

**Appendix 2 : Summary of Excluded Studies**

<b>Study</b>	<b>Reason for exclusion</b>
<p>Ashenden M, Gore C, Dobson G, et al. Simulated moderate altitude elevates serum erythropoietin but does not increase reticulocyte production in well-trained runners. <i>Eur J Appl Physiol.</i> 2000;81(5):428-35.</p>	<p>Inappropriate intervention (e.g. co-intervention or a non-EPO agent used)</p>
<p>Ashenden MJ, Hahn AG, Martin DT, et al. A comparison of the physiological response to simulated altitude exposure and r-HuEpo administration. <i>J Sport Sci.</i> 2001;19(11):831-7.</p>	
<p>Baumann C, Bond K, Rupp J, et al. Echinacea Purpurea Supplementation does not Enhance VO2max in Distance Runners. <i>Journal of Strength and Conditioning Research. J Strength Cond Res.</i> 2014;28(5):1367-72.</p>	
<p>Baumann C, Kwak D. Echinacea supplementation: does it really improve aerobic fitness? <i>J Exerc Nutrition Biochem.</i> 2016;20(3):1-6.</p>	
<p>Bellar D, Moody K, Richard N, et al. Efficacy of a Botanical Supplement with Concentrated Echinacea purpurea for Increasing Aerobic Capacity. <i>ISRN Nutr.</i> 2014;149549.</p>	
<p>Borisch S, Baertsch P, Friedmann B. Effects of strength endurance training in hypoxia on endurance capacity, blood volume on erythropoietin. <i>Int J Sports Med.</i> 2002;23(Suppl.2):S80.</p>	
<p>Brugniaux J, Schmitt L, Robach P, et al. Eighteen days of "living high, training low" stimulate erythropoiesis and enhance aerobic performance in elite middle-distance runners. <i>J Appl Physiol.</i> 2006;100(1):203-11.</p>	
<p>Marchand A, Martin JA, Collot D, et al. Combined administration of microdoses of growth hormone and erythropoietin: Effects on performance and evaluation of GH detection capability using anti-doping methods. <i>Drug Test Anal.</i> 2019. doi:10.1002/dta.2674.</p>	
<p>Parisotto R, Gore CJ, Emslie KR, et al. A novel method utilising markers of altered erythropoiesis for the detection of recombinant human erythropoietin abuse in athletes.</p>	

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<p><i>Haematologica</i>. 2000;85(6):564-72.</p> <p>Russell G, Gore CJ, Ashenden MJ, et al. Effects of prolonged low doses of recombinant human erythropoietin during submaximal and maximal exercise. <i>Eur J Appl Physiol</i>. 2002;86(5):442-9.</p> <p>Stevenson J, Krishnan S, Inigo M, et al. Echinacea-Based Dietary Supplement Does Not Increase Maximal Aerobic Capacity in Endurance-Trained Men and Women. <i>J Diet Suppl</i> 2016;13(1):324–38.</p> <p>Sutehall S, Martin-Rincon M, Wang G, et al. The Performance Effects of Microdose Recombinant Human Erythropoietin Administration and Carbon Monoxide Rebreathing. <i>Curr Sport Med Rep</i>. 2018;17(12):457-66.</p> <p>Whitehead M, Martin T, Scheett T, et al. Running economy and maximal oxygen consumption after 4 weeks of oral Echinacea supplementation. <i>J Strength Cond Res</i> 2012;26(1):1928–1933.</p>	
<p>Audran M, Gareau R, Matecki S, et al. Effects of erythropoietin administration in training athletes and possible indirect detection in doping control. <i>Med Sci Sports Exerc</i>. 1999;31(5):639-45.</p> <p>Bornø A, Aachmann-Andersen NJ, Munch-Andersen T, et al. Screening for recombinant human erythropoietin using [Hb], reticulocytes, the OFF hr score, OFF z score and Hb z score: status of the Blood Passport. <i>Eur J Appl Physiol</i>. 2010;109(3):537-43.</p> <p>Clyne N, Berglund B, Egberg N. Treatment with recombinant human erythropoietin induces a moderate rise in hematocrit and thrombin antithrombin in healthy subjects. <i>Thromb Res</i>. 1995;79(1):125-29.</p> <p>Durussel J, Daskalaki E, Anderson M. Haemoglobin mass and running time trial performance after recombinant human erythropoietin administration in trained men. <i>Eur J Appl Physiol</i>. 2013;8(2):e56151.</p> <p>Eklblom B, Berglund B. Effect of erythropoietin administration on mammal aerobic power. <i>Scand J Med Sci Sports</i>. 2007;1(2):88-93.</p>	Absence of or inappropriate control

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<p>Haile DW, Durussel J, Mekonen W, et al. Effects of EPO on Blood Parameters and Running Performance in Kenyan Athletes. <i>Med Sci Sports Exerc.</i> 2019;51(2):299-307.</p> <p>Juel C, Thomsen J, Rentsch R. Effects of prolonged recombinant human erythropoietin administration on muscle membrane transport systems and metabolic marker enzymes. <i>Eur J Appl Physiol.</i> 2007;102(1):41-4.</p> <p>Lundby C, Damsgaard. Exercise performance in hypoxia after novel erythropoiesis stimulating protein treatment. <i>Scand J Med Sci Sports.</i> 2006;16:35-40.</p> <p>Lundby C, Hellsten Y, Jensen M, et al. Erythropoietin receptor in human skeletal muscle and the effects of acute and long-term injections with recombinant human erythropoietin on the skeletal muscle. <i>J Appl Physiol.</i> 2008;104(4):1154-60.</p> <p>Robach P, Calbet J, Thomsen J, et al. The ergogenic effect of recombinant human erythropoietin on VO<sub>2</sub>max depends on the severity of arterial hypoxemia. <i>PLoS One.</i> 2008;3(8):e2996.</p>	
<p>Abellan R, Remacha A, Ventura R, et al. Hematologic response to four weeks of intermittent hypobaric hypoxia in highly trained athletes. <i>Haematologica.</i> 2005;90(1):126-27.</p> <p>Birkhoff WA, Heuberger J, Post TE, et al. Recombinant human erythropoietin does not affect several microvascular parameters in well-trained cyclists. <i>Physiol Rep.</i> 2018;6(24):e13924.</p> <p>Bodary P, Pate R, Wu Q, et al. Effects of acute exercise on plasma erythropoietin levels in trained runners. <i>Med Sci Sports Exerc.</i> 1999;31(4):543-6.</p> <p>Borrione P, Parisi A, Salvo R, et al. A peculiar pattern of expression of the transferrin receptor (CD71) by reticulocytes in patients given recombinant human erythropoietin (rHuEPO): A novel marker for abuse in sport? <i>J Biol Regul Homeost Agents.</i> 2007;21(3-4):79-88.</p> <p>Caldarazza Ienco E, Carlesi C, Logerfo A, et al. Resting and exercise-related oxidative stress markers in patients under erythropoietin treatment. <i>Amyotroph Lateral Scler.</i></p>	<p>Inappropriate outcome measures or analyses (e.g. outcomes not in inclusion criteria or missing between-group analysis between intervention and placebo group)</p>

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<p>2012;13(1):181.</p> <p>Clark B, Woolford SM, Eastwood A, et al. Temporal changes in physiology and haematology in response to high-and micro-doses of recombinant human erythropoietin. <i>Drug Test Anal.</i> 2017;9(10):1561-71.</p> <p>Kastner A, Grube S, El-Kordi A, et al. Common variants of the genes encoding erythropoietin and its receptor modulate cognitive performance. <i>Mol Med.</i> 2012;87(10):E90.</p> <p>Muza R, Jones J, Fulco C, et al. Recombinant erythropoietin administration reduces exercise-induced decline in regional cerebral oxygenation at 4500 m. <i>FASEB J.</i> 2012;26(1):1b1-1163.7.</p> <p>Remacha A, Ordonez J, Barcelo M, et al. Evaluation of erythropoietin in endurance runners. <i>Haematologica.</i> 1994;79(4):350-2.</p> <p>Viuff SL, Plenge U, Belhage B, et al. Effects of low-dose recombinant human erythropoietin treatment on cognitive performance. <i>Dan Med J.</i> 2017 1;64(9):1-5.</p>	
<p>Baraldi E, Montini G, Zanconato S et al. Exercise tolerance after anaemia correction with recombinant human erythropoietin in end-stage renal disease. <i>Pediatr Nephrol.</i> 1990;4(6):623-6.</p> <p>Braumann K, Nonnast-Daniel B, Boning D, et al. Improved physical performance after treatment of renal anemia with recombinant human erythropoietin. <i>Nephron.</i> 1991;58(2):129-34.</p> <p>Grunze M, Kohlmann M, Mulligan M, et al. Mechanisms of improved physical performance of chronic hemodialysis patients after erythropoietin treatment. <i>Am J Nephrol.</i> 1990;10(2):18-23.</p> <p>Guthrie M, Cardenas D, Eschbach J, et al. Effects of erythropoietin on strength and functional status of patients on hemodialysis. <i>Clin Nephrol.</i> 1993;39(2):97-102.</p> <p>Horina J, Schwabegger G, Brussee H. Increased red cell 2,3-diphosphoglycerate levels in haemodialysis patients treated with erythropoietin. <i>Nephrol Dial Transplant.</i> 1993;8(11):1219-22.</p>	Comorbidities present in study population

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<p>Huppmann M, Hief C, Schenk E, et al. Erythropoietin therapy in renal anemia. Effect on ergospirometry performance parameters. <i>Wien Med Wochenschr Suppl.</i> 1989;104(1):48-50.</p> <p>Jin B, Luo X, Lin H, et al. A meta-analysis of erythropoiesis-stimulating agents in anaemic patients with chronic heart failure. <i>Eur J Heart Fail</i> 2010;12(3):249-53.</p> <p>Mayer G, Thum J, Cada E, et al. Working capacity is increased following recombinant human erythropoietin treatment. <i>Kidney Int.</i> 1988;34(4):525-8.</p> <p>Nelson A, Hower C, Nguyen T, et al. Erythropoietin administration does not influence the GH--IGF axis or makers of bone turnover in recreational athletes. <i>Clin Endocrinol.</i> 2005;63(3):305-9.</p> <p>Normalisation of Hb level with epoetin alfa improves exercise performance in ESRD. <i>Erythropoiesis: new dimensions in the treatment of anaemia.</i> 2000;10(2):38-9.</p> <p>Quarello F, Martina G, Beltrame G, et al. Effects of erythropoietin on the cardiovascular system and the intradialytic hemodynamic behavior. <i>Minerva Urol Nefrol.</i> 1991;43(3):125-130.</p>	
<p>4th International Symposium for Hypoxia in Medical Research, Training and Rehabilitation. <i>Sleep Breath.</i> 2012;16(1).</p> <p>Alexy T. The pros and cons of erythropoietin use in the clinical practice. <i>Clin Hemorheol Microcirc.</i> 2013;54(2):174.</p> <p>Audran M, Lejeune M, Bonafoux B, et al. Analysis of human reticulocyte genes reveals altered erythropoiesis: potential use to detect recombinant human erythropoietin doping. <i>Haematologica.</i> 2004;89(8):991-7.</p> <p>Balestra C, Germonpré P. EPO and doping. <i>Eur J Appl Physiol.</i> 2010;109(5):1001-2.</p> <p>Bham B. Unhealthy competition. Advances in biomedical research provide new drugs and technologies in medicine, but also new ways for athletes to illegally enhance their performance. <i>EMBO Rep.</i> 2003;4(10):927-9.</p>	<p>Inappropriate study design (e.g. review article)</p>

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<p>Borrione P, Mastrone A, Salvo R. Oxygen delivery enhancers: past, present, and future. <i>J Endocrinol Invest</i>. 2008;31(2):185-92.</p> <p>Boyce E. Use and effectiveness of performance-enhancing substances. <i>J Pharm Pract</i>. 2003;16(1):22-36.</p> <p>Buemi M, Lacquaniti A, Cernaro V, et al. Down with the erythropoietin. Long live the erythropoietin! <i>Curr Drug Targets</i>. 2009;10(10):1028-32.</p> <p>Caetano Júnior P, Cunha T, Lemes L, et al. Effects of administration of human recombinant erythropoietin on physical performance: Study review. <i>Rev Andal Med Deport</i>. 2014;7(1):170-7.</p> <p>de Oliveira Carolina Dizioli R, de Bairros André V, Yonamine M. Blood Doping: Risks to Athletes' Health and Strategies for Detection. <i>Subst Use Misuse</i>. 2014;49(9):1168-81.</p> <p>Finnoff J, Chimes G, Murray T. Performance-Enhancing Drugs. <i>PM R</i>. 2010;2(4):285-93.</p> <p>Fisher J. Erythropoietin: physiology and pharmacology update. <i>Exp Biol Med</i>. 2003;228(1):1-14.</p> <p>Gaudard A, Varlet-Marie E, Bressole F, et al. Drugs for Increasing Oxygen Transport and Their Potential Use in Doping: A Review. <i>Sports Med</i>. 2003;33(3):187-212.</p> <p>Guezennec C. Doping: effective, consequences, prevention. <i>Ann Endocrinol</i>. 2001;62(1):33-41.</p> <p>Henry D. Changing patterns of care in the management of anemia. <i>Semin Oncol</i>. 1992;19(3):3-7.</p> <p>Jelkmann W. Use of recombinant human erythropoietin as an antianemic and performance enhancing drug. <i>Curr Pharm Biotechnol</i>. 2000;1(1):11-31.</p> <p>Opie L. Erythropoietin as a cardioprotective agent: Down but</p>	
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<p>not out. <i>Heart</i>. 2011;97(19):1537-9.</p> <p>Sgrò P, Sansone M, Sansone A, et al. Effects of erythropoietin abuse on exercise performance. <i>Phys Sportsmed</i>. 2018;46(1):105-15.</p> <p>Simon T. Induced erythrocythemia and athletic performance. <i>Semin Hematol</i>. 1994;31(2):128-33.</p> <p>Smith K, Bleyer A, Little W, et al. The cardiovascular effects of erythropoietin. <i>Cardiovasc Res</i>. 2003;59(3):538-48.</p> <p>Szygula Z. Sports anaemia, regulation of erythropoietin biosynthesis during physical effort and EPO doping. <i>Br J Sports Med</i>. 2010;44(S1):i17.</p> <p>Thompson C, Kemp G, Taylor D, et al. Bioenergetic effects of erythropoietin in skeletal muscle. <i>Nephron</i>. 1996;74(1):239-40.</p> <p>Varlet-Marie E, Gaudard A, Audran M, et al. Pharmacokinetic-pharmacodynamic modelling of recombinant human erythropoietin in athletes. <i>Int J Sports Med</i>. 2003;24(4):252-7.</p>	
<p>Boyaci F, Gokmen N, Erbayraktar S, et al. Effects of erythropoietin on the volume of infarction after spinal cord ischemia model. <i>J Neurol Sci Turk</i>. 2012;29(1):101-9.</p> <p>Cailaud C, Mechta M, Ainge H, et al. Chronic erythropoietin treatment improves diet-induced glucose intolerance in rats. <i>J Endocrinol</i>. 2015;225(2):77-88.</p> <p>Cayla J, Maire P, Duvallet A, et al. Erythropoietin induces a shift of muscle phenotype from fast glycolytic to slow oxidative. <i>Int J Sports Med</i>. 2008;29(6):460-5.</p> <p>El-Kordi A, Radyushkin K, Enhrenreich H. Erythropoietin improves operant conditioning and stability of cognitive performance in mice. <i>BMC Biol</i>. 2009;7(73).</p>	Use of animal models
<p>Bellamy-Zions J. Cracking Down on EPO Drug Use. <i>Canadian thoroughbred</i>. 2014;29(7):7.</p> <p>Burke E. Performance enhancement: blood boosting, erythropoietin, and steroids. Philadelphia, PA: Hanley &amp; Belfus 1994.</p>	Not an original scientific article

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<p>Hansen M. Learn how to optimize your performance like elite cyclists: the secret to improving your endurance. <i>Triathlete</i>. 2013.</p> <p>Jereski L. It gives athletes a boost: maybe too much: erythropoietin. <i>Business week</i>. 1989.</p> <p>Heuberger J, Posthuma JJ, Rotmans JJ, et al. Effects of exercise and erythropoietin on thrombotic risk in well-trained cyclists [abstract]. In: 26<sup>th</sup> International Society on Thrombosis and Haemostasis Congress;2017;Germany.</p>	
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