial duration, time to exhaustion at 105–110% VO2max or Wingate testing. The type of β2-agonist used made no difference.

Weak evidence was found that systemic β2- agonists improve anaerobic capacity and strength, but the results were inconsistent and only studies using systemic salbutamol were identified. Oral salbutamol was found to have a statistically significant effect on peak power, but not on total work, during a 30-secondWingate test. However, the number of participants and training levels were low. A statistically significant effect was found for oral salbutamol on strength in a few studies, but results were not consistent and the quality of the studies was low. Because of the great variation in study design and outcome parameters, studies investigating the effects of oral salbutamol on strength could not be pooled.

We found no published studies on the effects of systemic formoterol, salmeterol or terbutaline on physical performance.

Strength and Weaknesses

Our findings on inhaled β2-agonists are in agreement with earlier reviews on this topic,[1,15-17] confirming that there is no evidence that inhaled β2-agonists improve athletic performance in healthy athletes. The strength of our study compared with Kindermann's[15] review of randomized controlled trials differs in two areas. First, we systematically searched the literature for studies examining the effect of either inhaled or systemic β2-agonists, resulting in a broader database. There is a high likelihood that we identified all relevant studies. Second, we used meta-analysis, resulting in increased sample size, statistical power and objectivity, which enabled us to quantify effect size.[78]

A weakness of this review is that none of the included studies examined the effect of β2-agonists during actual performance. Therefore, the use of sensitive, valid and reliable performance protocols is important, and extrapolation of our findings to actual sports performance should be performed with caution. In this respect, it is important to note that time trials have greater validity than time to exhaustion, with better correlation to actual performance, and are also more reliable (coefficient of variation of <5%, compared with >10% for time to exhaustion).[79]

Open-end trials to exhaustion and submaximal tests should not be used as proxies for endurance performance.

A strength of this review is the application of systematic strategies to reduce bias by an assessment of the internal validity of the included studies. There were low risks of bias in the studies on inhaled β2-agonists. Also, the majority of studies had tested adequately for asthma and included highly trained athletes. The level of heterogeneity for the studies included in the meta-analysis was low (I2 is 0%).

The quality of the studies on systemic β2-agonists was variable, with only one study describing allocation concealment and no studies describing the randomization procedure. In two studies, differences in baseline characteristics of significance were evident.[75,76] Blinding was likely to be insufficient in the study using vitamin C as placebo.[76] It may have been inadequate in other studies, as side effects were reported in three studies when using salbutamol.[68,73,74] The data of Caruso et al.[70] were difficult to use, as they were presented as percentages in a diagram, and baseline values were lacking. Martineau et al.[76] also only presented the results as percentages in a diagram, although the authors did report the (imbalanced) baseline values. The training level of the subjects in all systemic studies was low to moderate and, therefore, not representative of the elite athletic population. This may have led to bias favouring a positive effect, as a downregulation in β-receptor sensitivity has been shown after long term aerobic training.[80] It is unclear whether identical subjects were used in some of the eight studies performed in the same research laboratory.

The included crossover studies did not always present the paired MD and standard error. In these cases, we calculated the numbers using the intervention-specific standard deviation and an imputed correlation coefficient of 0. Bias could have been introduced here if the real correlation coefficient was higher than 0. In order to reduce this source of bias, we performed a sensitivity analysis, whereby we repeated the measurement for the controlled trials included in the meta-analysis with a correlation coefficient of 0.5 to test whether this changed the results of our analysis. No significant effect was found.

Conclusion

No significant effects were detected for the inhaled β2-agonists salbutamol, formoterol, terbutaline or salmeterol on aerobic or anaerobic capacity or strength in healthy athletes. In view of the high prevalence of asthma in athletes, the considerable workload and high costs involved in providing a therapeutic use exemption, and the severe sanctions asthmatic athletes have to face when using

inhaled β2-agonists without written permission, these substances should no longer be included on the WADA list of prohibited substances. From a physiological point of view, there is no basis for imposing different criteria for the different types of inhaled β2-agonists, as is currently the case.[14]

The evidence base for assessing possible performance-enhancing effects of systemic β2-agonists is currently weak, and the available evidence pertains only to salbutamol. Future studies should consist of high-quality randomized controlled trials, assessing the effects of systemic β2-agonists, using reliable, valid and sensitive performance protocols for aerobic and anaerobic capacity and strength.

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Extended discussion on case 2 (common medications)

These two studies showed that inhaled glucocorticoids and beta2-agonists cannot be proven to enhance physical performance in regular dosages, and for beta2-agonists even in dosages that are slightly higher than normal medical practice. However, there are analytical difficulties in distinguishing the route of administration, or higher quantities that might be being used (Berges et al. 1999, Berges et al. 2000, Ventura et al. 2000, Pillard et al. 2015). For substances out of both groups so-called 'reporting levels' have been established, which means that laboratories should not report findings below a certain concentration. This concentration is not based on the analytical capabilities in finding low levels, but on the practical findings that virtually all 'regular users' of these medications do not lead to urinary concentrations above this level.

The situation described above makes clear that the place of glucocorticoids and beta2-agonists in the WADP is still highly controversial amongst anti-doping regulators. A closer look at these two groups of substances and the way they are regulated within the anti-doping framework is therefore warranted.

Glucocorticoids (up till 2014 mistakenly dubbed 'glucocorticosteroids' on the prohibited list) have anti-inflammatory effects and as such they play an important role in the immune system. The most common natural substance is cortisol. There are many exogenous medicines that fall within this group, which can be used to target many different medical problems such as allergies, asthma, and inflammations. This means that they are widely used, also within the athletic population for regular purposes. But because there have been examples of misuse as well they have been mentioned on the prohibited list since 1975, albeit with a variety of rules around them over the years (permitted after notification, permitted with certain application methods, permitted without systemic effects). Currently an analytical threshold is in place (30 ng/mL) below which the laboratory is instructed not to report a glucocorticoid AAF. In the years 2012-2014 higher levels were monitored (and as such no sanctions were involved) but in 2015 this practice was discontinued. These WADP rules have been complemented in the sport of cycling by additional consequences of glucocorticoid use, regardless whether this use has been medically justified or not. For example, the Mouvement Pour un Cyclisme Crédible ('Movement for credible cycling', a cooperation between various professional cycling teams) has rules that its members may not start cyclists in a

race if their endogenous levels of cortisol are low, sparking many debates in the few cases where this actually occurred.

There are frequent discussions about the necessity to ban this group of medicines in the world of sports in the first place. Historically, their potential to enhance performance has been sought in their main effect (anti-inflammation, which could be helpful to combat the physical stresses of severe and persistent endurance exercises) or in one of the side-effects of this medication: euphoria (which is expected to help, again especially during long-lasting exercises) or their impact on metabolism (an increased availability of substrates may be useful in endurance sports). More recently there have been claims that glucocorticoids play an important role in the proliferation of blood cells, and as such they might give a kick-start to the development of erythrocytes (again improving endurance performance, this time through increased oxygen transport in the blood stream). But actual performance enhancement has never been proven in scientific studies.

There is little debate about their fulfilment of the second criterion that is mentioned in the WADC as a potential property to consider a certain substance (or group of substances) for the prohibited list, as glucocorticoids are widely considered to represent a health risk. It may sound strange at first to outsiders of the world of medicine, but all medicines that are available to cure someone, possess in fact a health risk during use. All medicines have a long list of potential side effects, and glucocorticoids are no exception. Adrenal insufficiency, various infections, and osteoporosis are just a few of the problems that may occur. Besides these side effects when used as directed by medical professionals, it is clear that when a healthy person starts to use this medication the risks of health problems far outweigh the possibilities of health gains.

The third criterion, being a potential breach of the 'spirit of sport' is even more difficult to describe (Ritchie 2013). It will be discussed at length in paragraph 3.4; here it suffices to state that it is an ethical judgement whether or not a certain substance (or method) breaches basic sport values. With regard to glucocorticoids this criterion is mostly discussed on the basis that 1) they are being abused in sports (i.e. being used by healthy athletes without a proper medical reason) and 2) they are potentially very damaging to one's health (i.e. a repetition of the second criterion). Even though WADA does never publicly share their determination which substances fulfil which criterion, it is clear that most people responsible

for establishing the prohibited list feel that in the case of glucocorticoids all three criteria are fulfilled, but it is also true that in meetings where the status of these substances are discussed it is sometimes unclear whether the three criteria guide the discussion, or whether policy makers follow their own instinct first, and try to align this with the established criteria later. The application of the 'spirit of sport' criterion is often only implicit, and certainly not officially published.

It is clear that with this group of glucocorticoids there is a highly intricate entanglement of all relevant aspects which eventually should lead to one simple determination: are they doping, and should they therefore be prohibited in sports, or not? Regarding effectiveness, it is striking that many interpretations of glucocorticoid properties remain implicit, which spurs more and longer discussions. Attempts have been made to share findings and ideas regarding these substances (Montalvan & Duclos 2008, Orchard 2008, Duclos 2010, Pigozzi et al. 2012) but as long as WADA does not officially share their interpretation which of the three criteria can be applied to glucocorticoids and why, discussions on this subject will not even reach temporary conclusions. This is a clear area where more transparency and especially explicitness will aid in bringing the discussions forward.

Regarding beta2-agonists the above systematic review and meta-analysis settled a long discussion about the performance enhancing capabilities of these substances. It can readily be assumed that regular inhalations of anti-asthma medication do not enhance performance in non-asthmatic athletes. Systematic administration, however (oral, intravenously) is likely to improve muscular strength and as such a wide array of athletic performance characteristics. The latter conclusion is partly drawn on the basis of animal studies (Anonymous 1992). This distinction in the anti-doping rules highlights the importance of analytical possibilities to distinguish between methods of application (Dickinson et al. 2014, Pillard et al. 2015). Progress in this area has been made, albeit slowly and numerous beta2-agonists are available for which no distinction can be made.

The combination of the pharmacological potential and analytical challenge has led to frequent changes in anti-doping rules (Fitch 2006, 2013). The change as of 1 January 2009 had the most impact, as a requirement for asthmatic athletes was introduced to apply for a TUE for inhaled beta2-agonists, and the application should include the results of pulmonary tests that show the presence of asthma. This led to controversies all over the world, as not all countries and doctors require

such tests in their regular treatment regimens and not all pulmonary tests that were performed were accepted by WADA as sufficient proof. The result was that many athletes who had been using beta2-agonists for years had to undergo pulmonary challenge tests. This rather complex state of affairs satisfied most doctors – not because of the extra amount of work they had to perform but because there was a general feeling that beta2-agonists were prescribed too often and too soon to athletes who asked for them.

So in the end, the increased administrative efforts that were required in 2009 may have brought about chances for the good of mankind (Couto et al. 2013). But anti-doping policies are not meant to be an instrument in battling medical malpractice. The core of anti-doping policies is to enable doping-free sport and it can hardly be called effective if doping regulations force athletes and physicians to perform medical tests which otherwise would not have been necessary. This is an essential conclusion of case 2: anti-doping, no matter how important it may be, is a distinct and specific area of work, maybe even a profession in itself. One of the consequences is that those who work in anti-doping should stick to their own trade when drafting policies. This is difficult enough as it is, and it is safe to assume that one can only save one world at the time.

The current situation is that for some beta2-agonists the extensive pulmonary challenge test results are still necessary to receive approval for anti-asthma medication, but not for all. This has another peculiar effect, as it means that anti-doping policies have an impact on the choices that physicians make when treating asthmatic athletes: they might be inclined to choose the easy option for administrative purposes, which will undeniably interfere with their medical decision. It is a foretaste of the impact that anti-doping regulations have, or might have, on athletes, which will be further discussed in paragraph 2.5.

This case shows again that policy decisions often need to be taken in the absence of scientific data on the subject at hand. But such information can often be gathered relatively quickly if needed. A more coordinated research agenda may avoid that rule changes are necessary to accommodate for new scientific findings, and this may also guide discussions on the need to balance practical solutions and effective anti-doping measures. The frequent changes over the last decade in the prohibited list regarding respiratory medications still lead to misconceptions about these rules among athletes and the medical world. And while confusion may be unavoidable

to a certain degree, especially in a complex set of rules such as in anti-doping, it can hardly be called effective. The confusion could be diminished if WADA would publish its determination on the three criteria that guide the prohibited list, with respect to all (groups of) substances and methods that are on that list. Moreover, attempts to change general medicine prescriptions worldwide may be laudable but will not contribute to the effectiveness of anti-doping measures. In fact, using resources from anti-doping to rectify wrongs in other areas is principally ineffective for the purpose of anti-doping itself.

2.4.3 Case 3: Gene doping, or when to ban a potential doping problem

Introduction to case 3

One of the peculiarities of anti-doping policies is that throughout the history of doping regulations there has been an ambiguous relationship between the possibilities of detection and the prohibition of doping substances and/or methods. The first official prohibition of doping in sports, by the IAAF in 1928, does not mention possibilities of detection at all, and in fact no detection efforts were made for almost 40 years. Once the first lists of prohibited substances emerge in the course of the 1960s, anabolic steroids were not included because of two reasons. Firstly, there continued to be a scientific debate as to which extent these substances were actually performance enhancing. Secondly, there was no established way to detect their misuse in urine samples or otherwise, and as such it was not seen as a viable option to prohibit their use until 1976 (Todd 1987, Kicman & Gower 2003, Müller 2010). At that time, the IOC Medical Brochure for the 1976 Olympic Games explained the absence of steroids on previous prohibited lists as 'suitable analytical methods to determine all the drugs of this class had not been developed at that time' (Beckett 1976).

This approach changed in the 1980s. When the method of blood doping was openly used during the 1984 Summer Olympic Games the IOC decided to ban this practice, even though no chemical detection possibilities existed. Similar situations occurred later on with growth hormone (banned in 1989), erythropoietin (banned in 1990), insulin (banned in 1999), and gene doping (banned in 2003). Detection methods for these substances have been developed, but it has taken several years before this has been reached. The issue of gene doping is of particular interest as at the time of prohibition is was generally acknowledged that the practice of gene doping was not even possible yet (Friedmann & Koss 2001). This is the reason

why it is interesting to study the issue of gene doping in more depth, as an example of the relationship between doping policies and doping controls and, since at the time of writing no clear proof of actual gene doping practices have surfaced, as an example of current doping controversies. The following text is the full text of an article published in the journal *British Journal of Sports Medicine* in 2013.

GENE DOPING: AN OVERVIEW AND CURRENT IMPLICATIONS FOR ATHLETES

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Abstract

The possibility of gene doping, defined as the transfer of nucleic acid sequences and/or the use of normal or genetically modified cells to enhance sport performance, is a real concern in sports medicine. The abuse of knowledge and techniques gained in the area of gene therapy is a form of doping, and is prohibited for competitive athletes. As yet there is no conclusive evidence that gene doping has been practiced in sport. However, given that gene therapy techniques improve continuously, the likelihood of abuse will increase.

A literature search was conducted to identify the most relevant proteins based on their current gene doping potential using articles from Pubmed, Scopus and Embase published between 2006 and 2011. The final list of selected proteins were erythropoietin, insulin-like growth factor, growth hormone, myostatin, vascular endothelial growth factor, fibroblast growth factor, endorphin and enkephalin, α actinin 3, peroxisome proliferator-activated receptor-delta (PPARδ) and cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C).

We discuss these proteins with respect to their potential benefits, existing gene therapy experience in humans, potential risks, and chances of detection in current and future anti-doping controls. We have identified PPARδ and PEPCK-C as having high potential for abuse. But we expect that for efficiency reasons, there will be a preference for inserting gene target combinations rather than single gene doping products. This will also further complicate detection.

Introduction

Gene therapist Ted Friedmann and multiple Olympic gold medallist Johann Olav Koss were the first to describe the possibility of misusing the techniques and experiences of gene therapy in the athletic arena.[1] In 2006, before the Turin Winter Olympic games, the president of the World Anti-Doping Agency (WADA),

Dick Pound, called gene doping 'the new threat that is now a reality'.[2] Although Pound did not expect gene doping to pose a problem in Turin, he indicated that it could be a problem at the Summer Games, 2 years hence in Beijing. In fact, the problem did not materialise in China, in 2008, nor at the London 2012 Olympics, as far as the then available detection measures could determine. Yet again, we have to operate on the assumption that there may be athletes out there willing to test gene doping at the 2016 Rio de Janeiro Olympics. After all, an Olympic gold medal means considerable social and economic benefit.[3-7] Historical doping control statistics show that somewhere between 1.1% and 2% of all athletes test positively for doping.[8] The real number of doping users is expected to be higher, despite the fact that the governing bodies of sport place immense pressure on athletes by a strict liability rule that makes them responsible for everything in their bodies.[9] Although the detection of doping is constantly improving, it generally trails actual practice.[4,9] In a 2006 review, Haisma and De Hon[10] stated that gene doping was likely to enter sports within 5 years. Given that gene therapy techniques have improved considerably, the likelihood of gene doping has increased ever since.[9-12]

Today, most gene therapy studies examine hereditary diseases and cancer.[13,14] Gendicine (Recombinant Human Ad-p53 Injection) and Glybera (alipogene tiparvovec) are the first approved gene therapy products for human use in the USA and the EU, respectively. Gendicine is designed to place a p53 gene in cancer cells to inhibit cell growth and the Glybera gene therapy has been approved for treatment of life-threatening pancreatitis attacks in patients with lipoprotein lipase deficiency.[15-17]

The proteins selected for this systematic review include those reviewed by Haisma and De Hon[10] in 2006. Additional proteins were included if determined to be likely candidates for misuse in (potential) gene doping because of their physiological effects and current status in anti-doping regulations, or the possibility of gene isolation and manipulation using techniques available in gene therapy. The final list of selected proteins are erythropoietin (EPO), insulin-like growth factor (IGF), growth hormone (GH), myostatin, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), endorphin and enkephalin, a actinin 3, peroxisome proliferator-activated receptor-d (PPARδ) and cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C). These proteins are thus most relevant for the following systematic review, but they are not an exhaustive list of all possible proteins with an impact on athletic performance.

First, gene therapy and the risks and the safety related to gene doping are discussed. Subsequently, the properties and targets of the aforementioned therapeutic proteins are reviewed, as well as their current preclinical status. Next, animal models, gene therapy and gene doping are considered. Each protein was scored for potential benefits to athletes, experience in gene therapy, controllability of the risks and the chance of using the protein without detection. The scoring results were used to consider the degree to which the technique and protein was likely to be misused in sports, now or in the near future. Finally, detection methods including direct and indirect, as well as animal use of gene doping are addressed.

Methods

A general literature search was conducted to identify the most relevant proteins based on their current gene doping potential using articles from Pubmed, Scopus and EMBASE published between 2006 and 2011. The final list of 11 proteins included those reviewed by Haisma and De Hon in 2006. A systematic review of the 11 proteins was then conducted 10 by using the search terms 'gene doping' OR 'gene therapy' AND (protein).

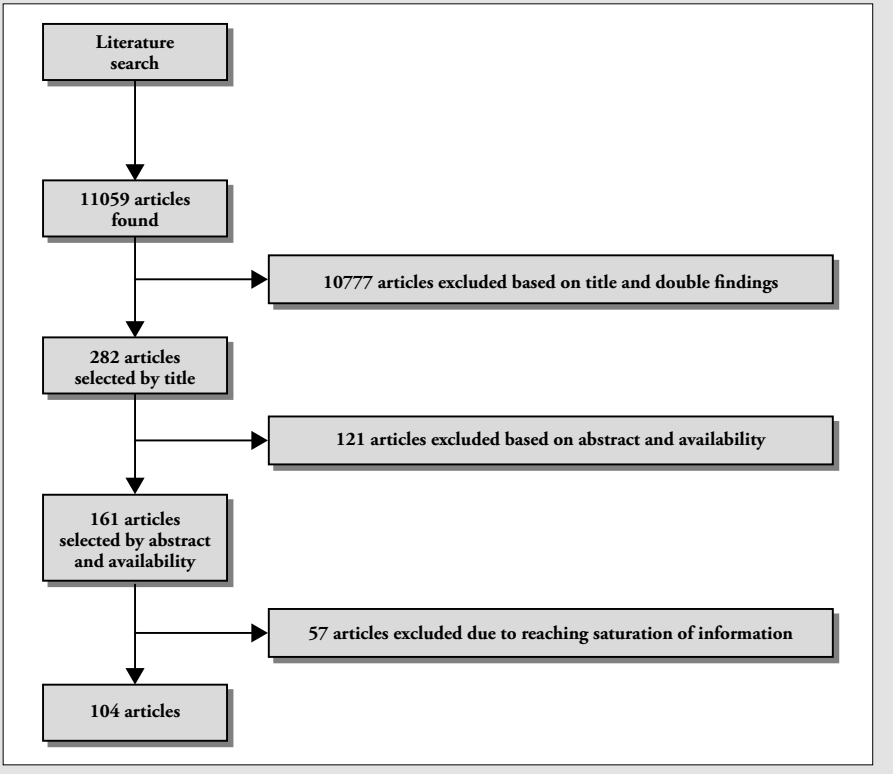
Exclusion criteria were:

- research before 2006;
- in vitro research;
- articles published in languages other than English.

Articles were judged by their title for relevance, that is, whether they concerned the appropriate protein and in adequate detail. If the title did not provide adequate certainty for inclusion, the abstract (if available) was judged. Articles describing the use of the protein in gene therapy or gene doping and review articles were preferred; although, primary research articles were also included in the sample. For each protein, articles were selected until a saturation point had been reached, that is, additionally identified articles offered no new information (see figure 1).

The search for eligible articles for the systematic review was completed on 31 December 2011 and included articles published from January 2006 through December 2011. Articles published before January 2006 were deemed to be included in a previous review and only those providing context that was critical to the analysis were added.[10] For each of the 11 identified proteins, an average of 10 articles were selected. As a supplement to the systematic search, a small number of important publications published before 2006 and after December 2011 were added.

Figure 1 This flow chart shows the overall selection process of the articles.



From gene therapy to gene doping

One of the most difficult steps in gene therapy is delivering the gene into host cells.[12] Three major techniques used for delivering genes are injecting naked DNA, viruses or modified cells.[3]

Direct injection of DNA into the target tissue

Initially, a desired gene can be produced in bacterial plasmids and then purified. Next, the gene can be directly injected into the target tissue. Unfortunately, direct injection of DNA is not very effective due to limited uptake and nuclear translocation (although electroporation of the target tissue increases the uptake.[18]) However, it is safer than using viral vectors, since there are generally fewer immune responses,[11,13,19] and considerably cheaper than other gene-transfer options.[20]

Introducing genetic material using a virus

Genetic material can be delivered to a target tissue by using a viral vector. Viruses have evolved to efficiently transfect cells with their genetic information and multiply, which makes them ideal for use in gene therapy. To prevent the virus from replicating, the viruses are tamed (all DNA or RNA coding for proteins allowing the virus to multiply and escape infected cells are removed) and therapeutic genes are inserted. Because of this inhibited replication, the viruses are less immunogenic.[9,12,14,19] The modified virus may be injected intravascularly or directly into a target tissue, or inhaled. Injection into the target tissue limits gene expression to the injection site, whereas intravascular injection usually results in systemic expression.[10,21] Inhalation is used if the lungs are the target tissue.[10,17,22] The viral vector contains a promoter that allows the inserted gene to be transcribed and translated, thus yielding the desired protein.[10]

Ex vivo gene therapy

For ex vivo gene therapy, stem cells are removed as in the case of patients with severe combined immune deficiency (SCID) and a therapeutic gene is introduced in vitro.[9,23,24] The genetically modified stem cells are then injected back into the patient's bone marrow. This can be done using plain DNA (with or without liposomes), a viral vector with electroporation or with a gene gun.[9,12] The technique allows for limited screening and sorting of the cells before reinjection, which increases efficacy and safety. Disadvantages are low efficiency and increased cost.[13,24]

Depending on the target tissue, the gene and the desired duration of transgene expression, multiple vectors can be used.[17,25,26] The most important properties are displayed in table 1.

Table 1 An overview of the properties of the most used viral vectors in gene therapy

Virus	Relative use(%)#	Package capacity (kb)	Tissues	Advantages	Disadvantages
Adenovirus	24	30 of dsDNA	Wide range	–No cell division required –Experience –No integration –Large capacity	–Short expression –Immunogenic when delivered systemically
Classic Retrovirus	20	8 of ssRNA	Wide range	–Experience	–Lack of specificity –Once caused leukaemia
Vaccinia virus	6	25 of dsDNA	Almost all cells	–Much experience –Antiviral agent exists –Well storable –No integration	–High immune response –Short effect
Adeno-associated virus (AAV)	5	4,5 of ssDNA	Neurons, muscle, brain, liver and haematopoietic cells	–Not pathogenic –Long effect –No cell division required –Almost no (<1%) integration	–Requires a helper virus to integrate –Lack of experience
Herpes simplex virus (HSV)	3	Up to 15 of dsDNA	Primary afferent neurons, epithelial and mucosal cells	–Can be present in a latent state –Low-immune response –No integration	–Can be present in a latent state –Neurotoxicity and cytohepathic problems
Lentivirus	2	8 of ssRNA	Macrophages, neurons	–Experience –No cell division required –Low-immune response	–Random integration –Errors in transcription
Plasmid vectors	19	10	Wide range	–Less immunogenic –Less oncogenic –No recombination with other viruses –Cheaper –No need to work with viruses	–Varying expression –Low efficacy

# The column ‘Relative use’ describes the use in gene therapy trials. Also see the Gene Therapy Clinical Trials Worldwide database.
ds = double stranded; ss = single stranded.
Adapted from the original table (all specific references have been removed).

Box 1 Risks of gene doping

Like all new medicines, gene therapy presents unsolved problems.[36] Until they are solved, large-scale use of gene therapy in the clinic is ruled out. Contrary to gene therapy and by implication of its illegal character, gene doping is not bound to safety regulations.[13] This box presents an overview of all risks involved with the application of gene doping in sports. Given the risks at this point, gene doping should be prohibited on safety grounds alone.[4,27,40]

Gene silencing

One limit to the effectiveness of gene therapy is gene silencing; thus, even when the target tissue is infected, it might not express the inserted gene.[22]

Immune reaction

Both the virus used and the protein itself can cause an immune reaction. How to handle this reaction appropriately is not completely clear.[9,13,14,32,76,86,98] The immune reaction against the protein can also induce a response against the endogenous protein, as happened with EPO in macaques resulting in anaemia.[9,10,19,36,54]

Integration

Though not all viruses integrate, those that do can present problems. Splitting up a tumour suppressor gene, or worse, increasing production of a proto-oncogene, can lead to cancer.[3,6,11,13,22,27,55] It is estimated that about one in every 10.000 retroviral insertions might be dangerous,[34] and one in every 10 could induce cancer.[9,20]

Infection of germ cells

The danger of the infection of germ cells with gene therapy also exists. This would transfer exogenous genes to future generations.[45] Though it is explicitly prohibited to target cells that reproduce,[10] and it is not likely gene therapy (which is not aimed at germ cells) would cause an infection of germ cells, this risk should be strictly monitored.[45]

Expression

Expression of gene therapy is hard to control, and overexpression could be dangerous. In addition to the effects of the protein itself, toxicity by accumulation is also dangerous.[6] Also, if a cell producing the desired product is infected by another virus, this could lead to overexpression of the protein.[12,30] Expression is controllable by an inducer drug (eg, doxycycline, which is approved for human use), but since this is detectable, it is less likely to be used for gene doping.[18,47]

Storage and usage

Gene therapy would require good storage and it is questionable whether those wishing to abuse it are knowledgeable about proper handling pro-

cedures.[41] Since professionals face difficulties with the non-linear dosage-expression relationship, it is likely those who have not been thoroughly educated could do worse.[13,41] Even more dangerous would be an attempt to produce gene doping in rogue laboratories, leading to unsafe products.[10,36]

Long term
Gene therapy is a new technology. Only short-term studies have been conducted, which means that the long-term effects are not yet clear.[85] There may still be problems with gene therapy products that simply have not been identified yet.[3,19,27,36,45]

It should be emphasised that the above-listed risks are only the foreseeable risks, as all the information was obtained in regulated and controlled settings.[13] The unknown risks present a much larger problem, because they are far more difficult to anticipate.[3]

Of the three gene therapy delivery methods described earlier, in vivo viral gene transfer is the most successful method for now.[12] In general, the benefits are efficacy and low cost; downsides are immune responses and poor controllability of integration and expression[19] (box 1).

Ex vivo viral gene transfer can be used to insert a gene to produce a desired protein, or increase or inhibit the transcription of an already present gene by influencing promoters. On the other hand, gene expression can also be prevented using antisense RNA sequences. RNA sequences bind to the original gene, prevent translation and cause destruction by the RNAse H or the siRNA pathway. Even splicing patterns can be altered by blocking splicing recognition sequences, thus allowing for the inclusion or exclusion of specific exons.[14,19,45]

Uses of gene therapy
Gene therapy can be used to treat a variety of illnesses. It may be applied to weaken or kill cancer cells by triggering apoptosis, to enable target cells to produce a protein that otherwise has to be administered or to upregulate the production of a specific protein.[3,31,34] Though a couple of gene therapy products have been marketed outside China to date, at least 1843 gene therapy trials have been conducted worldwide with thousands of patients suffering from cancer diseases, cardiovascular and neurological diseases and a range of other diseases.[10,15,19,34] Early clinical trials in Europe and the USA had limited results and even fatalities were reported from gene therapy;[9,46,47] however, examples of successful gene therapy include treatment

of SCID-X1 and Leber's congenital amaurosis.[17] The proof of concept of various transfer strategies in gene therapy shows that we are at least at the beginning of a gene therapy revolution for patients with monogenic diseases.[16,17,48]

Regulations

Regulatory oversight is stricter for gene therapy trials than for most clinical trials due to the potential risks.[35] Since the first documentation of fatalities during gene therapy, regulations have been tightened, primarily in Europe and the USA.[46,49] In the USA and Europe gene therapy is only allowed in cells that do not reproduce, preventing gene therapy from affecting following generations.[10]

Gene doping

When gene therapy is used to increase the performance of a healthy person, it is considered gene doping by WADA.[4,12] Gene doping presents the same advantages over regular doping as gene therapy does for regular medicine, but detection of gene doping is more difficult.[4,12] Since gene doping is a powerful tool to boost performances, it may have a significant impact on the professional sports world.[4,13]

Gene doping has been prohibited by the International Olympic Committee (IOC) since 2003. In 2004, WADA took responsibility for publishing the Olympic doping list, and they added gene doping.[4,10] The following new methods with the potential to enhance sport performance, are prohibited:

1. the transfer of nucleic acids or nucleic acid sequences;
2. the use of normal or genetically modified cells.[50]

Together with the performance-enhancing potential of gene doping, WADA uses two additional arguments for prohibiting gene doping. The first is the possible harm of gene doping for athletes. Second, is the violation of the value of fair play and the spirit of sport.[51]

As for gene therapy, every known gene can be used for gene doping. Currently, only about 500 genes in the human genome are used in existing drugs, thus a significant number of the remaining genes could bring new options for doping.[31] At least 100 genes are already linked to athletic performance and the number is increasing every year.[12,52] Although not all of these genes can be considered to be potential gene doping candidates, the increasing number of genes used in medications raises expectations for the potential advantages of gene doping.

The great benefits expected from gene doping make it likely that actual misuse is close at hand. As illustrated by the BALCO-affair, among other incidents, athletes are known to take more risks than average people.[53] BALCO was an American-based company that officially advised numerous world-class athletes on nutrition, but secretly instigated cooperation between chemists, trainers and athletes to purposely evade doping controls with new and undetectable doping substances. The fear is that athletes might not wait for gene therapy to be fully developed and tested before misusing it.[4,9,12,19,37,53]

Gene doping targets

Depending on the desired effect and the type of sport and athlete, gene doping might enhance performance. Athletes who compete in endurance sports, like marathons and long-distance swimming, may look to gene therapy to boost their oxygen supply or delay the sense of fatigue. Sprinters and weight lifters, who mainly need power, may consider gene therapy to increase muscle mass or improve their injury recovery time.[4,13,36] Boxers would appear to be most interested in improved pain tolerance from gene doping.[12]

Properties, targets and current status of protein drugs and gene doping

Erythropoietin

EPO increases oxygen supply to muscles, thereby increasing an athlete's endurance and performance.[10,13,36,54] EPO is a hormone with 165 amino acids produced mainly in the renal cortex and its production is quickly induced by hypoxia.[3,44,55-57] After being released, EPO binds to the EPO receptor stimulating erythropoiesis (the production of new erythrocytes),[40,41,54,58] which increases the number of haemoglobin carrying erythrocytes in the blood. Haemoglobin binds to oxygen with high affinity; although this affinity is reduced by heat or high carbon dioxide concentrations— conditions found in active muscle tissue.[54] Thus, EPO increases the oxygen supply for muscle tissue and muscles can work longer before they build up lactic acid.[56] The result is that maximal oxygen uptake in muscles is increased, which increases endurance.[59]

Recombinant human erythropoietin (rHuEPO) was introduced in 1988 as the protein drug epoetin-a in Europe (and in 1989 in the USA). It is used to treat anaemia caused by kidney disease, cancer or HIV, or for blood loss following surgery or trauma. Instead of giving a patient–donor blood to increase erythrocytes, the patient is injected with EPO to stimulate erythropoiesis.[5,44,54-56] Although

studies have shown the stimulation of steroidogenesis in Leydig cells by EPO leads to infertility over time,[44] EPO has also been found to have neuroprotective properties.[40-42,44]

The first documented illicit use of rHuEPO was in the 1989 Tour de France,[60] and more cases have since been documented.[61] Since EPO stimulates erythropoiesis, it increases the viscosity of the blood, thus raising the risk of microcirculation blockage, heart failure and strokes,[19] which makes overdosing and overexpression a risk.[3,9,19] EPO has been prohibited by the IOC since 1990 and is currently on the WADA prohibited list.[50,59,62]

Gene therapy with EPO was first tested in macaques in the late 1990s and was shown to double the number of red blood cells in 10 weeks, which increased aerobic capacity and performance. Unfortunately, EPO also made the macaques' blood rather viscous, although the macaques did not go into cardiac arrest and survived.[11,13,36] The macaques also had autoimmune reactions against EPO causing anaemia.[19,32] In a follow-up study, regulated gene expression allowed safe production of EPO for at least 6 years.[32] Furthermore, ex vivo gene therapy has been performed in mice causing expression of functional EPO.[24]

It has already been shown that EPO-screening of urine samples, as currently used in WADA doping controls, can identify EPO genetic therapy.[63,64] Since muscle tissue produces EPO with posttranslational modifications that differ from EPO produced by the kidneys, illegal use could be detected using isoelectric focussing (a technique using differences in pH-dependent electric charges).[63]

On the basis of the promising animal studies, Biomedica, a British company in Oxford, developed Repoxygen to be used in the treatment of cancer, diabetic neuropathy and Parkinson's disease. Repoxygen is a viral vector containing the EPO-gene and a hypoxia-response element used to treat anaemia. However, due to safety problems in in vivo testing—erythrocytosis, thrombosis and ischaemia and immune reactions—Repoxygen has not been clinically tested to date.[40-42] Despite the rather problematic safety profile of Repoxygen, a 2006 incident raised fear of abuse when a German track coach was accused of supplying Repoxygen to his athletes. However, the only evidence was email correspondence with a Dutch general practitioner about the issue.[79]

In conclusion, the potential benefits and experience with EPO gene doping are quite reasonable relative to other gene-doping candidates discussed below. Although in its infancy, given the availability of an EPO gene-therapy product, it is the most likely protein to be used for gene doping. However, the availability of a broad range of conventional EPO-products and the likelihood that the current

urine EPO-detection test would identify this type of gene doping rather easily speak against the use of EPO gene doping in the sport's arena.

Insulin-like Growth Factor

Although increased endurance offers major benefits for athletes like long-distance runners, EPO offers limited benefits for athletes for whom power is essential (eg, weight lifters). For this class of athletes, IGF may be more useful since it enhances muscle growth and performance. Medical researchers currently focus on developing methods to stimulate the endogenous production of IGF to prevent muscle loss due to a range of conditions such as degenerative muscle conditions, cancer, HIV or ageing.[5,36,65,66]

IGF-I is a polypeptide of 7.5 kDa, structurally related to insulin and produced as a result of hypothalamus-pituitary-liver axis activation. The hypothalamus produces growth-hormone-releasing hormone (GHRH), which stimulates the pituitary to release GH thus stimulating the liver to produce IGF-I.[44,65,67-70] IGF stimulates muscle repair and muscle mass hypertrophy after damage, for example, from overload or stress.[13,19,44,66] Increased expression of IGF leads to increased muscle power and mass making IGF a potential target for doping.[11,66,71,72]

The effects of IGF-I on muscle growth have not been tested on humans, but in IGF-I-deficient patients, insulin resistance, growth disorders and cardiovascular illnesses have all been documented.[73] Transgenic mice have been used to test the effects of IGF-I. They showed 20-50% larger muscle mass than regular mice and no age-induced muscle degradation.[36] The lifespan of these mice was decreased by 50%, possibly due to lower levels of antioxidative molecules, or cardiac hypertrophy.[73]

Although IGF-I is on the WADA prohibited list,[50] it is available on the internet[65] and anecdotal evidence proves IGF-I abuse.[74] The clear benefits of IGF—muscle growth and endurance—are desirable in many sports. The local effect of IGF allows for selective muscle growth; however, it is not expected to be one of the first targets for gene doping. The health risks of IGF gene doping, in particular, the possible clinical consequences of IGF-overexpression such as cancer and cardiac hypertrophy, are significant.[11,44]

Growth Hormone

Instead of applying IGF-based gene doping directly, it is possible to increase the production of IGF indirectly by aiming gene doping at the endogenous production of GH, that is, significantly more accessible.[74]

GH is mainly produced by the anterior pituitary gland.[75,76] The pulsatile regulation of the various GH isoforms differs in men and women and is controlled by the GHRH, which fluctuates with sleep, exercise, hypoglycaemia, age, gender, amino acid availability and low levels of IGF-I.[44,70,74,75] The effects of GH are regulated by GH-binding proteins.[70]

Since GH increases muscle strength,[75] it could be used to increase athletic performances in sports where strength is important.[23,75] In endurance sports when energy is scarce, GH promotes the use of lipids as fuel to conserve protein storage.[74,76]

Despite a 1989 ban by the IOC on GH, there is evidence of GH being used as doping.[19,51,67,74,75,77] A recent survey of 10th-grade boys in the USA showed that 5% had taken GH and 1.2% of college athletes admitted to have used GH in the last year.[74 77] GH-gene therapy tests in mice, rabbits, sheep and pigs have been performed with varying results.[70,78,79] In GH-deficient mice, a 48% growth in the injected quadriceps was found after 60 days.[79] The main concerns for GH use are the lack of control in expression and disruption of functional genes.[70,78] No results of gene therapy with GH in humans have been published to date. Since the results of animal studies are far from convincing and the effects of GH are less targeted than IGF and other proteins, GH is not likely to be used as a target for gene doping.[74]

Myostatin

In 2004, a German boy born with muscular thighs and strong upper arms was diagnosed with a myostatin gene deficiency. As a result, the anti-doping community's attention was then directed towards the effects of myostatin blocking.[5,13,80,81] In cows, a myostatin mutation leads to downregulation of myostatin, which increases muscle growth. 'Double muscled cattle' or 'Belgian Blue cattle' present with significantly more muscle mass than ordinary cattle.[12,36] These two examples made it clear that myostatin inhibition is yet another way to increase muscle mass, but it is more specific than the use of IGF or GH. As such, myostatin inhibitors are of interest to athletes who need muscles rather than speed; however, myostatin inhibitors are on the WADA-prohibited list.[5,50,81] Despite the risks of inhibiting myostatin, which include reduced cardiac and respiratory functioning, the inhibitors can be purchased on the internet.[81,82]

It is thought that myostatin is involved in sarcopenia (age-related muscle loss), although how this occurs exactly is unclear. Some tests have found increased myostatin protein and mRNA expression in aged human and rats; others find no difference.[83] Myostatin is overexpressed in muscle atrophy when there is

immobilisation, HIV infection, sepsis, burn or glucocorticoid excess, or specific skeletal muscle degeneration diseases.[83-85] These findings may lead to a new treatment for muscle atrophy using gene therapy to inhibit myostatin.[85,86] Myostatin is underexpressed in Duchenne and Becker muscular dystrophy, probably as an adaptive response to increased muscle growth.[83,84] Myostatin overexpression can induce cachexia and increased levels are associated with obesity and diabetes.[80,84]

Since the actions of myostatin inhibit muscle growth, blocking myostatin is a potential doping target.[84,87] Various in vivo methods of inhibiting myostatin are available, such as:

- using the myostatin propeptide, which binds to myostatin to prevent it from having an effect.[85,87,88] Although wildtype myostatin propeptide is unstable in vivo, it can be altered to extend stability;[84]
- using neutralising antibodies.[44,75,81,82,84,85,87,88] Research in mice showed less sarcopenia-related muscle loss when antibodies were injected;[89]
- applying follistatin in animal gene therapy studies to inhibit myostatin.[13,37,84-86] Follistatin is a glycoprotein that binds to myostatin preventing myostatin from binding to its receptor;[80]
- stimulating overexpression of a gene coding for a myostatin protein without its cleavage site to inhibit the production of myostatin.[81,90]

Gene therapy to inhibit myostatin is usually based on the adeno-associated virus (AAV) vector technology, since muscle cells are one of the natural hosts for AAVs.[85,86] There is long experience with all above-presented forms of myostatin gene therapy (except for antibodies) in animals; no clinical tests have been performed on humans.[80,82,84,86-88,91,92] Athletes might be tempted to use a myostatin-inhibiting form of gene doping. The effects of myostatin are significant, but the lack of experience and the poor controllability of the various methods of myostatin blocking make it hard to say whether it is already being misused.

Vascular Endothelial Growth Factor

Increasing blood flow through a muscle postpones fatigue. One protein regulating muscle blood flow is VEGF or VEGF-A,[93,94] also known as the vascular permeability factor.[95] Autocrine VEGF released by endothelial cells, regulates vessel homeostasis by acting as a survival factor for endothelial cells. Paracrine VEGF produced by any hypoxic cell stimulates vessel branching.[5,23,44,95-98] New capillary branches need additional hormones to become fully grown stable vessels.[98] When VEGF reaches

high levels in blood vessels, the blood vessel responds with increased permeability and vasodilation.[94,99] Since VEGF increases neovascularisation of ischaemic tissue, it might help patients with heart diseases. On the other hand, high dosages of VEGF can cause vessel leakage and abnormalities as well as tumour tissue growth.[95,97,100]

Gene therapy targeting VEGF-mediated angiogenesis has been tested in mice, rats, rabbits and dogs with generally positive results.[38,94,96] In a 10-year follow-up study on humans, VEGF gene therapy was found to be safe;[93,100] therefore, VEGF might be of interest to athletes combating exhaustion. Since VEGF increases blood perfusion in muscles, heart, liver and lungs, it is likely to increase endurance.[3,23,38,44] However, the risks of VEGF use mentioned above remain unmeasured and uncontrolled.[97,101] Controlling gene expression by adding a hypoxia-response element, for example, EPO, might make VEGF safer.[97] VEGF is a likely candidate for gene doping;[10] however, an immune response against VEGF has been detected using affinity-based biosensors and this is likely to make detection possible soon.[23] VEGF is on the WADA-prohibited list.[50]

Fibroblast Growth Factor

VEGF production is also modulated by a specific FGF2. FGF2 works partially in a synergistic manner with VEGF, producing some of the same intracellular effects. VEGF induces FGF2, which vice versa can induce VEGF expression. Inhibition of either VEGF or FGF2 shuts down angiogenesis.[102]

FGFs have multiple functions, some of which could be used in doping and these are discussed here. The family of FGFs includes 22 growth factors, produced by a variety of cell types.[99,102-106] The angiogenic effects of FGFs play an important role in muscle repair following exercise through the revascularisation process during muscle regeneration.[103] The modern clinical application of the principle of angiogenesis can be divided into two main areas: antiangiogenic therapies and proangiogenic therapies. Whereas antiangiogenic therapies are being employed to fight cancer and malignancies, which require an abundance of oxygen and nutrients to proliferate, proangiogenic therapies are being explored as options to treat cardiovascular diseases. One of the first applications of proangiogenic methods in humans was the use of FGF-1 for the treatment of coronary artery disease.[102,105] Clinical research in therapeutic angiogenesis is ongoing for a variety of atherosclerotic diseases, like coronary heart disease, peripheral arterial disease or wound healing disorders.[99,102,105] The risks of exogenous FGF include the possibility of increasing blood supply for tumours, or stimulating pathogenic heart remodelling.[105]

Adenovirus vectors and plasmids containing genes for FGF2 and FGF6 have been tested in human skeletal muscles and significantly increased muscle repair.[103] Phase II studies showed proteinuria as an effect of abnormal capillary network formation.[107] Most studies combine FGF gene therapy with IGF, PDGF or VEGF.[69,99,104,107-109] The synergistic effects of FGF with those proteins have been shown, but FGF alone has not been proven to be clinically effective.[105,109]

Most interesting for athletes is that FGFs increase muscle regeneration and neovascularisation. A combination of FGFs is most promising, especially for athletes recovering from injury and exercise.[103] It is most likely that the first use of FGF-based gene doping will be in combination with another protein. All FGFs and FGF-based gene doping are prohibited by WADA.[50]

Endorphin and enkephalin

A completely disparate approach for improving athletic achievements is diminishing the sensation of pain. This would specifically allow combat-sport competitors to achieve higher goals. For athletes in general, numbing the sensation of extreme exhaustion is beneficial; thus, analgesics are the most frequently used therapeutic class of drugs.[10,44,51] Most analgesics are permitted by WADA, but opiates are prohibited as they have addictive properties that can lead to abuse.

Chronic pain affects a large part of the general population and gene therapy with an endorphin or enkephalin may present a promising new approach for treatment.[29,35,101,110] Endorphins and enkephalins delay fatigue and increase endurance.[13] During exercise they diminish lactic acid-related pain and pain caused by earlier injuries.[13,51] Multiple gene therapy studies aimed at combating pain have been conducted, generally with positive results.[29] Gene therapy allows for local and specific treatment of pain, with few side effects and a low risk for abuse.[35] Since herpes simplex virus (HSV) targets neurons specifically, this is the virus generally used for gene therapy for pain.[110] Clinical trials using endorphin and enkephalin in HSV vectors are being performed in humans, but so far are restricted to cancer-induced pain.[51,110,111]

The pain-reducing effects of both endorphin and encephalin seem useful for athletes and early tests in humans are in progress. Given the fact that the brain is targeted, it may be difficult to detect endorphin or enkephalin gene doping in only blood or urine. It should be clear though, even for those without a biomedical education, that experimental medicines acting only on a partially understood brain system, pose a serious risk. Given the ambiguous doping qualities of endorphins and enkephalins it is rather unlikely that they are being used today for this purpose.

α actinin 3

In 2003, the association between athletic performance and α actinin 3 (ACTN3) genotype (instead of ACTN2) was demonstrated. 5 ACTN3 is mainly produced by skeletal muscle,[112] while actin and myosin are responsible for muscle contraction.[51] ACTN3 binds sarcomeres at the Z-lines. Although it was long thought that ACNT3 was only important for muscle structure, it is now clear that it is also important for muscle metabolism.[112] ACTN3 deficiency does not cause muscle disease, but rather it impairs power performance by shifting the characteristics of fast-type muscles to slow-type muscles.[112] When there is a deficiency of ACTN3, part of the action of ACTN3 is taken over by ACTN2.[36,51,112] ACTN3 expression increases strength (although androgens have a stronger effect than ACTN3113), while ACTN2 expression increases endurance.[51,113] No exogenous forms of ACTN3 or substances that influence ACTN3 transcription are known.

Sixteen per cent of humans worldwide have a polymorphism in both their ACTN3 genes that causes a deficiency, and in European and Asian populations this can be up to 50%.[112,113] It has been shown that female sprinters have a higher frequency of a functioning ACTN3 gene than the average population.[36] Since lacking the gene does not cause disease, it is not a lucrative topic of research. No trial with an ACTN3 gene therapy product has been published, although there are a few animal studies on knock-out mice. Mice missing the ACTN3 gene weigh less than wild-type mice and have smaller muscles and less strength. On the other hand, they were able to run 33% longer than wild-type mice and recovered faster from fatigue.[112,113] If translated to the sports arena, this indicates that increasing ACTN3 copies may be used in order to dope sprinters and diminishing ACTN3 copies as a means to stimulate endurance in marathon runners.[51] Although both the risk of abuse and the chance of being caught would be small, no gene therapy products for ACTN3 have been tested, not even in animals. This means that currently ACTN3 is an unlikely candidate for gene doping purposes.

Peroxisome Proliferator-Activated Receptor-δ

Another genetic predisposition for achievement in the elite sporting world is the gene coding for PPARδ. PPARδ—also known as PPARβ or NR1C2—is a protein for regulating the oxidation of fatty acids.[114-116] PPARδ also increases mitochondrial activity and muscular glucose uptake.[113] Overexpression of PPARδ decreases the accumulation of triglycerides in muscle cells and increases the oxidative capacity in muscle fibres.[114,117] This results in increased endurance and an enhanced response to endurance exercise.[13,19,113,115,117] Both endurance and power training strongly increase

the production of PPARδ.[115,118-121] Elite athletes have more PPARδ mRNA and protein than the general population.[19,51]

PPARδ agonists could be used for doping purposes and products claiming to boost performance with PPARδ are already for sale on the internet.[115] MBX-8025, GW742 and GW1516 (also known as GW501516) are ligands for PPARδ. They are being used in studies with patients who are obese or have diabetes mellitus type II or atherosclerosis.[23,114,117] GW1516 reduced the low-density lipoprotein and triglyceride plasma concentration, and increased fatty acid oxidation.[114] GW1516 has passed phases II and IV clinical trials for dyslipidaemia [122] and is detectable with mass spectrometry up to 4 days after intake.[122] Although GW1516 may be abused, the abuse might not go unpunished. Anticipating possible abuse, the WADA put PPARδ agonist GW1516 and PPARδ -AMP-activated protein kinase on the doping list in 2009.[13,50,122] PPARδ could also be targeted with gene therapy. PPARδ has been delivered to various cell types using an adenoviral vector; however, effectiveness differed according to cell type.[116] Gene doping using PPARδ is unlikely to be used soon, since it has only been tested in cells and not in vivo.

Cytosolic phosphoenolpyruvate carboxykinase

An even stronger effect on endurance than PPARδ is found with PEPCK-C. In one particular study, wild-type mice were exhausted after running 0.2 km and the transgenic mice overexpressing PPARδ after 1.5 km; but the transgenic mice overexpressing PEPCK-C ran for more than 4.9 km.[9]

PEPCK-C regulates glyconeogenesis in the liver and kidney, and glyceroneogenesis in the liver and adipose tissue.[9,123] Overexpression of PEPCK-C leads to hyperglycaemia.[124] On a normal diet, PEPCK-C overexpression induces insulin sensitivity; on a fat-rich diet it causes insulin resistance.[125] Despite all the evidence of PEPCK-C's importance in gluconeogenesis, (and, thus, diabetes), no gene therapy product targeting this protein has been investigated.[123] However, silencing vectors and decreasing PEPCK-C levels did prove to be effective in diabetic animals.[123] Its role in skeletal muscles is not clear yet, but it is hypothesised that an increase in triglycerides leads to improved athletic performance.[9,13]

There are two forms of PEPCK-C: one functions in the mitochondria and one in cytosol.[9] The PEPCK-C in cytosol is the most relevant for athletes, since the effects in trials with mice demonstrated convincing benefits for endurance.[9] No specific PEPCK-C stimulating agent is yet known.[50] Thiazolidinediones and glucocorticosteroids stimulate PEPCK-C production, but not specifically.[126] Glucocorticosteroids are on the WADA-prohibited list; however, to date, no gene

therapy product aimed at PEPCK-C specifically is known.[50] Since the expression of the PEPCK-C gene would be tissue-specific, detection would be nearly impossible;[9] thus, in addition to the significant effect of PEPCK-C, despite the lack of experience, PEPCK-C is a likely doping target (table 2).

Detection

Detection of gene doping is significantly more difficult than detection of doping with pharmaceuticals. This might make gene doping more attractive for athletes considering cheating.[23,44,127,128] Currently, no specific test to detect gene doping has been approved by the WADA or used by a WADA-accredited laboratory.[5,10,23,129,130]

Any detection method would have to comply with at least the following requirements. First, the doping detection method must be adequately selective to detect cheating athletes. Second, it should be accessible and easy to use on a large scale, while remaining reliable. Finally, it should be fast, as convicting an athlete years after the crime is not desirable (although legally possible up to 8 years after a doping violation has occurred).[13,128]

As stated earlier, athletes who engage in doping generally use pharmaceuticals to improve their performances, so the first gene dopers are likely to have had early access to gene therapy products. Detection efforts to identify gene doping by athletes should initially explore the current uses of known gene therapy for disease treatment.[12] Some detection methods might also help to determine the efficacy of gene therapy for disease while in development.[128]

Generally, detection methods can be divided into two groups: direct and indirect. Direct methods test for an illegal substance, or the genetic material or virus that delivered it. Indirect methods use the effect, immune response, differences in expression or metabolic changes for detection.[12,13,44] The direct detection of an illegal substance is preferred over indirect testing for legal reasons, but unfortunately, illegal substances are metabolised or cleared too quickly to be detected, in general.[12,23,75]

Table 2 This table summarises the likelihood of each protein being used for gene doping in a scale ranging from ++ (very high) to −− (very low)

Protein	Potential benefits	Experience in gene therapy	Risk control	Chance of undetected use	Likelihood of abuse
EPO	++	+	±	−−	++
IGF	++	−	−	±	−
GH	±	−	−	−	−
Myostatin inhibition	+	±	±	±	±
VEGF	+	++	−	−	++
FGFs	±	±	±	±	±
Endorphin & enkephalin	+	±	−−	++	−
ACTN3	+	−−	+	++	−−
PPARδ	++	−	+	±	+
PEPCK-C	++	−−	±	++	+

For each protein, the average of the possible methods is considered (ie, the multiple options for inhibiting myostatin taken on average, just like the various FGF's). If it is useful for athletes to abuse a protein, then it is marked in the first column as potential benefits. The experience in gene therapy-column has marks concerning the experience of gene therapy in humans. When fully developed, some proteins remain more dangerous than others and this is noted in the third column, risk control. The chances of getting away with the illegitimate use of a gene-doping product with a specific protein are given in the column chance of undetected use. The last column indicates the likelihood of present abuse.

ACTN3, α-actinin 3; EPO, erythropoietin; GH, growth hormone; IGF, insulin-like growth factor; FGF, fibroblast growth factor; PEPCK-C, cytosolic phosphoenolpyruvate carboxykinase; PPARδ, proliferator-activated receptor-δ; VEGF, vascular endothelial growth factor.

Direct Methods

Plasma levels

Measuring the plasma levels of a protein would not be an accurate method for detecting gene doping. Some endogenous mechanisms to control expression prevent high plasma levels and the plasma levels of some proteins are too low to detect.[19] Also fluctuation in physiological levels of a protein complicates this

method. Measuring various isoforms of a protein would be helpful. When an exogenous protein inhibits production of the endogenous variant, a difference in the isoform ratio would be detected; thus, detection would be possible for gene doping strategies targeting EPO and GH.[75]

Biopsy

A biopsy of an infected area would provide a sample in which the virus or the exogenous gene might be detectable in an athlete. Gene transfer has been shown to be detectable in a biopsy for up to a decade.[48] Since knowledge about the injection site is required, and biopsies are generally considered to be too invasive, methods using only blood, urine, serum, hair, saliva or a combination are needed.[6,23,36,75,128,130]

Virus

The presence of a virus might be detectable in the bloodstream, so blood samples could be tested with PCR to detect DNA or RNA or with other methods to test for viral proteins.[12,23,30] The difficulty with this technique is timing; the persistence of viruses varies from hours to months.[23,44] Testing for a virus in urine (persistence over several weeks) or saliva (persistence over several days) might be better.[23] The downside of this approach is a possible false positive, for example, an athlete who is infected with a normal virus.[12,36,75]

Introns

The genetic material commonly used in gene doping is complementary DNA (cDNA), which lacks introns; therefore, it can be discriminated from genomic DNA with PCR.[12,37,44,127,129] In mice injected intramuscularly with AAV-mediated gene therapy, PCR allowed detection in the blood for several weeks,[37] though in another test it was undetectable in blood after half an hour.[130] However, PCR is less useful for detecting doping using genes with introns because it presents problems with alternative splicing and efficacy.[12,127] In addition, it is conceivable that once a PCR detection method is introduced, gene-doping products based on genomic DNA will become available quite soon.

Post-translational modification

Since each cell type differs in post-translational modification, endogenous proteins would be distinguishable from the ones produced by gene doping. This is what caused the autoimmune reaction against EPO in macaques, resulting in anaemia.[19,32] Detection would be possible with isoelectric focussing.[6,10,12,19,23,44] The

method is useful until viruses target cells more specifically, or specific promoter regions are developed. However, it is possible that these target cells or promoter regions might also be detectable in the future.[12,23]

Barcoding
Genetically modified agricultural products have a genetic barcode, to help with identification. This could be done for gene therapy too, which would make the gene therapy products detectable with PCR. This approach requires global coordination in the pharmaceutical industry, which in the past has been proven to be difficult to achieve, and is likely to become practically irrelevant once gene-doping products are produced without barcodes.[6,12,51,129] Creating barcodes for identification could stimulate rogue laboratory production practices that eliminate barcodes.

Indirect methods

Immune reaction
Every virus induces a specific immune response in the host.[6,12,23,44] Plasmid vectors or the produced proteins can induce immune responses that can be detected and distinguished from common immune responses.[23] However, distinguishing common virus reactions from immune reactions remains a problematic issue.

Proteomic changes
Use of gene doping will probably change the transcription of other proteins as well. By tracking selected protein levels and gene transcription rates in a biomedical passport, dopers can be caught.[4,6,12,13,19,44,51,54,129] One risk of this method is the chance of a false positive or false negative, since changes in training or injuries can also induce changes in metabolism. Most research on possible detection methods of gene doping uses this approach, also because this approach is potentially quite useful to determine the efficacy of gene therapy trials; but the validity is as yet unproven.[37,47,54]

In conclusion, gene-doping detection is difficult, but with new techniques it might eventually be possible.[10,12,23,47] False positives are a nightmare to every anti-doping professional, so it is important to validate detection methods before applying them. It is likely that once a test has been developed, it will not be made public until it can be used for anti-doping, just as previously done for detecting hydroxyethyl starch or homologous blood transfusions among other prohibited substances in sport.

Animal use of gene doping

Since gene doping can increase performance, it is likely to be used in animal competitions as well. If money can be earned by betting or trading with superior animals, gene doping would be lucrative. If the achievements of horses, dogs, camels or pigeons could be improved, then it is quite possible that gene doping will be tried on these animals before human applications.

Conclusion

Before each post-2000 Olympic Game, the media have predicted gene doping. So far, all predictions have been proven wrong, based on the information that is currently available. Even though gene doping can be done with the lab skills of an undergraduate student, this does not mean that it is actually being applied in athletics. In addition, most currently available gene-therapy products still show a rather low efficiency of gene transfer and have side effects, some of which can be quite serious.[7] Thus, the question remains: is it likely gene doping is already being used and will be used at the 2016 Rio de Janeiro Olympics?

This is still a realistic option, despite all the efforts of anti-doping professionals. All proteins reviewed in this survey have the potential of performance-enhancing effects in sports and can be targeted with gene therapy. Some have already been tested in gene-therapy animal experiments and in clinical trials, like EPO and VEGF. These proteins are potentially the most likely candidates to be misused, but they are also the ones with the highest risk of detection and the ones that can be applied more cost-effectively by conventional means. Other proteins have only recently been selected for gene therapy research purposes. We have identified PPARδ and PEPCK-C as having high potential for abuse. But we expect that for efficiency reasons, there will be a preference for inserting gene target combinations rather than single gene doping products. This will also further complicate detection (table 3).

However, it is still fair to say that there is no clear proof that gene doping is already practised in major sporting competitions. Given the current niche status of gene therapy, it is not realistic to estimate the time period when gene doping will enter athletics. The interest is obviously there, and historically it is known that the determined cheat will try almost anything to boost their performance, regardless of the risks involved. Although gene doping is still largely theoretical, its implications for sports, health and ethics are significant and require further study.

Table 3 Classification of each reviewed protein as either functional for improving endurance, strength or pain tolerance

Aimed enhancement	Target gene
Endurance	EPO, IGF-I, GH, VEGF, FGF1, FGF2, FGF4, ACTN2, PPARδ, PEPCK-C, IGF-I
Strength	FGF6, FGF2, IGF-I, GH, myostatin, ACTN3
Pain tolerance	Endorphin, enkephalin

ACTN3, α-actinin 3; EPO, erythropoietin; GH, growth hormone; IGF, insulin-like growth factor; FGF, fibroblast growth factor; PEPCK-C, cytosolic phosphoenolpyruvate carboxykinase; PPARδ, proliferator-activated receptor-δ; VEGF, vascular endothelial growth factor.

Further reading

Gene Therapy Clinical Trials Worldwide–The Journal of Gene Medicine Clinical Trial site. www.abedia.com/wiley/index.html.

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Extended discussion on case 3 (gene doping)

During the past five summer Olympic Games the press has been describing the Games as 'possibly being the last Games without the issue of gene doping entering the athletic arena'. So far, this prediction has not come true, or at least there has been no proof for that, even though detection strategies currently do exist (Lasne et al. 2004, Beiter et al. 2011).

The case of gene doping illustrates that anti-doping can be fully transparent when discussing potential problems. When gene therapy pioneer Theodore Friedmann and multiple Olympic gold medallist Johann Olav Koss wrote their article on the 'impending' problem of 'gene transfer and athletics' this potential problem was only known to a very small group of gene therapy experts (Friedmann & Koss 2001). The IOC left all honours to newly founded WADA to convene a conference on this issue, and ever since discussions on the potential to apply this doping method, its unknown health risks, and the absence of any possible detection method have been held in the public domain (Sweeney 2004, Haisma & De Hon 2006, Schneider & Friedmann 2006, Baoutina et al. 2007, Azzazy et al. 2009, Friedmann et al. 2010, Møller et al. 2015). This is in stark contrast with the way in which the 'new doping drug of the 1990s', erythropoietin, was researched and handled at that time. With a much higher need for a direct detection method, as anecdotes of its use became more and more prevalent, ADOs avant la lettre struggled with the best way to tackle the new doping substance. Even though the principle of a direct detection method was published in 1995 (Wide et al. 1995), various IFs chose to lay their emphases on introducing maximum levels in certain haematological parameters. This indirect approach had two consequences: a dispensation procedure had to be put in place for those athletes who appeared to have naturally high levels of these parameters, and the use of erythropoietin was effectively allowed up to the agreed physiological limits (Videman et al. 2000, Hardie et al. 2012, Sorgdrager et al. 2013). The big advantage was that extreme values, including extremely dangerous values, did not occur anymore. As a temporary measure this approach was understandable, but in retrospect it steered away from a direct detection method, which was eventually implemented in the early 2000s (Lasne & De Ceaurriz 2000, Lasne et al. 2002). It also led to partially allowing doping use to happen, and this is highly likely to be one of the causes of the rife use of doping in the world of cycling for several years (Millar 2011, Hamilton & Coyle 2012, Hardie et al. 2012, USADA 2012, Sorgdrager et al. 2013, Aubel & Ohl 2014). Perhaps a more transparent approach towards erythropoietin and its detection would have led to a different path. Similar

dilemmas can be expected in the future, for example with the (already prohibited) Peroxisome Proliferator Activated Receptor δ-agonists or the (not prohibited) method of transcranial direct current stimulation.

Case 3 shows that a coordinated research effort can effect in practical outcomes, which is both laudable and up to a certain degree also reassuring. The transparent way in which this potential doping problem was discussed right from the moment it was identified has greatly helped to allow progress at the educational and detection levels. It is also reassuring that the lessons from erythropoietin, but also from blood doping, growth hormone, and insulin (where the prohibition preceded analytical possibilities by many years) seem to be taken at heart, in the sense that policy makers transparently chose for a time lag between the emergence of a new way of doping, the prohibition of this act, and the slowly developing efforts in trying to find a detection method (although it should be acknowledged that in the case of gene doping there was the luxury of no clear practical cases undermining anti-doping policies, with currently in 2016 still no proof of actual gene doping applications). With new doping substances and/or methods, chances are that new scientific barriers need to be taken. This costs time and money. In addition, detection strategies are never really 'ready' as analysts will continuously try to lengthen the detection period and improve the detection rate.

2.4.4 Discussion on the effectiveness of doping substances and methods

These three cases, described in four previous publications and discussed anew in the light of today, show the difficulties in assessing the performance enhancing properties of pharmacological substances. Regarding mind sports there are only very few studies available that look at the impact of certain substances on performance, making it necessary to extrapolate existing scientific knowledge into the world of sports. Locally administered glucocorticoids are not likely to have any impact on performance-related physiology, but the same substances can be used systemically and are being abused by athletes to gain an advantage. The same holds true for beta2-agonists, although the actual abuse of these substances seems to be less common. Yet, these pharmacological characteristics caused their presence on the prohibited list, which means that the rule makers have been looking for ways to prohibit (and detect) the routes of administration that can be expected to be performance enhancing and to distinguish these from those routes that are less relevant from a performance enhancement point of view. It has been proven to be

unavoidable that athletes who legitimately need these medications are forced to perform various administrative duties. Finally, gene doping is an example where profound performance enhancing characteristics can be expected but there does not seem to be a practical problem (yet).

These examples show the dilemmas of policy makers when deciding on the contents of the prohibited list. Many aspects need to be taken into account in this process and since it is a global list they are bound to disappoint many people. The most recent example in this regard is the meldonium-saga. At the time of writing this thesis it seems fair to conclude that WADA has been too eager to place this substance on the prohibited list (WADA 2016). This is highly remarkable as WADA has been very reluctant to place other substances on the list in recent years, such as nicotine or thyroid hormones. These two substances possess properties that are likely to improve sport performances. Nicotine through its cholinergic action and resulting improved cognitive performance (Marclay et al. 2011), which is beneficial for all sports that exist. Thyroid hormones speed up an individual's metabolism and as such stimulate weight loss (Roti et al. 1993), which can be deemed performance enhancing in all sports that include weight-bearing activities. Both substances elicit health risks (Roti et al. 1993, Marclay et al. 2011), and both substances are being (ab)used in sport (Parkinson & Evans 2006, Marclay et al. 2011). Hence, it seems rather simple to decide that these substances fulfil all three criteria mentioned in the WADC to add them to the prohibited list. Yet, WADA has decided not to do this, showing a relatively recent reluctance to add substances on the list. Unfortunately, the exact reasons for this decision are unknown as WADA very seldom explains the backgrounds of their decisions regarding the prohibited list.

Regarding the decision whether a substance or a method is performance enhancing or not, it is important to stress that established scientific methods to evaluate the effects of a substance will never be able to give 100% clear answers. This might be true for all scientific efforts but it is especially true in anti-doping related matters because of various intrinsic characteristics of doping research. Firstly, most doping substances are medicines, and medicines are developed to cure sick people. When healthy people seek a specific pharmacological effect for themselves, they most often need to substantially increase the dose of the substance involved. Such high dosages are unethical to give to subjects in a scientific experiment, and as such it is practically impossible to conduct studies with high methodological quality into

real-life conditions. Secondly, it can be expected that the physiology of elite athletes is unique. As such, it is important to study the effects of substances in people with such extraordinary physiological conditions: in the elite athletes themselves. But it is prohibited to administer doping substances to elite athletes in periods when they are actively competing in sport; this would create an uneven playing field, which is exactly what anti-doping regulations try to avoid. This is an archetypical vicious circle: in order to determine whether a certain substance should be prohibited, it needs to be administered in a group of people where it cannot be administered because it is prohibited. So far, it has never happened that a sufficient amount of truly elite athletes withdraw themselves from competition in order to volunteer for research into performance enhancing effects, for obvious reasons (Djerassi 2008). This status quo means that the decision whether something is actually performance enhancing needs to be taken on the basis of scientific results gathered under sub-optimal conditions, and on any practical experiences that are publicly known. These pieces of information can be sufficient to guide policy-related decisions, but it should be acknowledged that the scientific body of knowledge on athletic performance enhancement is difficult to overestimate.

This situation has led to a discussion whether erythropoietin and blood doping can actually be considered performance enhancing in endurance events. Despite many reviews that explain the physiological likelihood of this effect (Fisher 2003, Jelkmann 2009, Rasmussen et al. 2010, Jelkmann & Lundby 2011, Lundby & Olsen 2011, Schumacher et al. 2012), and practical experiences that it can be considered a game-changing doping method (Hamilton & Coyle 2012, USADA 2012, Sorgdrager et al. 2013), some scientists argue that scientific evidence for the performance enhancing properties of erythropoietin and blood doping in elite athletes is lacking (Lodewijkx & Brouwer 2011, Heuberger et al. 2012, Hardeman et al. 2014). However, this seems to be an extraordinary opinion outside the general consensus of scientific literature. Generally speaking a performance enhancement of 6-10% can be expected because of haematological doping given the effects of several existing pharmacological substances (Heuberger et al. 2012, Van Breda et al. 2014). Anabolic steroids can be expected to give even more gains for strength-related athletic achievements (Hartgens & Kuipers 2004, Sjoqvist et al. 2008, Heuberger et al. 2012, Van Breda et al. 2014). This aspect of doping is often neglected when critics of current anti-doping regulations state their case (Kayser et al. 2007, Miah 2007, Hunt et al. 2012).

The degree in which substances can be expected to improve athletic performances is important. After all, if this property would not exist, it would leave all discussions on possible prohibitions in the realm of health risks and the 'spirit of sport' (and as I will argue in paragraph 3.4 it would be questionable if anti-doping policies would be necessary in the first place if no performance enhancement can be expected). It is noteworthy to see that two reviews focussing on the effect of placebos find a possible performance enhancement of 1-5% in sport and exercise (Beedie & Foad 2009, Berdi et al. 2011). Strictly speaking, one could argue that substances and methods that elicit less effect than a placebo treatment are irrelevant to prohibit – if sugar water would do the trick, why resorting to medicinal products with many more potential side effects? There are many substances on the current prohibited list that are unlikely to fulfil this criterion, but the paucity of scientific data on potential performance enhancement on most substances make this an impossible criterion, at this moment.

From a principal point of view, it is important to acknowledge that science does progress, and as such viewpoints may change. And the prohibited list may change accordingly. Caffeine, for example is a rare example of a substance that has been taken of the prohibited list (Van Thuyne & Delbeke 2006, Del Coso et al. 2011). When WADA took over the responsibility to publish the global prohibited list from the IOC in 2003, the working group concluded that caffeine "is capable of enhancing performance at low levels of ingestion, urinary levels of caffeine concentration are an unreliable indicator of caffeine dose, it is not possible to distinguish casual, normal use of caffeine from doping attempts, and the ergogenic benefits of caffeine are small and realised by the vast majority of competitors most of whom are caffeine users" (WADA 2003a). This combination of very practical conclusions led to permitting caffeine use in elite sports. It has been monitored ever since, but the conclusion has remained the same: caffeine is not a doping problem. Pseudo-ephedrine, on the contrary, had been taken of the prohibited list in 2003 as well, but was re-introduced in 2010 based on new scientific literature as proof of the plasticity of the concept of 'knowledge' over time (WADA 2009a).

It is safe to conclude that the backgrounds for prohibiting certain substances or methods are too unclear. WADA has created an opportunity for itself to react swiftly to new emerging potentially problematic substances, but this has come at the cost of rather vague descriptions in the rules when something can be deemed worth prohibiting. This will be discussed more elaborately in paragraph 3.4 but it

is already safe to say that it would be preferable if the rules of this very important aspect of anti-doping regulations would become more clear and the process more transparent. Strangely enough, the transparency shown in 2003 with regard to caffeine and pseudo-ephedrine has faded.

This paragraph started as a discussion on the performance enhancing capabilities of existing pharmacological substances and ended up with discussions on the content of the prohibited list. This always seems to be the case in anti-doping related discussions, again highlighting the multidisciplinary aspect of anti-doping related matters. It seems that the contents of the Prohibited List International Standard holds the key, and perhaps the solution, to many doping-related discussions, despite the fact that it can be said beforehand that there will never be agreement between all scientists on what the prohibited list should contain, let alone agreement between all persons involved in anti-doping. There are two factors that are important in guiding these discussions: clarity (of opinions) and transparency (of decisions). Unfortunately, both are often lacking in practice.

2.5 The consequences of anti-doping policies

2.5.1 Case 4: Finding the athletes, or the burden of whereabouts regulations

Introduction to case 4

The IAAF was the first IF to introduce Out-of-Competition (OoC) doping controls, and the progress of world best performances suggests that such controls have impacted athletic performances, especially in women (Seiler et al. 2007, Berthelot et al. 2008, Lippi et al. 2008, Berthelot er al. 2010). Since the potential effect of anabolic steroid use on athletic performances is higher in women than in men (Franke & Berendonk 1997, Bahrke & Yesalis 2004, Hartgens & Kuipers 2004) this can be regarded as a strong indication that OoC testing leads to a decrease in anabolic steroid use.

For ADOs it was always difficult to locate the athletes in these periods, which eventually led to the introduction of the whereabouts requirements. Elite athletes have to submit some of their location details well in advance (up to three months). The obvious idea was to increase the effectiveness of locating athletes, but whether it has increased the effectiveness of anti-doping testing in the sense that it has led to more sanctions and/or less doping use is still debated. What is clear, is that many athletes find the whereabouts requirements in breach of their privacy as a citizen,

even though there is an obvious understanding that there is a need for some sort of whereabouts system in the specific setting of anti-doping (Hanstad et al. 2009, Waddington 2010, Overbye & Wagner 2014). This complex situation prompted a study into the impact of whereabouts requirements on elite athletes, instigated by an elite athlete herself who was wondering how her colleagues experience this relatively new obligation. The following text had been previously published in the *International Journal of Drug Policy* in 2014.

DOPING CONTROL, PROVIDING WHEREABOUTS AND THE IMPORTANCE OF PRIVACY FOR ELITE ATHLETES

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Abstract

Background: To improve anti-doping efforts in sports, the World Anti-Doping Agency (WADA) introduced the World Anti-Doping Program, in which (among others) regulations for providing athletes' whereabouts are described. Because the effectiveness and efficiency of this system depends on the co-operation and compliance of athletes, the perspective of elite athletes is important. This paper answers the following research questions: What is the perspective of Dutch elite athletes on the current whereabouts system in general and how important is their privacy in providing whereabouts in particular? In addition, this study explores how far the whereabouts system can be developed in the future. Are athletes willing to accept greater invasions of their privacy in order to reduce administrative effort and whereabouts failures?

Method: A structured questionnaire was completed by 129 Dutch elite athletes registered in the national and/or international testing pool.

Results: The results of this study indicate widespread dissatisfaction with the whereabouts system. Most respondents support anti-doping testing in general, but many athletes feel that WADA's whereabouts system is unacceptable in several respects. In terms of physical privacy, there was a great dissatisfaction. Nearly half of the athletes felt that the '1-hour time slot' limits their freedom, but on the other hand, most athletes disagreed with the statement that the distinction between their sport and private life is disturbed. For almost one in three respondents, the whereabouts system has a negative influence on the pleasure they experience in being an elite athlete. In terms of informational privacy, almost all athletes had confidence in the confidential treatment of their whereabouts information. Almost all athletes would accept giving their phone number to Doping Control Officials,

but only half of the athletes would accept sharing their location on their mobile phone. Furthermore, almost two in ten of the athletes would accept wearing a permanent wrist or ankle bracelet or accept being implanted with a GPS chip in order to facilitate future anti-doping testing.
Conclusion: The current whereabouts system needs to be improved in order to increase athletes' satisfaction with the anti-doping rules. The athletes themselves need to be engaged in this process. The results of this study indicate that a majority of the athletes are not likely to accept a greater violation of their privacy than the current whereabouts regulations already entail.

Introduction

For a long time in the past, doping tests were unsystematic and not very reliable, and consequently they were considered merely symbolic (Dimeo 2007; Houlihan 2004; Overbye & Wagner 2013a). In order to improve this situation, WADA was established in 1999, "the aim of which was to develop, coordinate, and harmonize anti-doping policy and procedures on a worldwide basis" (Hanstad et al. 2010; Hanstad et al 2009, p.31; Wagner 2009). Today, WADA strives to have a testing policy that ensures that athletes can be controlled at any time and at any place. Doping Control Officials must know where the athletes are in order to carry out random, unannounced, out-of-competition tests in addition to regular in-competition tests on the day of an athletic event. Therefore, in 2003, WADA introduced the World Anti-Doping Program, in which regulations for providing whereabouts were described (Hanstad et al. 2008, WADA 2008).

Since the revised World Anti-Doping Code became effective in 2009, athletes have had to provide much more detailed information about their whereabouts. Athletes are required to specify one specific 60-min time slot for each day, during which they will be available at a specified location for testing (WADA 2009a). For every day in the forthcoming quarter, these athletes have to identify where they will sleep, train, and compete in order to be located for out-of-competition drug testing at any time during those three months (cf. Dikic et al. 2011). Athletes can also be tested without notice at other moments of the day, but at those times they cannot be charged with a whereabouts failure (Waddington 2010, p.257). If athletes fail on three occasions to provide their whereabouts (which can be any combination of missed tests and failures to file appropriate whereabouts information) within a period of eighteen months, the athletes can be suspended from competition (WADA 2009b).

Because the success and credibility of the doping policy is partly dependent on the co-operation and compliance of athletes, it is important to understand the perspective of athletes on the whereabouts system (Alaranta et al. 2006, Bloodworth & McNamee 2010, Dunn et al. 2010; Sas-Nowosielski & Swiatkowska 2007, Striegel et al. 2002; Wagner & Hanstad 2011). Moreover, the anti-doping system is likely to be more effective if it has the support of athletes (Hanstad et al. 2009, Houlihan 2009, in: Waddington 2010). According to Houlihan (2009, in: Waddington, 2010), athletes will be more effectively motivated to comply with an anti-doping program if there is a perception by those subject to the regulations that those regulations are reasonable, that they are reasonably implemented and that they are enforced fairly.

In recent years, several systematic studies on elite athletes' perspective on the whereabouts system were performed. Hanstad et al. (2009) studied the perspectives of Norwegian elite athletes using a structured questionnaire that was conducted in 2006. In addition, in 2007, the British Athletes Commission (2007; in: Waddington, 2010) studied the perspectives of British elite athletes on WADA's whereabouts system. Although most athletes defended the necessity of doping controls, these studies indicated an outspoken dissatisfaction with the system of whereabouts in general.

These studies were published before the revised whereabouts system came into effect in 2009. According to Waddington (2010), because this revised whereabouts system places even more obligations on the athlete, future studies could reveal even higher levels of hostility by athletes towards the whereabouts system. In a more recent study with Danish elite athletes, Overbye and Wagner (2013a) showed ambivalent perceptions about the whereabouts system. On the one hand, there was a high degree of acceptance of the whereabouts system, as a 'necessary evil'. On the other hand, athletes indicated that the system interfered negatively in their everyday life and the joy of being an athlete decreased. The trust in the whereabouts system, especially how it operated in other countries, was remarkably low.

The current whereabouts system clearly constitutes (potential) invasions of the privacy of athletes, which, according to Schneider and Butcher (2001), could only be warranted by the need to protect others from serious harm. The question is therefore whether such invasions of the privacy of athletes can be justified and whether these justifications are accepted by athletes themselves. How do athletes perceive the whereabouts system, how does it affect their own interpretation of privacy, and how far are they willing to go with new technology to monitor their whereabouts?

Methods

Procedure and participants

Perhaps surprisingly, the number of athletes within a country that are required to share their whereabouts' information with anti-doping organizations is not exactly known. Athletes can be a member of the Registered Testing Pool of the National Anti-Doping Organization, of their International Federation, and/or (at certain times) of a major event organizer such as the International Olympic Committee around the Olympic Games period. There is no central institution that monitors these requirements.

In order to create a representative sample of Dutch athletes with a whereabouts requirement, we decided to approach all Dutch elite athletes who were likely to have a whereabouts requirement personally by email. This was done in two separate mailings in order to accommodate for the different event calendars of different sports. Those who did not go to the London Olympic or Paralympic games were emailed in July 2012 (with a reminder sent in August); those who did were emailed in October 2012 (with a reminder in November). In total, 888 athletes were approached. At that time, 452 Dutch athletes had a whereabouts requirement with the official National Anti-Doping Authority of the Netherlands. It was estimated that a total of 500 Dutch athletes had a whereabouts requirement at some organization at that time.

The total number of respondents was 157 (out of 888 approached), of which 129 had a whereabouts requirement (out of an estimated 500). The estimated response rate of our respondents is thus 26%. These represented 32 sports modalities and one hundred of these respondents were so-called 'A-status' athletes, which means that they perform at the top-8 level of the world in their respective specialism. Background information of the respondents and of the total group of approached athletes is given in table 1. Slight statistical differences were found in sports characteristics and level between the approached and respondent groups.

Table 1 Background information of athletes that were approaches by email (n = 888) and respondents with a whereabouts requirement (n = 129)

	Athletes that were approached by email (n = 888)	Respondents with whereabouts requirement (n = 129)
Gender		
Male	441 (50%)	53 (41%)
Female	445 (50%)	76 (59%)
Age		
<20 years	Unknown	11 (9%)
20–30 years		86 (67%)
≥30 years		32 (25%)
Sports		
Olympic/ Paralympic	656 (74%)	113 (88%)
Other	232 (26%)	16 (12%)
Team	486 (55%)	43 (33%)
Individual	402 (45%)	85 (66%)
Unknown	-	1 (1%)
Level		
Top-8	610 (69%)	100 (78%)
Other	278 (31%)	29 (22%)

Questionnaire

A questionnaire was designed to gather data on athletes' opinions about the whereabouts system in general and the importance of privacy in providing whereabouts in particular. The questionnaire was partly based on the questionnaire used previously by Hanstad et al. (2009). Opinions were assessed using a 5-point Likert scale (strongly disagree, slightly disagree, neutral, slightly agree, strongly agree; or never, sometimes, regularly, often, always). Open-ended questions allowed respondents to add qualitative comments to their responses.

Data analysis

Findings are presented in terms of descriptive statistics. For each Likert scale response, the percentage of athletes agreeing or disagreeing with each of the statements is pooled. Mann–Whitney U tests and Kruskal–Wallis tests were used to investigate differences between the subgroups identified in table 1. Significance was set at a level of 0.05. Qualitative comments were used to complement or reinforce the quantitative results. These qualitative comments are reported to provide a more detailed illustration of the athletes' perspectives. These statements

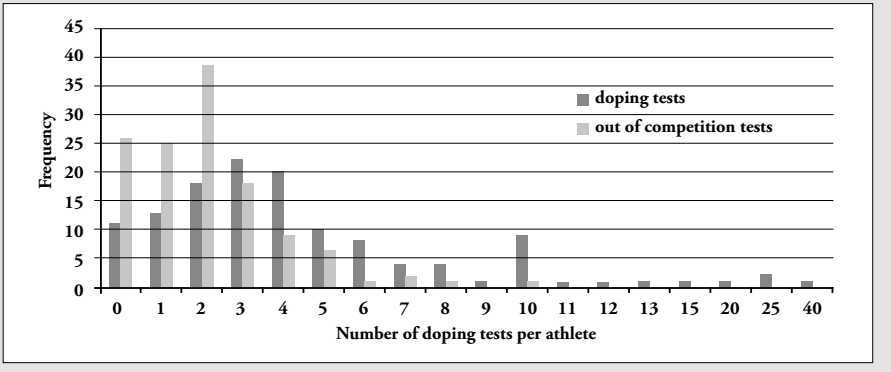
are presented not as representative of the entire group of respondents, but rather as illustrative comments on the kinds of issues that preoccupied athletes.

Results

Doping control experience

Fig. 1 shows the athletes' experience with doping control over the last 12 months. Eleven athletes (9%) stated that they had no doping tests and 26 athletes (20%) indicated that they had no out-of-competition tests in the previous year. Most athletes stated that they received one to four doping controls in total, of which one or two were out-of-competition controls.

Figure 1 Frequency chart of the total number of doping tests and the number of out-of-competition doping tests athletes had in the last 12 months (n = 128; 1 missing answer)



Experiences with whereabouts system

Table 2 shows the whereabouts-related backgrounds of the respondents. Almost all the athletes provide their whereabouts themselves. Two out of three of all respondents spend up to 30 min per week filling out their quarterly forms (whereabouts need to be sent in per period of three months) and spend another 1–10 min per week checking and (possibly) updating this information.

Around 9% of the respondents indicated that they do not always provide the (obligatory) information on their overnight address and their 'one-hour time slot'. A similar percentage received an official 'filing failure' and in addition to this 21% had experienced a definitive 'missed test' at least once. Only 29% stated that they were never afraid to miss a doping control during their 'one-hour time slot'.

Just over 40% agreed with the statement 'Providing whereabouts is a difficult task', while 12% took a neutral position. More specifically, if the responses 'regularly',

'often' and 'always' are added together, 20% of the athletes experienced technical failures in the whereabouts system itself. Furthermore, 17% could not change their whereabouts information because no computer was available and 26% could not do this because of a lack of Internet access. Such technical difficulties were more frequently reported for the internationally used ADAMS-system ("Anti-Doping Administration and Management System") than for the national system. In total, 21% disagreed with the statement 'I have confidence in the technical aspects of the current whereabouts system'. A recently introduced mobile application to provide and update whereabouts information was welcomed by most of the athletes, with 90% agreeing that it was an improvement to the existing system and 69% stating that it was easy to use (currently this mobile application is solely available for athletes who provide their whereabouts to the Dutch system, not to the international ADAMS-system).

Table 2 Whereabouts-related backgrounds

Experience		
<1 year	12 (9%)	(n = 126; 3 missing answers)
1–3 years	63 (50%)	
≥3 years	51 (40%)	
Platform		
ADAMS	41 (32%)	(n = 129)
Dopingautoriteit	86 (67%)	
Both	2 (2%)	
Person providing information		
Themselves	125 (97%)	(n = 128; 1 missing answer)
Family	12 (9%)	
Sport organization	1 (1%)	
Others	0 (0%)	
Time spent on quarterly updates		
≤10 min	30 (24%)	(n = 126; 3 missing answers)
11–20 min	37 (29%)	
21–30 min	25 (20%)	
31–60 min	21 (17%)	
≥60 min	13 (10%)	
Time spent on daily updates (in minutes per week)		
≤10 min	85 (67%)	(n = 127; 2 missing answers)
11–20 min	28 (22%)	
21–30 min	9 (7%)	
31–60 min	4 (3%)	
≥60 min	1 (1%)	

Table 3 Statements regarding doping and the importance of the whereabouts system

Statement	Agree – neutral – disagree (%)	n
1. The use of doping is a big problem in sport in general	80 – 12 – 9	127
2. The use of doping is a big problem in my sport	28 – 13 – 59	125
3. The use of doping is a big problem in Dutch elite sport	11 – 44 – 45	128
4. I think it is important that elite sport in general is free of doping	93 – 2 – 5	128
5. I think the whereabouts system is important in detecting users of doping	63 – 18 – 19	128
6. I think the whereabouts system is important in preventing the use of doping	59 – 20 – 22	128
7. A whereabouts system is necessary to carry out unnoticed out-of-competition tests	63 – 16 – 22	128
8. An anti-doping program can function well without whereabouts regulation	35 – 27 – 38	128

Perceived importance of whereabouts system

Doping is perceived by the respondents to be a problem for sports in general, although the problem becomes smaller when they look at their own direct environment. The whereabouts system is felt to be an important part of the anti-doping system by a majority of the athletes, but there is an ambiguous feeling whether an anti-doping program can function well without whereabouts regulations (table 3). This ambiguity does not interfere with the feeling that doping should continue to be banned: 90% of the athletes felt this way, with only 4% favouring an option where doping is allowed under medical guidance and 6% remaining unsure.

Statistical analyses revealed that females found the whereabouts system even more important than males, which was demonstrated by significantly different scores regarding statements #5, 7 and 8. Respondents from the sports of track and field and cycling agreed significantly more to statement #2 in comparison to respondents from other sports.

The current World Anti-Doping Code has a standard sanction for three whereabouts-failures in an 18-month period of 1–2 years of ineligibility, depending on the degree of fault of the athlete. Of all the respondents, 21% agreed with this sanction but 52% thought a lesser sanction was more appropriate. Only 1% thought that this particular sanction should be increased and 27% were unsure.

Table 4 Statements regarding privacy and privacy aspects of the whereabouts system

Statement	Agree – neutral – disagree (%)	n
9. I attach much importance to my privacy	72 – 14 – 14	125
10. I have nothing to hide, so I do not attach any importance to the effect of the whereabouts system on my privacy	49 – 18 – 33	124
11. I think it is good that athletes must be available for testing seven days a week, 24 h a day	35 – 16 – 49	125
12. I think my privacy is violated due to the requirement of providing whereabouts	30 – 23 – 46	125
13. I think anti-doping organizations interfere too much in my private life	26 – 22 – 53	125
14. The '1-hour time slot' limits my freedom	43 – 14 – 43	125
15. Despite the current whereabouts system, I feel free to seclude myself	60 – 23 – 17	122
16. I have confidence in the confidential treatment of my whereabouts information	89 – 6 – 5	123
17. The current whereabouts system has a negative influence on the pleasure I experience in being an elite athlete	28 – 14 – 58	125
18. I would accept giving my (mobile) phone number to Doping Control Official	94 – 2 – 4	125
19. I would accept sharing my location through my mobile phone with Doping Control Officials, so I can always be found for anti-doping testing	47 – 4 – 50	123
20. I would accept wearing a permanent wrist or ankle bracelet, so I can always be found for anti-doping testing.	18 – 2 – 79	125
21. If it would be possible in the future, I would accept implanting a microchip, so I can always be found for anti-doping testing	20 – 5 – 75	124

Privacy aspects of whereabouts system

The respondents feel that their privacy is important, but opinions differ on the degree to which it is compromised by the current anti-doping regulations. It is quite clear that their lives are greatly affected by these regulations already. Their thoughts on other possible and more extensive approaches to whereabouts control show that support for whereabouts measures quickly declines when permanent tracking systems would be introduced (table 4). Female respondents felt significantly more at ease with the current whereabouts regulations (more agreement with statement 15 and less with statement 17). At the same time, males were more inclined to wear a permanent bracelet as a possible alternative to for the current doping control whereabouts system.

Discussion

In this study, the perspectives of Dutch elite athletes on the current whereabouts system in general and their privacy with regards to providing whereabouts in particular were studied. Using a structured questionnaire, this study explored how the whereabouts system can be developed in the future. Are athletes willing to accept an even greater invasion of their privacy in order to reduce administrative effort and whereabouts failures?

In general, almost one in three agreed with the statement that the whereabouts system has a negative influence on the pleasure they experience in being an elite athlete. In terms of their experience with sending in whereabouts information, more than half of the athletes stated that providing whereabouts takes them a lot of time and that providing whereabouts is a difficult task. This is backed up by data that shows that two thirds of all respondents spend up to 30 min per week filling out their quarterly forms and spend another 1–10 min per week checking and updating this information.

The whereabouts application for mobile phones is used by slightly less than half of the athletes. Although most of them think it is easy to use and a good addition to the whereabouts system, some athletes experienced trouble and thought it has some limitations. In terms of providing whereabouts information, almost half of the athletes stated that they forget to provide their whereabouts sometimes, and even more than one in three stated that they forget to do so regularly, often or always. In addition, almost half of the athletes stated that they sometimes worry about being at the right place in accordance with their submitted whereabouts information, and even more than one in four stated that they worry about that regularly, often or always.

Although most athletes stated that they sometimes, regularly, often or always experienced problems when changing their whereabouts information, due to technical failures in the whereabouts system, or because they had no computer or no internet connection at their disposal, it is striking that more than three in four athletes agreed with the statement that they have confidence in the technical aspects of the whereabouts system.

One athlete (0.8%) got a suspension that was caused by three official 'missed tests' and/or 'filing failures' within an 18 month period (n = 126). Regarding the suspension of one to two years, which occurs after three official 'missed tests' or 'filing failures' within 18 months, most athletes stated that this sanction should be shorter. Athletes stated that the sanction would be fair if anti-doping tests were

consciously avoided, but they stated that it is not fair that an administrative failure can result in the same suspension as the use of performance enhancing drugs.

Most athletes in this study agreed with the statement that the use of performance-enhancing drugs is a big problem in sports in general. However, just one in four agreed that it is a big problem in their own sport and less than one in ten agreed that it is a big problem in Dutch elite sports. In addition, almost all athletes agreed that it is important that sports in general are free from the use of performance-enhancing drugs.

In terms of the importance of the whereabouts system in the anti-doping program, slightly more than half of the athletes agreed with the statement that the whereabouts system is important for detecting and preventing the use of performance-enhancing drugs and exactly half of them agreed that the system is necessary to carry out unnoticed out-of-competition tests. On the other hand, almost half of the athletes agreed that an anti-doping program can function without whereabouts regulation.

When discussing the issue of privacy in relation to modern sports, doping control and the whereabouts system, it is useful to distinguish between three types of privacy: physical privacy, informational privacy and decisional privacy (cf. Van Hilvoorde 2012). Physical privacy concerns access to people and personal spaces and is similar to the 'right to be left alone' (Teetzel 2007, Warren & Brandeis 1890). Informational privacy concerns access to personal information. This notion of privacy is closely related to the origins of the popular press. It has gained more relevance with the evolution of modern computer technology and developments in bioinformatics. Decisional privacy concerns interference with personal choices.

In order to protect the credibility of athletic performance, the distinction between professional and private life has almost disappeared in elite sport. Doping authorities claim the right to know where the athlete is at almost all times. To be able to test every athlete at any moment, athletes are required to be absolutely honest and open with respect to their whereabouts. This denies them privacy with respect to the 'right to be left alone'. The whereabouts system not only affects the individual's life as an athlete, but also their life as a private person (cf. Kayser & Broers 2012).

In terms of physical privacy, there was a great disparity in the athletes' perspectives on the extent to which the whereabouts system violated their privacy. Most athletes disagreed with the statement that the distinction between their sport and private life is disturbed. On the other hand, however, almost half of the athletes

stated that the '1-hour time slot' limits their freedom. This perspective is illustrated by the following quotations from two respondents:

"I think that it is important that sports stay free of doping, but it must not be exaggerated, it is about the sports. I think that there should be tests at competitions, not at home or at work/school. You have to pay attention to your 1 hour-timeslot, which costs a lot of energy that you need in training. I regularly notice stress from colleague athletes about having to change their whereabouts when training changes, which should not be the intention."

"Athletes should be innocent until proven guilty. It should, indeed, be possible to work with a GPS tracking system, but still doping tests should be held at convenient moments, not during an exam, selection, concert, date, family reunion, etc. If that would be possible, we will have a good system: a combination of freedom of movement and administration on one hand, and a doping agency that tests at more convenient moments on the other hand."

In addition, most athletes agreed with the statement that, despite the whereabouts system, they feel free to seclude themselves. However, half of the athletes disagreed with the statement that athletes should be available for testing seven days a week, at any time of the day.

The World Anti-Doping Code insists that the submitted whereabouts information "shall be maintained in strict confidence at all times, shall be used exclusively for purposes of planning, coordinating or conducting testing and shall be destroyed after it is no longer relevant for these purposes" (WADA 2009b, pp.87-88). A relevant question that we tried to answer in this research is: Do the elite athletes trust the confidentiality of their whereabouts information?

In terms of informational privacy, almost all athletes responded that they had confidence in the confidential treatment of their whereabouts information and in the fact that their information will not be used for purposes other than locating them for doping testing.

According to Carolina Klüft, Swedish Olympic heptathlon champion, the system was turning her into a nervous wreck. "It is bloody uncomfortable to know that my sloppiness and my spontaneity can make me equivalent to someone who uses drugs" (Roos 2006, in: Hanstad & Loland 2009, p.7). Klüft suggested implanting a data chip into her body so that doping agencies could follow her at all times. A similar statement was made by Canadian Olympic speed skating

champion Christine Nesbitt. After submitting her whereabouts for the forthcoming quarter she posted the following statement on Twitter: "Whereabouts, you are now complete for the next 3 months. I still wish I was just implanted with a GPS device for anti-doping to track me" (Nesbitt 2012).

How do Dutch athletes value these tracking technologies? When proposing new possible methods of tracking athletes' whereabouts in future regulations, only half of the athletes agreed with sharing their location on their mobile phone with Doping Control Officials so they could always be found for anti-doping testing without having to provide whereabouts manually. It is no surprise that a great majority of the athletes stated that they would be unwilling to wear a permanent wrist or ankle bracelet in order to be found for anti-doping testing. A great majority also disagreed with the proposal that they be implanted with a microchip with a GPS tracker. The following statements are good illustrations of the athletes' resistance against further invasion of their privacy:

"I think providing whereabouts is not pleasant, but I know it is the only way to keep sports free of doping. It is a violation of privacy, but there is no better alternative. I think implanting a microchip or sharing location by GPS is absolutely not appealing, because in that way, they can see where you are all the time. That is violation of privacy. I think it will be adopted shortly, however, because it would make tracking very easy."

"About that GPS system, we are not prisoners. People with money will find methods to avoid testing anyway."

Although a minority of the respondents was in favour of the use of new technologies, it is striking that 18% would even accept wearing a permanent wrist or ankle bracelet and 20% would accept wearing a microchip, as can be illustrated with the following statement by one of the athletes:

"Stop providing whereabouts, I agree with implanting a chip or I will wear a wrist or ankle bracelet all the time!"

The notion of Decisional privacy also involves the question of whether athletes should be involved in the discussion on doping rules and their application in sport. The decisions that are made regarding how the doping regulations are applied significantly affect the athletes themselves, which makes it at least questionable

that in relation to doping policy athletes are routinely relegated to the margins of the debate (cf. Houlihan 2004). Sports policy is generally made for athletes, rarely in consultation with athletes, and almost never in partnership with athletes. Although WADA's policy has the support of the Athletes' Committee within WADA, according to Waddington (2010), it is clear that the Athletes' Committee can hardly claim to be the legitimate representative of athletes in general. For one thing, the committee's members are appointed by WADA's Foundation Board and not chosen by their peers. The importance of the voice of the athletes themselves can hardly be exaggerated (cf. Alaranta et al. 2006, Bloodworth & McNamee 2010, Breivik et al. 2009; Dunn et al. 2010, Sas-Nowosielski & Swiatkowska 2007, Striegel et al. 2002, Wagner & Hanstad 2011).

The results of this study are in several respects similar to those of other studies (Hanstad et al. (2009) British Athletes Commission 2007, in: Waddington 2010, Overbye & Wagner 2013a, 2013b), in particular with respect to the widespread dissatisfaction with the whereabouts system. The athletes supported anti-doping testing, but felt that WADA's whereabouts system was unacceptable for several reasons.

With regard to whereabouts failures, the athletes' perspectives found in this study are consistent with the findings of Hanstad et al. (2009) in the Norwegian study. In both studies, athletes stated that it is not fair that an administrative failure to provide whereabouts results in the same suspension as the actual use of performance enhancing drugs. Another similarity between the studies is that they both reveal the paradox that most athletes stated that the use of performance-enhancing drugs is a big problem in sports in general, but only a minority of the athletes stated that it was a big problem in their own sport. Many anti-doping professionals find similar results in national surveys, but these results never reach scientific literature (personal communications). A minority of athletes also agreed with the statement that athletes should be available for anti-doping testing seven days per week. In line with other studies, one in four of the athletes reported that providing the whereabouts information affects their everyday life as an elite athlete.

The results of this study also show some remarkable differences with other studies. Regarding technical problems with the whereabouts system, in the study of Hanstad et al. (2009), 34.7% of the Norwegian athletes stated that they were not able to update their whereabouts due to technical problems. On the other hand, more than half of the Dutch elite athletes in this study stated that they sometimes, regularly, often or always have problems providing whereabouts due to technical problems. This difference in experience is remarkable since the questionnaire

of Hanstad et al. (2009) was conducted in 2006. Nowadays, due to technical improvements over the years, the system should be more reliable. The fact that our sample includes two subsets of whereabouts-platform users (the national Dopingautoriteit system and the international ADAMS-system) makes it difficult to draw a general conclusion regarding this finding.

The surveys of Hanstad et al. (2009) and the British Athletes Commission (2007, in: Waddington 2010) were conducted before the whereabouts system was revised. Because in the renewed whereabouts system athletes are required to provide their whereabouts in more detail, it was expected that in this study athletes would experience a greater invasion of their privacy. However, this difference was not found. An explanation may be that nowadays, due to the wide use of social media websites such as Twitter and Facebook, which broadcast location updates, the invasion of privacy involved in providing one's whereabouts is more accepted.

In all previous studies, a great dissatisfaction with the whereabouts system was found. In response to the criticism, WADA claimed that the whereabouts system is an acceptable and justifiable price athletes have to pay to compete in a fair and clean sport. From an institutional perspective, one can argue that athletes who choose to engage in elite sports must accept the rules of the activity. According to WADA, in principle every athlete is free to withdraw from the surveillance system by withdrawing from elite level competition in the sport. Therefore, Hanstad and Loland (2009) concluded, despite all the criticism, "that the system can be conditionally accepted as constituting justifiable anti-doping work".

According to Waddington (2010), WADA's argument about the voluntary character of the whereabouts system is based on an "individualized conceptualization of the elite athlete, who is presented as an asocial, isolated individual who is able to make a free and unconstrained choice" about participation in his or her sport and the whereabouts system. Young athletes simply do not have the freedom to choose to participate in their sport or to withdraw from their sport when they do not like the whereabouts system and it is questionable whether you could ask the same of athletes who make a professional career of their athletic ability.

The results of this study show serious dissatisfaction among Dutch elite athletes with the current whereabouts system. Many athletes experience violations of their privacy. Furthermore, most athletes would not accept future changes in the system that would mean a greater invasion of privacy. Despite all of the athletes' criticism of anti-doping testing and the whereabouts system in the past, WADA continues to develop a system that is increasingly invasive. Because the cooperation of athletes

is essential to developing and introducing changes in the whereabouts system, the athletes' perspectives should and could be taken more into account.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Extended discussion on case 4 (whereabouts)

This case highlights the general willingness of athletes to sacrifice personal freedom in order to support anti-doping regulations. Obviously, for some athletes it is simply a case of following the rules that exist, but most of them agree with the intrusions of their personal lives that accompany doping controls (providing a urine sample under supervision, having blood drawn at unexpected times) in a silent agreement that all athletes are treated the same. And it is true that correct and timely whereabouts information is crucial for performing OoC doping controls. The effects of various doping substances and methods last for many weeks and maybe even months after their last use, and in quite a few cases also past their detection windows (Hatton 2007, Catlin et al. 2008, Bowers 2009a). In order to be effective, unannounced OoC testing is crucial and this can only be done if the testers know where the athletes are, and more importantly: will be. The fact that this requires 24 hours a day, 7 days a week, 365 days a year availability by the athletes makes the whereabouts rule the subject of many human rights-centred debates.

The whereabouts rule and accompanied testing planning is a continuous subject of seeking balance. From a planning perspective it is important to know where the athletes will be in the upcoming weeks, but the current rule (filing whereabouts information per three month periods) requires methodological and quite frankly unrealistic planning from athletes and therefore unavoidably frequent changes in the whereabouts information. How much time to plan ahead is feasible to ask from athletes?

Some doping substances can only be detected for a few hours after their use, so frequent tests that can be performed at any time of the day are crucial. Yet it is highly intrusive already to test an athlete once, let alone more often in one day. It may also be felt necessary to test a certain athlete at night time, but waking up athletes for doping tests is certainly highly intrusive and occurs only under extremely exceptional circumstances. Obviously, rigorous testing is in its essence a service provided to non-using athletes but what level of privacy violations is acceptable for this cause?

These are important questions, not to say outright dilemmas (McNamee & Tarasti 2010), and while drafting the current rules they will all have passed the meeting tables. But it is important to keep in mind that any doping control at any time is asking a lot from athletes. The addition of whereabouts requirements to the array

of anti-doping measures seems to have pushed the willingness of cooperation amongst elite athletes towards a limit. Whilst not going over that limit, although this can be debated as well (MacGregor et al. 2013), it is remarkable how many athletes are feeling that there privacy is seriously limited (Hanstad et al. 2009, Waddington 2010, Overbye & Wagner 2014), and it is striking to see that those athletes are also more critical towards other anti-doping measures (Valkenburg et al. 2014). Based on the available literature it cannot be concluded what the cause and what the effect is of these sentiments, but fact of the matter is that in order to have an anti-doping system that works, cooperation with athletes is key (Striegel et al. 2002, Alaranta et al. 2006, Ntoumanis et al. 2014). It does not help either that it is generally acknowledged that many of the sanctions that have been laid down on athletes violating the whereabouts requirements have hit disorganised athletes more than cheating athletes (Dikic et al. 2011). This is a clear unintentional consequence of anti-doping regulations: sanctioning athletes not because they are cheating, but because they experience difficulties in keeping appointments. Since the above study was published the whereabouts rule has been slightly changed: the period in which two mistakes from the part of the athlete are 'allowed' (a third mistake will lead to an ADRV) has been shortened from 18 months to 12 months, decreasing the chances of running into problems because of missed tests and/or filing failures. But it is still a harsh decision to sanction an elite athlete with temporary ineligibility based on administrative mistakes.

Besides the evidence that OoC testing in general has had an impact on the performances in certain sport events, the world of anti-doping is in dire need of additional proof that the whereabouts rule changes have led to a noticeable effect on doping use habits. It is necessary to keep close relationships and discussions with past, current, and future elite athletes to continuously assess their willingness to adhere to anti-doping regulations and to feed this conversation with actual data. This is the best way to truly evaluate the various aspects of the issue of effectiveness of anti-doping policies.

2.5.2 Case 5: Commonly used supplements, or the impact of anti-doping policies on a non-doping issue

Introduction to case 5

Even more than regular medications (see case 2), the issue of nutritional supplements has an enormous impact on doping-related discussions. Following the principle of strictly liable athletes, who are responsible for everything that can

be found inside their bodies, supplements that contain doping substances can lead to severe sanctions, equal to confessed 'cheaters'. The current WADC introduced the principle of 'contaminated products' (including supplements) as a juridical road map to allow more lenient sanctions for athletes who unintentionally ingested tainted products, but the burden of proof to qualify for this outcome is still severe (WADA 2015c).

Starting in 2001, the Dutch NADO began to look for ways to help athletes in their search for doping-free supplements (Abbott 2004). These experiences led to a publication in a specific tennis issue of the *British Journal of Sports Medicine*, but this article is easily transferrable to all other sports. The following text is the full text of this article from 2007.

THE CONTINUING STORY OF NUTRITIONAL SUPPLEMENTS AND DOPING INFRACTIONS

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Abstract

Nutritional supplements can be a source of positive doping cases as some supplements contain prohibited substances without showing this on their label. This problem has existed for some time and has been extensively studied in the past 8 years. The sport of tennis has played a particular role in this problem because of some peculiar doping cases within its community.

This article focuses on this particular doping problem, explaining the background and reviewing the available literature. It presents the first 3 years of experience within the Netherlands Security System Nutritional Supplements Elite Sports ("Nederlands Zekerheidssysteem Voedingssupplementen Topsport" or NZVT) and explains the most extensive system established to combat this particular doping problem.

The NZVT experience has shown that paper based quality systems are still prone to possible contaminations, which leads to the conclusion that the best possible solution for athletes who wish to use nutritional supplements must include laboratory-based analysis for doping substances, preferably repeated for every new batch. The most important educational message, however, is to use a nutritional supplement only if it is deemed of benefit by a nutritional expert.

Abbreviations

BCAA	branched-chain amino acids
CLA	conjugated linoleic acid
DHEA	dehydroepiandrosterone
DSHEA	Dietary Supplement Health Education Act
HACCP	hazard analysis critical control points
IOC	International Olympic Committee
MDMA	methylenedioxymethylamphetamine
NOC*NSF	Netherlands Olympic Committee/Netherlands Sports Confederation
NZVT	Nederlands Zekerheidssysteem Voedingssupplementen Topsport (Netherlands Security System Nutritional Supplements Elite Sports)
OKG	ornithine-alphaketoglutarate;
WADA	World Anti-Doping Agency

Introduction

For more than a decade, it has been known that nutritional supplements can be "contaminated" with doping substances, which means that the contents of the supplements are not identical to the list of ingredients on the label. Tennis has played a particular role in this debate because of the complexity of the cases of Bohdan Ulihrach and Greg Rusedski, who tested positive for nandrolone or nandrolone prohormones in 2002 and 2003, respectively. In June 2007, Guillermo Coria sued an American nutritional company for the financial damages he suffered during his 2-year suspension after also testing positive for nandrolone in 2001. This problem is of major concern to elite athletes, who can test positive in a doping test without knowingly taking banned substances. This so-called "inadvertent doping use" has resulted in an unknown number of positive cases because doping tests often rely on the presence of metabolites of banned substances in urine, and cannot discern between intentional and inadvertent use. In this article, doping is defined as substances that are included on the list of prohibited substances of the World Anti-Doping Agency (WADA) or (before 2003) the International Olympic Committee (IOC).

The consequences of testing positive for a doping substance are severe. The sanctions for doping infractions, laid down in the World Anti-Doping Code, allow for mitigating circumstances to lower the standard 2-year ban.[1] But the use of unknown contaminated nutritional supplements is very seldom accepted as a reason to reduce a sanction, and the result of the particular competition is always nullified, which is a severe sanction in itself.

This has led to a situation where most international sports bodies advise athletes to abstain from using any nutritional supplements. This advice is deemed unsatisfactory by most athletes and nutritional experts, as supplements can help athletes to meet their nutritional needs.[2-3] Many studies have shown that supplements like carbohydrate drinks, creatine, and glucosamine can help some athletes to perform at their highest level.[4-10] It must be said, though, that the expectations of athletes tend to exceed the actual effects.

This article will review all relevant aspects of the relationship between supplement use and doping infractions. It will also present the results of the approach that has been taken in the Netherlands, often acknowledged to be the most all-encompassing effort to tackle this particular problem.[11] Finally, advice will be given for athletes and their support team (such as coaches, physical therapists, nutritionists and physicians) on how to reduce the risk of an unintentional doping infraction.

The doping risk of supplements

In the 1990s the IOC issued a public warning when certain supplements appeared to contain unlabelled pseudo-ephedrine, at that time a prohibited substance. This issue was brought to a head by sprinter Linford Christie, who tested positive for pseudo-ephedrine during the Olympic Games of 1988, but (as a rare exception) was not sanctioned because the likely source was a cup of ginseng tea.[12] Contamination of ginseng is often cited as a potential hazard.[13] Christie also tested positive for nandrolone in 1999. In the UK, the number of nandrolone positives jumped from an average of 3.4 in the years 1994-1998 to 17 in 1999; an increase from 0.08% to 0.29% of all the samples analysed.[14] A possible cause of this increase was the ingestion of contaminated nutritional supplements. A few years later, it was concluded that this statistical increase appeared to have been exceptional and was only present within the UK in 1999,[15] but from 2000 onwards the subject of nutritional supplements and doping entered the limelight. In subsequent years, more and more studies were published that confirmed the hypothesis that supplements could indeed cause unintentional doping infractions.[16-22] Other publications showed that unlabelled doping substances can be found in a variety of products[23-26] and thoroughly discussed the risks for elite athletes.[27-30]

The information on this issue came mainly from the WADA-accredited laboratory in Cologne that conducted an IOC-sponsored study in 2004.[18] This study showed that 14.8% of 634 freely available substances contained anabolic agents that were not declared on the label. These products were partly selected

because the producers of these substances also sold pro-hormone containing products. The risk of buying a contaminated supplement is about twice as high in products from such companies. The amounts that were found varied from 10 ng/g or parts per billion (ppb) to 190 mg/g or parts per million (ppm). Later studies found even higher and profoundly dangerous amounts of anabolic agents, up to 17 mg of unlabelled metandienone per tablet.[31-33]

The sport of tennis has had its own experiences regarding this subject. Bohdan Ulihrach and Greg Rusedski are rare examples of athletes who tested positive in a doping case, but were exonerated because they might have used contaminated supplements. The complexity in these cases lies in the fact that the source of their positive tests might have been supplied by the testing authority itself: the Association of Tennis Professionals (ATP). The tribunals, special enquiries, and task forces that studied these cases all named the nutritional supplements provided by the ATP organisation as the most likely source of the nandrolone metabolite. However, many minerals and vitamins that were available on the ATP tour have actually been tested, and the true source has never been confirmed. Because there were more (anonymous) cases within the ATP that were all linked, as demonstrated by an analytical anomaly noticeable in the mass spectrogram of the urine analysis, all of these tennis players have been cleared. Such exoneration by an anti-doping tribunal is extremely rare.

Characteristics of contamination

The fact that nutritional supplements can lead to a positive urine test has been consistently found in various studies. The risk of producing a positive doping test can be present for hours to days after the ingestion of one single supplement, depending on the substance, dose, and individual variation in metabolism.[16-18,21,24,34,35]

The difficulty of finding possible contaminations of a nutritional supplement was shown in one of the very first studies addressing this problem. A group from an anti-doping laboratory in Los Angeles, California, USA proved the existence of tablet-to-tablet variation in contaminations.[24] This variation was confirmed later that year[17] and is still likely to exist. The experiences from the laboratories show that contaminations can be present in the raw materials that are used, both in the active ingredients and in the substances used to make tablets or capsules. This type of contamination is often referred to as "cross-contamination". A second source of contamination might result from a lack of sufficient hygiene in the machinery that is being used during the production process.

Contamination problems in nutritional supplements can be found in any country. It concerns all types of nutritional supplements (box 1) and all forms, including powders, pills, capsules, and liquids. Likewise, experience shows that contaminations can occur with a multitude of doping substances (box 2).

Box 1:

Examples of nutritional supplements that have been contaminated with doping substances (in alphabetical order)

Branched-chain amino acids (BCAAs)
Carnitine
Chrysine
Conjugated linoleic acid (CLA)
Creatine
Glutamine
Guarana
Minerals
Ornithine-alpha-ketoglutarate (OKG)
Proteins
Pyruvate
Ribose
Saw palmetto
Tribulus terrestris
Vitamins
Zinc

Box 2

Examples of contaminations found in nutritional supplements (in alphabetical order)

4-Androsten-3,17-diol
4-Androsten-3,17-dion
5-Androsten-3,17-diol
19-Nor-4-androsten-3,17-diol
19-Nor-4-androsten-3,17-dion
19-Nor-5-androsten-3,17-diol
19-Nortestosterone (nandrolone)
Benzylpiperazine
Caffeine (off the WADA doping list since 1 January 2004)
Dehydroepiandrosterone (DHEA)
Ephedrine
Methandienone
Methylenedioxymethylamphetamine (MDMA or XTC)
Nor-pseudo-ephedrine
Sibutramine
Stanozolol
Testosterone

Even though these lists might not be complete, the variety of substances found indicates the magnitude of the problem. It also shows that contaminations in nutritional supplements are most likely to occur with substances that are part of the groups of anabolic agents or stimulants.

The problems surrounding nutritional supplements that contain unlabelled doping substances have often been attributed to the Dietary Supplement Health Education Act (DSHEA) that was passed in the USA in 1994. The DSHEA has often been accused of introducing a system where quality control is lacking.[13,28,36,37] This Act has undoubtedly played a large role in creating the problem of contaminated substances, because of the strong influence of the USA on the global market and the consequent spread of (traces of) anabolic agents and strong stimulants. But this problem does not only originate from the USA. Any facility that is part of the production or storage process of nutritional supplements, or that handles doping substances in addition to doping-free products, could be a source of the eventual downfall of an ignorant athlete. Globally there is a great difference in the quality procedures surrounding pharmacological medications and nutritional

supplements, but the difference between these two groups is not always as clear as it should be.[7,38-40]

In 2004 a new law was introduced in the USA, the Anabolic Steroid Control Act, which goes some way to recognising that there were flaws in the original legislation. It is not to be expected, however, that the chance of contamination will diminish rapidly. Not only is DHEA still freely available under the new law, but there are also many other countries and many other substances that can still cause doping problems. The Directorate for Health in the Netherlands, for example, has already found traces of designer steroids in regular supplements.

Initiatives to reduce the risk of using contaminated supplements

Over the years different approaches have been used to address the problem of contamination. Countries such as Norway, Switzerland, and the UK have tried to help the athletes and their nutritional advisors to choose supplements from companies that are deemed to be reliable. WADA has organised two symposiums to address the issue, but is primarily waiting for the industry to solve the problem that stems from their own production lines. The ATP is the only sports organisation that is actually involved in a system to provide athletes with nutritional supplements that are as doping-free as possible. After their unfortunate experiences, they started a system whereby a strict selection of tested supplements can be provided to athletes. The ultimate responsibility, however, still lies with the athlete.

Initiatives in Australia, Austria, France, Germany, and North America also include laboratory analyses in order to aid athletes in their decision when choosing between the large variety of available supplements. However, these systems do not always incorporate batch-by-batch analysis or the involvement of anti-doping organisations. As well as these official initiatives, some nutritional supplement companies conduct their own testing, but these results are not supervised by an independent third party and sometimes have considerably higher limits of detection. It is encouraging to note that in one study of 201 supplements, all produced under pharmaceutical guidelines, no unlabelled anabolic steroids were detected;[41] however, without confirmation on a larger scale it is too early to conclude that such supplements do not pose any risks to athletes.

The Dutch experience

The Cologne study, performed in 2001, showed that the Netherlands faced one of the biggest contamination issues in Europe.[18] Together with some high-profile

doping cases, this finding prompted a preliminary study, which would serve as an extra service to the Dutch athletes in their preparation for Salt Lake City 2002 and as an opportunity for the participating partners to devise a structural solution to the problem.

In November 2001, the athletes nominated to go to the Winter Olympics in Salt Lake City 2002 were given an opportunity to have their supplements tested for doping substances. They were asked to buy a supply of the nutritional supplements they were going to use during their preparation for the Olympics from a controlled sample of one batch. From this supply, a random selection of supplements was tested for several anabolic steroids, their precursors, and several stimulants.

The results of this preliminary study gave a clear insight of the seriousness, size, and scope of the problem. Of the 69 supplements that were submitted (mainly vitamins, minerals and creatine), 13 (19%) contained unlabelled doping substances.[42] Most products showed traces of caffeine and/or ephedrine, one product contained a small amount of 3,4-methylenedioxymethamphetamine (better known as MDMA or XTC), and five products contained anabolic steroids. By pure chance, two different batches of one single product were tested as well, yielding one positive and one negative finding.

These results were reported to the relevant public authorities. The local authorities took appropriate steps to eradicate the amphetamine traces from the public food supply, but concluded that this particular issue is not a concern from a public health perspective but is first and foremost a sport and a doping problem, as the trace amounts found in supplements would not endanger general health.

NZVT: maximal risk reduction

The results and experiences of this preliminary study were used to develop a structural solution to the issue of nutritional supplements and doping. The branch organisation for supplements producers and providers in the Netherlands (NPN), the Netherlands Olympic Committee*Netherlands Sports Confederation (NOC*NSF), and the Anti-Doping Authority of the Netherlands set up the Netherlands Security System Nutritional Supplements Elite Sports ("Nederlands Zekerheidssysteem Voedingssupplementen Topsport" or NZVT). This was strongly supported by the Ministry for Health, Welfare and Sports (VWS), the NOC*NSF Athletes Commission, and the National Institute of Public Health and the Environment (RIVM). All parties are involved on a not-for-profit basis; the producers pay only for the analysis. The NZVT consists of four elements:

Criteria enriched hazard analysis critical control points (HACCP) system. The companies and producers joining the NZVT system have to follow special procedures for the purchase of raw materials, production, and labelling of nutritional supplements. For quality control, a specific HACCP system has been developed by the branch organisation NPN, in which extra criteria is incorporated into the various stages of the production process to eliminate the risks of cross-contamination with doping substances. HACCP is an extensive set of regulations that ensures that any type of food is safe to be consumed.

Laboratory analyses. Laboratory analyses are conducted on every batch of nutritional supplements that wish to become part of the NZVT system. For this purpose, the NZVT Standard Analytical Procedure has been developed in cooperation with the participating laboratories. This procedure consists of sample taking, analytical processing, and the listing of relevant doping substances and their threshold levels relating to the doping list. Testing is performed for stimulants and anabolic steroids because these are the most likely sources of contamination.

Security analysis. The National Institute of Public Health and the Environment randomly conducts extra, double analyses as an extra security. This is performed by taking the same samples originally selected from the batches of nutritional supplements or by taking consumer units from these batches on the market. The security analyses are also conducted according to the NZVT Standard Analytical Procedure.

Communication to athletes. The batches of nutritional supplements that have been produced according to the NZVT-HACCP system standards are communicated to the athletes through a secured website (http://antidoping.nl/nzvt). Visitors to the website are informed that all statements regarding security guarantees are only applicable to the specified product/batch combination and that the "strict liability" rule, as applied in anti-doping cases, is not lifted. Website users are warned that other products and all other batches of the same product might not fulfil the NZVT requirements.

Table 1 Testing results of NZVT from 2003-2006

Year of analysis	No. of completed analyses	Positive cases
2003	99	1 (1.0%)
2004	72	3 (4.2%)
2005	53	0 (0.0%)
2006	72	2 (2.8%)
Total	296	6 (2.0%)

Testing results from NZVT

The NZVT was launched in November 2003 and the results of the laboratory tests are presented in table 1. It is striking to see that despite the HACCP-plus system and 3 years of experience, there are still some positive cases. Apparently, a quality system that is infallible on paper is still not a guarantee that doping free supplements will be produced. This is the reason why batch-by-batch analysis is still a prerequisite for producers to join the NZVT.

The six positive test results consist of two ephedra positives and four steroid positives (DHEA and 5-androsten-diol). The sources of these positives, as far as could be traced, were either raw ingredients or the material used to make capsules. In the production facilities of the end product, no doping substances are allowed, which prohibits cross-contamination at this stage. Naturally, the batch numbers of these positive cases were not posted on the NZVT-website, and the producers were free to bring these particular batches onto the market as they did not pose a major health risk to the general public.

The fact that contaminations easily occur was also shown in the early stages of the NZVT. Of the 96 products tested, 10 were shown to contain traces of (unlabelled) caffeine. As caffeine is an ingredient that is often used by the supplement industry, the presence of this substance in products where it is not intended to be an ingredient is another clear indication that cross contamination between different products made in the same production facility can easily occur. This underpins the necessity of producing legal supplements via completely separate production lines.

The NZVT is considered a success by athletes, their support personnel, and the parties involved in running the system. It gives willing producers of nutritional supplements the platform to express their commitment to a doping-free sport and shows their eagerness to go great lengths to produce a doping-free product. Despite the positive cases that sometimes still occur, the percentage of contaminated products is far lower than the previously found percentages in the Netherlands.[18,42] Most of all, the system gives athletes an opportunity to choose those products that can truly be called "athlete friendly". The website has been frequented daily by scores of visitors, which is satisfactory for a small country like the Netherlands with relatively few elite athletes. An evaluation during the Olympic Games in Athens showed that of all Dutch athletes who used supplements, 78% chose NZVT supplements. This amounts to 65% of all Dutch Olympic athletes, indicating that the primary message of the NZVT ("only use those products that are really useful") is also catching on.

Analytical issues

All NZVT analyses were conducted by one of four possible institutions: the laboratories accredited for the analysis of doping substances in nutritional supplements in Ghent (Belgium) and Cologne (Germany), the National Institute of Public Health and the Environment (RIVM) in Bilthoven (the Netherlands), and TNO Nutrition and Food Research in Zeist (the Netherlands). The methods used by the laboratories in Ghent, Cologne, and Bilthoven have been published elsewhere.[18,43-46]

Based on the published facts that a precursor of an anabolic steroid in an amount between 1–10 mg can cause a positive doping test,[18,24] and based on the fact that athletes easily use 50 g of supplements per day or more, a reporting threshold value of 10 ng/g or 10 ppb for all anabolic steroids is used in all tests. This value also allows for individual variations in metabolism. Excretion studies for stimulants are rare, but similar considerations led to the conclusion that for stimulants, a reporting threshold value of 100 ppb is opportune.

No 100% guarantee

The only way athletes are able to enjoy a 100% guarantee is when they decide not to take any supplements at all. But there are certainly some circumstances when dietary supplements provide an added benefit to diet and, in the world of elite sport where the ultimate goal is to reach one's best, it is not fair to deny athletes the use of legal substances that could improve their health, such as anti-oxidants and multivitamins. Although there are some studies that suggest that there is a relationship between (legal) supplement use and (illegal) doping use, these are only based on epidemiological data and causality has never been established.[47,48]

Two types of contamination can be identified. The first type is from malpracticing producers who do not care about consumer health or even deliberately spike products with known effective substances such as anabolic steroids or their precursors. Generally, such companies change identity quickly and most often sell their products over the Internet. Occasionally, the products might emerge in regular shops, but a country's health directorate is highly likely to pick up such products and take them off the market. Most of the time this type of company uses advertisements with unrealistic claims, and athletes and their support personnel should be able to avoid this type of supplement easily.

The second type of contamination is more subtle and more difficult to detect, and thus more of a concern to athletes with good intentions. The nature of the origin of such contaminations (mostly cross-contamination from other products,

frequently not in the facility where the end-product is made and packed and therefore always unexpected) makes it very difficult to pick up such contaminations, even for well-intentioned producers who follow strict quality procedures. Experience shows that such supplements can contain doping substances despite these extra efforts. Even though the level of such contaminations might be low, even very low amounts of doping substances can suffice to cause a positive urine sample for a window of several hours after the consumption of such a product.

Even athletes who are careful can test positive for doping because of a contaminated nutritional supplement. This is a discomforting thought, but an unavoidable consequence of the current situation in the nutritional supplement industry. However, 8 years after the sudden rise in nandrolone positives in the UK and the wealth of experience with this issue in the mean time, ignorance is no excuse for today's elite athletes.

Athletes should rethink whether there is an actual positive balance for them when determining the cost/benefit ratio of taking a particular supplement. Such an evaluation should preferably be performed with the aid of a nutritional expert. If it is concluded that supplementation could be beneficial, the athletes, with the aid of their support team, should select a product that has the slimmest possible chance of being contaminated.

How to deal with supplements in the field of practice

Many athletes tend to take supplements for a variety of reasons.[49-53] The first rule in any educational effort regarding supplements is that athletes should be cautioned against their indiscriminate use. Supplements can play a role in an athlete's diet, but confirmation of their added benefit should be sought with an appropriate expert before using them.

The second step is to try and identify those supplements that have the slimmest chance of being contaminated with doping substances. Companies that sell products containing doping substances should definitely be avoided, and it is prudent to disregard companies with unrealistic claims in their advertisements. This includes advertisements that mention "IOC approved" or "WADA tested" on their label, as no such approvals exist. The basic anti-doping rule remains that at all times athletes are responsible for the substances that are within their bodies, and a simple appeal based on an advertisement does not lift this rule of strict liability.

Athletes and their support personnel should be aware that no system is able to provide a 100% guarantee of doping free supplements. Contaminations can occur in many ways, which leads to possible package-to-package or even tablet-

to-tablet variation. No sampling protocol is able to cater for all these possibilities. However, there are protective systems that can be used to bring down the chances of ingesting contaminated supplements to very close to 0%. Such athlete-friendly systems should address the problems surrounding possible contaminations mentioned in this article, and well intentioned producers should acknowledge that contaminations can occur outside their control. Generally speaking, any system that ensures that the particular product is produced in a "doping -free environment", meaning that all parts of the production process are free of any substances prohibited by WADA, will provide an athlete with a trustworthy product. But as the NZVT experience has shown, even quality systems that are foolproof on paper cannot prevent contaminations with doping substances. Therefore, the best available option for athletes is to only use supplements that have been analysed in a knowledgeable laboratory on a batch-by-batch basis.

Conclusions

The problem of nutritional supplements and doping infractions is an issue that every sport organisation, including anti-doping organisations, has been obliged to address over the past 8 years. Tennis is a prime example of a sport where some trips and subsequent strides forward have eventually led to a practical solution that seems to serve athletes well. In the end, a situation where the strict liability rule in anti-doping is compromised is harmful to the entire anti-doping fight. The rulings on the cases of Rusedski and Ulihrach should remain very rare exceptions. It is precisely for this reason that some form of support system, preferably one with batch-by-batch analyses, is imperative for athletes and their support personnel. All organisations and individuals that love sport owe it to themselves to try and remedy the potentially disastrous situation of a well intentioned athlete unintentionally testing positive.

What is already known on this topic

Nutritional supplements can contain unlabelled substances that are on the List of Prohibited Substances as published yearly by the World Anti-Doping Agency.

They are a potential source for unintentional doping violations, leading to severe sanctions for well-intentioned elite athletes.

What this study adds

This article reviews 8 years of experience on this topic, and adds the results and experiences of the Netherlands Security System Nutritional Supplements Elite Sports (better known by its Dutch acronym "NZVT").

Guidelines for athletes, nutritionists, physicians, and others on how to choose a low-risk supplement are provided.

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Commentary

This paper highlights the issues arising from the use of nutritional supplements in relation to doping control. The authors draw attention to the risks associated with the use of untested supplements for athletes that can be subjected to doping control. In addition, they describe a quality system set up in The Netherlands to supply athletes with information about 'low-risk' dietary supplements. They also demonstrate the necessity for laboratory-based testing in addition to the HACCP procedures that are of utmost importance in ensuring the quality athletes expect. However, as stated in the article, additional efforts by governments, the industry and antidoping organisations have to be made to reduce (un)intentional malpractice in the supplement industry.

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Extended discussion on case 5 (nutritional supplements)

Case 5 highlights a prime example of how an athlete who has an adamant anti-doping attitude still can get caught in the juridical system of anti-doping regulations. When consuming a product that is considered to be 'regular food' can lead to an ADRV, it is only logical that athletes start to doubt just about everything they consume. And where the issues of meat contaminations are very rare, yet very disturbing as well (Le Bizec et al. 2000, De Wasch et al. 2001, Guddat et al. 2012), the fact that nutritional supplements may contain unlabelled doping substances has been known for such a long time (for over fifteen years now) that athletes, and especially their support personnel who tend to stick around longer in the world of sports, cannot plead ignorance anymore.

Different ADOs in the world have chosen different strategies to target this problem, with three basic pillars: 1) referring the problem to the supplement industry who at least in theory should be able to produce doping-free products; 2) increased education on the doping risks of supplement use; and 3) providing athletes with information on low-risk alternatives on the supplement market. These three pillars provide partial solutions with increasing personal attention to the individual athlete. Most ADOs restrict themselves to pillars 1 and 2, even though all ADOs are frequently confronted with athletes who blame the supplements they take for an AAF. It seems like the use of nutritional (or, in the eyes of purists more correctly: dietary) supplements is decreasing in the world of elite sports because of these efforts (Tsitsimpikou et al. 2009, Heikkinen et al. 2011).

This is a particular area where it is difficult to find the right balance in the approach towards athletes. Obviously, the risk is clear and well-known (Geyer et al. 2004, Van Thuyne et al. 2006, Parr et al. 2007, Geyer et al. 2008. Parr et al. 2008, Judkins et al. 2010, Kohler et al. 2010, Judkins & Prock 2012, Katz 2013), and it is impossible to accept a sole verbal 'supplement-excuse' as a reason for non-sanctioning an athlete with an AAF. This would equate to a situation where the use of a regular supplement can be used to mask intentional doping and as such would render anti-doping regulations useless. Because of the well-known history of supplements and doping it is also clear that an athlete who has shown flagrant negligence in choosing and using a certain supplement deserves to be sanctioned when an AAF has been established, even if this AAF can be traced back to that supplement. The degree of guilt on behalf of the athlete in every individual case is very difficult to fathom. Zooming in on the concentration of the substance found

in an athlete's sample during analysis does provide some extra information on the possible origin of the substance, but it can never be known for sure if a low concentration should be traced back to low-level cross-contamination in a recently consumed supplement or whether it may be a remnant from intentional use of a high dose of a prohibited substance days or even weeks before the doping control. In most cases the circumstances are not clear. Juridical panels need to make the ultimate judgment on the degree of guilt by the athlete who is confronted with such a case (for the difficulties of this process see also paragraph 2.3.2). This judgment is made easier when it is clear that the athlete was educated sufficiently on this issue, and even more easier when athlete-friendly alternatives were available while choosing a certain product.

From a principal point of view it is difficult to justify a call on athletes to refrain from all supplements, in order to eliminate all doping risks. The decision to use a certain supplement (or not) is a personal decision, but it is undeniably true that using supplements is a regular aspect of daily life of many people, and even more so in athletes whose health and physical condition is one of their prime assets in order to do what they do in life: performing in sports to the best of their abilities. Historically, dating back to the ancient Olympic Games, all sorts of concoctions have been used to improve athletes' performances. References mention the consumption of mushrooms, spices and even mother's milk by the professional athletes of those times (Birchard 2000, Papagelopoulos et al. 2004, Müller 2010). It would be inaccurate to compare these habits to 'doping' as there is no current knowledge about a ban on 'doping substances' in the competitive rules of that time. And as discussed in paragraph 2.2 the etymological backgrounds of the word doping do not go back this far in history. In fact, the use of mushrooms, spices and even mother's milk can be seen as supplemental to a regular diet, and as such as dietary, or nutritional, supplements. A historical comparison with today's multi-million market of vitamins, minerals, and proteins (and more) is thus far more correct than a comparison with doping use. Athletes try to be the best they can be and if something is not officially prohibited it is, by default, permitted. And many people in the world of elite sports would argue that an elite athlete even has a moral obligation to try something that is permitted and is potentially performance enhancing. This is a complicated issue, as there are some fears that the use of supplements and the use of doping might be interconnected (Backhouse et al. 2013) but at the same time the use of permitted alternatives to doping may be safeguarding athletes from the use of doping (Ntoumanis et al. 2014).

There is also an analytical part of this problem. Laboratories are constantly seeking to lower their detection thresholds of prohibited substances, with the aim to lengthen the detection period and as such increasing the chances to catch users of doping. But at some point it should be discussed whether even lower thresholds actually aid anti-doping efforts, or merely create a problem that has no health, performance or ethical sides to it because the concentrations found are extremely low. This is clear for endogenous substances, which sometimes are found in very low concentrations, but it is even more clear for exogenous substances that may be found in regular food, in botanicals, and also in supplements. Simply put: a drop of stanozolol in the ocean will contaminate the entire ocean, but this is completely negligible. But a drop of stanozolol in an Olympic-sized swimming pool can be detected by anti-doping laboratories already, and one might wonder how relevant this is. Here, also, a balance needs to be sought between the desire to provide clean athletes with the best analytical possibilities and the reality that any substance may be found anywhere, albeit in very low concentrations. An extra challenge regarding this issue is that WADA explicitly communicates minimum required performance levels to the accredited laboratories, which means that every lab must be able to detect and report substances at the stated concentrations. But the ISL also provides for the possibility to report even lower concentrations if the laboratory can produce these results reliably and within the scope of their own certified quality system. This means that a specific sample may result in an AAF in one particular accredited laboratory, but will bring up no findings in another lab. If the sample concerned stems from an athlete who intentionally brakes the anti-doping rules, this reasoning makes sense as one would not want to disregard analytical findings that are proven to be true. But if these low concentrations stem from a non-doping related source, for example from food consumption being a supplement or regular meat, the fact that an AAF needs to be investigated, with all concomitant time and stress, is even more disconcerting when one realises that all this would not have come about if the sample would have been analysed in a different laboratory. Again: balance is necessary.

I would like to argue that from a principal point of view supplement use is completely different from doping use. Both acts may have in common that in the world of sports they aim to improve one's performance, but equating doping to performance enhancement is untenable (this will be discussed more elaborately in paragraph 3.4). This is the crux of the issue of 'supplement use and doping': in its essence, the use of nutritional supplements is a completely different issue than the

use of doping because of their legality and, generally speaking, their physiological effects. There may be unclarities on the borderline between supplements and medicines (Geyer et al. 2008, Parr et al. 2008, Kohler et al. 2010, Katz 2013) but in their essence they are different entities.

Unfortunately, the current situation is that any athlete who uses supplements can only do this with the whole array of doping regulations, and its possible consequences, in his/her mind. The issue of nutritional supplement use has been dragged into the realm of doping regulations, because the principle of strict reliability (as explained in the WADC's comment to article 2.1.1) coupled to the rule that any proven concentration of most doping substances results in an ADRV leads inevitably to the practical consequence that any supplement becomes an inherent doping risk in today's commercial supplement market. Athletes need to take a wide array of precautions, and even then the athletes are told that they are taking a great risk and that this risk is entirely theirs. Obviously, this situation can be blamed on 1) the industry of nutritional supplement manufacturers, where clear examples of mislabelling and downright faulty production processes continue to surface; 2) the athletes, who in some cases are taking all sorts of supplements in a careless way; and 3) the fact that there is a grey area where the category of 'legal supplements' slowly merge into the category of 'pharmaceuticals'. These three issues are outside the scope of anti-doping regulations, but have become entangled with them nevertheless. Nutritional supplements are non-doping issues in its essence, and as such it would be logical if anti-doping regulators would accommodate for this fact more than simply saying 'athletes should not take them'.

It can be concluded that the issue of supplements and doping is a prime example of an unintentional consequence of anti-doping policies. As with the influence of anti-doping policies on medical (mal)practice (see case 2), it is interesting to see how doping regulations impact areas outside the world of sport. In fact, if athletes would not have been tested for doping substances, society might not have been aware that an array of officially registered pharmaceuticals can be found in regular supplements in varying concentrations – readily available for the general public including the more vulnerable groups such as elderly, children and pregnant women. Similar to the influence on medical (mal)practice, it is up to the anti-doping community to stick with its own trade and not try to clean up all the misconceptions in the world. But it can be expected from anti-doping professionals to acknowledge the fact that regular supplements pose serious risks to elite athletes, and to help

those athletes to find their way in a beautiful jungle full of doping risks that are not apparent at first, or second or third, sight. Because of the demands that are placed on elite athletes already (submitting whereabouts information, providing urine and blood samples, discussing their medical history with other doctors than their own, to name just a few examples) it is only fair to help them in their quest to be the best they can be, cleanly, and as such to guide them towards low-risk alternatives on the supplement market.

2.5.3 Case 6: Non-competitive fitness athletes, or the true importance of anti-doping policies

Introduction to case 6

The WADC is the core document of global anti-doping regulations. It is focussed almost solely on elite sports competitions, whereas several studies indicate that most illegal use of doping substances seems to occur in a non-competitive environment in gyms and fitness centres (Auge & Auge 1999, Kanayama et al. 2001, Bahrke & Yesalis 2004, Sagoe et al. 2014). This holds especially true when considering the absolute number of athletes in these two settings. For example, within the Netherlands there are approximately 500 athletes who are a member of a Registered Testing Pool and as such these can be defined as 'elite athletes with the highest priority in anti-doping testing'. The total amount of athletes who are competing at the highest national levels of their respective sports approximates 20,000. The best available estimate of intentional doping users in this group is 4.2%, or less than 1,000 individuals, although it should be debated whether this percentage is accurate for this relatively large group of athletes; the estimate itself is based on a group of 740 athletes and as such identifies approximately 30 intentional doping users (Duiven & De Hon 2015). But there are approximately two million members of fitness centres and as such any percentage of doping users higher than 1% in the latter group makes the percentage of doping users in elite sports not relevant as it will always be lower than the total amount of doping users in non-competitive sports. And this percentage is in fact about eight times higher, as the following study has shown (Stubbe et al. 2013). Although the exact numbers and percentages may be lesser known in other countries, the proportions are not likely to differ substantially (Johannisson et al. 2012).

A study was performed in order to gain more insight into the number of doping users in the Netherlands, and also to verify whether an alternative approach towards unearthing prevalence numbers related to this secretive act would have

additional value (see also paragraph 2.3.1). It was also aiming to expand on previous knowledge on the backgrounds of users of doping substances in non-competitive settings (Wiefferink et al. 2008), but this aspect will not be discussed in depth in this thesis. The following text is the full text of an article published in *Drug Testing and Analysis* in 2014.

PREVALENCE OF USE OF PERFORMANCE ENHANCING DRUGS BY FITNESS CENTRE MEMBERS

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Abstract

Studies on the use of performance enhancing drugs (PED) in fitness centres rely predominately on conventional survey methods using direct questioning. However, research indicates that direct questioning of sensitive information is characterized by underreporting. The aim of the present study was to contrast direct questioning of different types of PED use by Dutch fitness centre members with results obtained with the Randomized Response Technique (RRT). Questionnaires were conducted among members of fitness centres. PED were classified into the following categories: anabolic steroids, prohormones, substances to counteract side-effects, growth hormone and/or insulin, stimulants (to reduce weight), and miscellaneous substances. A total of 718 athletes from 92 fitness centres completed the questionnaire. The conventional method resulted in prevalences varying between 0% and 0.4% for the different types of PED with an overall prevalence of 0.4%. RRT resulted in prevalences varying between 0.8% and 4.8% for the different types of PED with an overall prevalence of 8.2%. The overall prevalence of the two survey methods differed significantly. The current study showed that the conventional survey method using direct questioning led to an underestimation of the prevalence. Based on the RRT results, the percentage of users of PED among members of fitness centres is approximately 8.2%. Stimulants to lose weight had the highest prevalence, even higher than anabolic steroids. The key task for future preventive health work is to not only focus on anabolic steroid use, but also include interventions focusing on the use of stimulants to lose weight.

Introduction

The prevalence of performance enhancing drugs (PED) in sports is not easy to evaluate.[1] Studies are difficult to compare due to varying ages, athletic backgrounds, selection variation, and analysis stratification.[2] Therefore, previous studies showed a wide variance in the prevalence of doping. A review by Laure[3] showed that 3-5% of children and adolescents, and 5-15% of adults report using doping substances in sports. Recent reviews show that prevalences seldom exceed 6%.[2,4,5] However, in high-risk sub-populations, such as competitive athletes or bodybuilders, the prevalence of PED use is higher. In a study including 82 competitive Hungarian athletes, 14.6% admitted using PED.[6] A study conducted by Blouin and Gouldfield[7] showed that the prevalence of steroid use among bodybuilders was 44.2%.

Over the last decade, studies have been conducted on the use of PED among fitness centre visitors.[8,9] A major limitation in these studies is that the results have been based on conventional survey methods using direct questioning. Despite the widespread use, direct questioning comes with considerable limitations.[10,11] Participating in research about PED can be threatening to athletes. Respondents may be reluctant to reveal sensitive information.

Recently, researchers have recognized this problem and made attempts to use indirect methods to obtain information on doping behaviour.[10] One notable example is a recent study which aimed to contrast self-reported doping use with objective results from chemical hair analysis.[10] Results showed an observed discrepancy between self-reports and objectively verified doping behaviour, which highlights the fact that a significant proportion of respondents simply choose to deny their current or recent behaviour. The authors concluded that there is a need for improved self-report methodology for future research in this sensitive domain, but also indicated that improvements are not likely to come from chemical validations, as this remains expensive. Petróczi et al.[10] claim that a more realistic promise for large-scale studies and online data collection efforts is held by measures of implicit social cognition.

The Randomized Response Technique (RRT) can be used when sensitive questions have to be asked and respondents can be expected to be reluctant to answer directly.[12] Examples of sensitive questions are questions about fraud, alcohol consumption, sexual behaviour, or use of drugs. A meta-analysis showed that randomized response designs lead to more valid answers compared to other conventional question-and-answer methods.[13]

Simon et al.[11] were the first to apply RRT in a study on doping-related behaviour of members of fitness centres. In this German study, 500 exercisers from 49 fitness

centres were interviewed using RRT. Participants were asked if they ever used PED. The RRT revealed a high prevalence of doping (12.5%), which confirmed previously estimated rates of drug use assessed by direct interviewing techniques and voluntary questionnaires based on a larger sample from the identical population.[14]

To our knowledge, no study compared RRT and the classic method of asking questions directly to investigate whether there are differences in prevalence of different categories of PED. Therefore, the aim of this study was to estimate the prevalence of use of different categories of PED by members (15 years and older) of Dutch fitness centres by comparing the conventional survey method with RRT. We hypothesize that the conventional survey method using direct questioning will lead to an underestimation of the prevalence, because we assume that PED users will be reluctant to directly answer questions about PED due to the danger of being detected through standard questionnaires.

Data and methods

To tackle the problem of response errors, two Web-based surveys were conducted. The first survey (i.e. the conventional survey) was conducted to compare the prevalence with earlier studies. The second survey using RRT was conducted to investigate whether there was an underestimation of the true prevalence caused by response errors due to social desirability. A design using RRT can be defined in various ways, but all designs have in common that a specified probability mechanism protects the privacy of the individual respondent.[15] The true status of the individual respondent is not revealed, because their observed answer depends not only on the true status but also on the misclassification design. There are several randomized response designs,[16] which all use a randomizing device that perturbs the answers of the respondents. In this study, we used the forced response method,[17] because it is one of the most efficient randomized response designs.[18] In the current study, the forced response method was implemented as a computer-assisted self-administered randomized response internet survey (see Lensvelt-Mulders et al.[13] where a best-practice for online implementation of the RRT is presented). The forced response design uses dice as the randomizing device. The binary responses are generated according to the known distribution of the sum of the outcomes of two dice. After the sensitive question is asked, the respondent throws two virtual dice. If the outcome of the two dice is 2, 3, or 4, the respondent answers yes. If the outcome is 5, 6, 7, 8, 9, or 10, they answer according to the truth. If the outcome is 11 or 12, they answer no.

Despite the fact that the respondents' privacy is protected by the RRT, it is not always perceived as such by respondents. Because the RRT forces respondents to give a potentially self-incriminating answer for something they did not do, it is susceptible to self-protective responses (SP), i.e. respondents answer no although they should have responded yes according to the randomizing device.[19] Although RRT performs relatively well, by eliciting more admittances of fraud than direct-questioning or computer-assisted self-interviews,[13] non-compliance probabilities might still be underestimated if SP is not taken into account. In this study the profile-likelihood method by Cruyff et al.[20] has been used to estimate the proportion of respondents who do not follow the randomized response design when answering the six questions about the use of PED. This method estimates the proportion of respondents that do not follow the design in the context of log-linear models, by detecting the respondents who systematically say no to every item in a subset of items. This method will yield prevalences of the use of each type of PED, corrected for the proportion of respondents who give self-protective responses.

To answer the question whether the prevalences obtained with the RRT differ significantly from the prevalences obtained with direct questioning (DQ), 90% confidence intervals were obtained for the differences between the RRT and the DQ prevalences, which can be used to perform a one-sided test for the difference in prevalences with 5% significance level.[21] This method uses the lower and upper limits of the confidence intervals for each separate prevalence. However, standard confidence intervals, based on theoretical standard errors, are not appropriate in this setting for several reasons. The distribution of prevalence estimates tends to be skewed. Also, when parameter estimates are on the boundary of the parameter space, which is likely to occur when studying sensitive behaviour, computing standard confidence intervals can result in confidence limits outside the interval [0, 1]. Therefore, for the DQ prevalences profile-likelihood 90% confidence intervals were obtained using the method described in Agresti.[21] For the RRT, estimating the proportion of self-protective responses, introduces extra variability in the estimated prevalences, and has to be taken into account. The non-parametric bootstrap method was used to obtain 90% bootstrap percentile intervals for the estimated prevalences, taking into account the variability caused by the use of the RRT as well as the extra variability induced by estimating the proportion of self-protective responses. Details about the set-up of this particular bootstrap method can be found in Cruyff et al. [20] and Frank et al.[16]

A total of 500 centres were randomly selected from the trade register of the Dutch Chambers of Commerce (which listed a total of 1839 of such centres). At least three

attempts were made to contact the owners of fitness centres by telephone. A total of 188 owners were reached of which 92 agreed to participate in this study (response rate = 49%). Fitness centres were divided at random into the conventional survey group (N=23) or the RRT group (N=69). Members of fitness centres received an e-mail with a link to the Internet questionnaires or received a flyer containing the link to the Internet survey. T-tests were conducted to test whether there were significant differences between respondents in the conventional and RRT group.

The current study was part of a large-scale study on health and lifestyle of members of fitness centres. Approval of the study was obtained from the Central Committee on Research Involving Human Subjects (known by its Dutch initials, CCMO). The survey contained items about physical and psychological health, sports injuries, eating habits, smoking behaviour, alcohol consumption, exercise behaviour and PED use. The concept of doping was not strictly defined as substances on the Prohibited List of the World Anti-Doping Agency (WADA). Firstly, not all substances on this list are of primary interest to fitness athletes looking for performance enhancement (for example corticosteroids and cannabinoids). Secondly, some relevant substances are not on the Prohibited List, for example thyroid hormones and oral antidiabetic medication. Therefore, these substances were included in the current study. PED were classified into the following categories: anabolic steroids, prohormones, substances to counteract side-effects (such as clomifene and tamoxifen), growth hormone and/or insulin, stimulants (to reduce weight), and miscellaneous substances (such as diuretics and thyroid hormones). For each category, examples of substances were given to ensure that the respondents understood the limitations between the substance categories correctly. Use of PED was defined as using these substances at least once in the preceding year. Legally available supplements, such as vitamins, minerals, and creatine, were explicitly excluded as being PED.

Results

A total of 718 athletes from 92 fitness centres completed the questionnaire. The majority of participants were female (64.0%), the average age was 43.4 (SD = 13.6) and the average body mass index was 25.5 kg/m^2 (SD = 8.2). The basic characteristics including the fitness motives are shown in table 1. We tested whether fitness centre members in the conventional group significantly differed from members in the RRT group. No significant differences in age, weight, length, and BMI ($p > 0.05$) were found between the two groups.

Table 1 Characteristics of members of fitness centres

Baseline characteristic	Value
Gender	
Male	35.7%
Female	64.3%
Miscellaneous	
Age (years; mean (SD))	43.4 (13.6)
Weight (kg; mean (SD))	76.1 (14.5)
Length (cm; mean (SD))	173.6 (10.7)
BMI (kg/m2; mean (SD))	25.5 (8.2)
Fitness motives#	
Positive health effects	79%
Tight and slim body	32%
Increase strength	32%
Fun and relaxation	31%
Reduce weight	21%

Participants responded to the items on a five-point scale ranging from one (not important) to five (important). Only the top five motives are shown with the percentages of respondents who found the motives important.

One out of ten members of fitness centres knew at least one person who used PED. As stated before, these drugs were classified into the following categories: anabolic steroids, prohormones, substances to counteract side-effects, growth hormone and/or insulin, stimulants (to reduce weight), and miscellaneous substances. A total of 693 respondents filled in items about PED use (direct questioning: N=246; RRT: N=447). Direct-questioning resulted in prevalences varying between 0% and 0.4% for the different types of PED, and an overall prevalence of PED of 0.4% (90% CI: [0.0%, 0.9%] (table 2). The results for the RRT were as follows: an estimate of 24% of the respondents gave self-protective responses (95% bootstrap percentile CI: [19%, 32%]). Taking the 24% of self-protective responses into account yields prevalences for the different types of PED that vary between 0.8% and 4.8% and an overall prevalence of PED of 8.2% (90% CI: [4.9%, 23.3%]) (table 2). The confidence intervals obtained with the RRT show that all estimated prevalences were significantly different from zero.

Table 2 Prevalences resulting from direct-questioning (DQ) and RRT and a comparison between RRT and DQ based on 90% confidence intervals (which corresponds to one-sided testing with α = .05)

Doping category	DQ	RRT	RRT - DQ
Overall prevalence PED listed below	0.4% [0%, 0.9%]	8.2% [4.9%, 23.3%]	7.8% [4.4%, 22.9%]
Anabolic steroids	0.4% [0%, 0.9%]	1.0% [0.4%, 6.9%]	0.6% [-0.2%, 6.5%]
Prohormones	0.0% [0%, 0.6%]	0.8% [0.2%, 3.7%]	0.8% [-0.03%, 3.8%]
Substances to counteract side-effects	0.0% [0%, 0.6%]	1.3% [0.6%, 6.9%]	1.3% [0.4%, 6.9%]
Growth hormone and/or insulin	0.0% [0%, 0.6%]	1.1% [0.4%, 4.5%]	1.1% [0.2%, 4.6%]
Stimulants (to reduce weight)	0.0% [0%, 0.6%]	4.8% [0.8%, 10.9%]	4.8% [0.8, 10.9%]
Miscellaneous substances	0.0% [0%, 0.6%]	2.8% [0.8%, 8.8%]	2.8% [0.7, 8.8%]

To answer the question whether the estimated prevalences obtained with direct questioning differ significantly from those obtained with the RRT, 90% confidence intervals are obtained for the difference between the RRT and the DQ prevalences for each PED separately and for the overall prevalence of PED (last column table 2). The results show that in general the RRT prevalences are significantly higher than the DQ prevalences, except for anabolic steroids and prohormones, where the difference is in the same direction, but not significant.

Conclusions and discussion

Based on the RRT results in this study, the percentage of users of PED among members of fitness centres in the Netherlands is approximately 8.2%. Use of these drugs predominantly concerns stimulants to reduce weight. These stimulants can be very dangerous, especially when used over a long period and injudiciously. Whereas most focus on the subject of PED use in fitness centres tends to be on anabolic steroid use, this is clearly not the only group of substances that is being abused. Professional medical advice is necessary to give members of fitness centres information about what is effective, dangerous and acceptable instead of forming opinions in a kind of trial and error process. In these processes the effects on figure are the main concern. Short-term side-effects play a minor role and long-term health risks may be nearly completely neglected.

RRT proved to be an effective method of obtaining estimates with a relatively high degree of reliability for evaluating use of PED in members of fitness centres. True prevalence rates of sensitive behaviours such as PED use may never be elucidated, but the mere fact that RRT yields significantly higher prevalence rates is an indication of a higher degree of validity, as proven in other (sensitive) areas where RRT has been used.[13] However, RRT has limitations. Randomized response designs are known to be less efficient than direct question designs, because the

proportion of forced responses does not deliver information about the sensitive behaviour, but are designed exclusively to guarantee the anonymity of the interviewees.[22] Therefore, it is necessary to collect larger samples than for the direct question method. However, the forced response design used in this study is one of the most efficient randomized designs currently available.[13]

Although studies have shown that RRT limits the influence of social desirability, its complexity and unfamiliarity for respondents could also lead to careful and not necessarily honest answers.[1,14,23,24] Therefore, Lentillon-Kaestner and Ohl[1] suggest not to use one way of questioning to evaluate doping prevalence. Data based on a combination of available techniques (i.e. RRT, questionnaires, observations, interviews, and possible chemical analyses) could help to give a reliable picture of doping prevalence and reduce the risks of inaccurate estimation.

Despite the fact that more participants were included in the RRT group than in the conventional group, due to the relatively small prevalence and the inferior test strength, it was not possible to carry out analyses focusing on determinants of PED use. To enable an analysis of determinants of PED use, it is advised to include fitness centres that are suspected to have many athletes using PED. However, selecting centres with a high prevalence of PED use is not the correct strategy to obtain estimates of prevalence of PED use, because the results of this selected group of athletes cannot be generalized to the population at large.

Furthermore, to investigate whether the participating fitness centres were representative for the whole fitness branch, we compared basic characteristics of these participating fitness centres with the Dutch National Fitness Monitor.[25] The findings showed that characteristics of centres participating in the current study did not significantly differ from characteristics of centres participating in de Dutch National Fitness Monitor.

Finally, we compared the characteristics of the respondents included in the RRT group with the characteristics of the respondents in the conventional survey group. No significant differences in age, weight, length, BMI and motives to engage in fitness were found between the two groups. Therefore, differences in prevalence of use of PED between the RRT group and the conventional survey group cannot be explained by differences in the characteristics of the respondents in the two groups.

The current study showed that the classical method led to an underestimation of the prevalence. This is in agreement with a study by Striegel et al.[14] They concluded that a standard questionnaire (classical method) fails to indicate a realistic prevalence of doping among elite athletes, leading to underestimation. Furthermore, Thevis et al. concluded in their study that surveys based solely on

questionnaires will result in underreporting of the prevalence of PED.[24] One reason for this could be that athletes see the danger of being detected through standard questionnaires with regard to doping. It can be concluded that RRT is more suitable for estimating the prevalence of use of PED in the future even though RRT necessitates more subjects and is thus a more expensive method to use. RRT resulted in prevalences varying between 0.8% and 4.8% for the different types of PED with an overall prevalence of 8.2% (90% CI: 4.9–23.3%). Stimulants to lose weight had the highest prevalence, even higher than anabolic steroids.

The key task for future preventive health work is to not only focus on anabolic steroid use, but also include interventions focusing on the use of stimulants to lose weight. Future studies are needed in order to identify those at risk of misuse.

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Extended discussion on case 6 (fitness athletes)

This study served three purposes: it provided an accurate measurement of doping use in Dutch fitness centres, it was a first step in introducing the method of Randomised Response questionnaire research to the Dutch policy partners in the field of anti-doping, and it revealed more of the backgrounds of doping use in this group of athletes. From its very early beginnings, anti-doping policies in the Netherlands have discerned competitive sports from 'cosmetic use' because of their socio-cultural differences. As a result, the two target groups of elite (competitive) sports and (mostly non-competitive) fitness enthusiasts, including bodybuilders, are often approached in different manners. But at the same time it is true that in the field of practice there are many interconnections between the supply-lines and doping-habits of the respective athletes who chose to dope. From a health perspective, the greatest gains of anti-doping measures can be expected from successful interventions in non-competitive fitness athletes (Sjoqvist et al. 2008, Health Council of the Netherlands 2010). This is all the more important as the non-medical use of anabolic steroids, the prime group of doping substances together with stimulants used in fitness centres, seems to be on the rise globally (Sagoe et al. 2014).

WADA is targeting the supply lines of the doping trade more and more, and as such is bound to be engaged with this non-competitive doping world more and more (Adams 2010, Paoli & Donati 2012). But officially their main target still is the world of competitive sports. As their mandate is historically inherited from the IOC this is understandable, but at the same time it cannot be denied that the issue of 'doping in sports' cannot be expected to be fought effectively when only a small percentage of the total amount of users is targeted. Moreover, it can be expected that engaging the expertise from this other world of doping users will provide interesting information as these fitness athletes are quite often relatively open about their experiences (Monaghan 2002).

There is a fundamental difference between the two groups of athletes. In non-competitive fitness most of the times there are no competition rules that prohibit these athletes from taking doping substances. This also means that officially the word 'doping' is out of context in the world of fitness, even though there is a great overlap in the substances of interest: anabolic steroids, various peptide hormones, insulin, diuretics, and stimulants, supplemented with thyroid hormones (Auge & Auge 1999, Kanayama et al. 2001, Monaghan 2002, Bahrke & Yesalis 2004,

Parkinson & Evans 2006). Likewise, there is no 'spirit of sport' defined for these athletes, even though for many fitness enthusiasts it goes without saying that they train in their best way possible without using any medication (Hoffman et al. 2009). To continue with the traditional list of 'doping' criteria, this group is equally interested in the performance enhancing properties of all sorts of substances, and since there is often no competitive interest, it can be expected that they focus even more on the strictly physiological aspects of these substances, limiting any possible placebo-effect (Auge & Auge 1999). And they are certainly knowledgeable about the health risks of these substances, even though these might be underestimated by the users themselves (Parkinson & Evans 2006, Health Council of the Netherlands 2010). Information that can be gathered in this group of athletes will thus include many relevant aspects, such as effectiveness of substances, health consequences of use, psychological determinants of use, and ways of acquiring these substances.

The lessons learnt from case 6 are that when an anti-doping strategy is focussing solely on competitive elite sports, it is likely that such efforts will only address a minority of the total amount of doping users, and as such of the doping issue. When targeting supply lines of elite athletes who use doping, it is unavoidable that connections with non-competitive fitness athletes are encountered. And, perhaps more importantly, when the health argument is used in explaining the importance of anti-doping regulations, it is not logical to exclude the target group of fitness and bodybuilding athletes from an anti-doping strategy. Apparently the performance enhancing argument used in elite sport should be seen in conjunction with an argument about the spirit of competitive sport to launch extensive and global anti-doping matters.

This leads to the conclusion that future anti-doping measures can be expected to be strengthened by more attention to fitness athletes, including bodybuilders, together with the target group that has received more limelight: athletes that perform in elite sports competitions. There are obvious differences between the two groups of athletes, and the strategies should certainly not be identical, but the effectiveness of efforts in both groups can be expected to increase if knowledge and experiences are shared. Moreover, the credibility of anti-doping measures will be increased if the existence of both groups of doping users is acknowledged more explicitly.

2.5.4 Discussion on the consequences of anti-doping policies

Cases 4, 5, and 6 show three examples of the consequences of anti-doping policies on athletes and their environment. All three examples seem to point at a misbalance between the general goal of anti-doping policies (the eradication of the use of doping in sport) and the unintended consequences that these policies bring about.

The pharmacological properties of many prohibited substances are such that their use in the weeks, and in some cases even months, preceding competition still has significant impact on the competition itself, without leaving traces of their metabolites in a human specimen. These properties have made the journey from prohibition of doping (early 20th century) to in-competition doping controls (1960s) to out-of-competition doping controls (1980s) to whereabouts-obligations (2000s) logical from a regulatory point of view, but the athletes have had to endure ever-increasing burdens. New regulations are always bound to encounter opposition, but sociological research in the past ten years has indicated that with the introduction of current whereabouts policies a significant proportion of elite athletes feel that the limits of what can be expected from them in regard of sacrifices in their private lives on behalf of clean sport are approaching (Hanstad et al. 2009, MacGregor et al. 2013, Overbye & Wagner 2014, Valkenburg et al. 2014). Close communication lines between policy makers and athletes are quintessential in any new plans regarding the whereabouts rules.

Regarding supplements there is a fundamental duty of all those involved in sport, including anti-doping professionals, to help athletes to perform the best they can within the limits of agreed regulations. The use of regular vitamins and other legal supplements is a logical part of any conditioning plan, if there is a potential to improve one's dietary status that their regular diet cannot provide (IOC 2011). Unfortunately the commercial reality of the supplement industry is as such that taking nutritional supplements goes hand in hand with running doping risks. Current anti-doping analyses are so sophisticated that they will pick up very low levels of contaminations of these freely available products. This is all the more problematic since the use of legal supplements can be regarded as an alternative to prohibited means of performance enhancement. This has led to a situation where athletes are advised against the use of supplements, unless these have been tested rigorously for their doping risks. So far the solution to this problem, that has been unearthed by the anti-doping community, has been sought outside the realm of anti-doping regulations. But ADOs have a moral obligation to help athletes to cope

with this situation beyond a 'just say no' approach to any supplement. Perhaps it is possible to agree on specific reporting thresholds of low-level findings during doping controls below which an AAF does not automatically lead to an ADRV. This might very well lead to less unintentional doping infractions without sacrificing many AAFs that are brought about by intentional doping users. It would also serve as a kind of protection against the ever-improving analytical possibilities, which can be expected to pick up low levels of prohibited substances in common food products such as milk (androstenedione) and chocolate (octopamine).

Case 6 is a slightly different issue, as it does not describe a specific burden for elite athletes but moreover the implicit backgrounds of existing anti-doping policies. By studying the backgrounds of a group of athletes that uses largely the same types of substances that spark so much controversy in elite sports it can be uncovered that apparently this use does not receive the same attention in this population of fitness and bodybuilding athletes. In sheer numbers of athletes, the latter group is much larger than the group of competitive elite athletes that is currently subjected to anti-doping regulations. It is also highly likely that experienced health risks and problems are much greater amongst fitness athletes, for both males and females. This leads to the inevitable conclusion that current anti-doping efforts are primarily guided by the desire to establish a doping-free competition for various reasons, but not primarily for the protection of the health of the athletes concerned. I would like to postulate that if more funds and attention is focussed on the largest group of doping users, the overall effectiveness of anti-doping policies can be expected to increase. Moreover, there is a moral obligation to address all risk behaviour that involves so-called 'doping substances', especially since concomitant health risks are one of the arguments to fight the use of doping.

These three specific examples highlight various consequences of anti-doping policies. It is also important to not just look at specific examples, but at real-life examples on a larger scale. The way in which professional cycling has evolved over the last 25 years provides a very interesting case study of an environment where various anti-doping measures have been implemented and brought about specific reactions that were not always intended. Literally all aspects of anti-doping policies come together in this 'field lab', obviously also including the aspects described in this thesis. The specific relationship between cycling and doping regulations is meticulously described elsewhere (Hoberman 2002a, Zorzoli & Rossi 2010, Millar 2011, Hamilton & Coyle 2012, Hardie et al. 2012, USADA 2012, Lentillon-

Kaestner 2013, Sorgdrager et al. 2013, Aubel & Ohl 2014, Møller & Dimeo 2014), but it is important to note that within an athletic community the use of prohibited methods can show large variation over the years as a result from policy decisions, based on the limited available evidence on doping use. Sub-conclusions are that athletes easily find ways to explain the 'necessity' to use doping under specific consequences especially under perceived 'unfair' circumstances. In some athletic cultures doping use is a fire waiting for opportunities to become a blaze. There is no proof nor conviction that the well-documented example in cycling would be limited to that particular sport.

This paragraph has described specific consequences on the daily lives of athletes and highlighted the potential frictions that well-intended anti-doping regulations may elicit. Obviously, any policy that tries to impact the playing field of athletes will also impact the lives of these athletes outside the athletic arenas. Since many substances that are prohibited possess a pharmacology that enables them to cause long-term physiological advantages for those who take them, this is unavoidable. It is up to the policy makers to decide, in conjunction with the athletes, to what degree these effects are still acceptable, and which are not. There needs to be an obvious balance between 'life as an athlete' and 'life as a human', and even when it can be assumed beforehand that there will be many differing opinions on this subject, it is necessary to come to a conclusion that is both fair and practical. Scientific studies are quintessential in this process to transcend from individual experiences to more generalised conclusions. With such data ADOs can explain policy decisions in a transparent way. Therefore, evaluation studies on all aspects of anti-doping policies remain to be necessary.

3.

PROPOSED WAYS TO BRING THE DISCUSSION FORWARD

The discussion on the issue of effectiveness in anti-doping and the cases described above allow to draw general conclusions regarding this subject. But since this thesis was also intended to be practical, it was deemed appropriate to also draw specific conclusions that may bring the discussions on this issue forward on a practical level. They can be seen as the practical consequences of the findings that have been described in this thesis and these will be described first.

3.1 Factors of a successful anti-doping policy

"Anti-doping policy is at a watershed. It is as though the individuals and organisations involved in the campaign against doping embarked on a sprint only to be told that the race has now become a marathon" (Houlihan 1999).

These words were written by Barrie Houlihan, professor of sport policy, in 1999. The words were predictive in nature, with the advent of WADA and the harmonisation accomplishments that were soon to follow. But the analogy with the marathon must mean that now, 17 years later, the campaign against doping has turned into an even longer event, such as an ultramarathon. Perhaps we should reserve the terms triathlon and ultrathlon for future policy evaluations.

The intention of this thesis was to discuss the issue of effectiveness in anti-doping policies from various angles, and ultimately to reach a conclusion on how effective current policies are, and how this may be improved. As strange as it may sound now, back in 2010 when this project started, the issue of effectiveness in anti-doping policies was barely discussed. Anti-doping professionals generally feel a personal pride in their work because they believe in the righteousness of their overall aim: a world of sport without doping. From that viewpoint anything one does 'for the right cause', whether it is an educational session that prevents just a single athlete from inadvertent doping use or a single doping control showcasing doping use in an athlete leading to a concomitant sanction, can be called a success. And such a

success justifies one's actions regardless of the amount of educational sessions one has organised, the number of doping controls one has planned and executed (or any other resource one has employed), and generally speaking regardless of the costs that have been involved. It is highly likely that this principal feeling impeded the development of discussions on the effectiveness of this work.

Fortunately, much has changed in recent years, and just the mere fact that the issue is currently discussed is an important improvement, even though a clear definition of 'success' is often absent (ASOIF 2010, Dikic et al. 2011, Hoberman 2013, Maennig 2014). This change in attitude amongst anti-doping professionals culminated in the Pound report for WADA's Executive Committee named 'Lack of Effectiveness of Testing Programs' and following discussions on this issue (Ayotte et al. 2013, WADA 2013). This report raised more questions than it answered, but it showed that WADA is taking this issue seriously. The next step is to give the concept of effectiveness relevant meaning. The reviews and case studies presented in this thesis provide several aspects that can help with this endeavour.

Doping may be seen as a 'wicked problem' in the sense that any solution will incorporate certain contradictory elements. Attempts to curb 'performance enhancement by any means' inevitably mean that the essence of competitive sport ('perform at one's best') is hampered. Calls for the protection of health are made by both defenders and critics of current anti-doping policies, which provides ample proof that the issue of 'health' itself will not lead to clear solutions. And the concept of the 'spirit of sport' is inherently vague, but at the same time it epitomises the value of sport. At the very least it is clear that any doping policy (anti or 'pro') involves many dilemmas that create huge challenges for all who are involved in doping issues: sport organisations, governments, and the athletes themselves.

But in this complex situation one can also find guidelines to steer towards solutions. When dilemmas are put into words it becomes possible to discuss their contents and to find common grounds. Transparent discussions are key to improve the current anti-doping framework (Kornbeck 2015). These discussions should be fed by scientific data, especially when they provide information on the effectiveness of a certain policy. There is an inherent obligation for all organisations and individuals that are involved to critically look at the issue of effectiveness and to reach common agreement on the ways in which this can be quantified. The opinions of the athletes

themselves are key in these efforts. These aspects will be discussed more profoundly in this chapter.

But what specific subjects are related to the issue of the effectiveness of anti-doping policies? In the first few months of this work an esteemed anti-doping colleague warned that the main conclusion of this work is already obvious: 'Some elements of anti-doping work are effective and others are not'. This may be true, but the main conclusion of this thesis is that in virtually all areas of anti-doping we simply do not know how effective the efforts are. A broader look at the world of public policies quickly learns that this situation is not limited to the field of anti-doping, but this does not mean that the issue is of little importance. Not just because of the general funds that are spent in anti-doping (an estimated minimum of 300 million American dollars per year; see paragraph 1.3) but first and foremost because of the promise of anti-doping activities to the athletes of the world. All elite athletes are confronted with burdening anti-doping measures (witnessed urine sampling and daily whereabouts sharing to name just two of them) and the least they deserve is an explanation what these measures bring to them.

The outcomes of the reviews and case studies that have been discussed in this thesis may be disconcerting at first sight. These are:

- very scarce research on the prevalence of doping use;
- even less research on the prevalence of other doping violations;
- a status quo in the field of biochemical analyses where some scientists have expressed concern about a lack of transparency on basic analytical information;
- likelihood of a high percentage of unintentional doping use among those who receive a doping-related sanction;
- no clear picture of ADRVs on a global scale until WADA's new initiative to publish general data in 2015;
- a harmonised Prohibited List International Standard that includes substances of little relevance for virtually every sport;
- elaborate administrative requirements for athletes with frequently occurring medical conditions such as asthma and persistent upper respiratory tract infections with a low likelihood that such use of medicines actually impact performances of healthy athletes;
- an existing doping method (gene doping) that is potentially highly performance enhancing but has not been detected yet;

- an overarching impossibility to study the effects of (potential) doping substances and methods in the population that matters most: elite athletes;
- a burdening whereabouts-requirement, which is necessary for finding the athletes outside their athletic environment but which simultaneously collides with basic privacy desires;
- practical barriers for and general discouragement of nutritional supplements, which under certain circumstances may even enhance athletic performance, thus providing an alternative for doping use;
- a promise to protect the health of athletes while existing regulations largely overlook an athletic activity that is undeniably associated with the use of doping products, namely fitness and bodybuilding.

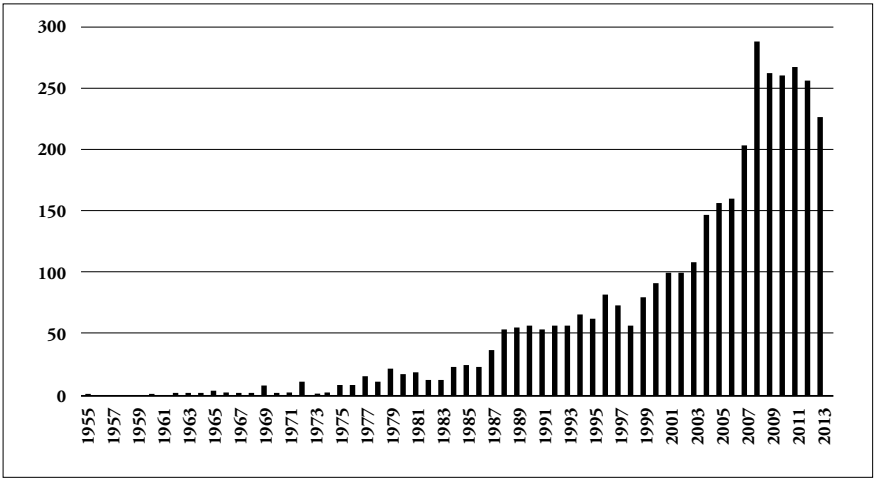
And this list of uneasiness may not be complete. But the good thing is that these issues have been discussed or are being discussed, and that solutions are being sought and implemented to aid all athletes. The results of the case studies in this thesis help to formulate potential answers in various areas of anti-doping.

Doping, as many other vices, is an example of an issue that when being counteracted there will always be a degree in which the 'good' will have to suffer under the 'bad'. It is up to the athletic community to strike the right balance between these two groups. Reliable information on the proportion of these two groups is an essential piece of this puzzle. It is up to the scientific world (both natural and social sciences) to provide further guidance in effectiveness discussions and to provide as much answers as possible to existing questions. This information is of essential value for the improvement of doping policies.

The good news is also that scientific work in doping is booming. Due to the increased WADA funds for scientific endeavours since 2001 and an increase in general interest in the subject the amount of publications on 'doping in sports' is increasing virtually every year (see figure 1 for an example). It is alarming that WADA's continuous science budget is under threat, but the continuity of scientific funds has so far been upheld with regular contributions by separate organisations and institutions to fill a voluntary anti-doping research fund (WADA 2014a). The influence of science, and its influence on anti-doping efforts, is paramount. Traditional efforts to improve analytical detection windows have yielded many successes, leading to literally dozens of new AAFs per year (as discussed in

paragraph 2.3.1). But many other available scientific disciplines seem to develop an interest in the subject, presumably because of a universal interest in sport.

Figure 1. Number of scientific articles per year with keyword 'doping in sports' within the international database of scientific articles on MEDLINE, which focuses on life sciences and biomedical information (source: www.pubmed.org).



Where the discussion above, including the numbers out of the Medline database, are primarily targeted on biochemical and medicine-related studies, a similar picture of increasing interest can be drawn about studies in the more sociological fields. A basic example, and an extremely important factor of successful anti-doping policies, is the application of education. This has not been made the main topic of this thesis; unfortunately one cannot discuss all relevant aspects of anti-doping within one manuscript. But a short discussion is opportune since scientifically based educational efforts potentially have a large impact on the behaviour of doping use (Donovan et al. 2002, Morente-Sanchez & Zabala 2013, Ntoumanis et al. 2014) even though education in itself is certainly not a panacea for all doping-related problems (Miah 2005, Hoberman 2013).

Most ADOs make a distinction within their educational efforts between 'transfer of knowledge' and 'building of values'. Both aspects are necessary to establish an athletic society that is free of doping. The issue of effectiveness is often discussed in this area. In most instances, however, these efforts are solely quantified in terms of contacts with athletes or with other groups of persons (questions answered,

presentations given, leaflets distributed, etc.). Although these indicators yield information on the exposure of target groups to the educational information that is deemed relevant (be it knowledge transfer or value building), they do not give any information on resulting changes within the individual (increased knowledge or changed values), let alone in actual (anti-)doping behaviour (Hoberman 2013). To demonstrate the importance of these differing levels of educational effectiveness, a model of doping behaviour is very helpful. Since the bench-breaking work of Donovan in this area (Donovan et al. 2002) and under the influence of WADA's financial support a lot of studies have been performed in this area, recently culminating in the review by Ntoumanis (Ntoumanis et al. 2014). Following the Theory of Planned Behaviour as introduced by Ajzen in 1991, they conclude that the decision to use doping, or not, is not made individually but is the final result of a combination of demographic, social-contextual, and psychological variables. The environment of the athlete is of great influence on doping behaviour. A similar model had been used in the Netherlands since 2003 (available in Dutch only; Wiefferink et al. 2005).

Ntoumanis et al. present an overview of all possible factors that play a role in this decision making progress, but as this particular scientific subject is still in its infancy further studies are warranted. It is certainly an area where more and more research is being performed. The past few years have seen a gradual shift towards more attention to sociological research, maybe even at the expense of analytical research. It is important to understand why athletes choose to dope, but the caveat here is that these reasons may vary between countries or sports (Morente-Sanchez & Zabala 2013). At the same time, such differences may reveal information on the reasons to dope or not. With better understanding in this area, educational efforts can be optimised. The review by Ntoumanis gives an excellent overview of the current state of knowledge.

An example of relevant research from another scientific field comes from professor of sport sciences Fabien Ohl. With Olivier Aubel he has described the backgrounds of doping use in cycling, and a roadmap for possible ways forward including closer supervision of athletes by their teams, smarter training methods, and widening the eyesight of athletes beyond their athletic careers (Aubel & Ohl 2014). These are promising recommendations indeed. It is interesting to see that sport sciences, political sciences and more and more scientific fields use their own theories and

expertise to study doping in various forms. It is part of the professionalisation of anti-doping, and encouraging for the future.

Besides the scientific and educational efforts, the anti-doping community is also focussing on broadening its perspectives. For many years WADA has been intensifying the links with the pharmaceutical industry in order to be maximally informed when new medications become available that have the potential to enhance athletic performance. This is an essential step in keeping the gap between 'hunters" and 'hunted' as small as possible. There is also more and more focus on combating doping trade, in cooperation with governments and intergovernmental institutions, which is a logical step since a global and complex issue like the use of doping cannot be solved by targeting the last rung of the ladder (the users). If the attempt to eradicate this behaviour should have any chance of success, all shackles in the chain (from production to storage to transport to use) should be targeted. Like the science to understand and combat doping use, this should be a multidisciplinary effort involving many organisations. The analogy of 'intermediate rungs' can also be used for targeting athlete support personnel, besides the traditional focus on the athletes themselves. This has become a requirement in anti-doping efforts for all ADOs in the 2015 version of the WADC (WADA 2015c). As such, there are many initiatives on various levels all working together to achieve one common goal, to eradicate doping in sport.

Another important factor is the increasingly loudening voice of athletes and their representatives in anti-doping debates in recent years. The article about the whereabouts requirements included in this thesis, written by an at that time active elite athlete, is just one clear example of this evolution. But there are more and more athletes, both currently active and recently retired, who express their opinions on anti-doping policies publicly. They have an important role in these debates as they are the prime reason why anti-doping policies exist in the first place.

The current situation paints a picture of many efforts that are being put in, many aspects of anti-doping that are highlighted, and many instruments to combat the use of doping in sports. Of course there is a financial limit as to what can be done, and there is a personal limit as to what can be expected from the people involved, mainly athletes and their support personnel. Improvements are always possible, and as such morally obligatory, but the basic foundations of current anti-doping work should suffice to be able to perform effective policies.

3.2 Towards improving anti-doping policies

The main thing that is lacking at this moment in time, is a reliable measure of success. Successes are not counted by the number of athletes that have been reached by educational materials, the number of press releases, or budgets that are kept at high levels despite global financial setbacks – they should be measured by reliable measures and materialised as a decreasing amount of doping use and/or doping impact on current athletic competitions. The latter can be materialised by determining either the perceived impact of doping on competitions or by a measure of performance. These new parameters would gain in strength if they are globally agreed upon, and established in comparable ways, much like the Performance Enhancement Attitude Scale as introduced by Petroczi is gaining more and more followers in education-related (anti-)doping research (Petroczi et al. 2008). It is only fair to look at WADA for this point, as WADA is the coordinating body on all doping-related issues. For years, WADA has regarded 'efficiency' and 'effectiveness' mainly as something that ADOs achieve when they do what they should do, i.e. adhering to the WADC and the International Standards. With the 2015 WADC a lot is expected from the extended International Standard for Testing, which now includes requirements in the field of investigations (WADA 2015c). It may be true that a lot can be gained in this area, but this does not address the issue of efficiency with regards to reaching a certain goal with a minimum amount of resources. It is certainly a laudable goal, but should rather be called 'performance' than 'efficiency'. A true measure of success in anti-doping policies has not been outlined as yet and as such an in-depth evaluation of new measures, such as the introduction of a new version of an International Standard, cannot take place.

This can partly be explained by the fact that current anti-doping policies are heavily influenced by its early beginnings. There are still discussions going on about the exact meaning and definition of the term 'doping', but the general consensus amongst policy-makers, the athletes and the public is that some substances and methods ought to be prohibited. From a practical point of view the definition problem is still solved by the publication of a prohibited list, even though this list has expanded much in the last 50 years, with only occasional retractions of certain substances. Testing for these substances still occurs through testing of bodily samples and the mere presence of a prohibited substance (or its metabolites) constitutes a doping offence, although this part of anti-doping policies has seen the greatest changes with the addition of blood-samples to urine samples and the introduction of non-analytical anti-doping rule violations (based on, for example, witnesses, police reports,

fluctuations in biological values). This testing is still performed by organisations which have a self-interest in the athletes that they test (NADOs predominantly test their own nationals, IFs solely test their own athletes) despite the obvious conflicts of interest that may arise, which means that the anti-doping framework possesses many checks and balances but ultimately relies on good intentions by all people who are involved. Finally, the effectuation of these policies with sanctions for athletes who have broken the rules has not changed, although the lengths of these sanctions have seen a striving for harmonisation up until the WADC of 2003, and since then a subsequent gradual move away from strict harmonisation taking specific circumstances of the case into account (WADA 2003b, 2009c, 2015c). The gradual changes that have been introduced reflect the very complex and intricate issues of the subject of 'doping', but this situation has also caused that the concerns that some people have with anti-doping measures have been addressed only superficially.

The fact that not much has changed on a principal level (which does not mean that not much has improved on a practical level) can indicate two different things: the anti-doping community has shown an inability to learn, or the choices that have been made in the early days of policy-shaping were right on target. Judging the overall picture, it seems fair to conclude that the latter answer is predominantly true. Introducing alternatives to these pillars of anti-doping regulations are likely to weaken the overall program as they would introduce loopholes for intentional doping users to get away with their breaking of the rules. But at the same time, it can be concluded that the world of anti-doping has lost some of its aureole of 'good intent' (Kayser et al. 2007, Hoberman 2013, Møller & Dimeo 2014) which all too often was regarded as an assurance of good outcomes, at least by many working in anti-doping. This 'good intent' might be present in most people involved in anti-doping, but the existence of predetermined schemes in order to intentionally circumvent anti-doping policies painfully showed that aureoles may sometimes be nothing more than mirages, such as the experiences in the former German Democratic Republic, various cycling teams, the BALCO-scandal, and just before the finalisation of this thesis the McLaren report which exposed a state-supported manipulation of the doping control program operated by various Russian organisations and institutions, to name just a few.

The fact that anti-doping rules are seen by many as an ethically right thing to do, has sometimes led to an ethical hubris reaching past the traditional realms of anti-doping. The examples of the influence of anti-doping regulations on the medical care

of asthmatic athletes and on the issue of (perfectly legal and mostly unproblematic) supplement use show that the lives of athletes as humans has been influenced much, and probably too much. These are clear unintentional outcomes of current anti-doping policies, and the way towards improvement lies with a stricter focus on the core of anti-doping: eradication of doping use in sport. Of course, the lives of athletes are also influenced by the fact that athletes need to provide highly personal medical and whereabouts information and are obliged to provide biological samples under supervision to complete strangers in order to comply with the anti-doping rules, but these activities can be explained by the intricate situation of applying effective anti-doping rules in a complex athletic world.

So here the word 'effective' is introduced, which has been shown to be very difficult to measure. But the world of anti-doping cannot anymore afford to disregard the calls for more insight into this word. ADOs need to be as transparent as possible in their efforts and outcomes, and even though transparency seems to be increasing (ASOIF 2010, WADA 2015a, 2015b) it could very well be that this is more transparent than what is currently being done. Critiques on anti-doping analyses, for example, have reached respectable scientific journals such as Nature (Berry 2008). These critiques need to be taken seriously and generally speaking more transparency will yield more public information on parameters of effectiveness, which is of crucial importance for a sustainable and supported anti-doping policy. In order to be able to do this in a meaningful manner it is necessary to establish harmonised overviews of data that shed light on these outcomes. This is difficult to establish and undoubtedly there will be some degree of uncertainty in the outcomes. But in the current society that stresses accountability it is not sufficient to point to the unmasking of certain doping users as an answer to the burdens, both physical and emotional, that are laid upon all athletes – most of which can still be expected to be no intentional doping users based on the evidence that is currently available.

Revisiting the list of disconcert above, I would like to propose that tipping the scales towards better balance would include:

- more research on the prevalence of doping violations is essential in order to come to an international agreement on a measure of success of anti-doping policies;
- the work of anti-doping laboratories may receive more credit if more transparency is sought in the basic research that has been performed to provide the foundation of legally binding analytical results;

- a concerted endeavour to decrease the percentage of unintentional breaches of the anti-doping rules. This should involve a wide range of possible measures including improved education, revisiting the contents of the prohibited list, and possible changes in analytical reporting rules, especially regarding low-level concentrations;
- collating more insights into the backgrounds of ADRVs. The relatively recent publication by WADA of a list of ADRVs is a good start to enable scholars to study this aspect;
- a prohibited list that acknowledges the fact that the world of sports includes many different sports with many different performance determining characteristics, and as such should seek to ban only those substances and methods that are relevant for the sport (or sport discipline) concerned;
- better acknowledgement of the fact that many athletes need to take medicines for legitimate medical reasons that may be part of the prohibited list. Strict anti-doping regulations should be based on clear information of misuse, or potential misuse, of medicines and as such these regulations should target only those groups of athletes where this potential misuse can be determined;
- continuation of the transparent and pro-active way in which the potentially game-changing 'doping of the future' gene doping has been addressed over the past 15 years;
- more research into the pharmacological effects of (potential) doping substances and methods while acknowledging the fact that not all physiological characteristics will be known when a decision on (non) prohibition should be made;
- continuous re-assessment of the necessity of requiring whereabouts-information, including studies into the effects of whereabouts on the ultimate goal of anti-doping: eradication of doping in sport;
- guiding athletes through the doping-risks of nutritional supplements by providing relevant information on risk-assessments, while acknowledging that using legal supplements may be an alternative for doping use;
- establishing more links between the anti-doping policies within the world of competitive sports and the world of fitness and body-building.

This is by no means intended as a complete set of possible improvements. If I may add one additional area where an evaluation of effectiveness can be helpful to strengthen anti-doping policies, it is the advent of biological passports which on the one hand require additional analytical and administrative efforts but on the

other hand are generally expected to yield more ADRVs both directly (based solely on passport values) and indirectly (through guiding doping controls to athletes with suspicious profiles). More data on these 'side effects' can be helpful to assess the value of this relatively new anti-doping tool. Another possible improvement, also regarding the analytical side of anti-doping, is the further advancement of the use of dried blood spots or even saliva in order to decrease the burden on all athletes during doping controls. And many more improvements can probably be imagined.

The case studies in this thesis have provided several examples of possible progress. They prove that anti-doping is highly multifaceted and far from being 'ready'. These examples include a general call for more evaluation research, more transparency, and more involvement of the athletes themselves. Those are the main avenues where progress can be made. They all focus on the core of anti-doping, as opposed to general calls for expansion of existing measures (more controls, more substances that should be banned, more available funds). The available evidence points to an importance of strengthening this core before other measures can be contemplated.

It is clear that anti-doping needs to focus: what is it that it tries to preserve in sports, and how far can we go to pursue the ideal of athletic achievements with 'intrinsic value'. Such a general agreement would provide more studies into the effects of anti-doping regulations, and as such also on the effectiveness of anti-doping policies. By focussing on effectiveness parameters, it is hoped that many aspects can be changed into more effective measures, with the case study of mind sports and the currently obligatory analyses of all doping substances on the prohibited list as a prime example of an area where improvements of efficiency can be easily achieved.

All successes are built on the combination of efforts in education and the control of doping use (including testing at the right times, world-class analyses, and knowledgeable juridical handling of any proof of doping). Various efforts aiming to eradicate doping use may supplement these. There is not just one factor that is most important; anti-doping is one of those subjects where every single issue needs to be optimally tuned. A multidisciplinary approach is key to improving anti-doping policies and this should be a continuous effort. The best that anthropology, chemistry, criminology, economics, ethics, governance, law, medicine, philosophy, physiology, psychology, sociology, and toxicology have to offer is necessary. Such optimisation is not strange in the world of elite sports: it is what every athlete and

every coach ambitions, and what every spectator expects. The least the anti-doping community can do is to work with the same commitment with which elite athletes try to be the best they can be.

A true multidisciplinary approach may also help to look at the anti-doping framework with 'foreign' eyes. The review of the magnitude of doping use showed that the prevalence of use of a permitted substance (nicotine) is comparable to the prevalence of use of prohibited substances, and the discussion on the effectiveness of substances showed that the anticipated effects of many prohibited substances can be expected to be lower than a placebo-effect in sports. Such conclusions may be uncomfortable, but they show that much work needs to be done in explaining the backgrounds of the existing rules.

What could be improved in anti-doping is an increased level of transparency. It is true that not all strategies and analytical intricacies can be shared, or at least not at all times, as such information would make the use of doping much easier for those who chose to do that and try to avoid detection. But in order to remain believable and to sustain the confidence of all stakeholders, including the public, ADOs need to be transparent in their efforts, successes and failures. To give just one example: scientifically speaking, the doubts on the results of the analyses of the Floyd Landis case have not been taken away completely by the debates that followed Berry's critical article in 2008. From a fundamental point of view, it is irrelevant that this particular athlete has admitted using several doping methods at a later stage. This sort of analytical results need to be completely clear and respected. No scientific effort provides 100% certainty, as effectively argued by Karl Popper and Imre Lakatos. But a scientist should always be ready to explain what has been done, and what the degree of certainty is in any doping analysis. It complicates things that in the field of anti-doping in-depth knowledge of all aspects of the applied analyses can be abused by knowledgeable people to minimise the risk of detection of intentional doping use so full transparency is likely to be counterproductive in the long term. Likewise, laboratories cannot provide their entire accreditation paperwork in each and every AAF that they report. This is a particular area where a clear balance should be sought between transparency and practicality (as a side-step: the current technical document specifying the contents of every laboratory documentation package that can be provided to an athlete who has been confronted by an AAF seems to have found this balance for the last issue pretty well).

More transparency will also help to focus the contents of the Prohibited List International Standard. This key document of anti-doping policies, it could even be argued that it is the practical definition of what doping really is, has been built on 50 years of opinions and experiences. In practice, the list is gradually expanding and very seldom a substance, let alone a group of substances, is taken off the list. This is a clear example of an element of the anti-doping framework that is out of balance: the prohibited list runs the risk of collapsing under its own weight. It also tries to harmonise the prohibition of doping substances across all sports, yet it allows for certain categories of substances to be prohibited in certain sports only. The list deserves a thorough update, firstly by banning only those substances that are relevant for the involved sports discipline and secondly by a clearer focus on the unethical deemed combination of relevant performance enhancement and health risks.

The criteria for putting substances and methods on the prohibited list are open and vague, which in itself is not wrong, but it has created the current situation of a prohibited list that is not explained in depth by WADA nor thoroughly understood by those who lack the historical understanding of the list. It is proposed to promote the criterion of the 'spirit of sport' to the core of all anti-doping efforts (see paragraph 3.4). As such, this concept would be the starting point in the process of prohibiting certain substances or methods instead of an optional downstream criterion. This would mean that potential substances and methods for the prohibited list would be discussed solely on the basis of (potential) performance enhancement and health risks. This assessment should be publicly released so the contents of the list is completely transparent and explainable, even though it can be expected that many disagreements will continue to exist. It is important to realise in these discussions that if regular medicines and/or so-called 'social drugs' are involved (beta-2 agonists, diuretics, stimulants, glucocorticosteroids, narcotics, and cannabinoids) the sanctioning regime quite often choses to lower the period of ineligibility because of a perceived lower degree of fault on the side of the athletes. Apparently, some prohibited substances are regarded as being less vulnerable to sport than others.

Finally, it is unavoidable for all ADOs, and especially WADA, to include efforts to counteract the use of doping substances in other groups than competitive athletes, such as non-competitive fitness athletes and even society as a whole. Anti-doping professionals possess a profound knowledge on these substances and have a potentially important role to play in educational efforts and policy deliberations on

all issues that include the unwanted use of substances and methods that are part of the prohibited list. From a fundamental point of view it is difficult to explain that so many efforts are being targeted at fighting doping in competitive sports, for a large degree under the pretence that this will decrease health risks in these athletes, while the athletes that use doping in non-competitive settings, in number a much greater group and as such a potentially greater health hazard on the population level, are not targeted by most of the ADOs in the world.

An analogy can be seen with the way how the IOC tackled the issue of doping in competitive sports after the establishment of the IOC Medical Commission in the 1960s: strong in words, but without a long-term philosophy (Hunt 2015). WADA is obviously well aware of the doping market outside competitive sports, but chose to focus predominantly, if not solely, on competitive sport in the first fifteen years of its existence. This should change in the future, and it is likely to change as well since WADA is increasingly targeting global cooperations to combat the illegal trade in doping substances, and has been setting up formal alliances with Interpol and the pharmaceutical industry in recent years. When targeting the illegal global trade in performance enhancing substances it is unavoidable that most of these efforts are targeted at non-competitive sport-related activities. It would be more transparent and more logical to officially acknowledge this fact without necessarily undermining the main objectives, which are targeted at competitive sport. The WADC is intended to serve athletes, and athletes are defined as those who compete in sport (WADA 2015c). But there is a world to win outside the realm of competitions and an organisation which prides itself in being the leader regarding the subject of doping cannot afford to disregard the largest group of users of doping substances, even though there might not be a formal sports rule that prohibits them to use these substances. In WADA's current strategic plan one of the objectives is literally (emphasis added): "WADA is recognized by the international community as the authority and the 'thought-leader' in the movement for doping-free sport in all its forms" (WADA 2014b). Such an increased involvement by ADOs in areas adjacent to traditional anti-doping is likely to benefit in two directions, as policies will undoubtedly be enhanced if knowledge and experiences are shared.

3.3 Measuring effectiveness of anti-doping policies

The main research question of this research was: How effective are current anti-doping policies? Such a broad approach was bound to lead to incomplete answers,

but the above has led to more insight into those aspects that contribute to successes in this area, and into areas that could benefit from improvements.
In a sense, each and every athlete that has been prevented from serious harm can be called a success. And, similarly, each competition that has started with equal chances for non-doping athletes in comparison to potential doping-cheats is a victory for doping-free sport. But if it takes too many resources to achieve such goals or if the side-effects of anti-doping policies are too severe these efforts are bound to lead to heavy criticism, and deservedly so.

What is needed in every evaluation of effectiveness, is a clear measure of effect. And equally important: such effect measures need to be transparently available. It can be concluded that this is a feature that has received too little attention in the past 50 years of anti-doping policies. The focus has been on individual cases, and each case 'won' was considered an important step forward in the overall goal: eradication of doping in sport. But have these cases been drops of water on a hot plate, or have they actually impacted competition in a way that the use of doping was diminished? Nobody knew exactly.

Over the last few years, it can be noticed that 'effectiveness' and 'efficiency' are words that are used more and more often in discussions on anti-doping. But so far, it seems that different persons talk about different things when they use these words. WADA mainly looks at compliance with the written rules in the WADC ('do stakeholders do what we agreed upon they would do?') while others would like to bring economic factors in the equation ('are anti-doping regulations worth what they currently cost?'). The Pound-working group on the perceived lack of effectiveness of testing programs did not even provide an explanation of what they considered to be the meaning of this word (Ayotte et al. 2013).

What the anti-doping community needs first and foremost, is a generally agreed upon measure of 'success'. There are numerous ways to do this, focussing on either the perception of the athletes themselves on the influence of doping use on their competitions, on changes in elite athlete performances, or on the number of ADRVs and/or AAFs or other measures of performances and successes by ADOs. Each of these measures has its pros and cons, and taken together these can build on each other's strengths which is likely to paint a highly relevant picture. In this thesis, it is proposed that establishing reliable measures of the prevalence of doping use in sports is the prime candidate to provide a valid measure of success, preferably with

a distinction between intentional and unintentional doping use. Prevalence figures will not be a panacea to silence all discussions in this area, as they will possess uncertainties and they will certainly not eliminate the complexities involved in the issue of doping. But they are able to provide essential information for measures of effectiveness. The tools to provide scientifically reliable data on these issues are readily available; they just need to be used more often.

Once consensus has been reached on one or more measures of success, meaningful discussions can take place on the issue of effectiveness. Only then a balance can be sought between the costs and impact of certain anti-doping measures and their effects on different groups of athletes: those who follow all anti-doping rules (out of principle or out of practical considerations), those who have decided to break (some of) these rules, and those who simply do not think too much about these rules. Doping policies (and note that the prefix 'anti' is not used here) will become stronger if the latter group is as small as possible, as these policies are strengthened with the involvement of the athletes themselves.

3.4 Revised instrumentalisation of the concept of doping

A pivotal subject in a new evaluation of the concept of 'effectiveness' is the instrumentalisation of the concept of doping. So at this point of this study it can be concluded that we are back where it all began: the definition of doping. But this is not a call for a new definition of doping; the best way to construct a clear and juridical waterproof definition of 'doping' is the current article 1 in the WADC: doping is one out of (currently ten) possible violations. But this definition steers away from the real contents of the discussion: what should we consider to be doping? This is a recurring question in all anti-doping related policy discussions. An article was written to discuss this issue and to propose a possible solution. The manuscript has been submitted to the International Journal of Sport Policy and Politics.

THE REDUNDANCY OF THE CONCEPT OF 'SPIRIT OF SPORT' IN DISCUSSIONS ON THE PROHIBITED LIST OF DOPING SUBSTANCES

O de Hon

Submitted to *International Journal of Sport Policy and Politics*. Re-printed with permission from Taylor & Francis.

Abstract

Doping is defined by the World Anti-Doping Agency as the occurrence of an anti-doping rule violation. These violations are mainly materialised by the content of the Prohibited List International Standard. A substance or method may be put on the prohibited list if it meets any two of the following three criteria: 1) the potential to enhance sport performance; 2) representing a potential health risk to the Athlete; and 3) a determination that it violates the 'spirit of sport'.

The concept of the 'spirit of sport' is explained in the fundamental rationale for the World Anti-Doping Code. This means that the decision that doping violates a fundamental principle of sport. One may not agree with this decision, but apparently there is some 'spirit of sport' that is deemed worthy of protection. This means that this concept is essentially present in all anti-doping rules and regulations, and as such also in all discussions on the Prohibited List. But this concept is subsequently offered as a possible criterion to add substances or methods to the prohibited list as well. It is unsatisfactory to call something both fundamental and optional.

It is proposed in this article to eliminate the spirit of sport-clause as an optional criterion in the determination whether a substance or method should be prohibited or not. This will focus discussions regarding the contents of the Prohibited List on the potentially performance enhancing and health risk properties of substances and methods. This would make discussions on this issue more transparent.

Preface

The issue of doping in sports continues to spark debate and controversy. The word 'doping' apparently invokes strong emotions in many people, and in order to guide

discussions on this subject there have been many attempts to define this concept of perceived unethical performance enhancement. Calling on the protection of athletes' health and on a basic belief that the integrity of sport should be protected, almost all competitive sports in the world currently have anti-doping regulations in place.

This article deals with the way in which 'doping' is currently defined in international competitive sport. It highlights the problems that are encountered in this definition, with a main focus on the concept of 'the spirit of sport'. It concludes with a proposal that might enable to focus future discussions in this area.

A short history of defining doping

The definition of 'doping', being the act in sports that is regularly considered as cheating and as such is prohibited by many sporting bodies and some governments, has proven to be problematic over the years (Houlihan 1999, Gomez 2005). The first known prohibition in human sports was laid down by the governing body of the sport of athletics, the IAAF, at its congress in Amsterdam, the Netherlands, in 1928. The IAAF handbook of that year reads 'Doping is the use of any stimulant not normally employed to increase the power of action in athletic competition above the average' (IAAF 1928). In the decades thereafter, several definitions have been proposed and also approved by respectable institutions, among which the Council of Europe and the International Olympic Committee (IOC). All of these had one thing in common: criticism on the definition of doping flourished before the ink was dry. This criticism always circled around the discussion on what can be considered 'normal' and when does 'supernatural' begin. It proved to be impossible to reach consensus on these issues (Houlihan 1999, Gleaves 2015, Schneider 2015).

The World Anti-Doping Agency (WADA) settled this discussion by providing a juridical waterproof definition. In the first World Anti-Doping Code (WADC) the definition of doping was brought back to its practical essence: doping is the occurrence of an anti-doping rule violation (WADA 2003b). The current WADC lists ten possible violations:

- presence of a prohibited substance or its metabolites or markers in an athlete's sample;
- use or attempted use by an athlete of a prohibited substance or a prohibited method;

- evading, refusing or failing to submit to sample collection;
- whereabouts violations;
- tampering or attempted tampering with any part of doping control;
- possession of a prohibited substance or a prohibited method;
- trafficking or attempted trafficking in any prohibited substance or prohibited method;
- administration or attempted administration to any athlete in-competition of any prohibited substance or prohibited method, or administration or attempted administration to any athlete out-of-competition of any prohibited substance or any prohibited method that is prohibited out-of-competition;
- complicity;
- prohibited association (WADA 2015).

The exact contents of these possible violations are not relevant for the discussion I would like to put forward in this article. From a juridical point of view the word 'doping' may be defined, but the core of doping and anti-doping policies comes down to the question why certain substances and methods are prohibited in the world of sports in the first place. This article focuses on this core and is intended to serve as a utility to discussions on what this core exactly is or should be.

Current meaning of the word 'doping'

Since WADA is the global organisation that promotes and coordinates the fight against doping in sport, it is their interpretation of the word 'doping' that is of main practical importance. Behind the official definition of doping, being one out of ten possible anti-doping rule violations, lies the materialisation of the word. All violations pivot around the exact content of the words "a prohibited substance or a prohibited method" and these words are materialised by the Prohibited List International Standard (PLIS). Use of the phrases 'mechanical doping', 'financial doping' or 'technology doping' are in fact derived from the original meaning of a substance that was deemed to possess pharmacological properties of invigoration (Müller 2010).

It was one of the first hallmarks of WADA to clearly write down what sort of substances and methods may be considered for this prohibited list, and at the same time WADA made some important changes in the prohibited list that up till then was collated by the IOC (WADA 2003a). Which substances and methods qualify to be included in the PLIS is explained in article 4.3 of the WADC, which states:

"A substance or method shall be considered for inclusion on the Prohibited List if WADA, in its sole discretion, determines that the substance or method meets any two of the following three criteria:

1. medical or other scientific evidence, pharmacological effect or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or enhances sport performance;
2. medical or other scientific evidence, pharmacological effect or experience that the Use of the substance or method represents an actual or potential health risk to the Athlete;
3. WADA's determination that the Use of the substance or method violates the spirit of sport described in the introduction to the Code." (WADA 2015)

An extra possible reason to prohibit a certain substance or method is when there is a potential to mask the use of a substance or method that is included in the PLIS.

Besides the obvious central role that WADA has in determining the contents of the PLIS, it is clear that two words are pivotal in this definition: 'potential', in the first two criteria, and 'considered', as a general concept. These words mean that practically all substances and methods one can think of may be made part of the PLIS. There can always be found someone in the world who may consider that a certain substance can potentially enhance athletic performances. The same holds true for the other two criteria, and WADA is entitled to follow this opinion. Obviously, in practice it is not so simple and on a global scale there are many discussions on the degree in which substances or methods fulfil the three criteria (Mottram 1999, Kuipers & Ruijsch van Dugteren 2006, Petrou 2006, Montalvan & Duclos 2008, Orchard 2008, Gleaves 2015). Where all three criteria can be deemed to be falling under the general header 'morality' (Malloy et al. 2007), the first two are mainly within the realm of (sports) physicians and coaches. They often lead to endless debates on the degree in which substances can be deemed ergogenic or detrimental to health. These debates also take into account the various performance determining factors in various sports, and often lead to debates on the influence of dosage. The scientific world has certainly not reached consensus yet on these issues, even though the profession of 'sport scientist' has existed for almost a century already and all pharmacological and toxicological handbooks meticulously outline possible side effects of all sorts of substances. I will discuss this labyrinth of opinions in more detail in paragraph 4. The third criterion, WADA's determination

whether something is a potential violation of the 'spirit of sport', is even more grey around the edges, which means that a more in depth discussion on this criterion is opportune.

Examining the 'Spirit of Sport'

Article 4.3.1.3 of the WADC mentions that the 'spirit of sport' is described in the introduction of the WADC. The difficulty with this reference, is that there is just one paragraph in the WADC called 'introduction' and this does not mention the spirit of sport at all (WADA 2015). The preceding paragraph, however, is called 'Fundamental rationale for the World Anti-Doping Code' and this provides the following description:

"Anti-doping programs seek to preserve what is intrinsically valuable about sport. This intrinsic value is often referred to as 'the spirit of sport.' It is the essence of Olympism, the pursuit of human excellence through the dedicated perfection of each person's natural talents. It is how we play true. The spirit of sport is the celebration of the human spirit, body and mind, and is reflected in values we find in and through sport, including:

- ethics, fair play and honesty;
- health;
- excellence in performance;
- character and education;
- fun and joy;
- teamwork;
- dedication and commitment;
- respect for rules and laws;
- respect for self and other Participants;
- courage;
- community and solidarity.

Doping is fundamentally contrary to the spirit of sport. To fight doping by promoting the spirit of sport, the Code requires each Anti-Doping Organization to develop and implement education and prevention programs for Athletes, including youth, and Athlete Support Personnel" (WADA 2015).

This description gives a certain feel to the concept of spirit of sport but is not entirely clear about it, as previously discussed by Loland and Hoppeler (Loland & Hoppeler 2011). The sentence "Doping is fundamentally contrary to the spirit of sport" borders to circular reasoning, but apparently it is about ethics, values, and Olympism. This last reference adds more words and concepts to this feel. The IOC's Olympic Charter states "Olympism is a philosophy of life, exalting and combining in a balanced whole the qualities of body, will and mind. Blending sport with culture and education, Olympism seeks to create a way of life based on the joy of effort, the educational value of good example, social responsibility and respect for universal fundamental ethical principles." It adds: "The goal of Olympism is to place sport at the service of the harmonious development of humankind, with a view to promoting a peaceful society concerned with the preservation of human dignity" (IOC 2015). The problem with 'ethical principles', however, is that they are not always universal. In fact, the motto of the IOC itself (the Latin phrase "Citius, Altius, Fortius", which translates into "faster, higher, stronger") may be seen by some as encouragement to use all the possible substances in the world, even if these may be formally prohibited, if these indeed have a potential to enhance your performance. But that is clearly not what is intended by either the IOC or WADA.

The issue of the spirit of sport has been discussed elaborately and very usefully by two scholars: McNamee (McNamee 2012) and Ritchie (Ritchie 2013). McNamee provides a comprehensive description of the process of prohibiting something on the PLIS, which leaves me with the possibility to describe the process in more general terms. He also argues that the concept of 'spirit of sport' may seem vague, but that it is necessary in order to have a meaningful doping prohibition. I will come back to this later. Ritchie provides a historical account of the creation of the concept of the spirit of sport, which is a must-read for all who discuss this issue. It gives more understanding to the backgrounds of the current text in the WADC.

Practical realisation of the PLIS

The PLIS is routinely renewed on (at least) an annual basis by WADA in order to follow new experiences and scientific findings. All stakeholders of the WADC are annually provided the opportunity to submit propositions to change the contents of the PLIS, after which a working group of non-WADA employees drafts a new PLIS. This is discussed in WADA's Health, Medical & Research committee and the final decision on the contents of the PLIS is made by WADA's Foundation Board and Executive Committee.

The PLIS is currently a list of more than 200 specifically mentioned substances and a few methods, arranged in fifteen groups based on their pharmacological similarities. But even more substances are prohibited, as most groups of substances start with the description "including but not limited to" or conclude with the words "and other substances with a similar chemical structure or similar biological effect(s)". This means that the PLIS is an open list, and potentially contains many more than 200 substances.

Because of the words chosen in article 4.3 of the WADC it is obvious that WADA's PLIS is a subject of major debate and even controversy (Kuipers & Ruijsch van Dugteren 2006, Petrou 2006, Montalvan & Duclos 2008, Orchard 2008, Huestis et al. 2011, Pluim et al. 2011, Heuberger et al. 2012, Pigozzi et al. 2012, Gleaves 2015). WADA's task is daunting indeed, as global agreement on these three criteria are simply utopian. With the anti-doping rules being an important part of general sport rules, it can be concluded beforehand that it will take great sportsmanship from many stakeholders to accept decisions that they personally would not make. The annual submissions are not officially published, but some stakeholders publish their contribution publicly. These insights make clear that the three criteria without further prioritisation have not resulted in a more unified approach. Each stakeholder puts different emphases on different aspects of the three criteria that are mentioned in the WADC. This is not strange, as the broad definitions of the criteria open the doors to just about any substance or method to be potentially prohibited. To provide just a few examples:

- 'the potential to enhance sport performance' would include six training sessions per week at the age of ten (a method currently employed in numerous sports) or psychological abuse of young athletes (which has proven to be performance enhancing in the past, or at least not sufficiently performance deteriorating to eradicate this kind of behaviour);
- 'potential health risk to the Athlete' would include eating three plates of spaghetti (risk of obesity), or taking ten ibuprofen pills before an athletic event (risk of stomach ulcers, or worse);
- 'violates the spirit of sport described in the introduction to the Code' would include all examples mentioned above (health, education, and joy being part of that 'spirit of sport' according to the Code).

These examples may seem trivial, but they are not. They could be seen as fulfilling the criteria as described in the WADC but during the past decade it has been decided not to do so. These decisions have not been published in reports, not in scientific articles, and most of the times not even in the minutes of the meetings where these decisions have been made. It is just the way it is, and where the decision to not ban any of the examples given above have received a great degree of support by those who are active in the athletic community, there are numerous examples where this support is not as broad. Creatine, for example, is still a permitted substance and the use of hypoxia-devices or thyroid hormones is also permitted, where various groups of stakeholders do not agree with this status.

As a summary of the current situation, it can be safely said that scientific experts will never exactly agree on the potentials of the first two criteria, let alone all stakeholders in the entire world. And the third criterion, about the spirit of sport, makes the discussions on this subject even more hazy. It does not help either that the 'spirit of sport' is explained, among other words, by the terms 'excellence in performance' and 'health', and as such it redirects to the other two criteria.

(As an aside: prohibiting any act might be seen as paternalistic, but if the organisation that decides on rules and regulations makes this particular decision, the rule is there, and apparently there was a reason why the rule has been implemented. Why are you not allowed to cut corners in athletics? Because it would not be fair to shorten the course just for you. Why are you not allowed to be in an off-side position in association football? Because it was deemed to be too easy to have a clear shot at the goal. Why has the off-side rule in field hockey been abandoned? Because it was deemed to benefit the game if the whole field could be used without interruptions. Why is doping banned in almost all sports? Because in the eyes of many apparently there is something more important than just winning. You might call it general health protection, you might call it the protection of the spirit of sport. Or you might define it as a certain act involving a listed substance or method in an International Standard, as is currently the case in almost all competitive sports.)

A more clear and distinct definition will aid to guide discussions on (anti-)doping policies. Agreeing and focusing on the core of doping will also better contribute to a more broadly supported solution to the issue of doping in sport. There continues to be a strong debate on the necessity to ban doping at all (Savulescu et al. 2004, Kayser et al. 2005). Both sides of the fence, those who support the general principles

of current anti-doping policies and those who support a more lenient approach to the medicalisation of society, and thus to sports as well, are seeing problematic issues in the current situation.

Bringing the discussion forward; a new appreciation of the 'Spirit of Sport'

It is probably true that there will never be a globally supported complete agreement on what substances and methods should be banned in sports, as athletes 1) do need to be protected against themselves at times according to many rule makers; 2) are deemed by many to have a fundamental right to a fair and safe competition in which they are not forced to engage in risky behaviour simply because their opponents dare to do just that; and 3) are role models to their admirers, who include children. These three issues are not specifically addressed in the WADC but they are always just around the corner when the PLIS is discussed (Wiesing 2011, Schneider 2015). As such, there are many more implicit criteria that play a role when the contents of the PLIS is discussed. In some instances, it seems that the PLIS is being used as an attempt to get rid of all sorts of vices in the world of sports. Obviously, if something is deemed to be a vice, measures can be taken against it. It can be argued that well-known champions should not drink and drive or assault their spouses. But there is a general consensus that such behaviour should not be dealt with in anti-doping regulations, which include anti-doping tribunals and long suspensions. The same could be argued regarding irresponsible pain killer use, or so-called 'social drug' use. Especially the use of cannabis is highly controversial in the field of anti-doping (Campos et al. 2003, Huestis et al. 2011). It may be true that 'real champions' do not engage in such behaviour, but anti-doping regulations are not about all possible misuse of any pharmacological substance. As an addition to this wide debate: any handbook in toxicology will explain in the introduction that it is not as much the substance that makes the poison, but the dose in which it is being used. This basic property of all substances makes it necessary to use a rather open definition of potentially important substances that may be banned in sports. It also means that there is a strong need for prioritisation in doping-related discussions. This would focus the process of creating and sculpting the PLIS.

In my eyes, the essence of doping is the unethical use of potentially dangerous substances or methods with an expected performance enhancing effect. As McNamee & Tarasti have stated before: "Performance enhancement per se, is of

course the heart of elite sport. The other criteria establish means by which it is unacceptable" (McNamee & Tarasti 2010).

The intrinsic problem of many substances is that higher doses of effective performance enhancing substances, such as anabolic steroids (Hartgens & Kuipers 2004, Health Council of the Netherlands 2010), show greater effectiveness in performance enhancement but at the same time yield greater risks of health problems. In competitive sports, this intrinsic property of such substances puts pressure on other athletes who have not (yet) used these substances, creating an ethical dilemma. It is as such all three of the current criteria that justify a prohibition, but not weighed in equal importance in all instances. And this is exactly why I would like to propose a new and clear weighting of the three criteria, that all play a role in the decision to ban certain substances or methods in sport.

In its essence, the decision to prohibit something is already an ethical judgment in itself. Apparently, there are things (substances, methods, anything) that justify a prohibition. With the decision to prohibit doping in sports, the rule-makers of that sport create an environment in which pharmacological shortcuts to physiological top-performances are officially prohibited with the clear intention to protect the sport from an unwanted influence. As such, the decision to prohibit doping in sports can rightly be called an attempt to protect (at least part of) 'the spirit of sport'. This spirit may be somewhat vague, but WADA, with the aid of the IOC, has provided long descriptions of what it is supposed to be. And as McNamee has argued, vagueness in itself is not a valid reason to disregard the entire argument (McNamee 2012). One may not agree with the descriptions that are provided in the WADC, but they are available. They have even been made available as a 'fundamental rationale'. Besides, numerous ethicists and philosophers have not agreed with the other two criteria either, claiming that performance enhancement is the essence of the human race and that health risks are inherent to life and that you may expect that athletes, with the aid of medical professionals, can cope with that risk, at least when they are adults (Savulescu et al. 2004, Kayser et al. 2005, Miah 2005, Kayser et al. 2007). Discussions on these concepts are both interesting and important, but they do not provide a justification that all three criteria are equally important.

McNamee argues that the concept of the spirit of sport is necessary in order to have a meaningful doping prohibition (McNamee 2012). I completely agree, but the ultimate consequence of this statement is that the spirit of sport is essential to

all anti-doping regulations. Not just as a possible 'one out of three' criterion, but as a central issue and a justification of why any substance or method is banned in the first place. I would like to argue that it would be more clear to everyone if the rule-makers put their ethical judgement where it belongs: right at the beginning of a chosen prohibition. This has been done in the early pages of the WADC, and by doing so it has been made clear that the influence of this ethical judgement should and will be present in all regulations of the WADC. Let us be frank about this central role of the spirit of sport in all anti-doping related regulatory texts.

Following this line of argument, this also means that it is unnecessary to include it as a possible criterion in the instrumentalisation of the PLIS. If the concept is fundamental to the prohibition of doping, as I think it is, it is redundant to offer it as a possible criterion at a later stage. Stressing this fact would take the 'spirit of sport' criterion out of the prohibited list-related discussions. As a consequence it would hopefully provide more clarity and focus in the discussions on this issue as well. It would position the criteria of 'potential performance enhancement' and 'potential health risks' as two equally important aspects in the practical decision to ban a certain substance or method, allowing more precise discussions than what is currently possible.

Back to the examples provided above. Abusing young athletes physically or psychologically? Surely unethical but these acts are better handled outside doping regulations as they require counselling and psychological guidance. It is also difficult to consider this cheating. Eating too much spaghetti? An unhealthy act that one quickly learns to avoid, or other help is needed. It might be even performance enhancing in some sports but eating disorders should not be handled by juridical panels. Swallowing ten ibuprofens before an event? Athletes should be protected from such behaviour, as it is medical misconduct and it puts them at risk. But a prohibition according to anti-doping regulations is not likely to provide a sufficient solution as long as one ibuprofen is deemed permitted. One could imagine the introduction of a threshold value that would point to an 'unhealthy ibuprofen dose' but this would effectively put all possible pharmaceutical substances on the PLIS, above a certain level. And to be consistent, this should not be just the case for pharmaceutical substances, but for all substances, which makes such an approach nearly impossible. All these examples show that simply prohibiting something 'because it does not feel right' is never possible within an anti-doping context.

There needs to be some kind of guidance, because in any discussion on the contents of the PLIS there are always many issues automatically involved.

If the criterion of the spirit of sport is taken out of article 4.3 of the WADC, discussions on the prohibition of substances or methods can focus on two criteria alone. Will it thus be able to provide a 100%-water-tight definition of doping? Probably not, and borderline decisions and interpretations will always need to be made by a committee that is given these powers. And WADA's working group on the prohibited list is the obvious candidate for this: it is well-equipped and profoundly knowledgeable. Maybe taking the 'spirit of sport' clause out of article 4.3 of the WADC does not even change the PLIS itself. But it would make discussions more transparent, and likely guide the issue of doping towards the abuse of medical substances. These decisions should be driven by science, while also taking into account the practical consequences that lie behind the decision to place something on the PLIS or not. There will be plenty of issues that can, and will, still be debated when it comes to the PLIS and as such the instrumentalisation of doping.

Conclusion

The only way to construct a clear and juridical waterproof definition of 'doping' is the current article 1 in the WADC: doping is one out of (currently ten) possible violations. But this definition steers away from the real contents of the discussion: what should we consider to be doping? Again, there is a juridical definition, which is 'all substances and methods that are mentioned in the Prohibited List International Standard'. But this is where the grey area starts, and hence where unclarities begin. First of all, the prohibited list has many open endings with use of the words 'and other substances with a similar chemical structure or similar biological effect(s)' and 'including but not limited to'. Ultimately, it takes a global agency with appropriate powers and authority to make clear where the line is drawn between prohibition and permission. But most problematic of all, the criteria that guide the contents of the prohibited list are optional and wide open to interpretation, and thus for discussion.

I would like to suggest a different weighting of the three criteria that have been identified by WADA to determine whether a substance or a method should be considered prohibited or not. It would be more clear if the concept of the 'spirit of sport' would be eliminated out of the formal definition of the prohibited list. The decision to ban certain substances and methods is an ethical decision in itself,

and this ethical judgement is already at the core of all anti-doping policies. It is redundant to introduce an extra ethical argument in the process of determining what should be banned and what should not be banned. Moreover, it is somewhat strange to offer this ethical criterion as an optional criterion, as this leaves the current situation where the two current criteria of performance enhancement and health risks suffice to prohibit something, possibly without an ethical judgement whatsoever.

I would like to call upon all anti-doping regulators to embrace the 'spirit of sport', as defined in the fundamental rationale of the WADC with a little help from the Olympic Charter. It is central to the prohibition of doping and is interwoven with all rules and regulations of the World Anti-Doping Programme. The decision that doping is contrary to the spirit of sport has been taken already, otherwise there would be no anti-doping measures at all. This state of affairs may be debated by anyone who takes issue with it, but let's not mix such discussions with the perceived (in)justification of banning certain substances or methods. Discussions on the content of the PLIS are better focussed when they deal solely with the issues of performance enhancement and health risks.

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4.

OVERALL CONCLUSIONS

4.1 Effectiveness in anti-doping

In the field of anti-doping in sport, it will never be possible to measure true effectiveness. The secret nature of the act of intentional doping use, together with the fact that no man or machine is infallible, means that a 100% reliable answer to the question 'has this particular athlete doped or not?' will never be given. As a consequence, a 100% reliable figure for the prevalence of doping use in a particular set of athletes can never be given. And since effective anti-doping efforts under ideal circumstances comes down to the minimisation of doping use by athletes, intentional or not, a 100% reliable measure of the effectiveness of doping use is impossible to give. In addition to this core piece of information, the issue of doping is very complex with many different aspects that play a role, and as such another measure of effectiveness is equally impossible to give. This first conclusion of this thesis may be disappointing at first sight, but it is by no means the endpoint of this discussion. Nor should it be.

First of all, trustworthy estimates on doping prevalence are possible. This sort of information is quintessential to reliably discuss the issue of effectiveness in this particular topic and the review on the prevalence of doping use in elite sports showed that there is a lot more to be known in this area. Moreover, the scientific principles how to increase this knowledge are already available. Randomised Response questionnaires and biomarker-based modelling are the prime candidates to provide this core information. Other measures are imaginable as well, for example measures of perceived doping-free competition and even 'old-fashioned' statistics of doping control results, but the strengths and weaknesses of such measures should be clearly outlined and considered when interpreting such numbers. Generally speaking, overviews of ADRVs provide more information than overviews of AAFs and WADA is currently providing both to the general public.

Information like this is necessary to give firm foundations to discussions regarding the use of doping, and also to be able to track successes or failures in doping

prevention over time. This would not necessarily have to cost a lot of money. Many data are already available or are already being collected and can be used for this purpose. For example: many IFs have had blood collection programs in place for many years already, and using these data in the Biomarker-based Prevalence Model would give extra information on the estimated prevalence of haematological doping in these groups of athletes. Also, retrospective testing by labs is already being performed at the request of various ADOs, most notably the IOC, but the success percentage of these efforts have not been officially communicated. It would, however, give additional information on the prevalence of previously undetected doping use. Likewise, continuing progress on the expansion of detection windows of certain doping substances can dramatically increase the number of AAFs associated with these substances. Even though this sort of information has one large caveat, as it should be kept in mind that 'mere' progress in chemical analyses may yield new knowledge on human physiology as well, and not necessarily on doping habits. But progress in analytical sciences provides information on the percentage of previously undetected doping use. The anti-doping world should not be afraid to publish these pieces of information because in the long run more is gained than lost with transparency. Obviously, anti-doping stakeholders will need to accept their vulnerability when such studies are being performed, as they may or may not support current policies.

A particular promising area in this regard are studies into the impact of anti-doping regulations on competitive performances. As yet these studies are rather rare. When expert mathematicians and statisticians cooperate with physiologists and biomechanics in order to elucidate the effect of doping, and anti-doping, on athletic performances this may yield valuable information on the effectiveness of anti-doping policies. In addition, attempts to quantify the perception of athletes (and others) about the impact of doping use on athletic competitions may complement this sort of information by providing information on the perceived effectiveness.

While gathering these pieces of information the anti-doping community should strive to try and make a distinction between intentional and non-intentional doping infractions. This is a difficult endeavour and it will never be possible to draw clear demarcation lines between the two categories, but this difference is of quintessential importance when conclusions are drawn and new policies are drafted.

Taken together, these various pieces of information will provide valuable input for discussions on the effectiveness of anti-doping policies. In order to streamline this process and in the light of harmonised policies it is highly preferable that international agreement is sought about the question which parameters would optimally feed these discussions. A balanced overview of an internationally agreed upon set of quantitative and qualitative data is quintessential for meaningful evaluations of the current situation and as such for the future development of effective anti-doping policies.

4.2 The intricacies of doping use

Doping use is not per se a sports-wide problem, but has selective origins and is limited by personal beliefs and socio-economic structures. This means that sports-wide measures, affecting all athletes, will always burden non-dopers as well. Yet, current anti-doping regulations are heavily anchored in the belief that harmonisation is key to a successful effort to fight doping. The situation in the 1980s and 1990s, where some sports fought doping with all sorts of measures while other sports barely conducted doping controls, called indeed for harmonisation and more equality between sports. Full harmonisation is currently still not achieved as not all professional sports are following the same anti-doping rules. But harmonisation in itself is not the solution either, as it can even hamper effectiveness, for example when the system of a harmonised list is continued to be as strict as it currently is. In order to be optimally effective, it will be necessary to loosen the reigns of harmonisation to a certain extent, enabling to focus attention and other resources on actual doping use by athletes and their support personnel.

The study on the lengths of doping-related sanctions showed that a high percentage of athletes that have violated anti-doping rules can be expected to have been considered to be at decreased fault by the applicable juridical panels. This is a strong indicator that the percentage of 'by-catch' in the total amount of ADRVs is higher than recommended. If this is indeed the case, this can seriously harm the anti-doping effort in the long run. Efforts to improve this situation brings more or less all aspects of the anti-doping system together: more and better education, a concise and relevant prohibited list for all sports (which likely is a less harmonised and more targeted list), controls in athlete groups where this is relevant and justifiable, clear analytical rules and technical documents that can optimally differentiate between potential 'cheaters' and 'non-cheaters', more understanding towards the practical world of athletes (for example regarding the use of nutritional

supplements). And so on. Such changes in the rules and regulations may result in an occasional 'cheater' to (temporarily) swim through the meshes of the fishing net but overall it can be expected that the balance between intentional cheaters and unintentional 'by-catch' will improve.

Doping in sports is likely to be a problem that will stay around for a long time to come. Any sport at the elite level is prone to doping use, given the existing pharmacological possibilities to increase strength and endurance and to improve precision oriented tasks and possibly even concentration. The current body of scientific knowledge in the area of athletic performance enhancement is scant, albeit growing, but since doping use implies illicit behaviour it is simply not possible to wait for definitive proof on all characteristics of substances or methods before they should be banned or not. It is unavoidable that policy-related decisions will have to be built on a certain degree of expert advice as a supplement to existing scientific literature.

The degree in which doping is able to influence performance in a purely pharmacological way should not be overestimated by those who fight against doping, but at the same time this degree should not be downplayed by critics of current anti-doping policies. Many of the substances and methods that are currently prohibited are highly likely to have a potential influence of several percentage points, which is sufficient to have a decisive influence on the outcomes of all possible sorts of competitions. It is fair to say that in certain sports there are undoubtedly more doping risks than others, but it would be difficult to name a sport that is immune to doping influences.

Also from a game-philosophical point of view it is completely logical to have some sort of doping prohibition in place. Without going into the intricacies of the connections between the concepts of 'games', 'sports' and 'play', I would like to put forward that the existence of an anti-doping framework fits into the classic definition of a game by Bernard Suits, being a voluntary attempt to overcome unnecessary obstacles (Suits 1995). If one accepts that games are the cradle of all sports, it is clear that sports participation requires the acceptance of a game-like situation, comparable to Suits' concept of a 'lusory attitude'. The use of doping can be seen as a short-cut to the best possible athletic performance. There are many reasons not to allow it, but from a fundamental point of view it is 'just' one of the unnecessary obstacles that marks a game. In my opinion the overall situation leads

to the conclusion that anti-doping policies are likely to remain for a long time to come, but not necessarily in the way they have been sculpted in the past 50 years.

4.3 Building anti-doping regulations

The current anti-doping framework is essentially still based on the set of rules that was established in the late 1960s: prohibition of certain substances that are judged to be undesirable in the world of sports, controlling for the use of these substances in bodily fluids, and sanctioning with disqualification and/or suspensions when the evidence is deemed clear enough to justify such a harsh punishment. All paragraphs and articles that have been added or changed in the anti-doping rules since that period 50 years ago have been expansions to these basic principles, trying to cover each and every aspect of anti-doping in all sorts of scientific specialties. It is as if a coat rack has been built on good intentions, and in the years afterwards this rack has grown and grown into an enormous set of rules. It needed to be fortified, braced and supported many times, but it is still there. To continue to use this analogy, and allowing a slight touch of personal preference: it does not seem to be necessary to re-address the core principles of the framework (a coat rack is still needed), but the current web of rules and regulations is bound to collapse at some point under its own weight (the rack is overloaded). There is a dire need to re-evaluate the main branches of the rack. Anti-doping regulations need to revisit its core before expanding.

This is a daunting task indeed. Whereas WADA is at the helm of the anti-doping framework, adaptations and changes are decided upon by all stakeholders, with some having more official influence than others. It involves a network of governmental and non-governmental institutions, of private and non-private organisations. It is a clear example of a multi-level governance network, polycentric and multi-layered, which provides an enormous coordination challenge. It is fascinating to see what WADA has achieved since 1999, but at the same time it is quite clear that many aspects of the anti-doping framework can and should be strengthened. The main influence probably comes from the general public, as this is a force that all institutions and organisations need to take into account. Currently, the voice of the athletes themselves, the prime stakeholders of anti-doping policies, is relatively weak in this entanglement of entities. This is a difficult issue as well, as active athletes tend to focus all of their energy into their own athletic career where a broad view and plenty of time are prerequisites to be able to participate in anti-doping debates. Over the past few years there seem to be more and more recently

retired athletes who take up this challenge and it can be expected that they can help to focus discussions on the subjects that truly matter to athletes. Providing more influence for these prime stakeholders can be expected to strengthen anti-doping policies.

One of the most important elements of the WADP is the Prohibited List International Standard, which defines what actually is prohibited and as such is considered a doping-problem. The prohibited list continues to spark debates on its contents. The current prohibited list is a wide heterogeneous collection of doping substances, both from a pharmacological point of view and from a performance-enhancement point of view. It is predominantly built on past decisions; it is very seldom when a substance, let alone a group of substances, is taken of the list. With just a slight exaggeration it can be said that it is better understood by historians than by experts in the field of medicine. Perhaps the anti-doping community should be somewhat less afraid to learn from practical experiences and increased scientific knowledge. Changes in the prohibited list are unavoidable as time progresses, and in fact they are necessary in order to maintain a credible list. And credibility to athletes, their entourage and the general public is key for a successful long-term anti-doping campaign.

It is true that many different opinions exist on the ideal contents of the prohibited list but in essence everyone is trying to construct a 'relevant' and 'meaningful' list following their own personal views. The current rules to consider substances and methods for the prohibited list allow for these individual differences to be brought in in each and every list-related discussion, and as such they are too broad to really guide the debate in this area. More focus is needed in order to streamline discussions. In this thesis it is proposed to promote the concept of the 'spirit of sport' away from the debates on the contents of the prohibited list into the core of anti-doping policies. By doing this, it is officially accepted that anti-doping rules are an ethical decision to limit the athletic potential of humans by any means to the potential by true means, or at least what is deemed true in the current timeframe. The next step is to debate the contents of the list, again and again, but now based solely on the potential enhancement and health-risk properties. It will hopefully guide discussions on the contents of the prohibited list towards what substances or methods can do – and not how they feel. After all, doping is prohibited in sport because it does not feel right in the first place.

4.4 Directions towards a more effective anti-doping policy

In just one single thesis it is impossible to cover every aspect of anti-doping and even to give appropriate consideration for the aspects that are discussed. This thesis has been set up as an exploration of the issue of 'effectiveness' as it was felt that this issue was not given sufficient attention yet in this field. It focussed on several aspects that were thought to be relevant, and because the strength of a certain concept is often surfacing when the limits are investigated, the focus has been on both the core principles and the grey areas of anti-doping. The conclusions on the core principles have been discussed above, and the case studies in this thesis offer potential improvements in specific aspects of the current anti-doping system:

- not all athletes should be tested for all prohibited substances. Too much harmonisation in this area is unexplainable and uses up scarce financial resources;
- anti-doping policies are not equal to regulations against misconduct in the world of medicine. There is an obvious great overlap between these two areas but the use of doping should be seen as the use of substances and/or methods that are deemed unfair and/or undesirable in the world of sports, and in the world of sports alone. Anti-doping efforts are doomed to fail if they become too pretentious;
- gene doping is a clear example of a possible threat to the integrity of sports that has been identified timely and where the scientific world has greatly aided anti-doping measures. The public discussions on this subject at a time when much was unknown are laudable. And even though much is still unknown today, this approach has proven that much can be gained from transparency. It is also a constant reminder that the prohibited list needs to be explainable both practically and theoretically;
- the whereabouts system can be considered to be a necessary tool in order to be able to perform a meaningful out-of-competition testing program, but it should not be forgotten how invasive these regulations are in the lives of elite athletes. Given its impact it is also imperative to feed discussions on this subject with reliable data on its effectiveness. Such high-impact rules should be drawn up and evaluated in close cooperation with the athletes themselves;
- elite athletes are expected to perform the best they can, and it is only logical to support them when they use perfectly legal means in this pursuit, such as the use of nutritional supplements. The fact that existing laws and regulations in this field have proven to be inadequate to provide full confidence in all freely available

supplements should not be held against the athletes, but at the same time the use of supplements (and a claim that they must have been contaminated with doping substances) should not become a handy excuse for intentional doping users. The least that ADOs can do for elite athletes is to point them into the right direction where they might find supplements with the greatest security that these are in fact free of doping. It is another example where the consequences of anti-doping measures should be balanced with the impact that these measures have on the personal lives of athletes;

- if the health aspects of doping use continue to be a prime reason for anti-doping policies, and the nature of many prohibited substances and methods makes this very likely, more focus should be paid to unorganised fitness enthusiasts who use substances and/or methods that are labelled as 'doping' in competitive elite sports. This group exceeds the number of doping-using elite athletes manyfold. In fact, those who work in anti-doping in elite sports may learn from the relatively open culture of doping use in this set of (often non-competitive) athletes.

These practical cases were deemed important enough to study independently from a policy point of view. By combining them there are also some general conclusions that can be drawn. Case 2 (on glucocorticoids and beta2-agonists) showed that low dosages of these regular medicines are highly unlikely to impact athletic performances if used by healthy athletes. Case 5 (on nutritional supplements) showed that legally available products that are regarded as safe by national health agencies still may contain low concentrations of banned substances with the consequence that these turn up in athlete's samples, leading to ADRVs. The clenbuterol experiences in regular meat (see 2.3.2) show a similar problem, which has led to the practical solution that athletes who test positive for clenbuterol in countries with known clenbuterol problems (China, Mexico) may escape sanctions rather simply, but only after enduring the agony of receiving a notice that an AAF has been found.

When taking these pieces of information together, I would like to propose that this is an area where a slight chance in balance may accommodate the well-willing, non-doping athletes and as such it will improve the overall effectiveness of anti-doping policies. One could think of a two-tiered system: at first, the current strict laboratory analyses focussing on the lowest possible concentrations of banned substances to identify potential ADRVs are applied. But as an extra precaution not all AAFs should lead to an ADRV if the concentration found is really low.

Without resorting to a system where a specific threshold value should be set for each and every pharmacological substance (see 3.2) it would be more sensible to have low-level AAFs followed up by an extra review, possibly including new doping controls, before a case is brought to a judiciary panel. This does not mean that all modes of administration of glucocorticoids and beta2-agonists are allowed – a distinction between local and systemic use can still be made. It neither means that all nutritional supplements are safe to use for elite athletes – the current status of supplement regulation (or lack thereof) still requires extreme caution for athletes in order to avoid high levels of banned substances in legally sold supplements. And finally it would not make the consumption of meat safe for athletes in all countries of the world – as long as there is a regulatory issue in certain countries, this will require extreme caution from an anti-doping perspective. In a black-and-white world such a two-tiered system would not make any difference at all on the outcome of case, and in fact it may be called ineffective as extra efforts are called for. But based on the cases presented in this thesis it is safe to assume that it will likely shift the balance between 'catching intentional cheats' and 'protecting the clean athlete' slightly towards the second goal, which would benefit anti-doping efforts in general. It would also steer away from the current practice where extremely low concentrations of prohibited substances may lead to an AAF in one laboratory but not in another.

This paragraph has given an overview of specific possible improvements, based on the cases that have been presented and discussed in this thesis. These can serve as a guide to future discussions on the effectiveness of anti-doping policies. The common principles of all specific conclusions and suggestions in this thesis can be summarised as a call for acquiring more relevant data, a multidisciplinary scientific approach, more focussed discussions on what the core of anti-doping policies should be, more transparency, increased involvement of the athletes themselves, and overall a better balance between the main task of anti-doping (the eradication of doping use) and the burdens placed on all athletes (who, as far as current data show, are in majority non-users).

4.5 Concluding remarks

All of the above aspects relate to effectiveness as they all provide focus in policy discussions and ultimately influence the daily work of anti-doping professionals. They are all linked to each other and attention should be given to each aspect

separately in order to maximise their impact on the overall goal of anti-doping policies. But this is not all that needs to be done.

Anti-doping policies are made and implemented both by sport organisations and by governmental institutions. They need to work together to try to achieve a common goal: to eradicate doping in sports and society. It is important to realise that this is an idealistic goal, which will likely never be achieved in practice. In the end, it is an essential choice for each and every policy maker to weigh the balance between repression and prevention. Especially in anti-doping both factors are of paramount importance. In fact, good prevention works repressive and good repression can have a great educational effect. It is yet another example that all aspects of anti-doping are of equal importance and it bears no significance to isolate one aspect and to try to quantify the effectiveness of this particular piece of the puzzle. And that every decision to change part of the anti-doping framework will inevitably lead to (profound) changes in other parts. An umbrella view is necessary in every policy decision as over the years 'anti-doping' has become a profession in itself. This means that it should not be left to experts in one specific field to decide on changing a rule or implementing a new one, although exactly these experts are needed to draft rules that are accurate and relevant. The crucial umbrella view should oversee many aspects in such a comprehensive area of anti-doping. Here, also, balance is needed: between the specific knowledge of experts and the practical consequences on the entire anti-doping system in order to avoid undesirable unintentional consequences. The major stakeholders in this balancing act are the athletes.

While shaping the anti-doping rules in such a way, it should be acknowledged that an individual athlete makes the choice to dope or not in a real-world context surrounded by many influences and that specific policy measures are likely to influence several of these factors (but not all). When discussing the effectiveness of anti-doping policies the most relevant aspect is to study the endpoint of this process: the decision to dope, or not. That is why reliable figures on doping prevalence are paramount regarding this topic.

Policy makers, researchers, athletes, and everybody else that is involved in the world of sports should realise that complete eradication of doping use in sports is a utopian goal, as there will always be some people who are willing to break the rules in order to get an unfair advantage. This is a basic criminological fact. This brings

an extra factor into the picture, which has both economic and human right-aspects: how far are we willing to go in order to bring the prevalence down? The closer the figure will come to zero, the more effort this will cost, according to the law of diminishing returns. It is important to weigh the burdens of anti-doping policies on all athletes in relation to the expected 'profit' of lowering the prevalence figure even more. This is an important balance that needs to be sought for the overall athletic population, apart from the finances that any extra efforts will require.

The current anti-doping framework would benefit from more precise measures of effectiveness and open and transparent discussions based on the outcomes of this necessary work. This way, there can be more focus on the issues that matter most, and a better balance can be sought between 'catching the cheats' and 'burdening all athletes'. A proposal for a more focussed definition of doping is given in this thesis (see paragraph 3.4 on a revised instrumentalisation of the concept of doping), but this work is by far not complete yet. Despite all the efforts and successes in the past, it can be concluded that in the world of anti-doping there has been insufficient attention to the measurement of true effectiveness. This might be understandable given the complexities of doping-related matters and because of the historical backgrounds of current anti-doping policies, but it is nevertheless a detrimental void. The prime victim of this insufficiency is not the general public and not the anti-doping professional. It is the dope-free athlete, many in number, who during an athletic career is repetitiously forced to battle against the cynics and the pessimists and all others that cannot imagine that performing at the elite level is possible without the aid of prohibited substances or methods. Only the athlete him/herself is able to state whether he/she has performed truly clean. Such an assessment is part of his/her personal satisfaction. It is up to the anti-doping professionals to help these athletes to convince the cynics and pessimists that elite sports is possible without the use of doping. It may not have worked in all sports in the past, but it is undeniably a laudable goal.

The outcomes of the studies presented in this thesis will certainly not be the end of discussions on the effectiveness of anti-doping efforts. Or at least: it should not be. In 2010, when the first discussions were initiated to start a thesis on this subject, the issue of effectiveness in anti-doping was only present on a very basic level in the daily lives of anti-doping professionals. Most ADOs were too busy just to cope with all aspects of the ever growing set of rules and regulations that accompany anti-doping. Effectiveness measures were reported as number of doping controls

performed, number of sanctions laid upon athletes or others, and financial reports of the money that went into education, controls, analyses, and the like. But how does somebody determine if what one is doing is actually contributing to the overall aim? That is the sort of studies that need to be done.

In the final weeks of writing this thesis, in 2016, the world of sports and in particular the world of anti-doping were shaken heavily by the exposure of state-supported doping use and covering-up of analytical results in Russia, dating back till at least 2011 (McLaren 2016). This asks serious questions about the level of support for the existing anti-doping framework in this and other countries. Cynics would say that the entire anti-doping framework should go back to square one to try to re-invent itself, or perhaps to abolish all anti-doping measures altogether. But anti-doping scandals, as any other integrity scandal, can present themselves at all times and in all countries. What should be done, is holding in-depth discussions on the reasons for prohibiting doping, engaging all relevant stakeholders, and to re-assess the (potential) effectiveness of doping policies. This should be the approach for any new challenge, for example the potential of medical and non-medical applications of transcranial direct current stimulation.

It is obvious that the field of studying the effectiveness of anti-doping policies is very new. This thesis is a first broad attempt to tackle the problem and to give examples and directions through which the issue of effectiveness can be addressed. This requires the effort of many experts as it is essential to fully appreciate and value the multidisciplinary character of the anti-doping framework. As Deetz stated, diversity can be expected to have very positive effects (Deetz 1996). It is clear that particularly the field of doping policies can be a fruitful terrain for collaborations between a wide array of scientific backgrounds, and both researchers and the subjects of such studies may benefit enormously from such a cooperation. The voice of the athletes themselves is indispensable in this process. This way, many improvements can be expected, and in fact this topic has already been receiving more attention in every year since 2010, when the work on this thesis started. This is very reassuring and hopeful, but this is a road that has just been treaded upon. There is much unknown territory that needs to be discovered. But it is a road that must be taken with all stakeholders working in cooperation. A system that fails too many athletes will ultimately implode, no matter how many good intentions have formed its basis. The issue of doping in sports is just too important to let that happen.

5.
EPILOGUE

As previously described, this thesis was intended as an objective analysis of current practices, without trying to give a final solution to doping-related discussions. The data in this thesis are intended to fuel these discussions, not necessarily to end them. It is clear that discussions that are based on beliefs and convictions can be both entertaining and helpful to reach a solution. The subject of 'doping in sports' is specifically invitational to critical appraisals. But such discussions are better held on the basis of accurate facts, and not on empty commonplaces.

In discussions on the necessity of anti-doping policies, several authors suggest to permit the use of all possible substances and methods 'under medical supervision' either completely or up to a certain degree (Fost 1986, Savulescu et al. 2004, Kayser et al. 2005, 2007, Miah 2007, Brissonneau 2008, Wiesing 2011). The idea is that doctors would always follow the principle of 'do not harm' in all of their patients, also when these 'patients' are healthy and fit athletes. A sub-argument to this idea is that elite athletic achievements are not necessarily accomplished in a healthy manner, as any performance that looks for, and consequently also may go across, the limits of what a human can achieve is potentially dangerous to that human's health. The idea is intriguing, and if applied it might render discussions on many aspects of current anti-doping policies useless. No prohibited list, no doping controls, no whereabouts; just medical guidelines giving a doctor, instead of an anti-doping panel, the authority to decide on what can be used, and what should not be used. It is fitting to conclude this thesis with a few words on this 'medical supervision solution'.

Most prohibited substances (and methods) are professionally prescribed (and performed) by licensed medical doctors. These doctors know what the potential risks are, and it is their daily profession to weigh potential benefits and possible side-effects with the final outcome to give a certain medicine or not, and if so which dose to use. A sensible doctor would make such a decision with the best interests of the concerned athlete in mind. Supporters of the 'medical supervision solution'

often claim that current anti-doping professionals are not always very sensible, and as such a different approach to doping is necessary. I have tried to show in this thesis that current anti-doping regulations are not always as rigid as some believe that they are and that much has been achieved in the past 50 years of anti-doping regulations. At the same time, improvements are indeed possible (Loland & Hoppeler 2011, Hoberman 2013, Møller & Dimeo 2014), and in an environment as high-demanding as elite sports 'possible' means 'necessary'. Anti-doping regulations may very well benefit from a more sensible approach in certain areas. But I am afraid that shifting more decision power towards medical professionals will not guarantee that all decisions are made in a sensible manner either.

In the end, a certain level of anti-doping regulation is necessary to protect athletes from parasite-like advisors, or supervisors, and possibly also from themselves. The current scientific body of knowledge clearly shows that substances like testosterone and erythropoietin are able to enhance most athletic performances and that greater amounts of these substances tend to give greater enhancements with concomitant greater risks of side-effects – both short-term and long-term. The field of practice has proven this various times already, with bodybuilders and cyclists being the prime 'ambassadors' of this reality because of several individual athletes out of these sports who have been very open about the doping experiences. It is not always clear which individual will be confronted with which effects, and this makes it impossible to detail one medical guideline. Various doctors will have various views, and in the past a certain sub-division of medical professionals have obviously exaggerated the health risks of doping substances, which does not increase the credibility of this profession (Todd 1987, Lopez 2011). The past has also shown that some doctors will be willing to advise more risks than others (Franke & Berendonk 1997, Hoberman 2002b). Some doctors will simply be more sensible than others. And especially in the high-performance athletic arena there is a great risk that sensibleness is lost in the battle to be the best. Changing the person or organisation that sets the rules and ultimately decides on what is permitted, or not, will not change this fact. The solution lies not solely in the WADA-offices or in medical hands or in the hands of the athletes themselves; it is a true combined effort.

The world of sport is just as life itself, with all imperfections that come with it. In an optimal situation sport is a reflection of the beautiful side of life. Only in retrospect it can be judged whether current anti-doping regulations will follow the path or former prohibitions against women's participation in sport or against

professionalism in sport – if that will be true, we will look back with embarrassment at the current timeframe with all these far-stretching anti-doping measures. Or maybe it will be the other way around, with future generations judging current discussions on 'relieving' athletes from strict anti-doping regulations to be inhumane and hubristic. It is impossible to make a final judgment on this issue at this time.

But it is clear that all doping-related discussions will benefit from openness. This thesis is predominantly a plea to gather more clear and transparent data to feed these discussions. This will bring the issue of 'doping in sports' forward. In the end, improvements in any area will come from the collective thinking power of mankind, not simply from a capsule, a pill or a syringe. And that is my own firm belief.

6.
APPENDICES

Appendix 1
Doping glossary

This is a list of the abbreviations that are used in the core texts of this thesis. Separate articles sometimes contain more abbreviations. If that is the case those abbreviations are explained in the articles themselves.

AAF	Adverse Analytical Finding
ADO	Anti-Doping Organisation
ADRV	Anti-Doping Rule Violation
IAAF	International Association of Athletics Federations, formerly International Amateur Athletics Federation
IF	International Federation
IOC	International Olympic Committee
ISL	International Standard for Laboratories
NADO	National Anti-Doping Organisation
OoC	Out-of-Competition
PLIS	Prohibited List International Standard
TUE	Therapeutic Use Exemption
WADA	World Anti-Doping Agency
WADC	World Anti-Doping Code
WADP	World Anti-Doping Program

Appendix 2
References

This list of references contains the literature that was used while writing the core texts of this thesis. Previously published articles, clearly marked in this thesis, contain their own original set of references.

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Appendix 3
Contribution of the author to this thesis

As explained in paragraph 1.6 (methodology) this thesis discusses the subject of effectiveness of anti-doping policies based on new discussions and reflections on this subject as well as a selection of previously published reports and articles. All texts have been reviewed and discussed anew to reflect the situation in 2016 and in the light of the general research question. In order to be completely transparent on the contributions to these texts by the author of this thesis (OdH), the following summary is given:

- the review on the prevalence of intentional doping use (paragraph 2.3.1) was set up, executed and written primarily by OdH. The other authors contributed with general suggestions and co-reading the manuscript;
- the review and data-analysis on the prevalence of unintentional doping use (paragraph 2.3.2) were set up, executed and written primarily by OdH. The other author contributed with general suggestions, co-reading various versions, and suggested to draft the 'practicality plots' (tables 10 and 11);
- the report on the subject of mind sports and doping was set up and written by OdH under supervision of the other author. The literature review was performed alone;
- the article (including the study) on corticosteroid inhalation was primarily set up, executed and written by first author Harm Kuipers. OdH helped in finding the funding for the study, and made suggestions for the study setup and co-read the article, like all other authors;
- the review and meta-analysis regarding beta-2 agonists was primarily performed by first author Babette Pluim, in close cooperation with OdH. Together they set up the study, performed the literature review and data extraction, and wrote most parts of the text. The other authors put in their specific expertises and co-read the manuscript;
- the review on gene doping was primarily written by first author Toon van der Gronde, a student who was supervised by both Toine Pieters and OdH during all parts of his master thesis and writing the manuscript. The fourth author put in his specific expertise and co-read the manuscript;
- the article (including the study) on whereabouts was primarily written by first author Diane Valkenburg, a student who was supervised by Ivo van Hilvoorde. OdH contributed to the setup of the study, to collating the questionnaire, and to writing and co-reading the manuscript;

- the article on supplements was set up and written primarily by OdH. The other author contributed with general suggestions and co-reading the manuscript;
- the article (including the study) on fitness centre members was primarily written and set up by first author Janine Stubbe. OdH contributed to the setup of the study, to collating the questionnaire, and to writing and co-reading the manuscript, like all other authors;
- the article on the Spirit of Sport was set up and written solely by OdH;
- all other texts in this thesis were written solely by OdH under supervision of professor Van Bottenburg.

Appendix 4
Curriculum Vitae

Olivier de Hon was born in Amsterdam, the Netherlands, on the same day Lasse Virén won his first of four Olympic gold medals. His time of birth coincided with half time of the Sunday afternoon football matches, although his hometown football club Ajax was travelling to Argentina to play in the Intercontinental Cup. The combination of sport and travel continued to colour his life afterwards, preferably in combination with each other.

He received his education in Zaandam (elementary school and high school), Brentwood, California, USA (high school), Amsterdam (university Master), and Utrecht (PhD). He worked small jobs at universities and in an elderly home, had a taste of academic speed skating research, before jumping into anti-doping research. After three years of working in an exercise physiology lab, he became a desk scientist for the Dutch national anti-doping organisation, anti-doping authority Netherlands (in Dutch: Dopingautoriteit). His main task is to provide a scientific background for the activities of this organisation. If answers cannot be found in scientific literature or within a network of scientific specialists, studies can be performed to find these answers.

He is a member of the scientific advisory boards of the Health Base Foundation (Netherlands based pharmacist medication surveillance) and of the 'Informed Sport' program (UK based nutritional supplements testing scheme), member of the USA Cycling Anti-Doping Committee, coordinator of the anti-doping work package of the sub2hrs-project (see www.sub2hrs.com), and advisor to the polyclinic for users of anabolic steroids in Haarlem, the Netherlands. Since 2015 he combines the scientific role with the position of manager of the support department of anti-doping authority Netherlands.

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List of publications:

Scientific journals - English

- De Hon O, H Kuipers & M van Bottenburg. Prevalence of doping use in elite sports – a review of numbers and methods. *Sports Med* 45(1):57-69, 2015.
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Book co-authorships

- Wassink H, W Koert, O de Hon, A Palsma & B Coumans. *Doping: de nuchtere feiten. [Doping: the sober facts].* Arko Sports Media/Dopingautoriteit, Nieuwegein, 2014.
- Stoele F, O de Hon & B Coumans. *Doping onder controle – 25 jaar dopingbeleid in Nederland (1989-2014). [Doping under control – 25 years of doping policy in the Netherlands (1989-2014)].* Arko Sports Media/Dopingautoriteit, Nieuwegein, 2014.

Various reports, book contributions and congress abstracts (an overview is available at request).

7.

MANY MANY THANKS

This has been a multidisciplinary scientific endeavour, but in order to reach a final result like this booklet, a true multidisciplinary support team is essential.

It starts with the home front: Ingrid and Ilse – no words can describe the joy and energy you give in my life.

The next circle of family and friends: always a pleasure to discuss important and non-important issues. And special attention for my parents, who have always fostered an environment where their children can grow, in every sense imaginable. I think you have succeeded.

My academic upbringing, from the early beginnings (thanks Coby) to today. There have been too many teachers and professors to mention them all, but I have been very fortunate to encounter numerous special characters who taught and teased in a very effective way. Two people deserve to be named publicly on this spot: Wouter van Solinge, who showed me the right track on the road towards a thesis, and Maarten van Bottenburg, who never lost his enthusiasm and conviction that this subject could actually turn into a final product with academic value.

My 'doping teachers': Fred Hartgens, Harm Kuipers, Frans Stoele, and Steven Teitler. Without them I would have lost my way in (anti-)doping matters a long time ago. For the last ten years I have been fortunate to work with Herman Ram, who excels in combining a positive individual approach and a critical overall view. Internationally I would specifically like to mention Joseph de Pencier, Graeme Steel, Hans Geyer and David Cowan who all possess the combination of profound in-depth knowledge and sincere individual interest. There have been many more coworkers, including all the colleagues at home and abroad that have sharpened my mind in countless discussions.

The time to write this thesis and to perform the extra analyses in order to compile a coherent manuscript was made available by means of a grant from the Dutch

Ministry of Health, Welfare, and Sports. Without this support the thesis would not have materialised.

And finally each and every discussion with an elite athlete. Sport brings joy to so many people, and elite athletes are the spotlight examples of this silver lining in life. The topic of doping interests almost all of them, and so it should. It is their input that drives our work and that ultimately determines the future of anti-doping policies.

COLOPHON

This thesis was defended in Utrecht on 18 November 2016

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STRIKING THE RIGHT BALANCE

Effectiveness of Anti-Doping Policies

Doping, and anti-doping, is in the news on a continuous basis. At the core of these stories and discussions is the question how effective anti-doping policies are to curb the use of doping in sports.

Anti-doping policies are based on ethical values, a juridical framework, laboratory analyses, educational efforts and the input of numerous other scientific disciplines. An evaluation of the effectiveness of these policies can only be made when this multidisciplinary aspect is truly appreciated. In this thesis various aspects of anti-doping policies are discussed, with specific emphasis on the extent of doping use (both intentional and unintentional), the effectiveness of doping substances and methods, and the consequences of current policies.

Valuable evaluations of the effectiveness of anti-doping policies can be performed, and they must be performed far more often. It is clear that improvements in the anti-doping framework can and should be made in order to strengthen it and to strike the right balance between all aspects that play a role in this intricate topic. The issue of doping in sports is just too important not to do that.