

## Beta<sub>2</sub> adrenoceptor agonists and the Olympic Games in Athens

Appendix A of the Olympic Movement Anti-Doping Code, the List of Prohibited Substances and Prohibited Methods dated 1<sup>st</sup> January 2003 states that Formoterol, Salbutamol, Salmeterol and Terbutaline are: “Permitted by inhaler only to prevent and/or treat asthma and exercise-induced asthma.” A simple notification from a respiratory or team physician stating that the athlete has asthma and/or exercise-induced asthma (or exercise-induced bronchoconstriction) **WILL NO LONGER BE ACCEPTABLE** as evidence for that athlete to inhale a permitted beta<sub>2</sub> agonist at the Olympic Games in Athens.

Athletes who request permission to inhale a permitted beta<sub>2</sub> agonist will be required to submit test results in support of that athlete having objective evidence of asthma and/or exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB). The measurement of FEV<sub>1</sub> and its change from baseline in response to either an inhaled bronchodilator or a bronchial provocation test is the minimum test information that is required to be measured and reported on the application form. Performance of spirometry must adhere to the guidelines of the American Thoracic Society (ATS), or the European Respiratory Society. The spirometer should be endorsed to ATS standards.

**It is now an essential requirement for this information to be submitted on the APPLICATION FORM provided. This form has been prepared a) to facilitate the computer entry of the test results and b) to facilitate the electronic submission of the form. The application must give information in respect of ONE or MORE of the following tests. These tests must have been conducted since the last summer Olympic Games in Sydney.**

1. **Bronchodilator test:** Evidence of a positive bronchodilator test is defined as a 15% or greater increase in FEV<sub>1</sub> calculated as a percent of the baseline FEV<sub>1</sub> after the administration of an inhaled permitted beta<sub>2</sub> agonist.
2. **Bronchial Provocation Tests:**
  - a) Evidence of a positive bronchoconstrictor response to provocation with either
    - i) an exercise challenge in the laboratory or
    - ii) an exercise test in the field or
    - iii) a eucapnic voluntary hyperpnea test in the laboratory (EVH : The Eucapnic Voluntary Hyperpnea Test is described by Anderson SD et al 2001, Br J Sports Med 35: 344-347).

A positive bronchoconstrictor response consistent with EIA or EIB is confirmed if there is a fall of 10% or more in FEV<sub>1</sub> within the 30 minutes of ceasing the challenge.

- b) Evidence of a positive bronchoconstrictor response to inhaling a hypertonic aerosol (e.g. 4.5% saline) as described (Methods for Indirect Challenge Tests. Clin Reviews in Allergy & Immunology 2003; Volume 24 pages 27-54 Anderson SD, Brannan JD).

A positive bronchoconstrictor response consistent with currently active asthma is confirmed if there is a fall of 15% or more in FEV<sub>1</sub> in response to the aerosol.

- c) Evidence of a positive bronchoconstrictor response to inhaling an aerosol of methacholine may be accepted as evidence of airway hyperresponsiveness, if the PC<sub>20</sub> FEV<sub>1</sub> is equal to or less than 2 mg/ml or the PD<sub>20</sub> FEV<sub>1</sub> is equal to or less than a cumulative dose of 1 µmol or 200 micrograms or 20 breath units in steroid-naïve subjects. In subjects on daily inhaled corticosteroid treatment of more than 3 months duration, a PC<sub>20</sub> FEV<sub>1</sub> equal to or less than 13.2 mg/ml or a PD<sub>20</sub> FEV<sub>1</sub> equal to or less than cumulative dose of 6.6 µmol, or equal to or less than 1320 micrograms or 130 breath units may be accepted as evidence of airway hyperresponsiveness. **Submission of laboratory worksheets is mandatory for methacholine tests (see below).**

In the application form, details of symptoms, allergies, current daily medications and other medications in the three months prior to the provocation test are required. The date that inhaled corticosteroids commenced must be included on the application form.

Information must be submitted on the application form which is available on the IOC website, <[www.olympic.org](http://www.olympic.org)>. This information should be; a) typed onto the form; b) all information requested should be answered; c) if possible, the application should be signed EITHER by the NOC Team Physician, a respiratory physician or the Head of the Laboratory conducting the tests with a copy sent to the NOC for their records and; d) submitted electronically. Submission of worksheets and graphic evidence (spirometry or flow volume tracings) for methacholine tests is mandatory. Submission of worksheets for the other tests is encouraged but not essential.

The inability or failure to provide any of the above confirmatory evidence, or, in the case of Methacholine challenge, if values for PC<sub>20</sub> or PD<sub>20</sub> or breath units are in excess of the values in Point 2c (above), may result in the need for testing with eucapnic voluntary hyperpnea or a field exercise challenge in Athens prior to the Games.

In the case of an athlete, with known but well controlled asthma recording a negative result, but still seeking approval, extensive documentation including consultations with their physician for treatment of asthma, hospital emergency department attendance or admission for acute exacerbations of asthma or treatment with oral corticosteroids will need to be submitted along with the negative test result for consideration by the panel. Additional information that will assist includes age of onset, descriptions of the individual's asthma symptoms, both day and night, trigger factors, medication use, past history of atopic disorders and/or childhood asthma, and physical examination, together with results of skin prick test or RAST to document the presence of allergic hypersensitivity. Should the athlete wish to submit a second test result, the opportunity for further testing would still be available in Athens.

**Peak Expiratory Flow (PEF) measurements are unacceptable.**

**Submission of bronchial provocation tests using pharmacological agents other than methacholine (e.g. carbachol, histamine, or adenosine monophosphate) will not be accepted.**

The Appendix contains additional information and references that will assist physicians to understand the different test options available and their subsequent interpretation. The essential APPLICATION FORM, the worksheets for the approved bronchoprovocation tests, this document and the following information are on the IOC website: <[www.olympic.org](http://www.olympic.org)>. To submit electronically you must download the Word for Windows files. These can be completed and saved. If you wish to print ONLY, you should use the pdf files. These cannot be saved so are unable to be used for electronic submission.

**Applications for athletes to inhale a beta<sub>2</sub> agonist in Athens should be forwarded to the IOC Medical Director as soon as possible after 13 August 2003 and before 6 August 2004.**

**Electronic submission is preferred ([patrick.schamasch@olympic.org](mailto:patrick.schamasch@olympic.org)).**

**Alternatively, the documents can be faxed to the IOC Medical Director on: 41 21 621 6357**

**Applications received during the year before the Games will be assessed by the panel and if approved, an approval form will be forwarded to the athlete with a copy to the NOC physician.**

**Later applications submitted at least one week prior to the competitive event will be accepted.**

**If the Independent Panel does not approve the application, there is an opportunity for the athlete to have either a eucapnic voluntary hyperpnea test or an exercise challenge test in Athens. It is important to note that**

- 1) To provide the optimal test circumstances to obtain a positive response, it is recommended that some medications are withheld for 8 - 96 hrs before the bronchial provocation test. (see Appendix)**
- 2) These tests may take up to 1 hour and 30 minutes**
- 3) The cost of the test will be US\$200 and payable by the NOC.**
- 4) The results of such investigation shall be final.**

As in Salt Lake City and Sydney, the Laboratory will report any urine test result with a level of Salbutamol greater than 100 ng/ml. If the athlete has not received an authority to inhale a permitted beta<sub>2</sub> agonist in Athens or is deemed not to have used it in accordance with their approved application, the sample will be deemed to have been positive control sample and action taken will be in accordance with the procedures for Positive Test Results.

**BACKGROUND to the decision to require documented evidence of asthma and/or EIA/EIB:**

In May 2001, the IOC (Medical Commission IOC-MC) convened a workshop to examine asthma, beta agonists and the Olympic Games. The workshop concluded that:

- At recent Olympic Games, there had been a large increase in the number of athletes notifying the need to inhale a beta<sub>2</sub> agonist
- Some athletes may have been misdiagnosed and did not have asthma and/or exercise induced asthma (EIA) or bronchoconstriction (EIB)
- There is no scientific evidence to confirm that inhaled beta<sub>2</sub> agonists enhance performance in doses required to inhibit EIA/EIB
- A skewed distribution of notifications of beta<sub>2</sub> agonists by sport was observed with a higher prevalence in endurance sports
- The geographic distribution of notifications of inhaled beta<sub>2</sub> agents was markedly skewed but correlated well to the reported prevalence of asthma symptoms in those countries
- There is some evidence that daily use of an inhaled beta<sub>2</sub> agonist may result in tolerance to the medication
- Inhaled corticosteroids may be under-used in athletes notifying the use of beta<sub>2</sub> agonists
- Eucapnic voluntary hyperpnoea (EVH) was considered to be the optimal laboratory based challenge to confirm that an athlete has EIA/EIB
- Beta<sub>2</sub> agonists when administered systemically do have anabolic effects

In October 2001, the IOC-MC appointed an Independent Panel of experts who established the necessary criteria for an athlete to be granted permission to inhale a permitted beta<sub>2</sub> agonist at the Olympic Games in Salt Lake City. A report of the implementation of these requirements for the Salt Lake City Games has recently been published. *J Allergy & Clinical Immunology* 2003;111:45-50.

The IOC-MC independent panel reviewed the requirements for the Salt Lake City Games and has made some minor revisions and some additions to the original criteria and recommended them for the Games in Athens.

**If team physicians require assistance or advice, please E-mail Ken Fitch, Moderator of the Independent Panel on [kfitch@cyllene.uwa.edu.au](mailto:kfitch@cyllene.uwa.edu.au)**

The Appendix contains

- Explanatory notes and references for interpretation of tests
- References pertaining to the tests
- A table containing the method of calculating predicted spirometry

Also present on the website

- The mandatory Application form as a Word for Windows document (Can be submitted electronically).
- A combined worksheet for EVH and exercise as a Word for Windows document (Can be submitted electronically).
- A combined worksheet for Hypertonic Saline and Methacholine as a Word for Windows document (Can be submitted electronically).
- A link to download Adobe Acrobat Reader 5.1 for viewing the pdf files provided. These files cannot be saved so are not able to be submitted electronically but they can be printed.
- A combined worksheet for EVH and exercise as a pdf file.
- A combined worksheet for Hypertonic Saline and Methacholine as a pdf file.

Yours sincerely

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## APPENDIX

## Explanatory notes and References for interpretation of tests

a) Predicted values for spirometry. See Table 1 for equations				
b) Interpretation of Spirometry				
	<b>FVC*</b>	<b>FEV<sub>1</sub>*</b>	<b>FEV<sub>1</sub>/FVC**</b>	<b>FEF<sub>25-75</sub>*</b>
<b>Normal</b>	>80	>80	>70	>67
<b>Mild Obstruction</b>	66-80	66-80	60-70***	50-66
<b>Marked Obstruction</b>	<66	<66	<60	<50
FVC = forced vital capacity; FEV <sub>1</sub> = forced expired volume in 1 second; FEF <sub>25-75</sub> = forced expired flow through the middle portion (25% to 75%) of FVC.				
*Percent predicted normal; **Absolute value; ***Many athletic persons have a low FEV <sub>1</sub> /FVC ratio because their FVC is higher than average. For measurement of spirometry see Johns and Pierce (1)				
c) <b>Positive response to a bronchodilator.</b>				
This is an increase in FEV <sub>1</sub> of 15% or more of the baseline FEV <sub>1</sub> and must exceed 200 ml.				
<b>Positive response to a provocation test</b>				
<b>Exercise</b> - a fall in FEV <sub>1</sub> of 10% or more from baseline in response to exercise in the laboratory or field. The field exercise should ideally be the one that brings on the symptoms of exercise-induced bronchoconstriction. To overcome the problem of some respiratory muscle fatigue the FEV <sub>1</sub> should not be recorded until at least three minutes after exercise. It would be usual for the reduction to be sustained over the next five minutes to be consistent with exercise-induced bronchoconstriction (4, 5, 7, 10)				
<b>Eucapnic voluntary hyperpnea</b> - a fall in FEV <sub>1</sub> of 10% or more from baseline performing hyperpnea with dry air for 6 - 8 minutes is consistent with a diagnosis of exercise-induced bronchoconstriction and responsiveness to hypertonic aerosols. To overcome the problem of some respiratory muscle fatigue the FEV <sub>1</sub> should not be recorded until at least three minutes after EVH. It would be usual for the reduction to be sustained over the next five minutes to be consistent with hyperpnea- induced bronchoconstriction (2, 3, 6, 7, 9).				
<b>Hypertonic Aerosol:</b> A fall in FEV <sub>1</sub> of 15% or more from baseline after a dose of 22.5 ml of 4.5 gm% saline (e.g. 4.5 g NaCl /100 ml water) has been delivered is a positive response and is consistent with a diagnosis of currently active asthma or exercise-induced bronchoconstriction. The aerosol response is usually reported as the dose required to provoke a 15% fall in FEV <sub>1</sub> (PD <sub>15</sub> ) but can also be reported as the maximum fall after the final dose of aerosol (4, 7, 9).				
<b>Methacholine:</b> A fall in FEV <sub>1</sub> of 20% or more from baseline at a dose less than or equal to 1 micromole, 200 micrograms or 2 mg/ml or 20 breath units when the subject is not taking inhaled corticosteroids is consistent with a diagnosis of airway hyperresponsiveness (AHR). For applicants taking inhaled steroids for at least 3 months, the PD <sub>20</sub> should be equal to or less than 6.6 micromoles, 1320 micrograms or PC <sub>20</sub> equal to or less than 13.2 mg/ml or 130 breath units, to be consistent with AHR (11). It should be noted that a negative response to methacholine does not exclude exercise-induced asthma in an athlete and in the event of a negative response, an alternative challenge is recommended (8).				
d) <b>Recommendation for Withholding Medications prior to challenge.</b>				
To provide the optimal test circumstances to achieve a positive response, it is recommended that some medications be withheld for 8- 96 hrs before the bronchial provocation test. No short-acting bronchodilators, sodium cromoglycate, nedocromil sodium, or ipratropium bromide for 8 hr. No long-acting bronchodilators or antihistamines for 48hr. No leukotriene antagonists for 4 days. Inhaled steroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least 4 hr prior to attendance at the laboratory and preferably none on the day of testing.				

### References pertaining to the tests

1. Johns DP, Pierce R. Pocket Guide to Spirometry (ISBN 0-07-471331-0). McGraw-Hill Australia. 2003.
2. Hurwitz KM, Argyros GJ, Roach JM, Eliasson AH, Phillips YY. Interpretation of eucapnic voluntary hyperventilation in the diagnosis of asthma. *Chest*, 1995; **108**: 1240-5.
3. Anderson SD, Argyros GJ, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnoea to identify exercise-induced bronchoconstriction. *Br J Sports Med*, 2001; **35**:344-7.
4. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness: Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J*, 1993; **6**(Suppl 16): 53-83.
5. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing - 1999. *Am J Respir Crit Care Med*, 2000; **161**: 309-29.
6. Smith CM, Anderson SD. Inhalational challenge using hypertonic saline in asthmatic subjects: a comparison with responses to hyperpnoea, methacholine and water. *Eur Respir J* 1990; **3**: 144-51.
7. Anderson SD, Brannan JD. Methods for 'indirect' challenge tests including exercise, eucapnic voluntary hyperpnea and hypertonic aerosols. *Clin Rev Allergy Immunol* 2003; **24**: 63-90.
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11. Anderson SD, Fitch K, Perry CP, Sue-Chu M, Crapo R, McKenzie D, Magnussen H. Responses to bronchial challenge submitted for approval to use inhaled beta<sub>2</sub> agonists prior to an event at the 2002 Winter Olympics. *J Allergy Clin Immunol* 2003; **111**: 44-9.

### Further Reading:

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Rundell, KW, Wilber RL, Szmedra L, Jenkinson DM, Mayers LB, Im J. 2000. Exercise-induced asthma screening of elite athletes: field vs laboratory exercise challenge. *Med Sci Sports Exerc* **32**(2):309-16.

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Anderson SD, Daviskas E. 2000. The mechanism of exercise-induced asthma is ..... *J Allergy Clin Immunol* **106**(3):453-9.

Gibson PG, Saltos N, Borgas T. Airway mast cells and eosinophils correlate with clinical severity and airway hyperresponsiveness in corticosteroid-treated asthma. *J Allergy Clin Immunol* 2000; **105**: 752-9.

Asthma and Exercise. Wilbur R, Lemanske R, Rundell K, Eds. Champaign, Human Kinetics, 2002.

**Table 1 METHOD OF CALCULATING PREDICTED VALUES FOR SPIROMETRY**

**Summary equations for Caucasian Adults aged 18-70 yrs. The lower 5 or upper 95 percentiles are obtained by subtracting from, or adding to, the predicted mean the figure for 1.64 residual standard deviation\* shown in the last column.**

Variable	Gender	Unit	Regression Equation	RSD	1.64 RSD
FVC	F	L	4.43H - 0.026A - 2.89	0.43	0.71
FEV <sub>1</sub>	F	L	3.95H - 0.025A - 2.60	0.38	0.62
FEV <sub>1</sub> /FVC	F	%	-0.19A + 89.10	6.51	10.7
FEF <sub>25-75</sub>	F	L.s <sup>-1</sup>	1.25H - 0.034A + 2.92	0.85	1.40
FVC	M	L	5.76H - 0.026A - 4.34	0.61	1.00
FEV <sub>1</sub>	M	L	4.30H - 0.029A - 2.49	0.51	0.84
FEV <sub>1</sub> /FVC	M	%	-0.18A + 87.21	7.17	11.8
FEF <sub>25-75</sub>	M	L.s <sup>-1</sup>	1.94H - 0.043A + 2.70	1.04	1.71

FEV<sub>1</sub> = Forced Expiratory Volume in One Second; FEV<sub>1</sub>/FVC = Ratio of FEV<sub>1</sub> to FVC;

FEF<sub>25-75</sub> = forced expiratory flow through the middle portion of the vital capacity;

H = standing height (m); A = age (yr)

§: between 18 and 25 yrs, use value of 25 yr in the equations as the allowance for age is made on a linear basis and this is valid over this range (Cotes, J.E. 1993. Lung Function Assessment and Application in Medicine. 5th ed. Blackwell Scientific Publications, Oxford).

\* The residual standard deviation (RSD) describes the spread of individual values about a multiple regression equation (Cotes, 1993). Because the numbers are high 1.64 RSD, rather than the usual 2.0 RSD, can be used to calculate the lower and upper limits of normal.

Taken from Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. 1993. Lung volumes and forced ventilatory flows. *Eur Respir J* 6:5-40.

**For Non-Caucasians, predicted values for the ethnic group should be used or an appropriate adjustment of the FEV<sub>1</sub> and FVC values (e.g. 80-90%) obtained from the equations above.**