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Review article

Effect of xenon and argon inhalation on erythropoiesis and steroidogenesis: A systematic review

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ABSTRACT

Background: Xenon and argon inhalation were included on the WADA Prohibited List in 2014 due to the reported positive effects on erythropoiesis and steroidogenesis that occur as a result of their application. Thus, the systematic review of studies supporting these notions is of interest.
Methods: A thorough search on the effects of xenon and argon inhalation on erythropoiesis and steroidogenesis, as well as their negative effects on human health and method detection was conducted. Pubmed and Google Scholar databases and the Cochrane Library were researched, as well as the WADA research section. The search was conducted in accordance with the PRISMA guidelines. All articles written in English and published between 2000 and 2021 were analyzed, as well as reference studies meeting the search criteria.
Results: At present, there are only two publications in healthy human subjects evaluating the effects of xenon inhalation on erythropoiesis that found no conclusive evidence of a positive effect on erythropoiesis. This research was published following the inclusion of this gas on the WADA Prohibited List in 2014 and had a high risk of bias. There were no studies available on the effect of argon inhalation on erythropoiesis. Furthermore, no studies were found on the effect of xenon or argon inhalation on steroidogenesis in healthy subjects and no studies relating to the effects of xenon or argon inhalation on erythropoiesis and steroidogenesis were found on the WADA website.
Conclusion: There is still inconclusive evidence to support the administration of xenon and argon inhalations on erythropoiesis and steroidogenesis and their positive effects on health. Further research is warranted to establish the effects of these gases. Additionally, improved communication between anti-doping authorities and all key stakeholders is required to support the inclusion of various substances on recognized prohibited lists.

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1. Introduction

Xenon is an inert gas that is present in the atmosphere. There are nine xenon isotopes, the most common of which is Xe 132. The narcotic effect of xenon has been previously reported in rats by inhaling 67% xenon and 33% oxygen [1]. The narcotic properties of the xenon-oxygen mixture (78% xenon 22% oxygen) were previously described during mice experiments [2]. The first studies involving human subjects reported that inhaling an 80% xenon and 20% oxygen mixture resulted in full anesthesia within 3–5 min [3].

In Russia, xenon has been officially approved for use as an inhalation anesthetic since 1999. By 2012, more than 10,000 surgical operations had been performed with the use of xenon anesthesia [4]. Xenon does not have teratogenic, mutagenic, carcinogenic, or allergenic properties and does not affect respiratory function [5,6,7,8]. The official recognition of xenon as an inhalation anesthetic and thus its subsequent clinical implementation has revealed several physiological effects, which have contributed to its widespread usage in clinical practice. There have been numerous potential applications of xenon documented including: treatment of withdrawal symptoms, drug addiction and depression, chemotherapy, analgesia and their possible cardiac, renal, and neuroprotective properties in the elderly population [9–16]. In addition to its use in anesthesiology, it has been examined as an adaptive recovery agent from extreme physical exertion in athletes and military personnel [17,18].

In September 2014, inhalation of xenon and another inert gas, argon with oxygen (hereinafter referred to as IX and IA) was added to the WADA Prohibited List under section S2.1 as hypoxia-inducible factor (HIF) stabilizers and activators [19]. To fully understand the circumstances that led to the inclusion of IX and IA on the Prohibited List, a clear chronology of events occurring must be established. On the February 7, 2014, the Russian city of Sochi opened the Winter Olympics and concurrently an article appeared in "The Economist" stating that xenon can improve athletic performance and that Russian athletes' participating in the Sochi Olympics may used xenon inhalation as a performance-enhancing substance [20]. The article further claimed that the official document released in 2010 by the State Research Institute of the Ministry of Defense set out guidelines for the administration of the gas to athletes. In the fore-mentioned report, it was allegedly recommended to inhale xenon pre-competition to eliminate lethargy and sleep disorders and to improve overall physical recovery. It was further recommended that xenon and oxygen may be used in a 50:50 ratio when inhaled for a few minutes prior to sleep. The report also stated that the effects last for 48–72 h, so it was suggested to repeat this procedure every 2–3 days.

On February 27th, 2014, immediately post-Olympics, the website www.insidethegames.biz published information that Russian athletes had used xenon during competition and that WADA President Sir Craig Reedie had said " it will take on the issue" [21]. Thus, WADA commenced a process to verify these statements.

Notably, IX had never previously been a banned substance and had been widely and legally employed by Russian athletes at major international competitions. For example, the use of xenon had been well-known for many years, prior to Athens 2004 and it had not been previously examined as "it wasn't an issue that needed to be addressed" (statement by David Howman, Director General of the World Anti-Doping Agency) [22]. Thus, there were no questions regarding the use of IX and IA. However, in contrast, the former WADA president and a member of the International Olympic Committee, Dick Pound, stated that, "undoubtedly that it is doping" [22]. Simultaneously, WADA president Sir Craig Reedy promised that "the topic of gas will be addressed at the next meeting after the Olympics" [23]. In April 2014, following the WADA Prohibited List Committee meeting, IX and IA were recommended for inclusion on the Prohibited List, where they have been included as Hypoxia-Inducible Factor (HIF) activators since September 1, 2014 [24]. It is important to consider that IX and IA were included in the same section (S2) of the Prohibited List as the long-established commonly used drugs with well-documented positive effects on erythropoiesis, erythropoietin (EPO) and darbepoetin (dEPO). Thus, in sports IX and IA became prohibited substances and a minimum two-year ban was imposed for their use.

Noteworthy, to be included on the Prohibited List, a substance or method must satisfy at least two of three criteria:

1. It has the potential to enhance or enhances sport performance;
2. It represents an actual or potential health risk to the athlete;
3. It violates the spirit of sport [25].

The third criterion is relatively vague and virtually any substance or method may qualify. However, at least one other criterion should be met. In this regard, the inclusion of IX and IA on the Prohibited List would have been based on WADA experts gaining compelling data on the positive effects on physical performance or negative effects on human health. This was potentially confirmed by WADA President Sir Craig Reedy's comment that the ban on IX and IA was based on research available to the agency indicating the positive effects on erythropoiesis and steroidogenesis [26]. Although, why these data were not previously mentioned warrants further research.

The ban may have been invoked due to a significant increase in its use among athletes, which may have been indicative of the unpublished evidence of its effectiveness in relation to performance or post-exercise recovery. For example, the banning of meldonium was implemented after its use was found to be extremely widespread at the 2015 European Games in Baku [27]. Therefore, the aims of this review were: 1) to examine the chronology of the emergence of xenon and argon detection methods in biological fluids and 2) to further examine the evidence base supporting the inclusion of IX and IA on the Prohibited List.

2. Materials and methods

2.1. Literature search

Two independent expert researchers conducted the search utilizing the Pubmed, Cochrane Library and Google Scholar databases. Additionally, the WADA website reporting on the effects of xenon and argon inhalation on various aspects of physical performance, erythropoiesis and steroidogenesis, and their negative effects on human health and methods for their detection in body fluids was also examined. These searches were conducted according to the PRISMA guidelines. All articles written in English and published between 2000 and 2021 were analyzed, as well as reference studies meeting the search criteria. A citation list of all articles that met the search inclusion criteria including articles on xenon detection in body fluids during doping control was also investigated.

The following words and word combinations were used for the search: “Xenon inhalation”, “Argon inhalation”, “Xenon and erythropoiesis”, “Argon and erythropoiesis”, “Xenon and steroidogenesis”, “Argon and steroidogenesis”, “Xenon and testosterone”, “Argon and testosterone”, “Xenon and erythropoietin”, “Argon and erythropoietin”, “Xenon and endurance”, “Argon and endurance”, “Xenon and performance”, “Argon and performance”, “Xenon and Sport”, “Argon and Sport”, “Xenon and Athletes”, “Argon and Athletes”, “Xenon Negative Effects”, “Argon Negative Effects”, “Xenon Inhalation Side Effects”, “Xenon Inhalation Adverse Effects”, Xenon Inhalation Adverse Events” “Argon Inhalation Side Effects”, “Xenon and Detection Methods”, “Argon and Detection Methods”, “Xenon and Doping”, “Argon and Doping".

The use of IX and IA in 2014 was documented in connection with Russian athletes, thus the above keywords and their combinations were also searched in the Russian-language scientific databases and CyberLeninka.

Information on all disqualified athletes was also searched on the rusada.ru and major winter sports federations’ websites in which Russian athletes participated at the Sochi Olympics. This was completed to identify athletes who had been disqualified for using IX and IA since the latter part of 2014, when it was banned. This timeline was adopted due to samples being taken during major international competitions (including the World Winter Sports Championships and the Winter Olympics) are now retrospectively analyzed within 10

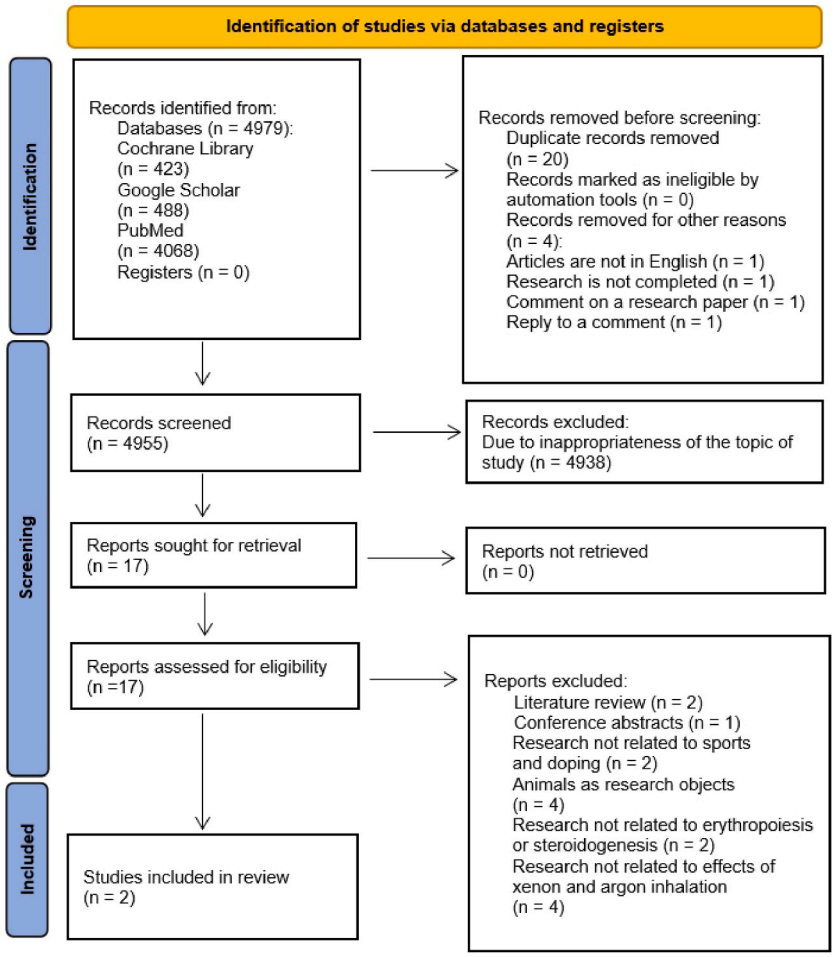

Fig. 1. Study selection process.

years of conclusion. This was completed to examine the use of prohibited substances and methods not found in the original analysis following the emergence of new detection protocols.

2.2. Study selection

The inclusion criteria were:

1) The article was a clinical study;
2) The subjects of the study were healthy individuals;
3) The study investigated the influence of xenon and argon on erythropoiesis and steroidogenesis;
4) The intervention was xenon or argon versus a placebo inhalation.

The exclusion criteria were:

1) Case reports, literature reviews, conference abstracts and other types of studies that are not clinical trials;
2) Articles in which xenon and/or argon inhalationused in combination with other substances;
3) Articles in which the effects of argon and/or xenon were studied on unhealthy individuals or animal models;
4) In vitro, surgical and anesthetic studies;
5) Effects not on erythropoiesis and steroidogenesis, but on other organs and systems that have been studied or the detection of xenon and/or argon in biological fluids has been investigated without studying the effects.

2.3. Data extraction

In order to assess studies for eligibility after the screening phase, articles were examined in full-text and tabulated in a table with 4 sections; 1) title, author of the article and year of publication; 2) number of participants and their physical status; 3) intervention; and 4) results.

2.4. Quality assessment

All identified studies have been assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [28]. Cases of disagreement in assessments of the risk-of-bias between the reviewers were resolved by discussion or with consultation with a third reviewer if required.

3. Results

Based on keywords, and combinations thereof, 4979 articles were collated: 4068 articles from PubMed, 423 from Cochrane Library and 488 articles from Google Scholar (See Fig. 1).

In the first phase, 20 duplicates were excluded, followed by four more articles, one of which was written in French [29], one was not completed [30], and the other two were a commentary and response to a commentary on the study by Stoppe et al. [31,32]. 4955

Table 1
Studies on the effects of xenon and oxygen inhalation on erythropoiesis and steroidogenesis in humans.

Article title	Number of participants and their physical status	Intervention	Results
Stoppe C et al., 2016	24 healthy individuals	Randomly assigned either to a group spontaneously breathing xenon 30% (Xe/O2 30%/60%) or a group breathing control gas (N2/O2 40%/60%) for 45-min.	The administration of xenon significantly increased erythropoietin levels 8-h after exposure, peaking at 24-h compared to the baseline values and remained traceable in blood and exhalation probes until 24-h after exposure. In contrast, no significant change was observed in the control group.
Dias KA et al., 2019	22 healthy individuals	Three subanesthetic concentrations of xenon: 30% fraction of inspired xenon (FiXe) for 20-min, 50% FiXe for 5-min, and 70% FiXe for 2-min. To determine the chronic effects, eight subjects breathed 70% FiXe for 2-min on seven consecutive days, and EPO, total blood, and plasma volume were measured. Phase II involved assessment of 12 subjects for EPO, total blood volume, maximal oxygen uptake, and 3-km time before and after random assignment to 4-week of xenon or sham gas inhalation.	FiXe 50% and 70% stimulated an increase in EPO at 6-h and at 192-h post-inhalation. Seven consecutive days of dosing significantly elevated plasma volume. Phase II showed no significant effect. Acute exposure to subanesthetic doses of xenon caused a consistent increase in EPO, and seven consecutive days of xenon inhalation significantly expanded plasma volume. However, this physiological response appeared to be transient, and 4-week of xenon inhalation did not stimulate increases in plasma volume or erythropoiesis, leaving cardiorespiratory fitness and athletic performance unchanged.

Regarding methods for detection of IX in biological fluids, several studies were found, notably one sponsored by WADA [42,43,44,45,46,47].

articles were screened by title and abstract. Due to the inappropriateness of the study topic, 4938 publications were excluded.

Seventeen publications were then screened in detail to ensure that the following criteria were met: two studies were literature reviews [33,34] and one study was the primary material [35] for the secondary analysis [36], which will be mentioned later in this article. Four studies on the effect of IX on erythropoiesis were performed with animals (rats and mice) [37,38,39] and another involving people after undergoing heart surgery [36]. In summary, only two publications written in English were found on studies involving healthy subjects that evaluated the effects of xenon inhalation on erythropoiesis (See Table 1) [40,41].

Studies on the effect of IX on steroidogenesis in healthy humans have not been found, nor have studies on the effect of IA on erythropoiesis or steroidogenesis. The first study on the effect of IX on erythropoiesis in healthy humans was not published until 2016, and the second study was published in 2019. This research recruited physically active subjects from the general population and the number of side-effects reported was minimal.

Prior to 2014, there were only three peer-reviewed scientific studies written in English, although conducted on animals (rats and mice) with simulated pathology or exposed to drugs using long-term high-dose IX inhalation. No studies reporting the effects of IX in humans were published prior to this date. None of these studies were initiated or funded by WADA. On the WADA website, there is also no study on the effects of IX and IA on erythropoiesis and steroidogenesis.

A search of the largest Russian-language databases did not yield a single publication on the effects of xenon and argon inhalation on erythropoiesis and steroidogenesis. A search for information on athletes disqualified for using or attempting to use IX and IA also failed to find any such cases since 2014.

From the analysis performed, the risk-of-bias is high (See Fig. 2).

It is important to note that in a study by Dias et al. the randomized trial investigating the effects of xenon was only Phase II of the study (Phase I was not randomized). Therefore, the risk-of-bias was only assessed in Phase II of this study.

The main criterion that influenced the result of the risk-of-bias analysis was Bias due to deviations from intended intervention (D2). In both studies, 14% of participants were excluded following randomization and thus this data were not analyzed further. This may have significantly affected the outcome in the context of small sample studies.

4. Discussion

The main findings of the current study are that a thorough search of English-language scientific databases found only two studies involving healthy human subjects investigating the effects of xenon inhalation on erythropoiesis, both of which were conducted and published after the inclusion of IX and IA on the Prohibited List. The studies involved physically healthy volunteers and the results either did not support the efficacy of IX as a modulator of erythropoiesis [40] or were obtained using potentially misleading statistical analysis [31,41,32]. Furthermore, as the analysis shows, both articles had a high risk-of-bias.

Regarding the effect of IA on erythropoiesis or steroidogenesis, no studies have been found in the academic domain. Until 2014 there were no studies on the possible effects of IX on erythropoiesis in humans, where Jelkmann et al. stated that the effects of xenon treatment on the blood level of EPO have never been reported. No human data are available for the HIF system and the production of EPO [33]. The author of this review acknowledged that compared to the numerous chemicals that increase HIF-dependent EPO synthesis in humans, the misuse of xenon in sport is a small problem [33].

It is important to note that before the banning of IX and IA in 2014, only three studies on the effects of IX on erythropoiesis were published and both were involving animals (rats and mice) with simulated pathology. Ma et al. demonstrated dramatic effects of xenon inhalation on both EPO levels and HIF-1 levels, a protein that stimulates EPO production in the body. In this study, the authors showed that exposure to a mixture of 70% xenon and 30% oxygen for 2-h resulted in a sustained increase of HIF-1α activity in adult mouse kidney and human kidney cells by enhancing the efficiency of HIF-1α translation involving the mTOR pathway [39]. It is important to note that such a protocol of using IX (70% for 2-h) xenon has never been employed in studies involving humans. Thus, Stoppe et al. stated that inhalation of 30% xenon and 70% oxygen used once a day for 45-min [41] was beneficial, while in a study by Dias et al. the maximum concentration of xenon was 70%, and inhalation was performed for 2-min [40].

In a study involving male and female mice, Limatola et al. studied the effects of inhaling a mixture of 70% xenon and 30% oxygen for 2-h on functional neurological outcome and cerebral infarct size after the onset of cerebral ischemia induced by middle cerebral artery occlusion. It was found that both females and males who received IX had improved functional outcome on the focal deficit scale and a smaller cerebral infarct volume. A stronger enhancement of HIF-1alpha compared to the control group who received 70%

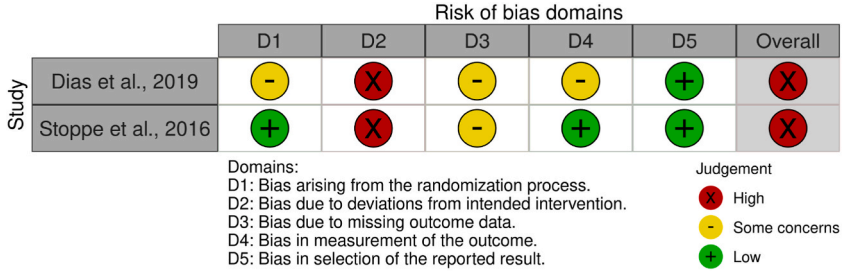

Fig. 2. Risk-of-bias in the studies included.

nitrogen inhalation was also reported [38]. In 2013, Jia et al. found that alpha HIF-2 α levels in mice that received 100 mg of the antibiotic gentamicin daily for seven days remained high for 48-h following IX application (70% xenon and 30% oxygen for 70-days), while mice placed in a low-oxygen chamber showed increases in EPO that lasted less than 2-h. However, the authors also found that pre-treatment with IX did not activate hypoxia-inducible factor 1α (HIF-1α) [37].

The first study investigating the effect of IX on erythropoietin levels in humans was published in 2015, one year after this method was banned by WADA. Stoppe et al. used data from 30 patients from an earlier randomized control trial (RCT) demonstrating the safety of xenon anesthesia in aortocoronary bypass surgery [36]. The authors noted that although erythropoietin concentrations after xenon anesthesia showed a significant increase on the first post-operative day, this did not result in a statistically significant increase in hemoglobin levels. The authors concluded that the observed association between xenon and erythropoietin and hemoglobin changes remain speculative and causes may be multi-factorial. Stoppe et al. further stated that the results can only be considered as a hypothesis. Interestingly, this was the first and the only study examining the possible effect of IX on testosterone level where no significant changes were found [36].

The first study investigating the effects of IX on erythropoiesis, involving healthy subjects (24 physically active volunteers), was only published in 2016–2 years following the substance ban. However, the study itself, was also conducted post-2014 [41]. In this RCT, Stoppe et al. concluded that xenon increased erythropoietin level in healthy volunteers, thus, the authors considered justification for placing IX on the WADA banned Prohibited List. The authors also reported increased erythropoietin levels in healthy volunteers following an acute 45-min exposure of xenon inhalation [41].

However, Balachandran et al. further commented on these findings and convincingly highlighted that the statistical methods used by the authors do not allow the conclusion that IX positively affects erythropoiesis in humans to be drawn. The main problem with the statistical analysis pointed out by Balachandran et al. was that the conclusion regarding the effectiveness of xenon was based on comparing the significant within-group change observed in the xenon group with a small change in the control group, and no comparison was made between groups [31]. However, the practice of comparing p-values within a group can be misleading [48]. The authors of this commentary emphasized that if a trial is to claim superiority, statistical tests comparing average differences between groups, i.e. group analysis of variance or two-sample *t*-test, should be performed and the conclusion that xenon increases EPO levels in humans is inappropriate and possibly misleading [31]. In their response, Stoppe et al. acknowledged that the observed results should be investigated more thoroughly in subsequent confirmatory studies [32].

In 2019, five years after IX was banned, a study by Dias et al. examined the acute and chronic effects of various IXs on 12 physically active volunteers from the general population and not athletes, which the authors considered to be a significant limitation of the study. The authors of the study particularly noted that it was the first study to examine each element of the cascade by which xenon inhalation is purported to take effect, starting with measurement of the hypoxia-inducible factor effector, erythropoietin, to hemoglobin mass and blood volume and athletic performance [40]. In this study, three different IX protocols were used: a 30% fraction of inspired xenon for 20-min; 50% for 5-min; and 70% for 2-min. The results showed that IX at 50% and 70% fraction of inspired xenon increased the EPO concentration after 6-h and 192-h after a single application. However, application of IX at a concentration of 70% for seven days showed no significant effect on EPO, hemoglobin mass, plasma volume, maximal oxygen uptake, or a 3-km time-trial. The authors further concluded that the physiological response of IX was temporary and 4-weeks of xenon inhalation did not stimulate increases in plasma volume or erythropoiesis, leaving cardiorespiratory fitness and athletic performance unchanged. Authors also found that acute xenon inhalation caused small prolonged increases in EPO, but short-term daily exposure did not provide superior benefits beyond an acute dose. The increase in plasma volume with short-term daily dosage was found. Therefore, authors concluded that xenon inhalation did not improve athletic performance, and stated that their findings do not support the use of xenon as an erythropoiesis-modulating agent in sports [40].

Furthermore, it should be noted that the protocols used in studies involving healthy individuals differed significantly from those described in the 2014 Economist article. Dias et al. referenced the Russian trainers to select the protocols for IX usage, rather than the protocols previously described in studies involving humans and animals. That is, at the time of the study there were no scientifically valid protocols for the use of IX in healthy volunteers to realize a potentially positive effect on performance and erythropoietin levels [40]. In the Dias et al. study, a statistically significant increase in plasma volume was highlighted when using IX at a concentration of 70% for 2-min during seven consecutive days. However, an increase in plasma volume alone does not cause a positive effect on performance, as evidenced by the lack of prohibition of other methods actively used by athletes to increase plasma volume. For example, endurance athletes actively use sauna [49], which, according to Scoon et al. may potentially increase plasma volume by more than 7%. Notably, in the same study, the authors reported that a 30-min sauna exposure for 3-weeks increased the ability to run to exhaustion by 32%, which may be equivalent to a 1.9% improvement in competitive running [50]. However, sauna remains a legal recovery method and is not included on the Prohibited List.

Importantly, an improvement in endurance performance and a significant increase in hemoglobin, of approximately 6%, with recombinant erythropoietin, which is prohibited in sport, only observed 2-weeks following the administration of recombinant EPO [50]. Therefore, an estimate of low and short-term erythropoietin levels following IX usage cannot be considered a reliable, worthwhile effect on physical performance, as was shown in the Dias et al. study where the authors found no positive effect of IX on performance during the 3-km run [40].

Following a search of the largest Russian-language databases, no articles on the effects of IX and IA on erythropoiesis and steroidogenesis were found. In addition, it should be noted that no significant adverse health effects have been observed in studies involving the use of xenon in humans, and its main global use is as an anesthetic in surgical procedures, including cardiac surgery. The possible non-compliance with the spirit of the sport of these particular inhalations is also questionable, given that helium and oxygen inhalation, for example, remain permitted and are actively used, including among athletes, but are not on the WADA Prohibited List

[51,52].

Another possible explanation for the inclusion of IX and IA on the Prohibited List may be the widespread use of both substances by a particular athletic group. To objectively determine the prevalence of a substance or method, accurate detection methods must be employed. A study by Thevis et al. showed that xenon can be determined from plasma and blood samples, with detection limits of approximately 0.5 nmol/mL to 50 nmol/mL, depending on the type of mass spectrometer used during routine sports drug testing [51]. Therefore, the detection of IX is possible using standard detection methods and provided data on the detection limit of xenon. Furthermore, Thevis et al. presented the first data on the determination of xenon from urine in the context of human sports drug testing [47]. This research also stated that, testing for xenon in samples submitted for sports doping control is required and presents the first data on the determination of xenon in human urine, indicating a detection limit of approximately 0.5 nmol/mL and a detection time of approximately 40-h following xenon anesthesia [47]. While in the Schaefer et al. study, the xenon detection time following standard anesthesia using an IX concentration of 60% was 24–48-h [45]. Thus, it is questionable that during the 2014 Sochi Olympics accurate information utilizing these methods was provided.

In summary, there were no data to suggest that the prevalence of IX in athletes of any nationality, or any data on the effects of IX on erythropoiesis and steroidogenesis in humans. The only data available on the effects of IX on erythropoiesis is based on studies in mice and rats with simulated pathology. Therefore, it is unclear why these substances and methods were included on the Prohibited List. Furthermore, following a structured re-evaluation of the 2020 Prohibited List, argon was removed, as it is considered to no longer meet the criteria for inclusion [53]. While in 2022 the Prohibited List maintained xenon as a prohibited HIF-activating agent [54]. Xenon remains prohibited, despite the fact that over the past eight years there has been no evidence of its positive effect on erythropoiesis and steroidogenesis, and data suggesting its wide prevalence prior to its inclusion on the prohibited list. There is also no evidence to support the notion that IX has a negative health impact and there is not a single case of disqualification for its consumption, which raises the question of its significance in enhancing any aspect of performance. Publishing data that justifies the decision to include a substance or method on the Prohibited List will promote key stakeholders trust. Demonstrating the evidence supporting these decisions would promote the process of transparency and reduce the opportunity for speculation [55]. The possibility to develop clear guidelines (e.g. the performance of RCTs and research in detection methods in bodily fluids) prior to the inclusion of various substances and methods should be considered.

5. Conclusion

Based on existing literature, there is no evidence that xenon inhalation can increase testosterone levels, and studies that have examined the effect of xenon inhalation on erythropoietin levels are inconclusive. Furthermore, there is no evidence of any significant adverse health effects. For IA, there is still no evidence to suggest it has any positive effects on steroidogenesis and erythropoiesis or any adverse health effects. Therefore, WADA should support high-quality research examining the actual effects of IX on erythropoiesis and steroidogenesis or potentially remove this substance from the Prohibited List. Finally, a study with retrospective analysis of all doping samples of Russian competitors at the Sochi Olympic Games for xenon should also be undertaken to determine the prevalence of IX use during these events.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Pubmed, Google Scholar databases and the Cochrane Library were researched, as well as the special research section of the WADA website. All the articles not mentioned directly in the manuscript, but screened in the process of research can be made available on request as worksheets.

Additional information

No additional information is available for this paper.

Declaration of competing interest

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

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