

EAACI consensus statement for investigation of work-related asthma in non-specialized centres

G. Moscato¹, G. Pala¹, C. Barnig², F. De Blay², S. R. Del Giacco³, I. Folletti⁴, E. Heffler⁵, P. Maestrelli⁶, G. Pauli², L. Perfetti¹, S. Quirce⁷, J. Sastre⁸, A. Siracusa⁹, J. Walusiak-Skorupa¹⁰ & R. Gerth van Wijk¹¹

¹Allergy and Immunology Unit, Fondazione 'Salvatore Maugeri', Institute of Care and Research, Scientific Institute of Pavia, Pavia, Italy;

²Division of Asthma and Allergy, Department of Chest Diseases, University Hospital Strasbourg, Strasbourg, France; ³Department of Medical Sciences 'M. Aresu', University of Cagliari, Cagliari, Italy; ⁴Department of Clinical and Experimental Medicine, Occupational Allergy Unit, Terni Hospital, University of Perugia, Perugia, Italy; ⁵Allergy and Clinical Immunology, University of Torino, ASO Mauriziano 'Umberto I', Torino, Italy; ⁶Department of Environmental Medicine and Public Health, University of Padova, Padova, Italy; ⁷Department of Allergy, Hospital La Paz-IdiPAZ and CIBER de Enfermedades Respiratorias CIBERES, Madrid, Spain; ⁸CIBER de Enfermedades Respiratorias, Ciberes and Department of Allergy, Fundación Jiménez Díaz, Madrid, Spain; ⁹Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy; ¹⁰Department of Occupational Diseases, Nofer Institute of Occupational Medicine, Lodz, Poland; ¹¹Section of Allergology, Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands

To cite this article: Moscato G, Pala G, Barnig C, De Blay F, Del Giacco SR, Folletti I, Heffler E, Maestrelli P, Pauli G, Perfetti L, Quirce S, Sastre J, Siracusa A, Walusiak-Skorupa J, Gerth van Wijk R. EAACI consensus statement for investigation of work-related asthma in non-specialized centres. *Allergy* 2012; DOI:10.1111/j.1398-9995.2011.0.2784.x

Keywords

irritant-induced asthma; occupational asthma; specific inhalation challenge work-exacerbated asthma work-related asthma

Correspondence

Gianna Moscato, M.D., Servizio di Allergologia e Immunologia Clinica, Fondazione Salvatore Maugeri, IRCCS, Via Maugeri 10, 27100 Pavia, Italy.
Tel.: 0039 0382 592941
Fax: 0039 0382 592086
E-mail: gianna.moscato@fsm.it

Accepted for publication 15 December 2011

DOI:10.1111/j.1398-9995.2011.02784.x

Edited by: Michael Wechsler

Abbreviations

FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HMW, high molecular weight; IIOA, irritant-induced occupational asthma; IS, induced sputum; LMW, low molecular weight; MCH, methacholine; MCH PC₂₀, provocative concentration of MCH causing a 20% fall in FEV₁; NAEB, nonasthmatic eosinophilic bronchitis; NAIIOA, nonacute irritant-induced occupational asthma; NSBH, nonspecific bronchial hyperresponsiveness; OA, occupational asthma; PEFR, peak expiratory flow rate; RADS, reactive airways dysfunction syndrome; SIC, specific inhalation challenge; WEA, work-exacerbated asthma; WRA, work-related asthma.

Abstract

Work-related asthma (WRA) is a relevant problem in several countries, is cause of disability and socioeconomic consequences for both the patient and the society and is probably still underdiagnosed. A correct diagnosis is extremely important to reduce or limit the consequences of the disease. This consensus document was prepared by a EAACI Task Force consisting of an expert panel of allergologists, pneumologists and occupational physicians from different European countries. This document is not intended to address in detail the full diagnostic work-up of WRA, nor to be a formal evidence-based guideline. It is written to provide an operative protocol to allergologists and physicians dealing with asthma useful for identifying the subjects suspected of having WRA to address them to in-depth investigations in a specialized centre. No evidence-based system could be used because of the low grade of evidence of published studies in this area, and instead, 'key messages' or 'suggestions' are provided based on consensus of the expert panel members.

Work-related asthma (WRA) is cause of disability and socio-economic consequences for both the patient and the society and is probably underdiagnosed (1). A correct diagnosis is important to reduce or limit the consequences of the disease (2). As much as 25% of adult asthmatic patients are estimated to have WRA (3), and thus, the possibility that non-occupational physicians such as allergologists or pneumologists face WRA in daily practice is high, and they may play a pivotal role in identifying the suspected cases. Nevertheless, the investigation of WRA still remains a difficult issue in the routine of nonoccupational physicians.

The last EAACI document on occupational asthma (OA) has been published in 1992 (4), and despite several other

comprehensive documents produced by other societies (2,5), an operative protocol for WRA assessment in the daily practice of allergologists is still lacking.

Methods

This consensus document was prepared by a EAACI Task Force consisting of an expert panel of allergologists, pneumologists and occupational physicians and was reviewed and accepted by the EAACI Executive Committee.

The literature was reviewed by the panel members, using a Medline search. A meeting was held to review the findings and reach informal consensus. Further consensus was reached by an informal iterative process by input of all panel members into the drafts of the document. The original aim of the Task Force was to advance recommendations using an evidence-based system. However, it was recognized that the quality of evidence of published studies in this area would be graded as low, based on case series and unmatched cohort studies. Therefore, no evidence-based recommendations could be provided, and instead, 'key messages' (see Key Messages Box) or 'suggestions' are provided based on consensus of the expert panel members (<http://www.chestnet.org/education/guidelines/currentguidelines>; accessed 13 November 2007).

In November 2010, the expert panel discussed the first written draft version of the document. Key messages, suggestions and changes were included in the draft, and the revised draft was discussed via e-mail communications, to achieve group consensus. All recommendations that received the agreement of all members were included in the final draft.

This document is not intended to address in detail the full diagnostic work-up of WRA, nor to be a formal evidence-based guideline (6). It is written to provide an operative protocol to allergologists and physicians dealing with asthma useful for identifying the subjects suspected of having WRA to address them to in-depth investigations in a specialized centre.

Definition and classification of work-related asthma

Work-related asthma comprises two major entities, that is OA, defined as a type of asthma 'caused' by the workplace and work-exacerbated asthma (WEA), which refers to asthma triggered by various work-related factors (e.g. aeroallergens, irritants or exercise) in workers who are known to have pre-existing or concurrent asthma (e.g. asthma that is occurring at the same time but is not caused by workplace exposure) (2) (Fig. 1). OA is currently one of the most common forms of occupational lung disease in many industrialized countries (7, 8).

Two types of OA are distinguished (2):

- Allergic, that is OA induced by sensitizers, which appears after a latency period necessary for the worker to acquire sensitization to the causal agent. It encompasses OA caused by most high (HMW) and some low molecular weight (LMW) agents (Table 1) for which an IgE-mediated mechanism has proven, and OA induced by some specific LMW agents in which the allergic mechanisms responsible have not yet been fully characterized.

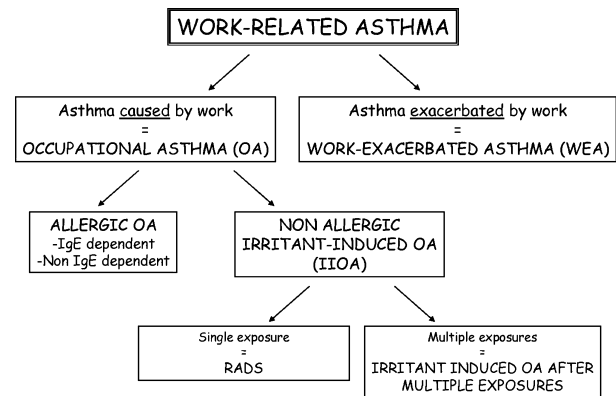


Figure 1 Classification of work-related asthma.

- Nonallergic, irritant-induced OA (HIOA). The most definite form of HIOA is the 'Reactive Airways Dysfunction Syndrome' (RADS), which occurs as an acute onset of asthma after a single exposure to very high concentrations of an irritating gas, vapour, fume or smoke (9). A less definite form, because of the paucity of reports and case studies, is HIOA after multiple exposure, where the onset of asthma is not so sudden and follows multiple exposures to high levels of irritants (10). Allergic OA is the most common type of OA, accounting for more than 90% of cases (11).

The investigation of WRA has a two-sided objective: demonstrating the presence of asthma and confirming its relationship to work (Table 2) (4). The starting point is a detailed clinical history, which must be confirmed by objective tests that partially differ for allergic and nonallergic OA (12). Because of the inflammatory basis of WRA, assessment of bronchial inflammation is helpful in the investigation of the disorder (13, 14). Moreover, because of the strict link between upper and lower airway inflammation, assessment of nasal inflammation is also suggested (15).

Assessment and diagnosis of occupational asthma

Assessment and diagnosis of allergic occupational asthma

Clinical history

In every adult whose asthma begins or worsens while working, WRA should be considered, and a detailed occupational and medical history should be collected (8, 16, 17). However, clinical history alone has a low specificity in the diagnosis of OA (18).

Occupational history aims at obtaining information on:

- past and current worker's job duties;
- substances and materials used in the work environment;
- use of protection devices;
- recent changes in work processes or materials;
- workplace environmental conditions;
- date of the last exposure at current job.

Table 1 Causal agents of occupational asthma and occupations at risk (from Ref. 16)

High molecular weight agents		Low molecular weight agents	
Occupation	Agent	Occupation	Agent
Baking, milling, pastry making	Flour(s), α -amylase, other enzymes, egg white	Spray painters, French polishers	Diisocyanates
Laboratory animal researchers and technicians	Rat, mouse, guinea pig, ferret, etc. proteins, egg	Electronic solderers	Colophony fume
Health-care workers	Latex	Health-care workers	Glutaraldehyde, methyl/butyl methacrylate
Detergent enzyme manufactures	Detergent protease, amylase, lipase, cellulase	Plastic and foam manufacturers	Diisocyanates, acid anhydrides, epoxy resins
Tea packers, coffee processors	Herbal teas, green coffee bean	Woodworkers, lumberjack	Red cedar, iroko, other tropical sawdusts
Sea food processors	Prawn, crab, other (shell) fish proteins	Textile workers	Reactive dyes
Other food processors	Garlic, egg, enzymes	Hairdressers	Persulphates
Flower and vegetable farmers	Pollens	Pharmaceutical manufacturers	Penicillins, morphine, cimetidine

Table 2 Investigation of work-related asthma (mod from Ref. 4)

History suggestive of occupational asthma and exposure documentation
Confirmation of bronchial asthma
Confirmation of work-related bronchoconstriction
Confirmation of sensitization to occupational agents
Confirmation of causal role of occupational agents

Medical history should focus on:

- Respiratory symptoms (i.e. chest tightness, wheezing, cough and shortness of breath).
- Associated symptoms:
 - (a) nose and eye symptoms (i.e. nasal congestion, rhinorrhea, sneezing, lachrymation, ocular itching) (19);
 - (b) skin symptoms (i.e. eczema, rash and urticaria);
 - (c) systemic symptoms (i.e. fever, arthralgias and myalgias).
- Date of symptoms' onset: after starting current job, or pre-existing and worsened by current job. In patients with symptoms' onset after starting current job, the presence of OA can be suspected, in those with pre-existing symptoms worsened by current job WEA can be postulated.
- Duration of employment at current job before symptoms' onset ('latency period'), duration of symptoms before diagnosis, information on individual risk factors (atopy, accidental exposures to irritants, pre-existent asthma and/or rhinitis, smoking habit).
- Relationship of symptoms to work exposure: immediate onset when entering the workplace; delayed onset beginning 4–12 h after starting work or after coming home; immediate onset followed by recovery, with symptoms recurring 4–12 h after initial work exposure (biphasic). Especially in the delayed-onset symptoms, most frequently presenting after exposure to LMW agents (e.g. isocyanates, reactive dyes, persulphates) may not be so obviously work related, and diagnosis may be delayed.

- Relationship between symptoms and periods at and away from work: at the onset of symptoms, improvement on weekends and holidays, and worsening on return to work, is the rule (positive stop-resume test). As exposure continues, symptoms may become persistent, and thus, a negative stop-resume test should not rule out the possibility of OA.

Exposure assessment

Work-related asthma results from the interactions between host factors and the environment, but at least in OA, there is evidence that exposure levels represent one of the major determinants for the development of the disease (20, 21). Therefore, the assessment and documentation of exposure is an important step in the diagnostic work-up of WRA. Every physician should be aware of occupations at risk for WRA and of the possible causative agents. An exhaustive list of agents and occupations is available in the EAACI website (http://www.eaaci.net/images/files/Pdf_MsWord/2010/occupational%20allergens%20list_june2010.pdf). A logistic regression model has been proposed to predict the OA hazard of chemicals (22). Review manufacturer's safety data sheets nearly always provide the necessary information on substances used. Levels of causative agents in the workplace environment or during specific inhalation challenge (SIC) should be measured when possible (23, 24).

The environmental study requires an exhaustive knowledge of all materials, and even intermediate or temporarily used substances, involved up to the final product, are obtained.

Assessment of the state of the agent such as a dust, aerosol, gas or vapour can be important because this can affect its interaction with the body and the way in which it must be analysed. Dermal absorption of chemicals may influence sensitization (25).

The web pages of various organizations publish sampling methods and analytic techniques for a variety of chemicals (<http://www.cdc.gov/niosh/nmam/nmamenu.html>, <http://www.osha.gov/dts/sltc/methods/index.html>, <http://www.skincinc.com/guides.asp>, 26). Quantification of allergenic proteins

requires the use of specific immunoassay techniques, usually inhibition immunoassays able to detect protein concentrations between 100 pg/ml and 1 ng/ml (27–31). A disadvantage of inhibition methods is that in most cases, there is no international standardization and that it may not be commercially available for many occupational allergens. In other cases such as pollens or fungi spores counts can be performed by optical microscopy based on morphologic criteria or by culture methods.

Basal physiologic assessment and serial measurements of lung function and bronchial hyperresponsiveness

Basal physiologic assessment. Physical examination and lung function testing are mandatory in the work-up of WRA to confirm objectively that the worker has asthma and to rule out other work-related conditions that can be confused with WRA.

Spirometry assesses airflow obstruction and its reversibility after inhalation of a bronchodilator agent (32). However, many patients with WRA may be completely asymptomatic and have normal pulmonary function when nonexposed to the relevant work agent, therefore the assessment of nonspecific bronchial hyperresponsiveness (NSBH) through direct challenges, such as methacholine (MCH) or histamine, is suggested (2, 33). Recently, also the use of indirect challenges (e.g. mannitol, adenosine monophosphate) has been shown to be very effective in diagnosing and monitoring asthma in occupational settings (34). The MCH challenge is a highly sensitive direct challenge with a high negative predictive value, while indirect challenges are highly specific but have a relatively low sensitivity compared with MCH (35). A basal positive MCH challenge supports the diagnosis of asthma in patients with asthma symptoms (12). However, the absence of NSBH does not exclude a diagnosis of OA particularly when the subjects are tested after they have been away from work (33). A recent systematic review (36) has shown, for HMW and LMW agents, a sensitivity of NSBH tests of 79.3% and 63.9%, respectively, and a specificity of 51.3% and 63.9%, respectively, when compared with SIC. Thus, NSBH challenge alone has a relatively high sensitivity and low specificity in predicting the diagnosis of WRA based on SIC. However, adding skin prick tests or specific IgE measurement can enhance sensitivity and specificity and may be an appropriate alternative to SIC in diagnosing OA in appropriate clinical situations when SIC is not available.

Moreover, in patients with a negative SIC, an increase in NSBH after exposure to the specific agent during the challenge (defined as a PC₂₀ MCH decreases between 1.8- and 3.1-fold from pre- to post-SIC) can be considered an early marker of bronchial response to further challenge exposure in the laboratory and/or at the workplace (37, 38).

In individuals with suspected WRA and normal respiratory function, and/or negative MCH challenge, serial measurements of lung function and NSBH have often been used to improve the diagnostic probability (2).

Cross-shift spirometry

Cross-shift spirometry and measurement of FEV₁ (i.e. performed during a work-shift) have been used in workers

exposed to occupational sensitizers and to detect workers with allergic OA. However, cross-shift changes in FEV₁ have a low sensitivity for discriminating subjects with OA from asymptomatic exposed workers (13).

Serial measurements of peak expiratory flow

Since 1979, serial measurements of peak expiratory flow rate (PEFR) have been used as an objective confirmation of the relationship between the workplace and asthmatic symptoms. One important advantage of serial PEFR is the measurement of lung function during a realistic exposure (39).

Cross-shift changes in PEFR have poor sensitivity in diagnosing OA (40). Recording of PEFR every 2 h is the preferable method, although the four times a day assessment (upon waking, at noon, at the end of the working day and at bedtime) is almost as satisfactory (41). During each measurement, three PEFR measures should be performed and recorded once all three readings are within 20 l/min (42). Although the optimal duration of PEFR recording has not been established, a period of 4 weeks, including a period of 2 weeks away from work, is recommended (2). Recently, Moore et al. (43) suggested a minimum of 2-hourly PEFR measurements on eight working days and three rest days. However, if there is no recording of work-related reduction in PEFR, the diagnosis of WRA cannot confidently be ruled out. Limitations of PEFR monitoring are need of good cooperation, possible falsification, feasibility of measurement away from work and no identification of the causative agent (39).

Serial measurements of nonspecific bronchial responsiveness

Because serial measurements of PEFR have several limitations, serial measurements of NSBH to MCH have been recommended to confirm a diagnosis of OA based on clinical history and monitoring of PEFR (33). To identify work-related changes in NSBH in workers with suspected OA, it is suggested that a MCH challenge test should be performed at a time the worker is working and reports respiratory symptoms (2).

Immunologic assessment of work-related asthma

Immunologic assessment of WRA aims to support the diagnosis of allergic OA. Skin tests and determination of specific IgE antibodies are necessary to demonstrate the sensitization to occupational allergens. Nevertheless, because sensitization alone does not mean allergy, the demonstration of the link between the specific sensitization and work-related changes in lung function is mandatory for the diagnosis of WRA.

In some cases, basophil activation tests (44, 45) or histamine release (46) has been used to detect an IgE response, but such tests have not been still validated and cannot be used in daily practice. Unfortunately, standardized tests are available only for a few allergens. Consequently, in many cases, patients are provisionally tested with noncommercially available, laboratory-made skin test extracts and IgE tests. Before accepting the results from such tests, proper control tests in nonexposed subjects and in case of new allergens additional challenge tests are required (47, 48). Then, a positive test outcome can establish a

working diagnosis. In addition, a positive test may guide the physician to the identification of a sensitizer among a series of agents. However, lack of standardization limits the value of negative test results. Although it has been shown that high concentrations of flour-specific IgE and clear skin prick test results in symptomatic bakers are good predictors for a positive challenge tests (49), commercial extracts show a wide variation with respect to sensitivities, negative predictive values and test efficiencies (50). In selected cases (e.g. bovine animal dander), SPTs demonstrated excellent negative predictive value for excluding OA (51). In spite of these limitations, it is important to select those allergens for testing that may elicit an IgE response (Table 1) (http://www.eaaci.net/images/files/Pdf_MsWord/2010/occupational%20allergens%20list_june2010.pdf).

In recent years, research has focused on specific allergen panels, instead of crude allergens. For instance, in latex allergy, it is possible to distinguish clinically relevant IgE reactivity for rHev b 1, rHev b 3, rHev b 5 or rHev b 6.0 from irrelevant IgE to recombinant latex profilin (rHev b 8) (52). With this approach, the appropriate allergens for allergenic extracts can be identified (53). Research to wheat lipid transfer protein Tri a 14 (54) attempts to refine the diagnosis of baker's asthma. The presence of IgE to cross-reactive carbohydrate determinants may bias the diagnosis of wood sensitization. Therefore, it has been suggested to measure such an IgE response to carbohydrate determinants to assess the relevance of individual wood sensitization (55). Although immunologic assessment cannot replace challenge tests, this approach may result in a more accurate diagnosis of allergic OA in future.

Specific inhalation challenges

Specific inhalation challenge exposes workers with suspected OA to suspected causing agents in a controlled setting to demonstrate a direct relationship between exposure to an occupational agent and asthma (2). It is considered a reference standard for the diagnosis of OA induced by some sensitizing agents (56). SICs have some limitation including possibilities of false-negative and false-positive results and lack of usefulness in the diagnosis of nonallergic OA. In addition, SICs are performed in only a few centres provided by specialized facilities and expertise and when a suspected workplace agent has been identified. On the basis of expert opinion and consensus, SIC is suggested when the diagnosis or causative agent remains equivocal in individuals with suspected allergic OA and when the worker's management is dependent upon knowing the exact cause of OA (2, 57).

When a potential causing agent is not identified or exposure cannot be reproduced in the laboratory, SIC can be replaced with a workplace challenge. It consists of monitoring spirometry at the workplace when the subjects perform the task suspected to cause asthma. Nevertheless, this method does not allow to distinguish between OA and WEA.

A 15–20% decrease from baseline FEV₁ is generally considered a positive response. When the appropriate agent

is applied, and the response is positive in workers with work-related asthmatic symptoms, SIC is considered confirmatory. False-positive responses are not common, but can occur in unstable asthma, in patients with marked airway hyperresponsiveness, or with exposures to irritating levels of an agent. False-negative responses can occur for a number of reasons: exposure to the wrong agent or process, an inadequate concentration or timing of the exposure, a loss of specific airway responsiveness away from exposure or the use of anti-asthma drugs (5, 57).

Assessment of inflammation

The assessment of airway inflammation is recommended in the investigation of WRA and may help to distinguish OA from WEA and allergic vs irritant-induced asthmatic reactions (58). Induced sputum (IS) is the most used method and may help in: (i) identifying occupational eosinophilic bronchitis with or without asthma (58, 59), (ii) supporting the diagnosis in a complex environment when the workplace sensitizer is unknown and (iii) monitoring airway inflammation before/after SIC. An increase in sputum eosinophil counts >3% after SIC often precedes the occurrence of functional changes on subsequent exposures (60). The best timing for the collection of IS is likely to be 7–24 h after exposure (15). Most subjects with allergic OA show an eosinophilic inflammatory response after exposure to the offending agent in the laboratory (58, 61–63) or in the workplace (64, 65). Neutrophils seem to play a role in OA because of LMW agents and especially isocyanates, but recent findings show that this type of asthma is associated with eosinophilia (66). Moreover, the increase in sputum neutrophils has not been validated to support or to confirm the diagnosis of OA, as it is also observed after exposure to irritant agents, and in a recent study (67), the levels of sputum neutrophils were not significantly associated with the final diagnosis and specific bronchial reactivity. Subjects with WEA showed no changes (64) or a neutrophilic type of airway inflammation (65, 68). The addition of sputum cytology to serial PEFR measurements and SIC in the investigation of OA improves diagnosis (62, 65–68). Therefore, airway inflammation should be evaluated before excluding the subjects from further investigations when the clinical history is highly suggestive, and functional tests and MCH or indirect challenges are negative (14). Fractional exhaled nitric oxide (FeNO) has been proposed as a surrogate marker of eosinophilic inflammation in asthma (69). Although the measurement of FeNO has some advantages over the analysis of IS in OA, the interpretation of FeNO is more difficult than sputum differential cell counts because it is less specific and several confounding factors (e.g. use of inhaled or oral corticosteroids, smoking status, prior diagnosis) may influence the results (15). For specific purposes, for example to discriminate positive and negative SIC (70), sputum eosinophil counts constitute a more reliable tool than FeNO. Nevertheless, FeNO measurement provides valuable information where analysis of sputum is unavailable (e.g. in daily practice) (71) or unsuccessful (72).

Assessment and diagnosis of nonallergic, irritant-induced occupational asthma

Diagnostic criteria for RADS, the acute form of IIOA, initially proposed by Brooks (9) and adopted by ACCP (2), are:

- absence of pre-existing respiratory disorder, asthma symptomatology or a history of asthma in remission and an exclusion of conditions simulating asthma,
- onset of asthma occurring after a single exposure or accident to an irritant vapour, gas, fumes or smoke in very high concentrations,
- onset of asthma symptoms within minutes to hours and < 24 h after the exposure,
- evidence of NSBH or bronchial obstruction persisting for at least 3 months of exposure avoidance,
- presence or absence of airflow obstruction confirmed by pulmonary function testing.

The same criteria could be adopted for diagnosis of IIOA after multiple exposures, except for the onset of asthma, which in this form occurs after multiple exposures to an irritant vapour, gas, fumes or smoke in high concentrations (10).

In patients with a suggestive history of IIOA who do not meet all these stringent criteria, some difficulties can arise in the diagnostic work-up. However, it is agreed that at least three general conditions should be fulfilled:

- a diagnosis of asthma.
- evidence of single or multiple exposures to high concentration of irritants (73),
- exclusion of pre-existent asthma.

Difficult diagnosis and misdiagnosis may often occur. In differential diagnosis of IIOA, WEA must be considered (see Chapter 5). In new onset asthma induced by a high-level respiratory irritant, if the involved agent is also a respiratory sensitizers, IIOA and concurrent OA with sensitization could be induced at the same time (74, 75). Mimicks of asthma resulting from irritant exposures include vocal cord dysfunction (76), hyperventilation and panic attacks. Finally, asthma-like symptoms with NSBH following irritant exposure may subside spontaneously. If NSBH or bronchial obstruction disappears after 3 months of exposure avoidance, a diagnosis of 'Acute Respiratory Injury' should be considered (77).

Assessment and diagnosis of work-exacerbated asthma

The mechanisms that induce WEA are unknown. The clinical features correspond to WRA symptoms, but there is no specific test providing evidence of a causal relationship (78).

The worsening of asthma symptoms at work (79) and PEF monitoring (80) do not differentiate OA from WEA. IS seemed to be more relevant, as there was no significant decrease in eosinophils in WEA at the workplace and outside of the workplace (65).

Work-exacerbated asthma has been diagnosed most commonly by self-report of worsened asthma symptoms on the job in workers with pre-existing asthma (79). Nevertheless, a

definite WEA diagnosis should be based on 'objective indicators' of worsening of asthma and of deterioration of pulmonary function related to work environment. If there is no documented workplace exposure to agents known to induce OA, WEA could be considered. Conversely, if there is documented exposure to sensitizing agents, SIC should be performed. An argument for differentiating between allergic OA and WEA is the presumed difference in prognosis with continued workplace exposure. In OA, the patients should be removed from the specific exposure as soon as possible. In WEA, the patient might be able to continue working with a close environmental control and optimization of asthma treatment.

Assessment and diagnosis of eosinophilic bronchitis

Nonasthmatic eosinophilic bronchitis (NAEB) is an important cause of chronic cough, being present in 10–15% of patients referred for specialist investigation (81). It is characterized by chronic cough in patients with no symptoms or objective evidence of variable airflow obstruction, normal airway responsiveness and sputum eosinophilia (82). It can be considered in the spectrum of work-related airway diseases (83) when it develops as a consequence of work exposure (http://www.eaaci.net/images/files/Pdf_MsWord/2010/occupational%20allergens%20list_june2010.pdf, 59). A diagnosis of NAEB requires the assessment of lower airway inflammation, after other causes of cough have been excluded (82), and the demonstration of the link between the disease and workplace exposure.

According to the most recent findings, the diagnostic criteria proposed by Quirce (59) can be reviewed as follows:

- Clinical history of isolated persistent cough (lasting more than 3 weeks) presents solely at work or that worsens at work, improving or disappearing after a consistent period off work.
- Sputum eosinophilia $\geq 3\%$ either in spontaneous or IS strictly correlated to workplace exposure. Increases in sputum eosinophils related to exposure to the offending agent should be firstly proved by IS performed during a period at work and off work and finally confirmed by SIC. Airway inflammation should ideally be measured by IS analysis (15, 84). FeNO measurement has also been proposed as alternative (72), but its role in the diagnosis of NAEB has not been formally evaluated (15).
- Spirometry within normal limits and not significantly affected by exposure to the offending agent.
- Absence of NSBH both at work and away from work. Patients with NAEB seem to be not responsive to either direct or indirect bronchial challenges (85).
- Other causes of chronic cough ruled out.

The diagnosis of occupational NAEB requires all the criteria fulfilled and the offending agent identified by means of SPTs or sIgE, when available, and confirmed by SIC. Basophil activation test has recently been proposed as a new tool in the diagnosis of occupational NAEB (86), but its usefulness needs to be further confirmed.

Diagnostic algorithms of work-related asthma

The evaluation of WRA requires training and expertise. The role of allergologists and/or of other specialists dealing with asthma is of primary importance in raising the suspicion of WRA from the clinical history, in performing the investigations in their daily practice (Fig. 2) and, if the suspicion is confirmed, in referring the patient to a specialized centre in

order to confirm the work-relatedness of asthma and make a definite diagnosis (Fig. 3). Table 3 summarizes the features of methods used in WRA evaluation.

The starting point of WRA evaluation is a thorough clinical and occupational history. Patients who are suspected of WRA should undergo immunologic tests (skin prick tests and/or serum sIgE) for evaluation of sensitization to common allergens, and the functional tests (spirometry, bronchodilation

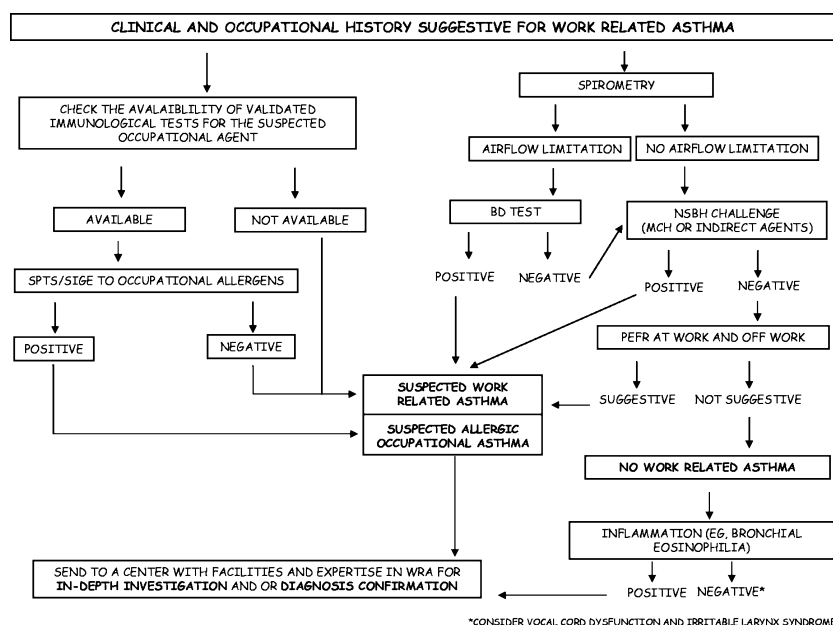


Figure 2 Investigation of work-related asthma in nonspecialized centres.

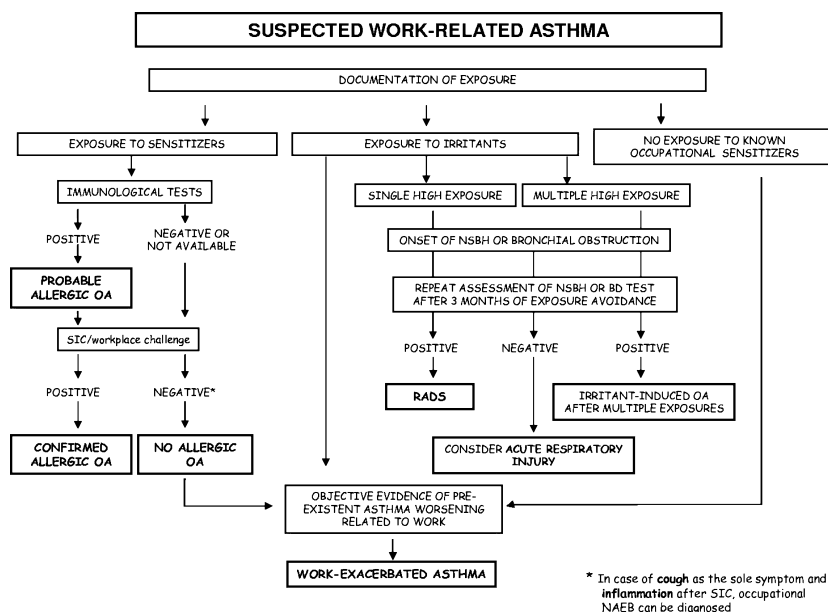


Figure 3 Investigation of work-related asthma in specialized centres.

Table 3 Methods used in work-related asthma evaluation

	Availability		Costs		Sensitivity	Specificity	Reproducibility	Notes
	Daily practice	Specialized centres	High	Low				
Clinical history/questionnaire	✓		✓	✓	✓		✓	Possible false-negative results (lack of standardized extracts)
Skin prick tests	✓		✓	✓	✓		✓	Not available for most low molecular weight agents
Specific IgE determination	✓		✓	✓	✓		✓	Not specific for OA, unless performed at work/off work
Mch test	✓	✓	✓	✓	✓		✓	Not specific for OA, interpretation not standardized
PEF at work/off work	✓			✓	✓		✓	Uncertain diagnostic performance
Assessment of airway inflammation		✓						
SIC in the laboratory		✓	✓			✓	✓	If negative, diagnosis not ruled out
SIC in the workplace		✓	✓			✓		Difficult to perform for organizational and safety issues

OA, occupational asthma; SIC, specific inhalation challenge.

test and/or nonspecific challenge tests with MCH or indirect agents) aimed at confirming or excluding the presence of asthma (Fig. 2). Asthma severity should be assessed according to GINA guidelines (32). Bronchodilation and NSBH challenge tests should be performed during a period at work. If one or both are positive, the suspicion of WRA is confirmed. If both bronchodilation and NSBH challenges are negative, serial monitoring of PEFR at least during a 2-week period at work and a 2-week period off work should be carried out. If PEFR monitoring shows a relationship between the workplace and asthmatic symptoms, WRA should be suspected, otherwise WRA might be excluded. The detection of sensitization to an occupational allergen in a patient with suspected WRA raises the likelihood of allergic OA, but this diagnosis should be confirmed in a specialized centre. When immunological tests are negative, or not available, but WRA is suspected, the patient should be referred to a specialized centre for further in-depth investigations. Nevertheless, if the clinical history is highly suggestive, airway inflammation may be evaluated (14). In the presence of bronchial inflammation, a work-related condition should be suspected, and the patient addressed to a specialized centre for the definite diagnosis. In the absence of bronchial inflammation, other possible conditions (e.g. nonasthmatic vocal cord dysfunction or irritable larynx syndrome) should be considered. In patients not currently employed in the suspected job/workplace at the time of examination, before excluding WRA, a comprehensive evaluation by a specialized centre is strongly suggested, to minimize the risk of a missed diagnosis.

Patients with suspected WRA should be addressed to centres and physicians specialized in WRA and equipped with facilities for performing SICs/workplace challenges and related investigations, as illustrated in algorithms 2 (Fig. 3).

Rhinitis in work-related asthma

There is evidence of a strict relationship between work-related rhinitis and WRA (87). In a recent study, at least one work-related rhinitis symptom was reported by 83% of subjects with WEA and 90% of those with OA, of them 73% with OA because of LMW and 99% with HMW-induced OA (88).

Moreover, rhinitis can exert substantial influence on the patients' quality of life, work productivity and asthma control (89, 90). Actually, the most important link between rhinitis and asthma is the presence of inflammation of the nasal and bronchial mucosae (15). Gaga et al. (91) showed eosinophil infiltration in the nasal mucosa of asthmatic patients irrespective of any signs of rhinitis. Allergen provocation of either the nose or the bronchi results in generalized airway inflammation. Moreover, the eosinophilic inflammation of the nasal mucosa exists even in patients with asthma (92) and with OA (93) without nasal symptoms. In addition, the eosinophil count in nasal lavage fluid is good predictor of sputum eosinophilia in subjects with asthma (94).

Thus, monitoring of nasal inflammatory cells may be used to measure the reaction to inhalation of workplace agent during SIC, simultaneously to evaluation of bronchial inflammation. The estimation of cell number and the biochemical examination

of the lavage fluid or secretion in the nose allow one to distinguish between the allergic and irritant effects of various substances on the respiratory system (95, 96). Specific allergic reaction comprises an increase of eosinophils and less pronounced but very characteristic increase in metachromatic cell number, and mediators in nasal mucosa (97). A simple, reproducible and easy-to-perform method for assessing nasal blown secretions during SICs has been described, and a cut-off value of 4% and/or 1×10^4 eosinophils/ml for a significant postchallenge eosinophil increase, useful for defining a positive nasal response in addition to symptom score, has been identified (98).

Conclusions

Work-related asthma is a frequent condition, but probably, it is still underestimated and underdiagnosed. A correct diagnosis is important for all forms of WRA to undergo the appropriate management and to reduce or limit the consequences. In OA, early diagnosis followed by early removal from expo-

sure is the most important factor that determines a favourable prognosis. Allergologists and other specialists dealing with asthma play a relevant role in identifying suspected cases, raising the suspicion of WRA from the clinical history, performing investigations in daily practice and if the suspicion is confirmed, referring the patient to a specialized centre to confirm the work-relatedness of asthma, and make the definite diagnosis.

Authors' contribution

This Position Paper is the result of the collaboration of a panel of experts who contributed to the document according to their different experiences and competences, coordinated by Gianna Moscato.

Conflict of interest

All authors have no conflict of interest to declare.

References

- Vandenplas O, Toren K, Blanc PD. Health and socioeconomic impact of work-related asthma. *Eur Respir J* 2003;**22**:689–697.
- Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D et al. Diagnosis and management of work-related asthma: American college of chest physicians consensus statement. *Chest* 2008;**134**:1S–41S.
- Sama SR, Milton DK, Hunt PR, Houseman EA, Henneberger PK, Rosiello RA. Case-by-case assessment of adult-onset asthma attributable to occupational exposures among members of a health maintenance organization. *J Occup Environ Med* 2006;**48**:400–407.
- Subcommittee on Occupational Allergy of the European Academy of Allergology and Clinical Immunology. Guidelines for the diagnosis of occupational asthma. *Clin Exp Allergy* 1992;**22**:103–108.
- Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;**62**:290–299.
- Bousquet J, Bieber T, Fokkens W, Humbert M, Kowalski M, Niggemann B et al. Consensus statements, evidence-based medicine and guidelines in allergic diseases. Editorial. *Allergy* 2008;**63**:1–4.
- Malo JL. Future advances in work-related asthma and the impact on occupational health. *Occup Med (Lond)* 2005;**55**:606–611.
- Moscato G, Galdi G. Occupational asthma and its relationship to occupational rhinitis. In: Pawankar R, Holgate S, Rossenwasser LJ, editors. *Allergy Frontiers: From Epigenetics to Future Perspectives. Volume 3: Clinical manifestations*. Tokyo, Berlin, Heidelberg, New York: Springer, 2009:303–320.
- Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985;**88**:376–384.
- Tarlo SM, Broder I. Irritant-induced occupational asthma. *Chest* 1989;**96**:297–300.
- Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational asthma. *Am J Respir Crit Care Med* 2005;**172**:280–305.
- Malo JL, Chan-Yeung M. Occupational asthma. *J Allergy Clin Immunol* 2001;**108**:317–328.
- Moscato G, Malo J-L, Bernstein D. Diagnosing occupational asthma: how, how much, how far? ERS Series “Controversies in occupational asthma”. *Eur Respir J* 2003;**21**:879–885.
- Malo J-L, Newman Taylor A. Defining occupational asthma and confirming the diagnosis: what do experts suggest? *Occup Environ Med* 2007;**64**:359–360.
- Quirce S, Lemièrre C, de Blay F, Del Pozo V, Gerth Van Wijk R, Maestrelli P et al. Noninvasive methods for assessment of airway inflammation in occupational settings. *Allergy* 2010;**65**:445–458.
- Cullinan P. Clinical aspects of occupational asthma. *Panninerva Med* 2004;**46**:111–120.
- Vandenplas O, Ghezzi H, Munoz X, Moscato G, Perfetti L, Lemièrre C et al. What are the questionnaire items most useful in identifying subjects with occupational asthma? *Eur Respir J* 2005;**26**:1056–1063.
- Malo JL, Ghezzi H, L’Archeveque J, Lagier F, Perrin B, Cartier A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991;**143**:528–532.
- Moscato G, Vandenplas O, Gerth Van Wijk R, Malo JL, Perfetti L, Quirce S et al. EA-ACI position paper on occupational rhinitis. *Allergy* 2008;**63**:969–980.
- Baur X, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin Exp Allergy* 1998;**28**:537–544.
- Jones MG. Exposure-response in occupational allergy. *Curr Opin Allergy Clin Immunol* 2008;**8**:110–114.
- Jarvis J, Seed MJ, Elton R, Sawyer L, Agius R. Relationship between chemical structure and the occupational asthma hazard of low molecular weight organic compounds. *Occup Environ Med* 2005;**62**:243–250.
- Bernstein DI, Campo P, Baur X. Clinical assessment and management of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI, editors. *Asthma in the Workplace*, 3rd edn. New York: Marcel Dekker, 2006:161–175.
- Nieuwenhuijsen M, Baur X, Heederik D. Environmental monitoring: general considerations, exposure-response relationship. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI, editors. *Asthma in the Workplace*, 3rd edn. New York: Marcel Dekker, 2006:235–274.
- Creely KS, Hughson GW, Cocker J, Jones K. Assessing isocyanate exposures in polyurethane industry sectors using biological and air monitoring methods. *Ann Occup Hyg* 2006;**50**:609–621.
- Lesage J, Perrault G. Environmental monitoring of chemical agents. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI,

- editors. *Asthma in the Workplace*, 3rd edn. New York: Marcel Dekker, 2006:297–318.
27. Luczynska CM, Li Y, Chapman MD, Platts-Mills TAE. Airborne concentrations and particle size distribution of allergen derived from domestic cat (*Felis domesticus*). *Am Rev Resp Dis* 1990;**141**:361–367.
 28. Swanson MC, Heederik D. Quantification of bio-active protein aerosols. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI, editors. *Asthma in the Workplace*, 3rd edn. New York: Marcel Dekker, 2006:275–296.
 29. Lillienberg L, Baur X, Doekes G, Belin L, Raulf-Heimsoth M, Sander I et al. Comparison of four methods to assess fungal amylase in flour dust. *Ann Occup Hyg* 2000;**44**:427–433.
 30. Quirce S, Swanson MC, Fernández-Nieto M, de las Heras M, Cuesta J, Sastre J. Quantified environmental challenge with absorbable dusting powder aerosol from natural rubber latex gloves. *J Allergy Clin Immunol* 2003;**111**:788–794.
 31. Renström A, Gordon S, Hollander A, Spithoven J, Larsson PH, Venables KM et al. Comparison of methods to assess airborne rat and mouse allergen levels II. Factors influencing antigen detection. *Allergy* 1999;**54**:150–157.
 32. GINA report, global strategy for asthma management and prevention. 2010. Available at: <http://www.ginasthma.com/>.
 33. Burge PS, Moscato G, Johnson A, Chan-Yeung M. Physiological assessment: serial measurements of lung function and bronchial responsiveness. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI. *Asthma in the Workplace*, 3rd edn. New York: Taylor & Francis, 2006:199–226.
 34. Cockcroft D, Davis B. Direct and indirect challenges in the clinical assessment of asthma. *Ann Allergy Asthma Immunol* 2009;**103**:363–369.
 35. Cockcroft DW. Direct challenge tests: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010;**138**:18S–24S.
 36. Beach J, Russell K, Blitz S, Hooton N, Spooner C, Lemièrè C et al. A systematic review of the diagnosis of occupational asthma. *Chest* 2007;**131**:569–578.
 37. Vandenplas O, Delwiche JP, Jamart J, Van de Weyer R. Increase in non-specific bronchial hyperresponsiveness as an early marker of bronchial response to occupational agents during specific inhalation challenges. *Thorax* 1996;**51**:472–478.
 38. Sastre J, Fernández-Nieto M, Novalbos A, De Las Heras M, Cuesta J, Quirce S. Need for monitoring nonspecific bronchial hyperresponsiveness before and after isocyanate inhalation challenge. *Chest* 2003;**123**:1276–1279.
 39. Moscato G, Godnic-Cvar J, Maestrelli P, Malo J-L, Burge PS, Coifman R. Statement on self monitoring of peak expiratory flow in the investigation of occupational asthma. *J Allergy Clin Immunol* 1995;**96**:295–301.
 40. Park D, Moore VC, Burge CBSG, Jaakkola MS, Robertson AS, Burge PS. Serial PEF measurements is superior to cross-shift change in diagnosing occupational asthma. *Eur Respir J* 2009;**34**:574–578.
 41. Malo J-L, Côté J, Cartier A, Boulet L-P, L'Archevêque J, Chan-Yeung M. How many times per day should peak expiratory flow rates be assessed when investigating occupational asthma? *Thorax* 1993;**48**:1211–1217.
 42. Chan-Yeung M. Assessment of asthma in the workplace. *Chest* 1995;**108**:1084–1117.
 43. Moore VC, Jaakkola MS, Burge CB, Pantin CF, Robertson AS, Vellore AD et al. PEF analysis requiring shorter records for occupational asthma diagnosis. *Occup Med* 2009;**59**:413–417.
 44. Caballero ML, Gomez M, Gonzalez-Munoz M, Reinoso L, Rodriguez-Perez R, Alday E et al. Occupational sensitization to fungal enzymes used in animal feed industry. *Int Arch Allergy Immunol* 2007;**144**:231–239.
 45. Ebo DG, Bridts CH, Mertens MH, Stevens WJ. Coriander anaphylaxis in a spice grinder with undetected occupational allergy. *Acta Clin Belg* 2006;**61**:152–156.
 46. van Toorenbergen AW, Dieges PH. Immunoglobulin E antibodies against coriander and other spices. *J Allergy Clin Immunol* 1985;**76**:477–481.
 47. Jansen AP, Visser FJ, Nierop G, de Jong NW, Waanders-de Lijster de Raadt J, Vermeulen A et al. Occupational asthma to amaryllis. *Allergy* 1996;**51**:847–849.
 48. Groenewoud GC, de Graaf in 't Veld C, vVan Oorschot-van Nes AJ, de Jong NW, Vermeulen AM, van Toorenbergen AW et al. Prevalence of sensitization to the predatory mite *Amblyseius cucumeris* as a new occupational allergen in horticulture. *Allergy* 2002;**57**:614–619.
 49. van Kampen V, Rabstein S, Sander I, Merget R, Bruning T, Broding HC et al. Prediction of challenge test results by flour-specific IgE and skin prick test in symptomatic bakers. *Allergy* 2008;**63**:897–902.
 50. van Kampen V, Merget R, Rabstein S, Sander I, Bruening T, Broding HC et al. Comparison of wheat and rye flour solutions for skin prick testing: a multi-centre study (Stad I). *Clin Exp Allergy* 2009;**39**:1896–1902.
 51. Koskela H, Taivainen A, Tukiainen H, Chan HK. Inhalation challenge with bovine dander allergens: who needs it? *Chest* 2003;**124**:383–391.
 52. Ebo DG, Hagendorens MM, De Knop KJ, Verweij MM, Bridts CH, De Clerck LS et al. Component-resolved diagnosis from latex allergy by microarray. *Clin Exp Allergy* 2010;**40**:348–358.
 53. Raulf-Heimsoth M, Rihs HP, Rozynek P, Cremer R, Gaspar A, Pires G et al. Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (*Hevea brasiliensis*). *Clin Exp Allergy* 2007;**37**:1657–1667.
 54. Palacin A, Varela J, Quirce S, del Pozo V, Tordesillas L, Barranco P et al. Recombinant lipid transfer protein Tri a 14: a novel heat and proteolytic resistant tool for the diagnosis of baker's asthma. *Clin Exp Allergy* 2009;**39**:1267–1276.
 55. Kespohl S, Schlunssen V, Jacobsen G, Schaumburg I, Maryska S, Meurer U et al. Impact of cross-reactive carbohydrate determinants on wood dust sensitization. *Clin Exp Allergy* 2010;**40**:1099–1206.
 56. Beach J, Rowe BH, Blitz S, Crumley E, Hooton N, Russell K et al. *Diagnosis and Management of Work-Related Asthma*. Evidence Report/Technology Assessment No. 129. Rockville, MD: Agency for Healthcare Research and Quality, 2005.
 57. Vandenplas O, Cartier A, Malo J-L. Occupational challenge test. In: Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI, editors. *Asthma in the Workplace*, 3rd edn. New York: Marcel Dekker, 2006:227–252.
 58. Lemièrè C. Induced sputum and exhaled nitric oxide as noninvasive markers of airway inflammation from work exposures. *Curr Opin Allergy Clin Immunol* 2007;**7**:133–137.
 59. Quirce S. Eosinophilic bronchitis in the workplace. *Curr Opin Allergy Clin Immunol* 2004;**4**:87–91.
 60. Vandenplas O, D'Alpaos V, Thimont J, Huaux F, Lison D, Renaud J. Sputum eosinophilia: an early marker of bronchial response to occupational agents. *Allergy* 2009;**64**:754–761.
 61. Maestrelli P, Calcagni PG, Saetta M, Di Stefano A, Hosselet JJ, Santonastaso A et al. Sputum eosinophilia after asthmatic responses induced by isocyanates in sensitized subjects. *Clin Exp Allergy* 1994;**24**:29–34.
 62. Lemièrè C, Chaboillez S, Malo JL, Cartier A. Changes in sputum cell counts after exposure to occupational agents: what do they mean? *J Allergy Clin Immunol* 2001;**107**:1063–1068.
 63. Fernández-Nieto M, Sastre B, Sastre J, Lahoz C, Quirce S, Madero M et al. Changes in sputum eicosanoids and inflammatory markers after inhalation challenges with occupational agents. *Chest* 2009;**136**:1308–1315.
 64. Lemièrè C, Pizzichini MM, Balkissoon R, Clelland L, Efthimiadis A, O'Shaughnessy D

- et al. Diagnosing occupational asthma: use of induced sputum. *Eur Respir J* 1999;**13**: 482–488.
65. Girard F, Chaboillez S, Cartier A, Côté J, Hargreave FE, Labrecque M et al. An effective strategy for diagnosing occupational asthma: use of induced sputum. *Am J Respir Crit Care Med* 2004;**170**: 845–850.
 66. Ferrazzoni S, Scarpa MC, Guarnieri G, Corradi M, Mutti A, Maestrelli P. Exhaled nitric oxide and breath condensate pH in asthmatic reactions induced by isocyanates. *Chest* 2009;**136**:155–162.
 67. Malo JL, Cardinal S, Ghezzi H, L'Archevêque J, Castellanos L, Maghni K. Association of bronchial reactivity to occupational agents with methacholine reactivity, sputum cells and immunoglobulin E-mediated reactivity. *Clin Exp Allergy* 2011;**41**:497–504.
 68. Quirce S, Gala G, Pérez-Camo I, Sánchez-Fernández C, Pacheco A, Losada E. Irritant-induced asthma: clinical and functional aspects. *J Asthma* 2000;**37**:267–274.
 69. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;**35**:1175–1179.
 70. Lemière C, D'Alpaos V, Chaboillez S, César M, Wattiez M, Chiry S et al. Investigation of occupational asthma: sputum cell counts or exhaled nitric oxide? *Chest* 2010;**137**:617–622.
 71. Desai D, Brightling C. Cough due to asthma, cough-variant asthma and non-asthmatic eosinophilic bronchitis. *Otolaryngol Clin North Am* 2010;**43**:123–130.
 72. Pala G, Pignatti P, Moscato G. The use of fractional exhaled nitric oxide in investigation of work-related cough in a hairdresser. *Am J Ind Med* 2011;**54**:565–568.
 73. Shakeri MS, Dick FD, Ayres JG. Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review. *Occup Med* 2008;**58**:205–211.
 74. Leroyer C, Perfetti L, Cartier A, Malo JL. Can reactive airways dysfunction syndrome (RADS) transform into occupational asthma due to "sensitization" to isocyanates? *Thorax* 1998;**53**:152–153.
 75. Perfetti L, Bramé B, Ferrari M, Moscato G. Occupational asthma (OA) with sensitization to diphenylmethane diisocyanate (MDI) presenting at the onset like a reactive airways dysfunction syndrome (RADS). *Am J Ind Med* 2003;**44**:325–328.
 76. Galdi E, Perfetti L, Pagella F, Bertino G, Ferrari M, Moscato G. Irritant vocal cord dysfunction at first misdiagnosed as reactive airways dysfunction syndrome. *Scand J Work Environ Health* 2005;**31**:224–226.
 77. Rabinowitz PM, Siegel MD. Acute inhalation injury. *Clin Chest Med* 2002;**23**:707–715.
 78. Vandenplas O, Malo JL. Definitions and types of work-related asthma: a nosological approach. *Eur Respir J* 2003;**21**:706–712.
 79. Tarlo SM, Leung K, Broder I, Silverman F, Holness DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. *Chest* 2000;**118**:1309–1314.
 80. Chiry S, Cartier A, Malo JL, Tarlo SM, Lemiere C. Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. *Chest* 2007;**132**:483–488.
 81. Berry MA, Parker D, Neale N, Woodman L, Morgan A, Monk P et al. Sputum and bronchial submucosal IL-13 expression in asthma and eosinophilic bronchitis. *J Allergy Clin Immunol* 2004;**114**:1106–1109.
 82. Brightling CE. Chronic cough due to non-asthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**:116S–121S.
 83. Tarlo SM, Malo JL; Third Jack Pepys Workshop on Asthma in the Workplace Participants. An official ATS proceedings: asthma in the workplace: the Third Jack Pepys Workshop on Asthma in the Workplace: answered and unanswered questions. *Proc Am Thorac Soc* 2009;**6**:339–349.
 84. Keatings VM, Evans DJ, O'Connor BJ, Barnes PJ. Cellular profiles in asthmatic airways: a comparison of induced sputum, bronchial washings, and bronchoalveolar lavage fluid. *Thorax* 1997;**52**:372–374.
 85. Singapuri A, McKenna S, Brightling CE, Bradding P. Mannitol and AMP do not induce bronchoconstriction in eosinophilic bronchitis: further evidence for dissociation between airway inflammation and bronchial hyperresponsiveness. *Respirology* 2010;**15**:510–515.
 86. Pala G, Pignatti P, Perfetti L, Caminati M, Gentile E, Moscato G. Usefulness of basophil activation test in diagnosis of occupational nonasthmatic eosinophilic bronchitis. *Allergy* 2010;**65**:927–929.
 87. Moscato G, Vandenplas O, Gerth Van Wijk R, Malo JL, Perfetti L, Quirce S et al. EAACI position paper on occupational rhinitis. *Respir Res* 2009;**10**:16.
 88. Vandenplas O, Van Brussel P, D'Alpaos V, Wattiez M, Jamart J, Thimpont J. Rhinitis in subjects with work-exacerbated asthma. *Respir Med* 2010;**104**:497–503.
 89. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population based study of young adults. *Am J Respir Crit Care Med* 2000;**162**:1391–1396.
 90. Vandenplas O, D'Alpaos V, Van Brussel P. Rhinitis and its impact on work. *Curr Opin Allergy Clin Immunol* 2008;**8**: 145–149.
 91. Gaga M, Lambrou P, Papageorgiou N, Koulouris NG, Kosmas E, Fragakis S. Eosinophils are a feature of upper and lower airway pathology in nonatopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000;**30**: 663–669.
 92. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003;**58**:691–706.
 93. Moscato G, Pala G, Perfetti L, Frascaroli M, Pignatti P. Clinical and inflammatory features of occupational asthma caused by persulphate salts in comparison with asthma associated with occupational rhinitis. *Allergy* 2010;**65**:784–790.
 94. Amorim MM, Araruna A, Caetano LB, Cruz AC, Santoro LL, Fernandes AL. Nasal eosinophilia: an indicator of eosinophilic inflammation in asthma. *Clin Exp Allergy* 2010;**40**:867–874.
 95. Palczynski C, Walusiak J, Ruta U, Gorski P. Nasal provocation test in the diagnosis of natural rubber latex allergy. *Allergy* 2000;**55**:34–41.
 96. Paczyński C, Walusiak J, Ruta U, Gorski P. Occupational asthma and rhinitis due to glutaraldehyde: changes in nasal lavage fluid after specific inhalatory challenge test. *Allergy* 2001;**56**: 1186–1191.
 97. Raulf-Heimsoth M, Wirtz C, Papenfuss F, Baur X. Nasal lavage mediator profile and cellular composition of nasal brushing material during latex challenge tests. *Clin Exp Allergy* 2000;**30**: 110–121.
 98. Pignatti P, Pala G, Pisati M, Perfetti L, Banchieri G, Moscato G. Nasal blown secretion evaluation in specific occupational nasal challenges. *Int Arch Occup Environ Health* 2010;**83**:217–223.