NEW YORK STATE OF OPPORTUNITY.

Workers' Compensation Board

Medical Treatment Guidelines

Occupational / Work-Related Asthma

May 2020

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The NYS Workers' Compensation Board would like to thank the members of the New York Workers' Compensation Board Medical Advisory Committee (MAC). The MAC served as the Board's advisory body to adapt the American College of Occupational and Environmental Medicine (ACOEM) Practice Guidelines to a New York version of the Medical Treatment Guidelines (MTG). In this capacity, the MAC provided valuable input and made recommendations to help guide the final version of these Guidelines. With full consensus reached on many topics, and a careful review of any dissenting opinions on others, the Board established the final product.

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A. General Guideline Principles

The principles summarized in this section are key to the intended application of the New York State Medical Treatment Guidelines (MTG) and are applicable to all Workers' Compensation Medical Treatment Guidelines.

A.1 Medical Care

Medical care and treatment required as a result of a work-related injury should be focused on restoring functional ability required to meet the patient's daily and work activities and return to work, while striving to restore the patient's health to its pre-injury status in so far as is feasible.

A.2 Rendering of Medical Services

Any medical provider rendering services to a workers' compensation patient must utilize the Treatment Guidelines as provided for with respect to all work-related injuries and/or illnesses.

A.3 Positive Patient Response

Positive results are defined primarily as functional gains which can be objectively measured. Objective functional gains include, but are not limited to, positional tolerances, range of motion, strength, endurance, activities of daily living (ADL), cognition, psychological behavior, and efficiency/velocity measures which can be quantified. Subjective reports of pain and function should be considered and given relative weight when the pain has anatomic and physiologic correlation.

A.4 Re-Evaluate Treatment

If a given treatment or modality is not producing positive results, the provider should either modify or discontinue the treatment regime. The provider should evaluate the efficacy of the treatment or modality two to three weeks after the initial visit and three to four weeks thereafter. Recognizing that treatment failure is at times attributable to an incorrect diagnosis should prompt the clinician to reconsider the diagnosis in the event of an unexpected poor response to an otherwise rational intervention.

A.5 Education

Education of the patient and family, as well as the employer, insurer, policy makers and the community should be a primary emphasis in the treatment of work-related injury or illness. Practitioners should develop and implement effective educational strategies and skills. An education-based paradigm should always start with communication providing reassuring information to the patient. No treatment plan is complete without addressing issues of individual and/or group patient education as a means of facilitating self-management of symptoms and prevention of future injury.

Time Frames

A.6 Acuity

Acute, subacute and chronic are generally defined timeframes for disease stages:

Acute – Less than one month,
Subacute – One to three months, and
Chronic – Greater than three months.

A.7 Initial Evaluation

Initial evaluation refers to the acute timeframe following an injury and is not used to define when a given physician first evaluates an injured worker (initial encounter) in an office or clinical setting.

A.8 Diagnostic Time Frames

Diagnostic time frames for conducting diagnostic testing commence on the date of injury. Clinical judgment may substantiate the need to accelerate or decelerate the time frames discussed in this document.

A.9 Treatment Time Frames

Treatment time frames for specific interventions commence once treatments have been initiated, not on the date of injury. Obviously, duration may be impacted by disease process and severity, patient compliance, as well as availability of services. Clinical judgment may substantiate the need to accelerate or decelerate the time frames discussed in this document.

A.10 Delayed Recovery

For those patients who fail to make expected progress 6-12 weeks after an injury, reexamination in order to confirm the accuracy of the diagnosis and re-evaluation of the treatment program should be performed. Assessment for potential barriers to recovery (yellow flags/psychological issues) should be ongoing throughout the care of the patient. However, at 6-12 weeks, alternate treatment programs, including formal psychological or psychosocial evaluation, should be considered. Referrals to mental health providers (i.e.: psychology/psychiatry) for the evaluation and management of delayed recovery do not indicate or require the establishment of a psychiatric or psychological condition. The evaluation and management of delayed recovery does not require the establishment of a psychiatric or psychological claim.

Treatment Approaches

A.11 Active Interventions

Active interventions emphasizing patient responsibility, such as therapeutic exercise and/or functional treatment, are generally emphasized over passive modalities, especially as treatment progresses. Generally, passive and palliative interventions are viewed as a means to facilitate progress in an active rehabilitation program with concomitant attainment of objective functional gains.

A.12 Active Therapeutic Exercise Program

Active therapeutic exercise program goals should incorporate patient strength, endurance, flexibility, range of motion, sensory integration, coordination, and education as clinically indicated. This includes functional application in vocational or community settings.

A.13 Diagnostic Imaging and Testing Procedures

Clinical information obtained by history taking and physical examination should be the basis for selection and interpretation of imaging procedure results. All diagnostic procedures have variable specificity and sensitivity for various diagnoses.

When a diagnostic procedure, in conjunction with clinical information, provides sufficient information to establish an accurate diagnosis, a second diagnostic procedure will be redundant if it is performed only for diagnostic purposes. At the same time, a subsequent diagnostic procedure (that may be a repeat of the same procedure, when the rehabilitation physician, radiologist or surgeon documents the study was of inadequate quality to make a diagnosis) can be a complementary diagnostic procedure if the first or preceding procedures, in conjunction with clinical information, cannot provide an accurate diagnosis, and is permissible under the MTG.

It is recognized that repeat imaging studies and other tests may be warranted by the clinical course and to follow the progress of treatment in some cases. It may be of value to repeat diagnostic procedures (e.g., imaging studies) during the course of care to reassess or stage the pathology when there is progression of symptoms or findings, prior to surgical interventions and therapeutic injections when warranted, and post-operatively to follow the healing process. Regarding CT examinations, it must be recognized that repeat procedures result in an increase in cumulative radiation dose and associated risks.

A.14 Surgical Interventions

Contemplation of surgery should be within the context of expected functional outcome. The concept of "cure" with respect to surgical treatment by itself is generally a misnomer. All operative interventions must be based upon positive correlation of clinical findings, clinical course and imaging and other diagnostic tests. A comprehensive assimilation of these factors must lead to a specific diagnosis with positive identification of pathologic condition(s). For surgery to be performed to treat pain, there must be clear correlation between the pain symptoms and objective evidence of its cause. In all cases, shared decision making with the patient is advised. The patient should be given the opportunity to understand the pros and cons of surgery, potential for rehabilitation as an alternative where applicable, evidence-based outcomes, and specific surgical experience.

A.15 Pre-Authorization

All diagnostic imaging, testing procedures, non-surgical and surgical therapeutic procedures within the criteria of the Medical Treatment Guidelines and based on a correct application of the Medical Treatment Guidelines are considered authorized, with the exception of the following procedures: Lumbar Fusion, Artificial Disc Replacements, Vertebroplasty, Kyphoplasty, Electrical Bone Growth Stimulators, Spinal Cord Stimulators, Intrathecal Drug Delivery (Pain Pumps), Osteochondral Autograft, Autologous Chondrocyte Implantation, Meniscal Allograft Transplantation and Knee Arthroplasty

(Total or Partial Knee Joint Replacement). These are not included on the list of pre-authorized procedures. Providers who want to perform one of these procedures must request pre-authorization from the carrier before performing the procedure.

Second or subsequent procedures (the repeat performance of a surgical procedure due to failure of, or incomplete success from the same surgical procedure performed earlier, if the Medical Treatment Guidelines do not specifically address multiple procedures) also require pre-authorization.

A.16 Personality/Psychological/Psychosocial Evaluations

In select patients, diagnostic testing procedures may be useful when there is a discrepancy between diagnosis, signs, symptoms, clinical concerns or functional recovery. Psychological testing should provide differentiation between pre-existing depression versus injury-caused depression, as well as post-traumatic stress disorder, and other psychosocial issues that may include work or non-work-related issues when such conditions are identified in the patient.

For those patients who fail to make expected progress 6-12 weeks after an injury and whose subjective symptoms do not correlate with objective signs and tests, reexamination in order to confirm the accuracy of the diagnosis should be made. Formal psychological or psychosocial evaluation may be considered.

A professional fluent in the primary language of the patient is strongly preferred. When such a provider is not available, services of a professional language interpreter must be provided.

Frequency: One time visit for evaluation. If psychometric testing is indicated by findings in the initial evaluation, time for such testing should not exceed an additional two hours of professional time.

A.17 Personality/Psychological/Psychosocial Intervention

Following psychosocial evaluation, when intervention is recommended, such intervention should be implemented as soon as possible. This can be used alone or in conjunction with other treatment modalities.

- Time to produce effect: two to eight weeks.
- Optimum duration: six weeks to three months.
- Maximum duration: three to six months. Counseling is not intended to delay but to enhance functional recovery. For select patients, longer supervision may be required, and if further counseling is indicated, documentation of the nature of the psychological factors, as well as projecting a realistic functional prognosis, should be provided by the authorized treating practitioner every four to six weeks during treatment.

A.18 Functional Capacity Evaluation (FCE)

Functional capacity evaluation is a comprehensive or more restricted evaluation of the various aspects of function as they relate to the patient's ability to return to work. Areas such as endurance, lifting (dynamic and static), postural tolerance, specific range-of-motion, coordination and strength, worker habits, employability, as well as psychosocial, cognitive, and sensory perceptual aspects of competitive employment may be evaluated.

Components of this evaluation may include: (a) musculoskeletal screen; (b) cardiovascular profile/aerobic capacity; (c) coordination; (d) lift/carrying analysis; (e) job-specific activity tolerance; (f) maximum voluntary effort; (g) pain assessment/psychological screening; (h) non-material and material handling activities; (i) cognitive; (j) visual; and (k) sensory perceptual factors.

In most cases, the question of whether a patient can return to work can be answered without an FCE.

When an FCE is being used to determine return to a specific job site, the treating physician is responsible for understanding and considering the job duties. FCEs cannot be used in isolation to determine work restrictions. The authorized treating physician must interpret the FCE in light of the individual patient's presentation and medical and personal perceptions. FCEs should not be used as the sole criteria to diagnose malingering.

An FCE may be considered at time of MMI, following reasonable prior attempts to return to full duty throughout course of treatment, when the treating physician is unable to make a clear determination on work status on case closure.

A.19 Return to Work

For purposes of these guidelines, return to work is defined as any work or duty that the patient is able to perform safely. It may not be the patient's regular work. Ascertaining a return to work status is part of medical care, and should be included in the treatment and rehabilitation plan. It is normally addressed at every outpatient visit. A description of the patient's status and task limitations is part of any treatment plan and should provide the basis for restriction of work activities when warranted. Early return to work should be a prime goal in treating occupational injuries. The emphasis within these guidelines is to move patients along a continuum of care and return to work, since the prognosis of returning an injured worker to work drops progressively the longer the worker has been out of work.

A.20 Job Site Evaluation

The treating physician may communicate with the employer or the employer's designee, either in person or by telephone, to obtain information regarding the demands of the patient's pre-injury job, including a description of the exertional demands of the job, the need for repetitive activities, load lifting, static or awkward postures, or any other factors that would pose a risk of re-injury or impedance of convalescence. When returning to work at the patient's previous job task/setting is not feasible, given the clinically determined restrictions on the patient's activities, inquiry should also be made about modified duty work settings, and a similar set of questions should be posed by the physician about work activities/demands in modified duty jobs.

Ideally, the physician would gain the most information from an on-site inspection of the job settings and activities; but it is recognized that this may not be feasible in most cases. If job videos/CDs/DVDs are available from the employer, these can contribute valuable information.

Frequency: one or two calls:

- First call: Patient is in a functional state where the patient can perform some work.

- Second call: Patient has advanced to state where the patient is capable of enhanced functional demands in a work environment.

The physician shall document the conversation.

Other

A.21 Guideline Recommendations and Medical Evidence

The Workers' Compensation Board and its Medical Advisory Committee have not independently evaluated or vetted the scientific medical literature used in support of the guidelines but have relied on the methodology used by the developers of various guidelines utilized and referenced in these Guidelines.

A.22 Experimental/Investigational Treatment

Medical treatment that is experimental/investigational and not approved for any purpose, application or indication by the FDA is not permitted under these Guidelines.

A.23 Injured Workers as Patients

In these Guidelines, injured workers are referred to as patients recognizing that in certain circumstances there is no doctor-patient relationship.

A.24 Scope of Practice

These Guidelines do not address scope of practice or change the scope of practice.

Occupational / Work-Related Asthma

B. Introduction

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. Increased airway responsiveness to a variety of stimuli is typical. Work-related asthma (WRA) presents with symptoms of asthma that begin or become worse at work, usually in the context of exposure to a new chemical or environmental change. (WRA) includes both occupational asthma (OA,) and work exacerbated asthma (WEA). OA includes sensitizer-induced asthma, resulting from sensitization to an antigen in the workplace, and irritant-induced asthma, resulting from reactive airways disease, which has been provoked by workplace exposures to irritants. Each has the potential for considerable acute morbidity, long-term disability, and adverse social and economic impacts.

B.1 Occupational Asthma (OA)

OA is defined as new onset asthma in the workplace and can be caused by exposure to either a workplace sensitizer or an irritant. OA is further classified into OA with latency and OA without latency.

B.1.a OA With Latency

- OA with latency is seen in all instances of immunologically (sensitizer) mediated asthma.
- Sensitizers are agents that initiate an allergic (immunologic) response.
- The latency period, which represents the time between the first exposure and the development of symptoms, can vary from weeks to years. It reflects the time for induction of an immunological response to the workplace allergen.
- There is typically a latency period of at least a few months between first exposure and becoming sensitized, leading to asthma symptoms during re-exposure.
- Sensitizers are divided into high molecular and low molecular weight chemicals.
- This distinction helps define typical mechanism of asthma, symptoms and latency.
- Prolonged exposure to low level irritants can also result in OA with latency.

B.1.b OA Without latency

- Irritant exposure (gases, fumes, vapors and aerosols) is an inflammatory, not an allergic response.
- OA without latency can occur after exposure to irritant gas, fumes, or chemicals, such as nitrogen oxide, ammonia, and chloride.

B.1.c Work-Exacerbated Asthma (WEA)

WEA occurs in individuals with existing/concurrent asthma that worsens because of specific workplace exposures to irritants such as:

- Gases, fumes, vapors and aerosols
- Allergens, or physical conditions.

Table 1. Specific High and Low Weight Chemicals (Sensitizers) and Occupations

Category	Chemical	Occupational Activities
High Molecular Weight: (Direct sensitizers) • Stimulate the production of specific immunoglobulin E (IgE) antibodies. • During re-exposure, the agent cross-links specific antibodies on mast cells and activates them to release inflammatory mediators leading to asthma symptoms	• Grains and flours, in particular wheat, soya and: • enzyme additives to these products • Animal proteins from urine, dander, fur, hair or saliva • Latex	• Bakers and food processors, dock workers (exposed to shipping of the materials) • Veterinarians, and laboratory researchers or their assistants • Health care workers
Low Molecular Weight: • Are incomplete antigens, called haptens that • combine with a protein to produce a sensitizing agent	• Acid anhydrides (plastics, dyes, adhesives and resins) • Di-isocyanates (rigid foam, binders, coatings, elastomers, and paints) • Platinum salts • Aluminum • Cleaning agents • Wood dusts • Colophony • Fluxes	• Chemical production workers. • Cosmetologist • Refinery workers. • Smelters • Jewelry/alloy production workers • Cleaning services • Sawmill workers/carpenters • Electronics manufacturing

B.1.d Etiology

Asthma is primarily a disease of airway inflammation and reactivity. The cardinal symptoms of asthma are episodic shortness of breath, wheezing, and cough.

B.1.e Diagnosis of Work-Related Asthma

B.1.e.i Signs and Symptoms of Work-Related Asthma

Asthma is primarily a disease of airway inflammation and reactivity. The cardinal symptoms of asthma are episodic shortness of breath, wheezing, and cough, compared to the predominant symptoms of bronchitis that are cough and sputum production.

Specialized pulmonary history and diagnostic history is required for a diagnosis of occupational asthma. The American College of Chest Physicians published the following criteria in 1995 https://doi.org/10.1378/chest.108.4.1084 for establishing a diagnosis of WRA, all of which are required:

- a history compatible with occupational asthma;
- presence of airflow limitation and its reversibility;

- in the absences of airflow limitation, the presence of nonspecific airway hyperresponsiveness; and
- demonstration of work-relatedness of asthma by objective means.

B.1.e.ii Complications and Comorbid Conditions Relevant to Work

Asthma may present in complex ways with a variety of secondary symptoms and problems that affect daily life and work. For example, asthma may trigger chronic cough and secondary hoarseness that indirectly interferes with some jobs (e.g. voice changes, or the ability to carry on a conversation). Gastroesophageal Reflux Disease (GERD) is often associated with asthma, may be triggered by the effect of bronchodilator medications on the lower esophageal sphincter, and may make asthma symptoms worse. Vocal cord dysfunction is distinct from asthma but may often coexist with it, or may be triggered by GERD or exposure to irritants.

B.2 Occupational / Work-Related Asthma

B.2.a History Taking and Physical Exam

Occupational exposure history, presentation, and diagnostic screening test results form the foundation for diagnosis and treatment plans.

B.2.a.i History of Present Illness

The History of Present Illness (HPI) should document:

- Occupational and non-occupational pulmonary exposures.
- Occupation: current/past and types of work activities (such as: bakers and food processors, dock workers, veterinarians and laboratory workers, chemical, jewelry and alloy production workers).
- Time spent at each job, including jobs held years to decades in the past.

Exposures to:

- Dusts: grains, flours and wood.
- Metals (Platinum salts, aluminum).
- Chemicals or substances exposure: gases, fumes, vapors (especially ammonia, isocyanates, solvents), smoke and aerosols.
- History of exposure should include non-occupational exposures to these agents with a description of exposure, duration of exposure, and intensity of exposure.
- Intensity of exposure: ideally with environmental measurements (industrial hygiene data) or at least a qualitative description of intensity of exposure, e.g., daily, weekly, monthly, yearly, etc.
- Include questions detailing the individual's responsibilities and exposure (e.g. did you work in the office, etc.).

Symptoms:

- Symptoms and when symptoms began
- Including complaints of:
  - Throat tightness
  - Shortness of breath
  - Difficulty with inspiration or expiration

    - Harsh breath sounds
    - Cough
    - Sputum production
    - Recurrent bronchitis
    - Chest tightness

Duration, onset and frequency of symptoms

- Symptom development including:
    - Aggravation and alleviation of symptoms in relationship to work environment
    - Changes in work environment
    - Changes in symptoms in relation to days worked and not worked (especially improvements on weekends or holidays when not at work)
    - Progression of symptoms
    - Seasonal pattern to the symptoms

Document if:

- Symptoms began after a one-time, high-level workplace inhalation exposure to an irritant gas, fume, smoke, vapor or aerosol.
- Pulmonary imaging and testing.
- Previous treatments.
- Relationship to work: This includes a statement of the probability that the illness or injury is work-related.
- Ability to perform job duties and activities of daily living.
- Workplace history of room size, ventilation and current and past use of any PPE.

B.2.a.ii Past Medical History

- Past medical history including but not limited to prior pulmonary exposures and treatments (include childhood asthma, prone to bronchitis, hay fever, eczema and pneumonia).
- Review of systems includes, but is not limited to, symptoms of rheumatologic,neurologic, endocrine, neoplastic, dermatologic and other systemic diseases.
- Detailed smoking history (including marijuana, vaping, etc.).
- Detailed medication history including use of pulmonary medications, angiotensin converting enzyme inhibitor and beta-blockers.
- Vocational and recreational pursuits.
- Prior imaging studies.
- Past surgical history.
- Allergy history (including history of atopy).
- Family history of atopic disease.

B.2.a.iii Physical Examination

An occupational pulmonary physical examination should include the following elements:

- Vital signs, including measured respiratory rate, O2 saturation.

- Overall functional abilities, including ease of movement, walking and changing positions, dressing and undressing while assessing signs and symptoms of dyspnea.
- Assessment of respiratory status (e.g., rate, depth, use of accessory muscles, nasal flaring).
- Inspection for stigmata of pulmonary disease as well as potential etiologies including:
  - Mucous membrane abnormalities
  - Nasal polyps/swelling/discharge
  - Clubbing
  - Anterior-posterior chest diameter
  - Purse lip breathing
  - Peripheral edema

- Palpation for:
  - Chest wall abnormalities
  - Adenopathy and neck masses

- Percussion for resonance to identify:
  - Aeration
  - Diaphragm level
  - Suggestion for fluid interface or consolidation

- Auscultation for:
  - Inspiration to expiration ratio
  - Adventitious breath sounds (crackles, wheeze, rales, rhonchi)
  - Pleural rubs, as well as timing, location and persistence of lung findings

- Cardiac examination with attention to findings of cor pulmonale and heart failure.

- Dermal examination for signs of disease (i.e. erythema nodosum (Sarcoidosis)).

- Cardiac examination with attention to findings of cor pulmonale and heart failure.

C. Exposure Assessment

Information on work exposures may be obtained from Material Safety Data Sheets (MSDSs), industrial hygiene data, employer records, and union health and safety personnel information. In general, at least one source of objective information is needed for evaluation of cases of suspected occupational asthma. The MSDS is usually the initial source of information, although sensitizing ingredients in low concentrations may not be listed, and identifying them may require a phone call to the technical staff of the manufacturer. Published literature may also be helpful.

It is important to establish:

- All known exposures in any environment to any chemicals or substances including gas, fumes, vapors, dusts, and aerosols, particularly known or suspected asthmagens.
- Workplace history of room size, ventilation, current and past use of personal protective equipment, other co-worker reports, exhaust hoods, remodeling, recent change in processes, and industrial hygiene reports (if available).
- MSDSs should be reviewed, if available, for both health effects information and personal protective equipment recommendations by the manufacturer of materials used.

For exposure assessment, the standards and methods of evaluation widely used are those promulgated by the American Conference of Governmental Industrial Hygienists (http://www.acgih.org).

For workplace risk assessment, the *NIOSH Pocket Guide to Chemical Hazards* provides a concise summary of toxicologic information

C.1 Environmental History

Exposures outside the workplace are also important to evaluate and document. Patients should be queried regarding primary place of residence, its age, location, type, remodeling history, heating, ventilation, flooring, and past water damage. Hobbies such as automobile repair, woodworking, photography, ceramics, and gardening may expose individuals to agents that can cause or exacerbate asthma.

D. Diagnostic Testing

D.1 Spirometry in Work Related Asthma

Spirometry testing is an essential component in the evaluation and management of persons with possible work-related asthma. Spirometry with or without bronchodilator administration has four distinct potential roles when WRA is a concern:

- Determining whether asthma is present;
- Exclude other “asthma-like” conditions;
- If asthma is present, helping inform the conclusion about whether the asthma is work related; and
- Monitoring response to therapy (and possible return to work).

Recommended - as an initial evaluation method for diagnosing work-related asthma.

D.1.a Spirometry with Bronchodilator Response Testing

Recommended Is recommended to document and quantify airflow obstruction noted on spirometry.

Rationale for Recommendation - Indications for spirometry with or without bronchodilator for the evaluation of work-related asthma include signs and symptoms associated with a history consistent with work-related asthma. Spirometry with bronchodilator is an essential test for the evaluation of pulmonary function and would be performed in most cases.

Variability of airflow obstruction fundamentally distinguishes asthma from other obstructive disorders. Comparison of spirometry results before and after administration of a bronchodilator and variability of results when repeated over many days are effective and simple methods of assessing such variability.

When considering WRA, spirometry with bronchodilator is used primarily to document and quantify airflow obstruction. For this purpose, the forced expiratory volume in one second (FEV_1) and the ratio of the FEV_1 to the forced vital capacity (FEV_1 /FVC ratio) are most useful.

Asthma is confirmed by demonstrating airflow obstruction (e.g., by reduction in both FEV_1/FVC ratio and FEV_1) or by a positive metacholine challenge. Repeated spirometry, or spirometry followed by repeated peak flow measurements, is used to demonstrate that the obstruction is present and that it is variable rather than fixed.

Important caveats to consider:

- Serial measurements can be used with clinical correlation to track progression and variability under different conditions and exposures, with the understanding that improvement in the measurements does not always correlate well with an improvement in the disease.
- Because asthma is characterized by variability, airflow obstruction is an indicator of status at any one time and does not necessarily reflect trends over time but can indicate worsening of disease if it is much worse than a previous FEV_1 measurement.
- Therefore, its main value is in demonstrating variability (e.g., ruling out
- irreversible obstruction).

The measurements of greatest utility in spirometry for the evaluation of airways disease are:

- Forced expiratory volume in one second (FEV_1), expressed in liters and/or as a percentage of predicted values,
- FEV_1 before and after (pre/post) administration of a bronchodilator, usually albuterol (salbutamol),
- Pre/post FEV_1, which is measurement of FEV_1 before and after (pre/post) a work shift, taking into account diurnal variation,
- Ratio of FEV_1 to forced vital capacity (FEV_1/FVC), expressed as a percentage,
- Peak expiratory flow (PEF), expressed primarily in liters per minute, which is particularly useful in following workers in whom reactive airways are demonstrated, and
- Of less central importance, forced expiratory flow rate (FEF_{25-75}), which is the volume expired between 25% of FVC and 75% of FVC, often called midflows.

Methods

- Accurate results depend upon use of proper equipment, proper test performance, and qualified interpretation.
- Spirometry can be done alone or with pre- and post-bronchodilator testing.

- Pre- and post-bronchodilator testing is performed by establishing baseline airflow and then determining whether volumes increase with administration of a bronchodilating agent.
- The American Thoracic Society (ATS) defines a 12% improvement in the FEV_1 or an absolute value increase of at least 200 mL after bronchodilator administration as indicating reversibility of airflow obstruction in FVC or FEV_1 values.
- Rarely, subjects may have a paradoxical response to the bronchodilator resulting in increased obstruction; this is a transient effect associated with highly reactive airways responding to a nonspecific stimulus and slow response to the agent.
- Changes in peak flow are to be expected and are used to monitor progress in treatment but not for diagnosis.

Interpretation of Spirometry

- Spirometry with or without bronchodilator cannot differentiate occupational asthma from non-occupational asthma, and must be interpreted with additional information from the history or supplemental testing.
- Failure to demonstrate reversible airway obstruction on a single test day does not exclude the diagnosis of asthma or of airways reactivity in general.

The American Thoracic Society and European Respiratory Society (ATS/ERS) have published statements on how to conduct and interpret spirometry. OSHA has also recently issued guidance on best practices for occupational spirometry testing.

D.1.b Peak Expiratory Flow Rates (PEFR)

PEFR is defined as the maximum flow achieved during expiration, delivered with maximal force, starting from the level of maximum inspiration and using simple portable meters. Serial PEFR measure the circadian rhythm, which has lower values in the early hours of the morning and maximal in the afternoon. The differences are more pronounced in individuals with bronchial asthma.

PEFR must be performed by the patient outside of a medical setting to be useful in evaluation of occupational asthma. PEFR can be easily obtained both at and away from work to document presence or absence of changes in flow that are potentially related to the work-place environment or exposures.

Peak Expiratory Flow Rates – Serial Measures

Recommended - for confirming a diagnosis of work-related asthma, in patients already diagnosed with asthma by other methods. The physician or qualified staff should train the patient on the proper use of the meter and the importance of accurate recordings.

Indications – To assist in screening patients with a history consistent with WRA.

Rationale for Recommendation - Serial PEFR is recommended as an initial method for investigating suspected OA and WRA. It is desirable to initiate serial PEFR early in the evaluation of WRA when patients are more likely to still be exposed to a putative cause of asthma. Serial peak expiratory flow measures may

add information on airway resistance both at work and at home and are thus recommended.

Method – Assessment of serial measurements of PEFR at and away from work is an accessible method of confirming the relationship between the exposure and bronchoconstriction and has been recommended as a first-line investigation in suspected cases of occupational asthma.

- Standards for PEFR devices and their performance have been published by ATS and the subcommittee on Occupational Allergy of the European Academy of Allergy and Clinical Immunology group with recommendations for total duration and frequency of PEFR measurements both at and away from work.
- The optimal frequency and duration of serial PEFR has not been agreed upon. Generally, workers are instructed to record PEFR every two to three hours for four weeks, including periods at and away from work, while maintaining a diary indicating their activities, as well as, any symptoms they might be experiencing including use of bronchodilators. Dedicated diary cards are available at www.occupationalasthma.com.
- Each measurement session should include three or more forced expiratory maneuvers with the best of the attempts recorded and used for analysis.
- The best of three PEFR readings should be recorded on each occasion provided the best two readings were within 20 L/minute of each other.
- A recording period of four weeks, including a period of at least two weeks away from suspect exposure is recommended, although longer periods increase the value of the test. PEFR measures should be obtained upon awakening, mid-day, at the end of the shift, and before bedtime (or comparable times for non-day shift workers), although some investigators recommend every two hours while awake.
- Use of a freely downloadable automated data plotting and analysis system may limit human variability in interpreting the PEF values, and can be particularly useful for practitioners without extensive prior experience (www.occupationalasthma.com).

Advantages and Limitations – PEFR Can provide objective evidence of relationship between work and asthma worsening. PEFR is heavily dependent upon the worker's efforts, including reliable performance of a forced expiratory maneuver and accurate recording of the results PEF measures cannot differentiate between OA and work exacerbated asthma.

Evidence for the Use of Peak Expiratory Flow Rates

D.1.c Non-Specific Bronchial Provocation Test

Bronchoprovocation with methacholine, histamine, cold air, or exercise challenge is used to establish the diagnosis of asthma, particularly when asthma is suspected and spirometry is normal or near normal. Methacholine and histamine challenges are the most commonly available tests. Methacholine is preferred to histamine because it is associated with fewer side effects, and lung function measurements are more reproducible. Nonspecific bronchial provocation testing is thought to reflect the increased sensitivity of the airways to inhaled nonspecific stimuli or irritants that is reported by many patients with asthma. These stimuli are thought to evoke airflow limitation predominately by an effect on airway smooth muscle, although the mechanisms preceding this effect differ. Increased

methacholine reactivity may resolve a few months out of exposure, but has been demonstrated to persist for more than 13 years out of exposure.
Method –There are two methods for inhaling aqueous solutions of pharmacologic stimuli: (1) the 2-minute tidal breathing protocol; and (2) the 5-breath dosimeter protocol. The method of performing nonspecific bronchial provocation tests is to first measure baseline lung function and to calculate a target FEV_1 that indicates a 20% fall in FEV_1. Inhalation of a placebo or diluent (0.9% NaCl) is optional. Inhalation of the bronchoconstrictor agent methacholine typically starts at a concentration of 0.031 to 0.0625 mg/mL, and then increases by doubling or quadrupling concentrations up to 16, 25, or 32 mg/mL, depending on the protocol. Following each inhalation, the FEV_1 is measured and the test is stopped when the FEV_1 has fallen by 20% from baseline or diluent value. The response is usually expressed as a provocative concentration (PC_{20}) producing a 20% fall in forced expiratory volume in 1 second. The presence of asthma is usually defined as a ≥20% fall in the FEV_1 at a methacholine dose of 4 mg/mL or below. Methacholine 4-16 mg/ml is considered borderline full categorization of bronchial responsiveness based on methacholine PC_{20} mg/mL dose.

Recommended - for use (e.g., methacholine) in diagnosing asthma if the clinical history is compelling and other tests (spirometry and bronchodilator responsiveness) are unhelpful.

Recommended - for use (e.g., methacholine) in diagnosing work-related asthma as other steps are required to establish the work-relatedness of the asthma.

Criteria and Standards for Use – Bronchial challenge testing should be done according to the 1999 ATS statement and the 1993 European Respiratory Society statement (updated 2008)
https://journal.chestnet.org/article/S0012-3692(08)60285-8/abstract

Indications/Contraindications – NSBP is not generally recommended if the baseline FEV_1 is <65% of predicted. Absolute contraindications for methacholine challenge testing include:

- severe airflow limitation (FEV_1<50% predicted or <1.0L), heart attack, or stroke in previous three months;
- uncontrolled hypertension (systolic BP>200 or diastolic BP>100); and
- known aortic aneurysm.

Relative contraindications include:

- moderate airflow limitation (FEV_1 <60% predicted or <1.5L;
- unable to perform acceptable-quality spirometry;
- pregnancy;
- nursing mothers;
- recent upper respiratory infection; and
- current use of cholinesterase inhibitor medication (for myasthenia gravis).

D.1.d Mannitol Bronchial Provocation Test

Not Recommended - for use in diagnosing work-related asthma; other steps are required to establish the work-relatedness of the asthma.

Evidence for the Use of Nonspecific Bronchial Provocation Test

D.1.e Specific Immunological Testing

Specific immunological testing to suspected allergens is commonly used to aid in the diagnosis of allergic rhinitis and occupational asthma. These tests are performed to evaluate type I (IgE) hypersensitivity reactions to specific allergens, and can be useful in the diagnosis of certain cases of occupational asthma caused by immune or allergic mechanisms, in contrast to irritant-induced asthma. However, the presence of specific antibodies is an indicator of an immune response, and does not necessarily have a causal relationship with occupational asthmatic symptoms. Hence, demonstration of sensitization to an occupational agent by specific IgE and/or skin testing alone, without demonstrating the work-relatedness of the asthma, is insufficient to establish a diagnosis of OA.

Detection of IgE to a specific allergen is accomplished by skin prick testing (SPT), and serum IgE testing when kits are available for the specific allergen. Three methods of detecting serum IgE antibodies have been employed to assess antigenicity to occupational antigens: 1) RAST; 2) ELISA; and 3) ImmunoCAP.

The sensitizing agents known to induce occupational asthma are traditionally divided into high molecular weight (HMW) and low molecular weight (LWM) antigens.

D.1.e.i High Molecular Weight Agents

Occupational asthma induced by HMW agents, which are mainly proteins of animal or plant origin, is often associated with the production of allergen-specific IgE antibodies.

Examples of HMW asthmagens include:

- proteins of biological origin, such as laboratory animals;
- enzymes used in the detergent or food industries;
- grain proteins found in bakeries; and
- natural rubber latex proteins prevalent in health care workers.

Such proteins are considered complete allergens, capable of causing the elaboration of specific IgE antibodies.

D.1.e.i.a IgE Specific Immunological Testing for High Molecular Weight Specific Antigens

Recommended - for workers with symptoms consistent with occupational asthma to certain high molecular weight specific allergens and when standardized antigens and assay protocols exist. High molecular weight allergens for which there is sufficient evidence in quality studies include flour dusts, bovine danders, laboratory, and other animal allergens. Natural rubber latex (NRL) allergy can be confirmed by serum IgE testing, but the assay does not include all potential NRL allergens, such that a negative result does not necessarily exclude the diagnosis of NRL allergy.

D.1.e.i.b IgG Specific Immunological Testing for High Molecular Weight Specific Antigens

Not Recommended - as a diagnostic tool for select workers with symptoms consistent with occupational asthma to high molecular weight specific allergens.

D.1.e.ii Low Molecular Weight Agents

Become allergenic only after binding with one or more autologous serum, epithelial, or tissue proteins.

Common LMW agents include:

- diisocyanates;
- colophony fume, liberated from cored solder in the electronics industry;
- complex platinum salts; and
- the family of acid anhydrides, which are common constituents in the manufacturing of resins.

D.1.e.ii.a IgE Specific Immunological Testing for Low Molecular Weight Specific Antigens

Not Recommended - for workers with symptoms consistent with occupational asthma to low molecular weight specific allergens.

Method –The majority of LMW antigens do not have commercial assays that have been validated for specific antibody testing.

Indications – To be used for allergens that have been shown to have acceptable sensitivity, specificity, positive predictive value, and negative predictive value using a validated method in investigational studies.

Advantages and Limitations – Not all occupational asthma is believed to have IgE and/or IgG mediated immune responses, but data suggest IgE is involved in subsets of symptomatically exposed workers, especially to HMW antigens.

Evidence for the Use of Specific Immunological Testing

D.1.f. Skin Prick Testing

Skin tests are used, in addition to a directed history and physical exam, to exclude or confirm sensitization in IgE-mediated diseases, including asthma. There are two types of skin testing used in clinical practice. These include percutaneous testing (prick or puncture) and intracutaneous testing (intradermal). If local tissue mast cells have surface IgE specific for the allergen being tested, it will cross-link the IgE and trigger the release of preformed histamine from mast cells which in turn causes increased vascular permeability and development of a wheal; inflammatory mediators initiate a neural reflex causing vasodilatation, leading to erythema (the flare). Test results often report the size of the wheal and the size of the flare in

millimeters, as W/F mm/mm and compared to the negative saline control response. Results may also be reported on a scale of 0 to 4+, where 1+ is erythema smaller than a nickel in size, 3+ is wheal and erythema, and 4+ is a wheal with pseudopods and erythema. Most of the literature suggests that with a negative skin prick test result, a positive intradermal skin test (IDST) result adds little to the diagnostic evaluation of inhalant allergy. IDST is only indicated and should be selectively used when there is a compatible or compelling history and a negative or equivocal SPT result. Many studies have demonstrated that the prick skin test response correlates much better with clinical allergy.

Skin prick testing has been used to assess allergy to asthmagens in various types of patients and occupational settings. Workers should be referred to a physician with experience in skin prick testing for interpretation to assess atopy, as well as to the potential causative allergen. Skin prick testing should be performed by trained and qualified personnel, and the tests supervised by and interpreted by a physician experienced in the technique.

D.1.f.i Skin Prick Testing to High Molecular Weight Allergens

Recommended - for select workers with symptoms consistent with occupational asthma to specific allergens and where validated, commercial skin testing extracts are available. High molecular weight allergens for which there is sufficient evidence are natural rubber latex, wheat and rye flour, grain dust, alpha-amylase, bovine danders, and laboratory and other animal allergens.

D.1.f.ii Skin Prick Testing to Low Molecular Weight Allergens

Recommended - for select workers with symptoms consistent with occupational asthma to specific allergens, and where skin testing extracts are available. Low molecular weight allergens for which there is sufficient evidence are reactive dyes, halogenated platinum salts, and trimellitic anhydride.

D.1.f.iii Skin Prick Testing to Other Allergens Not Covered Above

Not Recommended - for allergens not covered above. When specific allergens have not been evaluated in quality studies with reported specificity and sensitivity, skin prick testing for these allergens cannot be recommended. Skin prick testing is also not recommended if suspected cause is non-allergenic.

Rationale for Recommendations - Multiple studies include skin prick testing as part of the diagnostic protocol, although most include skin prick testing as a test for atopy rather than a diagnostic test for occupational asthma.

Method **–** The performance of skin prick testing has been the subject of a practice guideline by the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI).

Indications – Prick skin testing should be performed with allergens that have acceptable sensitivity, specificity, positive predictive value, and negative predictive value. Allergens associated with occupational asthma and that meet these criteria include: natural rubber latex, wheat and rye flour, grain dust, alpha-amylase, reactive dyes, bovine danders, laboratory and other animal allergens, halogenated platinum salts, and trimellitic anhydride.

Harms – Rare risk of severe asthmatic or anaphylactic reactions.

Advantages and Limitations –The risk of fatality due to skin prick testing is extremely remote, and severe/anaphylactic reactions are rare. Nevertheless, this risk cannot be completely excluded in highly susceptible subjects, such as individuals with a history of previous anaphylactic reactions, pregnant women, those who have uncontrolled asthma, or have high degree of reactivity. Skin testing should not be performed in pregnant women and only in other high risk individuals where the consequence of the result outweighs the risk.

Evidence for the Use of Skin Prick Testing

D.1.g Specific Inhalation Challenge

Specific inhalation challenge (SIC), also called specific bronchial provocation test (SBPT), is performed by generating an exposure to the suspect asthmagen that simulates workplace conditions, and following the subject's lung function for an asthmatic response. It is used when other methods have failed to establish the diagnosis; or a reference standard as there is no other definitive diagnostic test.

Recommended - for use in diagnosing work-related asthma with latency for highly select cases, where the diagnosis of occupational asthma is highly suspected, but has not been established by less invasive means. This testing should only be performed in appropriately equipped facilities, with direct medical supervision throughout the testing.

Method - These tests may have serious complications that include fatalities. There are few centers that can safely and accurately perform these tests, and should have the proper equipment and Asthmagen exposure should be done after a control day where the patient is not exposed to the suspected sensitizer and lung function is monitored for stability. The testing may be performed once, but may need to be repeated on another day or with a higher dose to identify positive responses. Patients should stop using short-acting beta 2-agonist agents eight hours before testing and longer acting medications 24 hours before testing. Positive responses, defined as a 20% fall in the FEV_1, may present in an immediate pattern (within 30 minutes of the exposure), is typical for HMW agents; a delayed pattern (two to eight hours after the exposure) is typical for LMW agents; or a dual pattern demonstrating both early and late responses to that may be present with both LMW, and some HMW agents. Full method and criteria for positivity of specific inhalation challenges with diisocyanates may be further reviewed in this reference.

Indications – Most patients with suspected sensitizer-induced OA do not require this test, as their OA can be diagnosed with less invasive means.

The indications for SIC include:

- evaluation of a worker who has left the workplace and is unable or unwilling to return to work utilizing serial measurements of lung function
- initial documentation of a new cause of occupational asthma
- identification of a specific causative agent when there is work exposure to multiple substances;
- confirmation of the diagnosis of occupational asthma and identification of causative agent, when other objective methods are not feasible, are less efficient, or have failed to provide definitive results.

Harms – Excessive bronchoconstriction and exacerbation of asthma; infrequently systemic and anaphylactic reactions

Advantages and Limitations – Specific bronchoprovocation testing is not considered necessary in a worker with a history of OA in whom work-related airway obstruction is confirmed in association with exposure to an agent known to cause OA, or when the worker has been shown to be sensitized to that agent. Limitations to the validity of the SIC include:

- The challenge exposure does not replicate the work exposure
- The OA is caused by a mixture of agents, and not one single agent
- The worker has been out of exposure for too long, and has lost immediate reactivity to the agent
- The patient has unstable asthma with variations in airflow independent of exposure.

Rationale for Recommendation - SIC is recommended only for highly select cases, particularly where assurance of an accurate diagnosis is important.

Evidence for the Use of Specific Inhalational Challenge Testing

D.1.h Nitric Oxide (Fractional Exhaled Nitric Oxide, FENO)

Measurement of total exhaled nitric oxide (FENO) is a test used for detection of endogenous inflammatory signals. FENO is acknowledged to assess pathological rather than physiological changes in asthma. The fraction of nitric oxide in expired air increases with uncontrolled asthma and decreases with anti-inflammatory therapy. FENO is considered to be a surrogate marker of eosinophilic inflammation in asthma. Other factors such as smoking (generally lower), use of inhaled steroids (lower), exercise (lower), height (increase), gender (higher in males), atopy (increase), recent pulmonary infections (higher), ambient air levels of NO, and other pulmonary function testing (lower) may alter FENO results. These factors, if not well described or controlled for, may make comparisons from one diagnostic study to another difficult.

Recommended – for the select assessment of those with moderate to severe asthma to monitor treatment and control if strict protocols are in place and the test is well understood both by the examiner and the clinician interpreting the test.

D.1.h.i Exhaled Nitric Oxide Testing for Diagnosis of Asthma

Recommended- Exhaled nitric oxide testing for establishing a diagnosis of asthma in select cases when additional evidence is required for

confirmation of a clinically-grounded diagnosis of asthma when pulmonary function tests / provocation tests are nondiagnostic.

D.1.h.ii Exhaled Nitric Oxide Testing for Selective Monitoring of Asthma

Recommended - Exhaled nitric oxide testing for selective use in monitoring airway inflammation in patients with moderate or severe asthma.

This may be particularly useful when biologicals are used in the treatment of asthma.

Criteria and Standards for Use – Use criteria and standards as described in the ATS 2011 statement for the Interpretation of Exhaled Nitric Oxide Levels for Clinical Applications.

Evidence for the Use of Nitric Oxide Testing

E. Management of Occupational Asthma (OA)

The goal of treatment is to minimize asthma exacerbations by reducing work exposures (e.g., by limiting sources of exposure, improving ventilation) and optimizing standard medical management with non-work environmental control measures and pharmacologic treatment. The patient may be able to stay at the same job with reduced exposures, depending on the severity of asthma and extent of exacerbating factors at work, but a job change to a workplace with fewer triggers may be necessary if this approach fails to adequately prevent work-related exacerbation of symptoms. When a patient with WEA can no longer tolerate a work setting, the clinician and patient should carefully balance the potential benefit of removal from work with the benefits (financial and psychological) of continued working.

The medical management of OA, however, includes measures aimed at early diagnosis and early avoidance of further exposure, either by relocation of the worker or substitution of the hazard, as these offer the best chance of avoiding further jeopardizing the asthmatic condition. The pharmacologic management of occupational asthma is similar to that used for other forms of asthma and should follow well recognized and published medical guidelines. Patients with sensitizer-induced OA should be removed from further exposure to the causative agent in addition to providing other asthma management.

If medical removal is not possible, exposure should be minimized to as low as possible by means of worker relocation. Relocated workers should have increased medical surveillance to demonstrate the absence of worsening of disease. Workers with OA may still deteriorate even with low exposure to the causative agent. Worsening of the disease in these circumstances should prompt recommendation for removal from exposure. In patients with irritant-induced OA, a trial of minimizing exposure by means of use of respiratory protective equipment could be indicated as initial management, in addition to providing asthma medication. Again, increased medical surveillance is recommended and, if worsening of the disease is demonstrated, a recommendation for removal of exposure is encouraged. In these cases, relocation to a different job and a different environment could be considered. Determining the most effective treatment for OA requires having precise information on the effect of different management options.

E.1 Persistence of Exposure

Recommended – informing that persistence of exposure to the causal agent is likely to result in a deterioration of asthma symptoms and airway obstruction.

E.2 Avoidance of Exposure

Recommended – informing that complete avoidance of exposure is associated with the highest probability of improvement, but may not lead to a complete recovery from asthma.

E.3 Medical Removal

Once a diagnosis of OA is confirmed, the patient should be advised that the prognosis is improved by early and complete removal from exposure. Symptoms and functional impairment associated with OA may persist for many years after avoidance of further exposure to the causative agent. Persistence of exposure to the agent causing occupational asthma is more likely to be associated with the persistence of asthma, and an accelerated decline in FEV_1, compared with complete avoidance of exposure.

E.3.a Management of Sensitizer-Induced Asthma (Reduction of Exposure)

Recommended – removal from exposure

Rationale for Recommendation - available evidence indicates that many asthma cases will worsen in continued exposure.

E.3.b Management of Irritant-Induced Asthma (Reduction of Exposure)

Recommended - exposure reduction to the lowest levels possible, including the use of personal protective equipment.

Recommended - careful medical monitoring must be performed to ensure early identification of worsening asthma. Progression of the asthmatic condition should prompt total removal from exposure.

E.4 Respiratory Protective Devices

Not Recommended - are considered the last level of protection from noxious exposures; especially in the long-term and in patients with severe asthma.

Not Recommended - as a stand-alone intervention, however may be used for mild cases in lower exposure settings, on short- term basis in conjunction with other efforts to reduce or eliminate exposure and with pharmacologic therapy, especially in irritant induced OA.

Not Recommended – for severe or moderately severe asthma in worksites with medium or high exposures

Not Recommended – as a stand-alone intervention

Utilization - Appropriate medical monitoring is required keeping in mind that progression of the asthmatic condition should prompt a recommendation for avoidance of exposure. Evaluating the ability of the worker to wear a respirator as per OSHA 1919.134 standard and selection of appropriate respirator are essential.

F. Medications

F.1 Pharmacological Treatment of Work-Related Asthma

Treatment does not differ from the treatment of non-work-related asthma.

Recommended – should follow accepted standards for the treatment of non-work-related asthma.

F.2 Anti-Asthma Medications Alone

Not Recommended - as a reasonable alternative to environmental interventions such as exposure reduction or medical removal, but may be indicated in conjunction with such interventions.

F.3 Immunotherapy to Manage Sensitizer Induced Asthma

Recommended – for consideration in settings where occupational asthma due to a specific HMW allergen has been established, when only one or a few allergens have been linked clinically to disease, when there is a standardized commercial allergen extract available for treatment, good control with pharmacotherapy cannot be established and the causative agent cannot be completely avoided for economic, professional or other reasons.

F.4 Immunotherapy to Manage Irritant-Induced Asthma

Not Recommended

F.5 Biologicals - a new class of asthma agents, especially the monoclonal antibodies, anti-IgE, anti-eosinophils and anti-mediator medications

Recommended - in specific situations with increased levels of IgE, or eosinophils for use by specialists with experience in the use of these medications.

G. Treatments

G.1 Manage and Minimize Potential Complications of Asthma

G.1.a Immunization

Recommended – pneumococcal pneumonia and influenza vaccinations

G.1.b Additional Recommendations

- Monitor for acute flare-up,
- Aggressive management of respiratory infections, and
- Specific management of allergic / irritant co-morbidities of the upper respiratory tract (rhinitis, sinusitis, GERD).

H. Prognosis

The long-term consequences of OA are variable and require prolonged follow-up. Symptoms and functional impairment associated with OA may persist for many years even after avoidance of further exposure to the causative agent. Outcomes are best in those patients with a shorter duration of exposure after onset of symptoms.

Improvement or resolution of symptoms or of preventing deterioration is more likely in workers who have:

- No further exposure to the causative agent,
- Relatively normal lung function at the time of diagnosis, and
- Shorter duration of symptoms prior to diagnosis.

OA may become a chronic condition, similar to non-OA, and may require similar prolonged medical management. Patients with confirmed or possible OA should be closely followed up with respiratory questionnaires and spirometry testing while risks of continuing exposure remain. Patients with confirmed OA who have left work, or who have no ongoing asthmagen exposure risk, should be regularly followed up as clinically indicated.

I. Prevention and Exposure Control

Control of workplace exposure consists of elimination, substitution, engineering controls, administrative controls, and personal protective equipment (PPE). Elimination of the agent or total substitution of the agent are considered the best strategies for eliminating exposure. Engineering controls involve eliminating the potential exposure without any need for the employees to participate. Administrative controls, such as work practices, involve processes to minimize exposure. Personal protective equipment relies on the employees' use to decrease exposure. Prevention strategies should also include educational information regarding the risk of sensitization disorders, the importance of exposure control measures, indicators of work-related asthma, and the steps to take if asthma symptoms occur in relationship to work exposures.

Use of PPE, particularly respirators, is considered less effective than eliminating or minimizing exposures at the source or in the environment. The success of respiratory personal protection requires an ongoing commitment by employers and employees to the selection, cleaning, maintenance and storage of equipment, as well as training, fit testing, and medical monitoring of users. Respirators are best used as an interim measure while efforts to control exposures at the source or in the environment are being implemented, or when controls at these other levels are not possible. Respirators have often been used in conjunction with other control activities at the source and/or environmental level.

Appendix I – Asthma Management Guidelines (by Others)

Asthma Treatment Guidelines (by Others)

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Management Topics Evaluated	Results	Comments
Chung 2014 Guidelines ERS/ATS Task Force on Severe Asthma	NA	Pharmacological treatment	Treatment of severe asthma relies heavily on the maximal optimal use of corticosteroids and bronchodilators. There is potential for benefits of biological agents.	Recommendations on treatment for severe asthma. No specific mention of OA or WEA.
Baur 2012 Guidelines ERS Task Force Report	NA	Reduction of exposure Removal from exposure Personal respiratory equipment Pharmacological treatment	Reported insufficient evidence that treatment with inhaled corticosteroids and long-acting beta 2-agonists is able to prevent long-term deterioration of asthma is subjects who remain exposed to the agent causing occupational asthma.	Specific to OA and WEA. Authors address their recommendations for both diagnosis and treatment of OA and WEA.
Tarlo 2008 Consensus guideline, literature review document American College of Chest Physicians Consensus Statement Supported by Schering-Plough Corporation.	NA	Removal from exposure Minimizing exposure Inhaled corticosteroids Other antiinflammatory agents Immunotherapy	Removal from work is beneficial in relation to both symptoms and pulmonary function. There is limited evidence that minimizing exposure is a safe, or appropriate method of management. It seems beneficial to initiate early treatment an early treatment with inhaled corticosteroids in subjects with sensitizer-induced OA in addition to removal from exposure. Evidence of other anti-inflammatory agents is weak. Immunotherapy may be an effective management option when a commercial extract is available and the causative agent cannot be completely avoided for economic, professional, or other reasons. It is most effective when it targets 1 allergen or a few	A thorough look at the available evidence with good overall organization. Addressed several issues in relation to diagnosis and treatment of OA and WEA. Noted limitations in the literature. No summary table of recommendations, no level of evidence noted. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.

			allergens. Immunotherapy is not indicated to treat irritant-induced asthma.	
Beach 2005 Consensus guideline, literature review document Sponsored by Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.	NA	Removal from exposure Reduction of exposure Use of PPE Inhaled Corticosteroids Immunotherapy	Less than half of the studies with removal (complete or reduction of exposure) reported improved FEV_1. 14/15 studies reported removal resulted in decreased hyper-responsiveness on NSBP testing. The majority of studies reported improved symptoms after removal from exposure and reduction of exposure. Use of PPE also reported reduction of symptoms, but did not eliminate symptoms. Studies reported improved PD_{20} in patients tested with inhaled corticosteroids. Immunotherapy to wheat flour extract appeared to be safe and resulted in improvement in symptoms and lung function.	Good summary details of studies included. No level of evidence provided for statements. No level of confidence provided. Authors noted small numbers in most treatment/management studies and that most corticosteroid agent studies reported efficacy but these were done primarily with di-isocyanate induced OA. Concluded that workers with OA often require medication treatment long after diagnosis, but no clear trend was identified based on LMW versus HMW asthmagen division.
Newman 2005 Guidelines for Occupational Asthma Supported by British Occupational Health Research Foundation (BOHRF)	NA	General management of OA	Occupational asthma should be diagnosed early and treated appropriately.	No official recommendations based on literature review. Appears to be mainly consensus recommendations. Not specifically addressing any one type of management.
Nicholson 2005 Consensus guideline, literature review document Commissioned by BOHRF	NA	Removal from exposure Minimizing exposure Medications	Employees should avoid further exposure to causative agents in the workplace. Physicians treating patients with OA should follow published guidelines for the medical management of OA.	Authors follow a grading protocol with recommendations. Recommendations are broad in management sections. No mention of arms/benefits. No level of confidence noted.

Management of OA with Inhaled Corticosteroids

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Malo 1996 RCT-crossover Supported in part by Glaxo Canada Ltd. No mention of COI.	8.0	N = 44 patients with occupational asthma between ages 20-60 years	Active group received beclomethasone dipropionate, 250 µg, in 2 inhalations daily: morning and evening vs. placebo group inhalers containing only Freon propellant. Active preparations were administered for 12 months with follow-up at 3, 6, 9, and 12 months. Placebo preparation administered either before or after 12-month active period. This crossover period lasted 6 months with follow-up at 3 and 6 months.	Greater clinically significant improvement seen in group that received active treatment first. However, both groups reported significant improvement in clinical and behavioral variables, whereas placebo period saw deterioration. For those who started with active treatment, reductions in nocturnal symptoms and coughing were -1.1 ($\pm$0.32), p <0.001 and -0.88 ($\pm$0.2), p <0.001, respectively. Compared to same group during placebo phase: 0.89 ($\pm$0.23), p <0.001 and 0.64 ($\pm$0.16), p <0.001. FEV_1 and FVC significantly deteriorated in both active-drug and placebo periods.	"This study shows that adding inhaled corticosteroids to removal from exposure to several high-and low-molecular-weight occupational agents results in a significant improvement in the clinical symptoms of occupational asthma, the most important reductions being in nocturnal symptoms and coughing."	Twelve dropouts from refusal to carry on. First group had 12 months of treatment; second had 6 months of active treatment. Medication given after withdrawal from exposure. There were differences based on high or low molecular weight substances. Data suggest treatment with inhaled corticosteroids can be beneficial but is more beneficial if used early after removal from exposure compared to delayed use.
Maestrelli 1993 RCT No mention of industry sponsorship or COI.	5.0	N = 15 subjects exposed to TDI in workplace and diagnosed with OA by SIC	7 had beclomethasone dipropionate (BDP, 1mg) twice a day vs. 8 with placebo twice a day. Both groups evaluated at 2, 4 and 5 months.	10 participants (6 in placebo, 4 in treatment) had no significant fall in FEV_1 at any time after TDI challenge. Severity of reaction to TDI decreased in both groups at 6 months. PD_{20} FEV_1 increased after 2 months in treatment group (p<0.05).	"These results indicate that long-term treatment with inhaled beclomethasone persistently decreases nonspecific airway responsiveness to methacholine, but it does not modify the effect of cessation of occupational exposure on the airway sensitivity to TDI."	At baseline, beclomethasone treatment group had longer exposure to TDI compared to placebo group. Small numbers in study. Data suggest treatment with beclomethasone can help with nonspecific airway responsiveness, but does not alter FEV_1 decline.
Mapp 1987 Cross-over clinical trial	6.0	N = 24 sensitized subjects to TDI	Beclomethasone 1 mg BID Theophylline 6.5 mg/kg BID Verapamil 120 mg BID Cromolyn 20 mg QID Administered for 7 days	After exposure to TDI, subjects treated with placebo, verapamil or cromolyn developed a late or dual asthmatic reaction with a decrease in PD_{20} FEV_1.	"These results suggest that only high-dose inhaled steroids can completely block TDI-induced late asthmatic reactions."	Cross over study design, blinding of assessor not described. Baseline characteristics minimal, but similar. Data suggest that beclomethasone can help

No mention of industry sponsorship or COI.				Subjects treated with beclomethasone developed no asthmatic reaction or increase in airway responsiveness. Theophylline developed a less severe early and late asthmatic reaction.		treat patients with TDI-related asthma by decreasing hyper-responsiveness of airways.

Management of OA with Immunotherapy

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Sastre 2003 RCT No mention of industry sponsorship or COI.	5.5	N = 24 patients allergic to natural rubber latex (NRL), average age 33.8 years	Active group (n = 16) received standardized SIT with crude latex vs. placebo group (n = 8) received placebo extract spiked with aluminum hydroxide buffer with 0.01 mg of histamine hydrochloride. Both groups received treatment for 6 months.	Post-treatment comparison of active group vs. placebo yielded cutaneous tolerance index difference of 8.9 ($p < 0.01$); reduction in scores for latex use test and rubbing test ($p = 0.026$ and $p = 0.072$, respectively).	"…the clinical efficacy observed during this 6-month trial was shown mainly on cutaneous symptoms, although a significant improvement of rhinitis and asthma symptoms was observed during controlled specific inhalation challenge."	Patients had urticaria, rhinitis or asthma; 16 randomized to active treatment and 8 to placebo (15/24 had diagnosis of asthma). No significant difference in methacholine reactivity, VAS results, symptom scores, or medication use between groups.
Armentia 1990 Case-control study No mention of industry sponsorship or COI.	4.5	N = 26 patients (16 had active treatment; 10 had placebo)	Injections of what flour extract were done once a week. Treatment was done for 10 or 20 months.	After 20 months of immunotherapy there was a decrease to hyper-responsiveness to methacholine, skin sensitivity ($p = 0.02$) and specific IgE to wheat flour ($p<0.05$). Placebo group had no noticeable changes in testing after 10 months of placebo treatment.	"Our study shows with objective measurements that immuno-therapy with wheat flour results in a significant clinical and immune response in our asthmatic patients."	8 participants in 20 months of active treatment group. Small sample size. Data suggest immunotherapy in wheat flour allergy can decrease symptoms, but study overall had small number of treated participants; larger studies need to be completed.

Studies and Guidelines Addressing Removal/Reduction of Exposures

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Management Topics Evaluated	Results	Comments
Banks 1990 Observational study	NA	Reduction of exposure.	Workers with reduced but continued exposure to TDI had continued symptoms of OA. Serial evaluations of participants showed no improvement in bronchial methacholine testing and some showed 15% decline.	Only 6 participants. No comparison to removal from exposure or full continued exposure.

Beach 2005 Consensus Guideline, literature review document Sponsered by Agency for Healthcare Research and Quality. U.S. Department of Health and Human Services.	N/A	Removal from exposure. Reduction of exposure. Use of PPE. Inhaled Corticosteroids. Immunotherapy.	Less than half of the studies with removal (complete or reduction of exposure) reported improved FEV_1. 14/15 studies reported removal resulted in decreased hyper-responsiveness on NSBP testing. The majority of studies reported improved symptoms after removal from exposure and reduction of exposure. Use of PPE also reported reduction of symptoms, but did not eliminate symptoms. Studies reported improved PD_{20} in patients tested with inhaled corticosteroids. Immunotherapy to wheat flour extract appeared to be safe and resulted in improvement in symptoms and lung function.	Good summary details of studies included. No level of evidence provided for statements. No level of confidence provided. Authors noted small numbers in most treatment/management studies and that most corticosteroid agent studies reported efficacy but these were done primarily with di-isocyanate induced OA. Concluded that workers with OA often require medication treatment long after diagnosis, but no clear trend was identified based on LMW vs. HMW asthmagen division.
de Groene 2012 Cochrane Review	NA	Removal from exposure. Reduction of exposure.	Compared to continued exposure, removal from exposure increased the likelihood of reporting absence of symptoms, improved FEV_1 and decreased NSBH. Compared to continued exposure reduced exposure also increased the likelihood of absence of symptoms, but did not affect FEV_1.	Good summary study findings in paper. Used statistics in order to develop conclusions. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Merget 1999 Observational study	NA	Removal from exposure. Reduction of exposure	For the majority of subjects with OA due to platinum salts transfer to low exposure areas may not be associated with a more unfavorable outcome as compared with complete removal from exposure sources.	Single survey of 83 workers. Authors noted that reduction and removal had similar outcomes in terms of symptoms and FEV_1 values.
Fishwick 2012 Consensus Guideline, literature review document British Thoracic Society.	NA	Removal from exposure. Medications	The patient should be advised that the prognosis is improved by early and complete removal from exposure. The pharmacological management of OA does not differ from the management of asthma that is not work related.	Minimal references. No grading of articles. No summary table of recommendations, no level of evidence noted. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Nicholson 2005 Consensus Guideline, literature review document Commissioned by British Occupational Health Research Foundation.	NA	Removal from exposure. Minimizing exposure. Medications.	Employees should avoid further exposure to causative agents in the workplace. Physicians treating patients with OA should follow published guidelines for the medical management of OA.	Followed a grading protocol with recommendations. Recommendations are broad in management sections. No mention of arms/ benefits. No level of confidence noted.
Paggiaro 1994 Study summary document	NA	Removal from exposure. Reduction of exposure.	Removal from occupational exposure is associated with recovery of asthma in about 50% of subjects. Delay in diagnosis, in the removal from occupational exposure and in drug treatment may rsult in persistent chronic dysregulation of airway tone and in progressive deterioration of lung function.	Looked at several studies of OA due to TDI. Good summary of results. No specific guidelines or level of evidence.

Paggiaro 1984 Observational study	NA	Removal from exposure. Continued exposure.	Stopping occupational exposure to TDI frequently did not produce an improvement of the TDI bronchial asthma, and persistence of the occupational exposure causes a more rapid decline in the respiratory function.	Followed 27 patients over 2 years. 12 were removed/left exposure. Included both employees with and without OA.
Tarlo 2008 Consensus Guideline, literature review document. American College of Chest Physicians Consensus Standard Sponsored by Schering-Plough Corporation.	NA	Removal from exposure Minimizing exposure Inhaled corticosteroids Other antiinflammatory agents Immunotherapy	Removal from work is beneficial in relation to both symptoms and pulmonary function. There is limited evidence that minimizing exposure is a safe, or appropriate method of management. It seems beneficial to initiate early treatment an early treatment with inhaled corticosteroids in subjects with sensitizer-induced OA in addition to removal from exposure. Evidence of other antiinflammatory agents is weak. Immunotherapy may be an effective management option when a commercial extract is available and the causative agent cannot be completely avoided for economic, professional, or other reasons. It is most effective when it targets one allergen or a few allergens. Immunotherapy is not indicated to treat irritant-induced asthma.	A thorough look at the available evidence with good overall organization. Addressed several issues in relation to diagnosis and treatment of OA and WEA. Noted limitations in the literature. No summary table of recommendations, no level of evidence noted. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Vandenplas 2012 Consensus Guideline, literature review Task Force was funded by the ERS. No COI stated.	NA	Consequences of persistent exposure. Pharmacological treatment. Immunotherapy. Avoidance of exposure. Reducing exposure through engineering controls. Reducing exposure through PPE.	Asthma symptoms persisted in 93% of subjects who remained exposed and 66.3% in subjects removed from exposure. Some evidence of inhaled corticosteroids benefit. Immunotherapy had evidence showing improvement in asthma control in patients with flour and latex allergy. Studies reported decline in FEV_1 after removal was similar in healthy adults. 7/10 reviewed studies were LMW antigens. Reducing exposure was associated with a lower level of improvement when compared to complete removal. Use of PPE lead to a significant reduction in symptoms, but failed to provide complete protection.	Good summary tables provided of studies that were included in the statements. Addressed several issues in relation to diagnosis and treatment of OA and WEA. Noted limitations in the literature. No summary table of recommendations. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Vandenplas 2002 Observational study	NA	Removal from exposure. Reduction of exposure.	Reduction of exposure to latex should be considered a reasonably safe alternative that is associated with fewer socioeconomic consequences than removal from exposure.	Single study design. Total of 36 subjects followed for 56 months (range 12-92). Noted decreased symptoms and improved PC(20) values in both removal and reduction to exposure groups. Removal groups had more work-related disability and loss of income compared to reduction.
Anees 2006 Retrospective study	NA	Removal from exposure	Mean rate of FEV_1 decline after removal from exposure was 26.6 ml/year. Mean rate of FEV_1 decline was not related to duration of symptomatic exposure or smoking. No evidence inhaled	Various types of exposures included in this study including flour, latex, wood, isocyanates, metal, oils, etc. With the various exposures it is difficult to assess

			corticosteroids after removal from exposure had a major beneficial effect on step-up in FEV_1.	effects removal from any one causative agent. Various treatments also make determination of treatment effectiveness difficult.

Appendix II – Evidence Tables

Evidence for the Use of Peak Expiratory Flow Rates

There are 2 high-[107, 125] and 6 moderate-quality[109, 111, 113, 114, 121, 122] studies incorporated into this analysis.

Author/ Year Study Type	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Perrin 1992 Comparative Study	7.5	61	Spirometry both at work and way from work, skin prick test, specific IgE, specific inhalational challenge	PEF every 2 hours after at least 2 weeks away from work and 2 weeks at work.	Patients with a history suggestive of occupational asthma	4 weeks or more	PEF values	PEF vs. FEV_1: Sensitivity of 81% and specificity of 74%.	"[V]isual analysis of PEF is an interesting tool for investigating occupational asthma, although sensitivity and specificity values do not seem satisfactory enough to warrant using it alone."	PEF testing varied by center. Different participants had different assessments. Various possible sensitizers included in study. Data suggest supervised PEFs may be helpful in investigating occupational asthma.
Park 2009 Controlled Clinical Trial	7.5	76	Serial PEF over 3 weeks	Cross-shift PEF, calculated by taking the pre-shift and post-shift values. Over a 3-week period.	36 patients diagnosed with occupational asthma by specific inhalational challenge testing; 44 diagnosed clinically with non-occupational asthma and had serial PEF data from a period when not at work.	Participants measured their PEF at 2 hour intervals over a 3-week period, including both work days and rest days.	PEF values	Cross-shift cut-off value of -5 L/min with specificity of 90.9%, sensitivity of 50%. Serial analysis using mean work/rest day PEF comparison had sensitivity 66.7% and specificity of 100%.	Serial PEF monitoring in morning/day shift workers has reasonable sensitivity in diagnosing occupational asthma, and is superior to monitoring cross-shift changes in PEF.	No mention of health status of participants (e.g. upper respiratory tract symptoms, or medication use). Data suggest cross-shift PEF readings are insufficiently sensitive to diagnose occupational asthma.

Burge 2009 Comparative Study	6.5	556	Stenton method	Skin prick test (SPT), specific inhalation challenge testing	236 records from workers with independently diagnosed occupational asthma and 320 records from controls with asthma	Uncertain	Sensitivity and specificity of Stenton method	Records with ≥1 non-waking time point difference sensitivity 77% and specificity 93% for diagnosis of occupational asthma vs. independent diagnosis. Records with ≥2 had sensitivity of 67% and specificity of 99%.	"It does not usually identify the cause of occupation asthma, but can be used to confirm successful relocation as its specificity is high."	PEF measurements unsupervised and requested every 2 hours. Different PEF meters used in study. Data suggest using discrete lower boundary points for PEF may help diagnose occupational asthma.
Moore Occup Med 2009;59(6):413-7 Comparative Study	6.5	311	Serial measurement of peak expiratory flow	OASYS-2 Computer System	712 serial PEF records; 389 serial PEF records from workers diagnosed as having occupational asthma based on independent clinical investigations	Uncertain	Workday Specificity (WSP), Workday Sensitivity (WSE), Rest day Sensitivity (RSE), and Rest Day Specificity (RSP)	For 8 working days and at least 3 rest days, WSE: (≥8) = 62%, (7) = 92%, WSP: (≥8) = 57%, (7) = 96%, RSE: (≥8) = 34%, (7) = 89%, 100%. RSP: (≥8) = 60%, (7) = 81%.	"To be sensitive and specific in the diagnosis of occupational asthma, the area between the curves between the rest and workday curves, score requires 2-hourly PEF measurements on eight workdays and three rest days. This is a short assessment period that should improve patient compliance."	OA diagnosis was made prior to study by non-uniform methods (i.e., specific bronchial challenges, methacholine testing, and relevant history). Data suggest OASYS-2 computer system decreases the number of PEF recordings needed in serial PEF measurements.
Anees 2004 Comparative Study	5.5	141	Peak expiratory flow	None	81 workers with independently confirmed occupational asthma and 60 asthmatics without occupational exposure	Readings obtained for 4 weeks duration, 8 readings per day, at least 4 consecutive days in each work period.	FEV_1/FVC, sensitivity, specificity	Sensitivity 81.8% for records of 4 weeks' duration and 70% for those of 2 weeks' duration (specificity 93.8 and 82.4%, respectively).	"Peak expiratory flow records for the diagnosis of occupational asthma should be interpreted with caution if they do not satisfy the suggested minimum data quantity criteria."	OA diagnosis was made prior to study by non-uniform methods (i.e., history suggestive of OA, SIC, IGE or methacholine challenge test). Data suggest PEF measurements may aid in OA diagnosis.

Moore Occup Med 2009;59(6):418-23 Comparative Study	5.0	67	Serial measurement of peak expiratory flow	OASYS Computer System	67 peak flow records from 72 workers who had reported symptoms suggestive of occupational asthma	Uncertain	Comparison of records diagnosed with positive specific IgE, occupational rhinitis, non-occupational asthma, normal, or no diagnosis made between serial measurements and OASYS.	79% of workers with diagnosis of occupational asthma had confirmatory PEF results with OASYS.	"The OASYS program is a sensitive tool for the diagnosis of detergent enzyme occupational asthma, but the levels of exposure and specific IgE sensitization to enzymes do not affect the magnitude of PEF response in symptomatic workers."	OA diagnosis was made prior to study by non-uniform diagnostic criteria. Data suggest serial PEF analyzed by OASYS-2 system may aid in diagnosis of sensitization to detergent enzymes.
OTHER STUDIES										
Leroyer 1998 Comparative Study	9.0	20	Peak expiratory flow	FEV_1 un-supervised, specific inhalational challenge	20 patients with clinical history of occupational asthma	None	PEF values, FEV_1 values.	PEF: sensitivity = 73%, specificit y = 100% Unsupervised FEV_1: Sensitivity = 55%, specificity = 89%	"[U]nsupervised FEV1 is not more accurate than unsupervised PEF monitoring in the diagnosis of occupational asthma."	Small numbers – 55% (11/20) confirmed to have occupational asthma by SIC testing. Data suggest unsupervised FEV_1 not better than unsupervised PEF measures for diagnosing occupational asthma.
Weytjens 1999 Clinical Comparative Trial	9.0	57	Specific inhalational challenge, spirometry	Peak expiratory flow	37 with an immediate asthmatic response and 20 controls without an immediate asthmatic response	48+ hours	Spirometry PEF	Mean changes in PEF not different from changes in FEV_1 at any time ($p = 0.13$). 20% fall in PEFc to sensitivity = 92%, specificity = 95%, PPV = 97%.	"PEF, corrected for inaccuracies of the mini-Wright meters, is a satisfactory tool for detecting an immediate ≥ 20% fall in FEV1 after exposure to occupational allergens."	Agents used not well described. PEF measures monitored by research staff and not done independently by workers. Data suggest for immediate asthmatic responses PEFc are comparable to FEV_1 measures for decreased lung function.

Evidence for the Use of Nonspecific Bronchial Provocation Test

There are 9 high-[65, 85, 140, 141, 146, 152, 156, 160, 169] and 22 moderate-quality[50, 53, 69, 131, 132, 136, 137, 139, 144, 151, 153-155, 157, 158, 162, 170-175] studies incorporated into this analysis. There are 9 other studies in Appendix 1.[134, 143, 145, 176-181]

Author/Year Study Type	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
STUDIES NOT SPECIFIC TO OCCUPATIONAL ASTHMA										
Methacholine										
Hunter 2002 Diagnostic, Cross-sectional Study	10.0	110	Spirometry	Methacholine	N = 21 healthy control subjects (no symptoms of asthma and non-smokers) vs. n = 69 with asthma (have FEV_1 values >65%) vs. n = 20 diagnosed with asthma "pseudo-asthma."	None	Skin prick test. Peripheral blood eosinophil count. Twice daily PEF.	Spirometry: Sn: 61% Sp: 60% PPV: 84% NPV: 31% Accuracy: 61% +LR: 1.5 -LR: 0.65 PC20: Sn: 91% Sp: 90% PPV: 97% NPV: 78% Accuracy: 91% +LR: 9.1 -LR: 0.10	"[T]he methacholine PC20 is the most sensitive marker of mild asthma."	Pseudoasthma defined as no change in symptoms with withdrawal of treatment and symptoms improved with other treatments (i.e., GERD, OSA, dry cough). Tests done by blinded observer. Both asthma and pseudoasthma patients included. Data suggest methacholine is more sensitive and specific than spirometry and PEF.
Hedman 1998 Diagnostic Study	9.5	230	Rapid methacholine challenge test	Clinical diagnosis with ATS guidelines. PEF Spirometry	Patients referred to clinic due to dyspnea, wheezing or a cough of unknown reasons.	None	Sensitivity, Specificity, Positive Predicted Values, and Negative Predicted Values of MIC based only distribution of PD_{15} FEV_1 and PD_{20} FEV_1 in clinical material	Sensitivity: PD_{15} FEV_1 (84%), PD_{20} FEV_1 (77%) Specificity: PD_{15} FEV_1 (69%), PD_{20} FEV_1 (82%) PPVs: PD_{15} FEV_1 (50%), PD_{20} FEV_1 (60%) NPVs: PD_{15} FEV_1 (92%), PD_{20} FEV_1 (91%)	"The Bayesian analysis approach showed that the present rapid methacholine challenge is as capable as previous methods in distinguishing between normal and asthmatic subjects."	Patients diagnosed as asthmatics clinically and after spirometry. Data suggest rapid methacholine challenge testing has sensitivity of 77% and specificity of 82% with PD_{20} FEV_1.

								(p<0.0001)		
Di Lorenzo 2007 Diagnostic Study	9.0	115	Methacholine inhalational challenge test	Spirometry Allergen skin prick testing Peripheral blood eosinophil testing, serum ECP levels, sputum induction after recovery.	60 patients with mild asthma (Asthma Patients), 30 patients with GERD and asthma-like symptoms (GER Patients), 25 control (Healthy Control Subjects)	None	FEV_1/FVO ratio, Maximum PEF A%M, MCh PC_{20}/FEV_1, Blood Eosinophils, Serum ECP levels, Induced sputum eosinophils	For primary outcomes: FEV_1/FVC ratio (Healthy Control Subjects: 81.3±1.3 vs. Asthma Patients: 76.6±0.4, p<0.001; Asthma Patients: 76.6±0.4 vs. ECP levels (Healthy Control Subjects: 4.6±0.8 vs. Asthma Patients: 17.4±0.8, p<0.001; Asthma Patients: 17.4±0.8 vs. GER Patients: 5.6±0.8, p<0.001).	"[T]he MCh PC_{20}/ FEV_1 and the induced sputum eosinophil counts are the most sensitive and specific markers of mild bronchial asthma, able to discriminate asthma from asthma-like symptoms by GERD."	Blinded observer but some details unclear. Study participants referred to specialty clinic. PPV and NPV influenced by prevalence of disease of this sub-population. Data suggest methacholine challenge testing and sputum eosinophils are more sensitive and specific tests in diagnosing asthma.
Goldenstein 2001 Diagnostic Study	8.5	121	Methacholine Inhalation Challenge (MIC)	Peak Expiratory Flow Variation (PEFvar), Post-bronchodilator, FEV_1 (post BD FEV_1)	At least 7 years old, English speaking, and had recurrent (≥3 months) asthma-like symptoms	3-4 weeks	Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value of MIC, Post-BD FEV1, Best Mean Daily PEFvar, and Best Period PEFvar.	Sensitivity: MIC = 85.71%, Post-BD PEFvar = 53.7%. Specificity: MIC = 100%, Post-BD FEV_1 = 100%	"Based on our results, relying on PEFvar as a diagnostic tool for asthma as suggested by NHLBI may lead to underdiagnosis, undertreatment, and/or delay in early intervention. Our findings warrant a reconsideration of the NHLBI guidelines recommendation of the utility of PEFvar."	Duration that participant was experiencing symptoms unclear. Data suggest methacholine challenge testing has most reliable sensitivity and specificity vs. PEF and bronchodilator testing.
Cirillo 2006 Cross-sectional Study	7.5	726	Methacholine Inhalation Challenge (MIC)	Spirometry	680 males, 46 females, Navy soldiers referred to Navy Hospital, La Spezia, Italy, for	Uncertain	Difference (DFF) and the Ratio (RFF) between FEV1 and $FEF_{25-75\%}$	Mean DFF increased significantly in patients with negative (9.0±7.2) to severe (28.1±7.8)	"[I]n the context of a normal FEV1 in allergic patients, a DFF > 20 (or an RFF > 1.24) may be considered as an approximate predictor of the existence of	With wide range of diagnoses, difficult to ascertain which subgroup if any had more robust results. Data suggest FEF 25%-75% when compared to FEV1

					periodic first visit.			responses to BHR testing (p<0.001).	moderate-to-severe BHR. Of course, these indexes are 'soft data' and must be used as first approximation only."	can help predict a positive response to methacholine challenge testing.
Yurdakul 2005 Diagnostic Study	7.5	123	Skin prick test, blood tests	Spirometry, non-specific bronchial challenge test with methacholine.	100 patients admitted to asthma outpatient clinic and 23 non-smoking healthy control subjects.	Two weeks	Spirometry, PEF monitoring, methacholine, aeroallergens, total IgE, and eosinophil count.	Methacholine challenge test had highest sensitivity (96.5%) vs. other tests. Specificity (78.4%) of methacholine lower than total IgE (84.6%), reversibility test (95%), and PEFR variability (81.8%).	"[M]ethacholine airway responsiveness is the most valuable diagnostic tool for asthma. In addition, there is significant correlation between methacholine airway responsiveness and some patient symptoms."	Good description of study. Larger study population, though not occupational asthma. Data suggest methacholine challenge testing helpful in diagnosis of asthma.
Nensa 2009 Diagnostic Study	6.5	155	Spirometry with methacholine challenge	Body plethysmo-graphy with methacholine challenge	Patients with bronchial asthma undergoing methacholine challenge testing	1 period of testing	FEV_1 and body plethysmo-graphic data	Body plethysmography showed a positive MCH challenge test based on sReff in 113/155 (75%) participants. Spirometry showed a positive MCH challenge test based on FEV_1 fall of >20% in 50/155 (32%)	"[W]e would recommend sReff and sGaw as the reliable parameters for classification of AHR. Additional investigations on healthy subjects and patients with asthma and COPD should be performed to compare sensitivity and specificity of body plethysmography and forced spirometry for MCH-challenge tests."	Not specific to occupational asthma. Included patients with chronic cough. No specificity or sensitivity calculated. Data suggest body plethysmography is abnormal more often with a methacholine challenge vs. spirometry in healthy patients, those with chronic cough, and those with bronchial asthma.
Histamine vs. Methacholine										
Higgins 1988 Controlled Clinical Trial	5.0	203	Histamine challenge test	Methacholine challenge test	108 random tested non-asthmatics and 95 people who reported at least a wheeze in the past year	None	PD_{20}	More subjects had a measurable PD_{20} with methacholine. 108 non-asthmatics = 25 vs. 11, p<0.01; 95 reported with	"We have shown that when used in an epidemiological study methacholine produces more measurements of non-specific bronchial reactivity	No OA. No real diagnosis of asthma in 95 people who had reported a "wheeze or asthma" by questionnaire sometime over the past 12 months.

								wheeze = 67 vs. 48 p<0.01.	than histamine, with less unwanted effects."	
Hypertonic Histamine										
Koskela 2005 Diagnostic Study	6.0	47	Hypertonic histamine challenge	Skin prick test, Challenge solution of hypertonic saline, isotonic histamine, and hypertonic histamine	N = 15 healthy subjects vs. n = 16 asthmatic subjects (steroid-naïve) vs. n = 16 asthmatic subjects (with steroid treatment)	Healthy subjects between April and August. Asthmatic subjects between September and April.	FEV_1 and PEF values for challenge tests	Isotonic histamine: At 56%, 100%, & 77%; 1.1 (0.5-2.7) vs. Hypertonic histamine: at 81%, 100%, and 90%; 0.5(0.2-1.2) mg/ml; p = 0.047. Results as stated are not interpretable.	"[T]he diagnostic accuracy of histamine challenge can be improved by using a hypertonic challenge solution. Hypertonic histamine challenge may also be more capable to detect the effects of inhaled corticosteroid treatment than the conventional, isotonic histamine challenge."	Small numbers in each group. Baseline differences in age and smoking. Co-interventions not well described besides smoking and inhaled steroids. Data suggest in steroid naive patients, hypertonic histamine challenge is more sensitive than isotonic histamine.
Purokivi 2008 Diagnostic Study	5.0	138	Hypertonic Histamine Challenge (HHC)	HHC provocation based asthma diagnosis vs. FEV diagnosis	N = 30 clinically diagnosed asthmatics, n = 26 healthy control subjects, n = 82 non-asthmatic symptomatic subjects	Ultrasound nebulizer at 0.44-0.48 mL/min output with hyper-tonic phospate aerosol for 2 mins/kg. Challenge continued until FEV ≥20% from baseline.	Cough/con-centration ratio (CCR) in mg/mL, coughing frequency (CF), ROC curves, Area under curve (AUC) values, used to assess sensitivity, specificity, and accuracy.	CCR (asthmatics): 302 (166-562) mg/mL, CCR (symptomatic controls): 29.5 (20-43.7); p<0.001. CF>0.5 % (healthy controls): 6.31 (3.47-11.5) Asthmatic subjects vs. healthy controls = disparity of 80% sensitivity, 96% specificity. Diagnostic accuracy: p<0.001.	"[T]he cough response to hyperosmolar airway challenges can be utilized in the differential diagnosis of asthma. Since this response is independent of patient cooperation, it may be especially useful among subjects who cannot perform spirometry in a reliable manner."	Baseline characteristics minimal, but similar. Co-interventions and medications not well described. Data suggest calculation of coughing vs. concentration of histamine during histamine challenge test may be useful in diagnosing asthma and other lung diseases vs. healthy patients.
Mannitol										
Anderson 2009	8.5	509	Mannitol, Methacholine	Exercise, clinical diagnosis	Age 5-50 years. FEV_1 >70%	5 visits	Exercise test: ≥10% fall in FEV_1	Sensitivity/ specificity of mannitol to identify	"In this group with normal FEV1, mild symptoms, and mild	Not occupationally related. Ages of participants were 5-

Diagnostic Study					78% atopic Clinically suspected to have exercised induced broncho-constriction		Mannitol: 15% fall in FEV_1 at $\leq$ 635 mg cumulative dose or >10% fall in FEV_1 between tests; MCC: PC_{20} <16	EIB was 59%/65%, for methacholine it was 56%/69%. BHR mild. Mean EIB % fall in FEV_1 in subjects positive to exercise 19%, (SD 9.2), mannitol PD_{15} 158 mg (CI: 129, 193), and methacholine PC_{20} 2.1 mg/ml (CI: 1.7, 2.6). Prevalence of BHR same: exercise (43.5%), mannitol (44.8%), methacholine (41.6%) with test agreement between 62-69%. Sensitivity and specificity for clinician diagnosis of asthma 56%/73% for mannitol, 51%/75% for methacholine. Sensitivity increased to 73% and 72% for mannitol and methacholine when 2 exercise tests were positive.	BHR, the sensitivity and specificity for both mannitol and methacholine to identify EIB and a clinician diagnosis of asthma were equivalent, but lower than previously documented in well-defined populations."	50 years of age. Blinding done of the mannitol and methacholine assessors. Co-interventions well described. Data suggest Mannitol and Methacholine have similar SP and SN in diagnosing mild exercise induced broncho-constriction.
Koskela 2004 Diagnostic Study	6.5	47	Mannitol Challenge	Cold Air Challenge, Histamine Challenge, and skin prick test	N = 10 healthy subjects vs. n = 37 asthmatic patients	Repeated after 3 and 6 months of treatment of budeso-nide	FEV_1 values for Mannitol Challenge	Asthmatic patients coughed mere during the Mannitol Challenge than healthy subjects. Cough-to-dose ratio (CDR) is 8.3 coughs per 100mg [95% CI, 0.4 to 3.0]; p<0.0001.	"Coughing during mannitol challenge is associated with asthma and occurs independently of bronchoconstriction … [T]he measurement of the mannitol-provoked coughing may be	Small numbers. Patients were recently diagnosed and had more cough + sputum than dyspnea + wheeze. Data suggest mannitol more sensitive in demonstrating

									useful both in the diagnosis of asthma as well as in the assessment of the effects of an anti-inflammatory therapy on this common disorder."	airway hyperresponsivenes s than cold air challenge.
Miedinger 2010 Diagnostic Study	6.5	284	Mannitol Challenge and Methacholin e Challenge with BPT (Bronchial provocation test)	Skin prick test, spirometry, questionnaire , and oral exhaled nitric oxide (FeNO)	Military subjects	January 2007 – October 2007	FEV_1 and FVC values with spirometry, methacholine, and mannitol challenge tests	BPT with mannitol and methacholine have similar sensitivity and specificity. Methacholine PD_{20}: sensitivity 43%, specificity 92%, PPV 55%, and NPV 88% Mannitol PD_{15}: sensitivity 41%, specificity 93%, PPV 55%, NPV 88%.	"BPT with mannitol has a sensitivity and specificity similar to methacholine for the diagnosis of physician-diagnosed asthma in military conscripts but is less costly to perform without the need to use and maintain a nebulizer."	Physician diagnosed asthma as "gold standard." Recruits ages 18-19 so many may not have seen MD. Data suggest BPT with mannitol has similar sensitivity and specificity as methacholine testing.
Lipworth 2012 Prospective, Randomized Parallel-Group Trial	6.0	157	Mannitol	Clinical investigation. Spirometry PEF FeNO	Patients with mild to moderate asthma	12 months	Inhaled corticosteroid dose. Mannitol challenge testing		"Using mannitol resulted in exposure to a higher dose of ciclesonide, which was associated with equivocal effects on exacerbations without associated adrenal suppression."	Good baseline characteristics given. Randomized trial. Study of general population with asthma. Question was for control of asthma using Mannitol testing, not diagnosis of asthma. Data suggest mannitol testing can be used to help titrate medication in mild to moderate asthma but in this study resulted in a higher dose of steroid use compared to clinical judgment with no significant difference in clinical outcomes.

Anderson 1997 Diagnostic Study	5.5	50	Mannitol	Hypertonic saline challenge. Methacholine	43 patients with asthma; 7 healthy controls	None	Challenge testing spirometry		"[T[his study clearly demonstrate that a dry powder preparation of mannitol…can provoke airway narrowing in asthmatic subjects who are sensitive to a wet aerosol preparation of 4.5% NaCl and methacholine."	Methacholine (considered gold standard) performed on 25/43 (58%) cases. All cases had hypertonic saline testing performed; 7 controls did not have methacholine or hypertonic saline testing. FEV_1 at baseline ranged from 54.2-129.0 % predicted. Data suggest mannitol challenge is a possible test for asthma in mild to moderate asthmatics.
STUDIES TARGETING OCCUPATIONAL ASTHMA										
Methacholine vs. SIC, symptoms, need for medications, or specific sensitization										
Munoz 2004 Diagnostic Study	8.0	26	Specific inhalational challenge by pour method	Skin prick test, Total IgE levels, Methacholine Challenge Testing	8 patients with diagnosed OA due to persulphate salts vs. 8 with asthma and no prior exposure to persulphate salts vs. 0 healthy patients with no history of asthma	None	Spirometry after challenge testing	*Methacholine testing*: 6/8 (75%) of patients with OA had positive test. 7/8 patients with asthma (88%) had positive methacholine test. *Pour test*: Sensitivity = 100% Specificity = 87.5%	"The procedure described in this study allows patients with bronchial asthma to be distinguished from those with persulphate salt induced OA."	Small numbers. No details on how they determined the 8 patients with asthma did not have exposure to persulphate salts. Data suggest methacholine testing is a valid test for patients with persulphate salt induced OA.
Dellabianca 1996 Diagnostic Study	8.0	40	Ultra-sonically nebulized distilled water	Specific inhalation challenge Methacholine	Patients referred to center because of probable occupational asthma due to low molecular weight chemicals	One period of testing	FEV_1 and FCV values during the different tests	*Ultrasonically nebulized distilled water*: Sensitivity: 65% Specificity: 80% *Methacholine*: Sensitivity: 75%-90%	"[I]n the assessment of low molecular weight chemical-induced asthma diagnosed with the specific challenge as the "gold standard," UNDW challenge proves	Patients diagnosed by specific inhalation challenge testing, not as well described as other testing. Data suggest combination of methacholine and ultrasonically

								Specificity: 60% *Combination of UNDW and methacholine*: Sensitivity: 85% Specificity: 85%	more specific than methacholine for occupational asthma, but is considerably less sensitive."	nebulized distilled water results in higher sensitivity and specificity for occupational asthma.
Paggiaro 1986 Diagnostic Study	6.5	114	Challenge test with toluene diisocyanate (20 ppb for 15 minutes). Workers classified by reactions to challenge (immediate, late, and dual).	Methacholine challenge test	114 furniture workers with bronchial asthma induced by toluene diisocyanate.	8 hours after challenge	PD_{20}, FEV_1	Late reactions in non-smoking subjects was significantly greater than the other two groups (immediate and dual) ($p<0.01$).	"[A]sthmatic subjects sensitive to toluene diisocyannateose with a dual reaction at the time of diagnosis have a greater degree of airway obstruction and more evident non-specific bronchial hyper-responsiveness."	All had prior diagnosis of TDI asthma. Non-specific inhalational challenge test done differently on different participants making conclusions difficult. Data suggest smoking and atopy may affect hyperreactivity reactions with specific inhalational challenge testing.
Moller 1986 Diagnostic Study	6.5	12	Inhalation challenge with toluene diisocyanate (TDI)	Pulmonary function tests (PFT), bronchial challenge test with methacholine , Spirometry	12 patients with possible TDI asthma.	Uncertain	FEV_1, FVC, (PD_{20})	5 workers showed no significant bronchospasm to TDI challenges at high or low doses; but 3/5 had positive methacholine tests. 8 of 12 had serologic measurements of specific IgE to TDI-HSA, MDI-HSA, or HDI-HSA.	"In the present study, 12 workers with suspected TDI asthma were evaluated by bronchial challenge to TDI. Seven persons demonstrated sensitivity to low levels of TDI (reactors), confirming isocyanate sensitization."	Small numbers. Addressed removal from work. Co-interventions not well described. Several workers with clinical history suggestive of asthma to TDI did not react on SIC. Data suggest methacholine test is nonspecific enough that 60% of patients negative to SIC still positive to NSBP testing.
Sastre 2003 Diagnostic Study	6.5	22	Specific inhalational challenge with isocyanates	Methacholine challenge	22 patients with a clinical history of di-isocyanate induced asthma	None	Spirometry after and methacholine testing	1st round of testing – 13/22 (59%) had positive response. After 2nd round, 2/22 (11%) had negative response PC_{20}: 2/9 with	"PC20 should be systematically assessed before and after isocyanates. This is especially relevant in the absence of	Small numbers. No controls for non-occupational asthma possibilities. Data suggest PC20 may help decrease false

								negative on round 1, PC_{20} fell within asthmatic range after test.	significant changes in FEV1 during."	negatives in testing with isocyanates.
Shirai 2003 Diagnostic Study	6.5	21	Inhalation challenge. Non-specific challenge tests to metha-choline	Immuno-logical assessment	Patients suspected of having green tea induced asthma on basis of a suggestive clinical history (had worked at different green tea factories).	None	EGCg; Sensitivity; FEV_1; PC_{20}	Skin sensitivity to EGCg had positive correlation with EGCg; PC_{20} (r = 0.760; p = 0.0048), and methacholine PC_{20} had positive correlation with EGCg PC20 (r = 0.717, p = 0.0108).	"[B]ronchial responsiveness to EGCg can be highly satisfactorily predicted by skin sensitivity to EGCg and bronchial responsiveness to methacholine."	Small numbers. Data suggest use of skin prick testing in conjunction with methacholine challenge test may aid in diagnosis of green tea related asthma with methacholine challenge test.
Cote 1990 Diagnostic Study	6.0	48	Asthma symptoms; requirement for anti-asthma medications	Spirometry with methacholine challenge	Male workers with diagnosis of occupational asthma to red cedar who stayed in same industry after diagnosis.	Minimum 1 year, average of 6.5 years	Asthma signs and symptoms after continued exposure	10.4% improved, 62.5% were stable, 37.5% worsened. None of the patients completely recovered.	"[A]mong cedar asthmatics who remained exposed to cedar dust for an average of 6.5 yr, over one-third showed marked deterioration of their asthma symptoms. There is also no way to predict who will deteriorate. A decrease in the amount of exposure to cedar dust does not prevent deterioration of asthma. This suggests that the ideal management of cedar asthma is removal from exposure."	All diagnosed with occupational asthma by testing then followed forward. Data suggest continued exposure to cedar dust in confirmed asthmatics prevents resolution of symptoms and worsens symptoms in 37.5%. MCC test used to monitor course of asthma.
Vogelmeier 1991 Diagnostic Study	6.0	43	Specific inhalational challenge test to isocyanates	Methacholine challenge test	A = 19 workers clinical history consistent with occupational asthma vs. B = 14 workers	None	Methacholine then spirometry	A = 13/19 (68%) positive, B = 3/14 (21%) positive, C = 1/10 (10%) positive. Methacholine:	"[T]he methacholine test in patients with suspected diisocyanate-induced asthma is only of limited	Small numbers. There were 21% and 10% false positives on testing. Data suggest methacholine testing

					with asthma not exposed to isocyanates vs. C = 10 healthy workers without asthma			A = 10/19 (53%), B = 14/14 (100%), C = 0/10 (0%)	diagnostic value; at least in doubtful cases a diisocyanate challenge should be performed."	not sufficient alone to diagnose diisocyanate-induced asthma.
Karol 1994 Diagnostic Study	5.5	63	Methacholine challenge test	SIC IgE to TDI	63 patients exposed to TDI with symptoms consistent with occupational asthma	None	Methacholine challenge testing SIC IgE levels	No difference in geometric mean of serum IgE level for responders and non-responders at (68 vs. 69 IU/ml).	"[O]ccupational history was not a good indicator of current sensitivity to TDI. Methacholine responsiveness was a good predictor of response to TDI. TDI-specific antibodies of both the IgE and IgG classes, assessed with well characterized haptenated serum albumin conjugates, were found in only a few individuals… suggest that the early-onset response might reflect an IgE-mediated mechanism, whereas the mechanism of the late onset response is yet uncertain."	Small numbers. All suspected to have an adverse response to TDI. No mention of co-interventions or other prior asthma testing. Data suggest patients with airway hyper-responsiveness with methacholine and having symptoms consistent with TDI asthma more likely to have positive result with SIC to TDI.
Lam 1979 Diagnostic Study	5.5	193	Methacholine testing	Skin prick testing.	86 patients with OA – 33 nonatopic healthy volunteers; 30 non-occupational asthma patients; 17 chronic bronchitis	None	Spirometry in relation to methacholine challenge test. Comparison to previous spirometry	Patients with non-occupational asthma had lower FEV_1 than those with occupational asthma ($p<0.001$). Patients with occupational asthma removed from exposure for a mean of 0.8 years	"The findings in this study of a decrease in bronchial reactivity after removal from exposure and an increase following re-exposure to the offending agent suggest that nonspecific	Testing protocol varied by patients making a comparison difficult. Baseline characteristics different between groups. Not all had testing to red cedar. Data suggest bronchial

					patients; 16 atopic non-asthmatics			had better lung function than currently exposed group (p<0.02).	bronchial reactivity is the result rather than the predisposing factor in occupational asthma."	hypersensitivity a result of occupational asthma, and removal from exposure improves lung function.
Park 1998 Diagnostic Study	5.0	70	Serum Specific IgE	Skin prick test Broncho-provocation test SDS-PAGE	N = 43 male workers in animal feed industry exposed to grain dust composed of corn, rye, wheat, barley). 31/43 were process workers who mixed and carried materials (intermediate exposure group and high exposure group according to exposure intensity measured by dust air sampler); 12/43 office workers classified as low exposure group. 27 Controls never exposed to grain dusts and demonstrated negative skin tests to 50 common inhalant allergens.	Testing over 2 different days.	IgE levels. ELISA results. Skin prick test. Inhalational challenge testing. Symptom questionnaire.	7/15 (47%) employees with respiratory symptoms had airway hyper-responsiveness to methacholine. 6/15 (40%) had positive grain dust inhalational challenge testing. IgE testing positive in 6/15 (40%) symptomatic. Smoking had association with IgE test. (p<0.05).	"[G]rain dust can induce an immunologic, IgE-mediated response in exposed workers."	Differing tests protocols as symptoms determined testing protocol. Cases defined by possible exposure and results of symptoms questionnaire. No specificity or sensitivity for IgE testing. Data suggest IgE tests more likely positive if exposed to grain dust and have positive symptom questionnaire.

Histamine vs. SIC, symptoms, need for medications, or specific sensitization										
Vandenplas 2001 Diagnostic Study	9.0	45	Natural rubber latex clinical diagnostic testing	Question-naire Immunologic testing skin prick test. Spirometric lung function tests (PC20 values <16 mg/mL indicative of bronchial hyper-responsive-ness) with NRL challenge (SIC) and other common asthma inducing present at occupation.	45 with suspected occupational asthma, exposed to airborne NRL	Not specified	Sensitivity, specificity, positive predictive values, negative predictive values (p = 0.05 considered significant)	Thirty-one demonstrated positive SIC results to NRL gloves. At baseline (%): sensitivity was 87, specificity was 14, PPV was 75, and NPV was 50. Non-specific bronchial responsiveness (NSBH) (%): sensitivity was 90, specificity was 7, PPv was 75, and NPV was 25.	"[C]ombining the assessment of NSBH and immunologic tests with the open questionnaire is not reliable as an SIC in diagnosing NRL-induced [occupational asthma] among subjects referred to demonstrate the causal relationship between asthma and occupational exposure to NR, although measurement of NSBH and immunological tests are useful for excluding NRL-induced occupational asthma."	Small numbers. Evaluated workers' compensation cases and found no correlation in the present of latex induced asthma. Data suggest a combination of clinical history and skin prick testing have greatest sensitivity and specificity vs. SIC for occupational asthma compared to histamine challenge testing.
O'Brien 1979 Diagnostic Study	5.0	63	TDI inhalation challenge test	Histamine inhalation test and exercise test	63 workers occupationally exposed to toluene di-isocyanate (TDI).	Uncertain	FEV_1, FVC, PEFR	Differences in histamine inhalation tests between TDI highly sensitive with asthmatic reactions to concentrations of 0.001 ppm and TDI non-sensitive groups with reactions to concentrations of 0.001-0.02 ppm (p<0.005) and TDI non-sensitive group (p<0.01).	"[S]ubjects giving asthmatic reactions to TDI tests, seventeen out of thirty-one (55%) had increased histamine reactivity and eighteen out of twenty-nine (62%) had exercise-induced asthma."	Not all received same testing protocols making comparisons difficult. No mention of co-intervention. Data suggest TDI may induce asthma and spirometry, histamine inhalational testing, and specific inhalation challenge testing all aid in diagnosis of asthma.
Mannitol vs. SIC, symptoms, need for medications, or specific sensitization										

Koskela 2003 Diagnostic Study	8.0	37	Skin prick test, IgE testing, Histamine challenge, Exhaled NO measure-ment, Mannitol challenge, sham inhalational challenge, PEF(twice daily for a week before testing and every 4 hours during testing)	Bovine specific inhalational challenge	37 dairy farmers with suspected occupational asthma to bovine dander who were referred for bovine dander specific inhalational challenge testing	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other testing results	11/37 (30%) classified as positive response to b. *Skin prick test:* r = 065 (p = 0.0001) Sn = 100% Sp = 50% PPV = 46% NPV = 100% *IgE:* Sn = 82% Sp = 100% PPV = 100% NPV = 93% *Histamine:* Sn = 82% Sp = 65% PPV = 50% NPV = 89% *Mannitol:* Sn = 20% Sp = 94% PPV = 67% NPV = 89% *Exhaled NO:* Sn = 27% Sp = 77% PPV = 33% NPV = 71%	"[A]lthough is the 'gold standard' for the documentation of occupational asthma, the high prevalence of respiratory symptoms and bronchial hyper reactivity in farmers may lead to a very high demand for access to this expensive test… Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bs."	Patients with suspected occupational asthma by clinical presentation and spirometry. Data suggest patients with positive SPT and bIgE testing do not require SIC testing.
Miedinger 2007 Diagnostic Study	7.5	101	Mannitol Challenge and Metha-choline Challenge with bronchial provo-cation test	Skin prick test, spirometry, questionnaire, and oral exhaled nitric oxide (FeNO)	101 firefighter subjects being tested for asthma. Diagnostic standard for asthma wheezing plus hyper-responsiveness to bronchial challenge testing.	Uncertain	FEV_1 and FVC values with spirometry, methacholine and mannitol challenge tests	Bronchial airway challenge with mannitol (PD_{15}) was more sensitive (92%), specific (97%), PPV (86%), and NPV (98%) when testing for asthma.	"Asthma was considerably underdiagnosed in firefighters. The combination of a structured symptom questionnaire with a bronchial challenge test allows to identify patients with asthma and should routinely be used in the assessment of active firefighters and may be of help when	All firefighters. Data suggest asthma under diagnosed in firefighters. Mannitol challenge testing had highest sensitivity and specificity.

									evaluating candidates for this profession."	
Lemiere 2012 Diagnostic Study	5.0	30	Mannitol Metha-choline FeNO Sputum	Historic diagnosis of OA by SIC	30 patients previously diagnosed with OA to different substances. Removed from exposure.	None	Spirometry FeNO Sputum cell	50% were never smokers. 9/30 (30%) had positive mannitol test. 13/30 (43%) had PC20 <4. Positive mannitol had lower FEV_1 (p = 0.01), higher fraction of exhaled nitric oxide levels (p = 0.03).	"[T]he mannitol BPT is a useful test for assessing the impairment/ disability and disease activity of workers with a previous diagnosis of OA because this test has the ability to differentiate the subjects according to the severity of airway responsive-ness and collection of sputum to be made at the same time."	Patients diagnosed previous with occupational asthma and removed from work. Various substances included in diagnosis of OA. Baseline characteristics showed baseline FEV_1 as 95.9-101.8 of predicted for all participants. Data suggest mannitol is not as sensitive as methacholine but may be more specific.

Evidence for the Use of Specific Immunological Testing

There are 6 high-[141, 185, 197, 200, 210, 211] and 12 moderate-quality[142, 162, 182, 183, 186, 198, 199, 202, 208, 209, 212, 213] studies incorporated into this analysis. There are 5 other studies in Appendix 1.[143, 188, 194, 206, 207]

Author/Year Study Type	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
High Molecular Weight Antigens										
Van Kampen 2008 Diagnostic Study	8.5	107 bakers	IgE to wheat and rye flour	SIC SPT Symptoms	Bakers	None	IgE STP SIC	In bakers with OA: IgE to wheat Sn: 87% Sp:68% PPV: 74% NPV: 82% IgE to Rye Sn: 61% Sp: 94% PPV: 95% NPV: 56% SPT to wheat Sn: 68% Sp: 74% PPV: 74% NPV: 68% SPT to rye Sn: 78% Sp: 84% PPV: 91% NPV: 66%	"Both flour specific IgE and SPT with flours, can be used effectively for the prediction of the outcome of specific challenge tests with flours in symptomatic bakers."	Workers were bakers with symptoms of rhinitis, cough, wheezing, and shortness of breath with a mean age of 40 years. All were seeking claims for compensation due to occupational asthma. A positive challenge test was defined as either nasal or bronchial reaction. Data suggest SPT and/or IgE can be used to aid in diagnosis of bakers' allergy to wheat or rye flours. This data not specific to just OA, but also included rhinitis symptoms.
Wiszniewska 2011 Diagnostic Study	8.5	151 diagnosed with OA by SIC; 287 had rhinitis symptoms	IgE to flours	SPT SIC Spirometry NSBP Nasal Lavage	Bakers	None	IgE STP Spirometry Symptoms	In baker's with OA: *SPT* Sn: 41.7% Sp: 85.9% PPV: 73.3% NPV: 61.4% *IgE* Sn: 61.6% Sp: 77.3% PPV: 71.5% NPV: 68.5%	"Results in our study indicate that neither SPTs to occupational allergens nor evaluation of serum allergen-specific IgE alone or combined with nonspecific bronchial hyper-reactivity are characterized by	Study included workers with rhinitis and OA. Data suggest that IgE and SPT can be useful in the diagnosis of both occupational asthma and rhinitis in bakers.

									sufficient diagnostic accuracy to replace specific inhalational challenge test.”	
Park 2001 Diagnostic Study	8.0	151	Serum specific IgE to reactive dyes; skin prick test	Bronchial provocation testing with methacholine, specific inhalational challenge	42 patients with occupational asthma from reactive dyes; 93 asympto-matic factory workers; 16 unexposed controls	None	Skin prick test, IgE testing	Skin prick test: Sens: 76.2% Spec: 91.4% PPV: 80% NPV: 89.5% IgE testing: Sens: 53.7% Spec: 86% PPV: 62.9% NPV: 80.8% Combined: Sens: 83.3% NPV 91.7%	“SPTs and ELISAs may be valuable tools for screening, diagnosis, and monitoring occupational asthma resulting from exposure to reactive dyes; these two tests might complement each other for such a diagnosis.”	Well-defined cases and controls. Data suggest a combination of SPT and IgE is more sensitive and specific than either test individually.
Koskela 2003 Diagnostic Study	8.0	37	IgE testing to bovine dander	Bovine specific inhalational challenge (bSIC); skin prick test; Histamine challenge exhaled NO measurement Mannitol challenge Sham inhalational challenge; PEF, twice daily for a week	37 dairy farmers with suspected occup-ational asthma to bovine dander who were referred for bovine dander specific inhalational challenge testing	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other testing results	Skin prick test: Sn = 100% Sp = 50% PPV = 46% NPV = 100% IgE: Sn = 82% Sp = 100% PPV = 100% NPV = 93% Histamine: Sn = 82% Sp = 65% PPV = 50% NPV = 89% Mannitol: Sn = 20% Sp = 94% PPV = 67% NPV = 89	“Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bSICs." “A diagnosis of occupational asthma from exposure to bovine allergens could be made without performing a bSIC in asthmatic patients with a bIgE concentration of >5 IU/L.”	Patients with suspected occupational asthma by clinical presentation and spirometry were referred for testing. Data suggest patients with a positive SPT and high specific bIgE levels do not require SIC bovine testing to diagnose OA.
Walusiak 2004	6.5	287	IgE to flour	SPT SIC NSBP	287 bakers	2 years	SPT IgE SIC	25/287 (8.7%) diagnosed with OA by SIC.	“The results of our study indicate that SPT to common	Baseline testing done during first month of training, meaning there

Diagnostic Study				Symptoms			Symptoms	23/25 (92%) had positive SPT and IgE testing.	occupational allergens should be performed in apprentice bakers before starting vocational training."	was at least some exposure to work allergens before testing. Average age of worker at study start 16.2 years. Data suggest hypersensitivity to occupational allergens develops during vocational training and SPTs for common allergens, and elevated IgE level, are significant risk factors for development of OA.
Park 1991 Diagnostic Study	5.5	309	IgE to reactive dyes	Broncho-provocation tests, skin prick tests	78 (25.2%) employees had work-related lower respiratory symptoms associated with or without nasal, skin, or eye symptoms.	None	IgE	25 (8.1%) of 309 demonstrated >2+ of A/H ratio to Black GR, 21 (6.8%) reacted to Orange 3R. RAST-inhibition tests of black GR had significant inhibitions by black GR-human serum albumin conjugate and minimal inhibitions by unconjugated black GR. Orange 3R	"These findings suggested that reactive dyes could induce immunologic responses, most likely IgE-mediated."	Author addressed whether reactive dyes induced a type 1 immune response. Co-interventions and past medical history of participants not well described. Not all participants appeared to receive the same testing protocol. Data suggest reactive dyes may induce an IgE mediated immunologic response in exposed workers.
Tiikkainen 1990 Diagnostic Study	5.0	62	IgG to wheat flour	IgE SPT SIC	Bakers with allergic symptoms	None	IgG SIC results Symptoms	36/42 (86%) cases considered to have a wheat flour allergy based on symptoms and test results. Overall level of IgG to wheat flour higher in exposed bakers	"We conclude that the development of IgG subclass antibodies to flour depends particularly on antigen exposure, but the role of these antibodies in the pathogenesis of environmentally	There was a wide range of time exposed to wheat flour in the cases. No good baseline data on cases or controls. Data suggest IgG levels indicate exposure to wheat flour, but do not correlate with allergic symptoms or a

								than controls. No correlation found between IgG levels and symptoms.	induced allergy remains uncertain."	diagnosis of wheat flour allergy.
Doekes 1999 Diagnostic Study	5.0	41	IgE to Asper-gillus niger derived phytase	Symptoms	Feed plant workers exposed to phytase in an animal feed plant with reported respiratory symptoms. Internal and external controls.	None	IgE levels Symptoms Air sampling	External controls: 1/19 (5%) had a positive result. 3/19 (16%) had at least a borderline result. Internal controls: 1/11 (10%) had a positive result. 3/11 (27%) had at least a borderline result. Exposed cases: 4/11 (36%) had a positive result. 8/11 (73%) had at least a borderline result.	"Phytase is a potentially important new occupational allergen causing specific IgE immune responses among exposed workers."	Small number of cases. No baseline characteristics to compare cases and controls. No diagnostic test done to confirm diagnosis. Data suggest IgE assays could be useful in the diagnosis of respiratory allergies in exposed workers to Aspergillus niger phytase. Relationship with common mold allergy is not clear.
Park 1998 Diagnostic Study	5.0	70	IgE to grain dust	Skin prick test; Broncho-provocation test; SDS-PAGE	Workers of animal feed industry (n=43 exposed to grain dust composed of corn, rye, wheat, and barley and male). Of 43, 31 were process workers who mixed and carried materials (intermediate exposure group and high	Testing over 2 different days.	IgE levels. ELISA results. Skin prick test. Inhalational challenge testing. Symptom questionnaire	7/15 (47%) employees with respiratory symptoms had airway hyper-responsiveness to methacholine. 6/15 (40%) had positive grain dust inhalational challenge testing. IgE testing positive in 6/15 (40%) Smoking had association with IgE test. ($p<0.05$).	Grain dust can induce an immunologic, IgE-mediated response in exposed workers."	Different protocol for different participants. Cases defined by possible exposure and results of symptoms questionnaire. Data suggest IgE tests more likely positive if exposed to grain dust and have positive symptom questionnaire.

					exposure group according to exposure intensity measured by dust air sampler); 12/43 were office workers and classified as low exposure group. Controls (n = 27) never exposed to grain dusts and demonstrated negative skin tests to 50 common inhalant allergens.					
Douglas 1995 Diagnostic Study	4.5	24	IgE levels to salmon	Spirometry, PEF pre and post shift; Symptom questionnaire	24 patients with occup-ational asthma in automated salmon processing, in group of 291 employees	One period of testing	IgE antibody production	Associations with increasing symptom severity: IgE levels: (p<0.001); IgG levels: (p = 0.037). Occupational asthma higher in workers who smoked compared to non-smokers (p<0.001).	"We have shown an 8.2% prevalence of occupational asthma caused by exposure to respirable aerosols containing salmon-serum antigens generated by processing machinery."	No specific inhalational challenge to confirm diagnosis. Data suggest salmon proteins may increase asthma type symptoms in workers exposed after as little as 2 weeks. Smoking increased risk of developing occupational asthma.
Crimi 1999 Diagnostic Study	4.5	23	Reverse Allergo-Sorbent Test (REAST)	Skin Prick Test, Nasal Challenge Test, Bronchial Challenge	Non-smoking subjects with mixed allergies (15 females, 8 males)	At least 1 week	Asthma diagnosis using methacholi ne challenge	IgE density and nasal challenge score (p <0.0001), bronchial challenge score	"IgE density as calculated by REAST procedure, … In rhinitis subjects with multiple	Small numbersl 11 asthmatics studied. Diagnosis of asthma was compared against methacholine challenge testing. Data suggest

				Test, Methacholine Challenge Test (MIC)			vs. SPT, RAST, nasal challenge, and bronchial challenge	(p < 0.001), and maximum late FEV fall (p <0.005). Amount of specific IgE and bronchial challenge score (p<0.001).	sensitizations, IgE density appears in satisfactory agreement with the nasal response to the inhaled allergens, ... In asthmatic subjects the confounding effect of non-specific airway responsive-ness blunts the predicting value"	that specific serum IgE expressed as density does not correlate well with the in vivo response in asthmatic subjects.
Kim 1999 Case Reports	4.5	16	IgE to citrus red mite (CRM)	Skin prick test, Airway reversibility, Specific bronchial challenge test	16 citrus farm workers complaining of respiratory symptoms.	Uncertain	IgE, FVC, FEV_1	All patients had strong reactions to the skin prick test of CRM extract. 62.5% of patients had isolated positive reactions to CRM.	"CRM-derived allergens may be important factors in the development of both occupational rhinitis and asthma in farmers cultivating citrus fruits."	Skin prick testing and IgE testing performed on all participants. Data suggest allergic reactions can occur to citrus red mite and occupational asthma may also occur but further testing is needed.
Platts-Mills 1987 Diagnostic Study	4.0	179	IgE and IgG to rat allergens	Reported symptoms, skin prick test	125 lab workers exposed at different levels to rat allergens, 54 pregnant women not exposed	None	IgE, IgG, SPT, symptoms of asthma or rhinitis	SPT positive in 19/30 of symptomatic and 2/135 asymptomatic employees (p<0.01%). IgE ab to rat antigen 16/30 2/135 (p<0.01%). IgG positive in all 20 employees with positive IgE but also in 30% of asymptomatic employees.	"The correlation between IgE ab and positive skin test to rat urine strongly supports the view that this is the major allergen of rat urine…the incidence of IgG antibodies to this protein correlates with exposure to animals."	No good baseline data on cases versus controls. Asthma diagnosis was done by employee report. Data suggest IgG is a marker of ever being exposed to rat allergens. IgE is more of a marker of having symptoms associated with rat exposures.
Low Molecular Weight										
Budnik 2013 Diagnostic Study	8.0	43	IgE to MDI by fluor-escence	SIC SPT IgG	Workers exposed to MDI with presumed OA	None	IgE level SIC results Spirometry Symptoms	10/12 (83%) had positive SIC. 4/10 (40%) had positive IgE. No	"Isocyanate-specific IgE antibodies are not always detectable but their	Small numbers of positive SIC patients (10). Data suggest IgE antibody testing is

			enzyme immune assay detection method (semi-automatic ImmunoCAP100)	Histamine challenge spirometry Symptoms	sent to referral clinic			SIC positive patients had negative IgE. 5/10 (50%) had positive SPT. No SIC positive patients had a negative SPT.	presence can be predictive of isocyanate asthma and supportive for the diagnosis of occupational asthma. In order to better compare between the studies, the methods for the immuno-logical analysis of the IgE and IgG antibodies need standardization and validation."	supportive in the diagnosis of occupational asthma if they are found to be present. An absence of IgE does not rule out a diagnosis of occupational asthma to MDI. Results based on their own characterized conjugates which are not same as commercially available tests.
Tee 1998 Diagnostic Study	8.0	101	RAST IgE to isocya-nates	SIC PEF Clinical symptoms SPT	Patients with clinical symptoms consistent with OA sent to a hospital based clinic	Varied	IgE levels SIC PEF SPT	58 considered to have OA caused by isocyanates. 46/58 (79%) had positive SIC. Patients with SIC confirmed diagnosis: IgE RAST $\geq$2: Sn: 28% Sp: 92% IgE RAST $\geq$3: Sn: 20% Sp: 100%	"IgE to isocyanates is a more specific than sensitive index of occupational asthma. With a RAST score of 3 or greater, it is wholly specific and therefore diagnostic of isocyanate-induced asthma. The sensitivity of specific IgE measurement is highest when blood is taken less than 30 days from last exposure, which is consistent with the observed half-life."	SIC done on 70/101 (69%) of workers. Some of the diagnoses made by retro-spective review of symptoms. Cross-reactivity of IgE was seen. Data suggest RAST IgE testing within 30 days of exposure can aid in diagnosis of OA. Methods for immunological analysis of isocyanates Ag was RAST which is not commercially available for isocyanates.
Cartier 1989 Diagnostic Study	7.5	62	IgE and IgG to isocyanat es by ELISA	Specific inhalational challenge, Skin prick test	Patients who underwent specific inhalational challenge testing for isocyanates	Up to 2 weeks	IgG and IgE levels after testing to isocyanates.	Increased specific antibodies: IgE only – 0/62 IgG only – 13/29 (45%), 7/33 (21%)	"[T]he levels of specific IgG to the more recent types of isocyanates (HDI and MDI) bear a satisfactory association, in terms of sensitivity and specificity, to the	All patients had SIC testing and then were tested for IgE and IgG levels. Data suggest IgG levels are better correlated than IgE with IgE, which suggests an immunologic mechanism.

								Both IgE and IgG – 8/29 (28%), 1/33 (3%)	results of specific inhalation challenges, suggesting an immunologic mechanism is involved."	
Bernstein 2002 Diagnostic Study	7.0	75	IgE testing to di-isocyanates by ELISA	In vitro MCP-1 production testing Methacholine challenge testing SIC to a diisocyanate encountered in workplace (TDI, MDI or HDI)	54 diisocyanate-exposed workers who had prior histories consistent with OA, 9 non-asthmatics, 12 asthmatics with no diisocyanate exposure	One period of testing	In vitro MCP-1 levels	In vitro MCP-1: Sn = 79% Sp = 100% IgE: Sn = 21% Sp = 89%	"[A] strong association between diisocyanate antigen enhancement of MCP-1 and DA suggest that further investigation and validation of cellular immunoassays could enable development of more sensitive and specific diagnostic tests that could be useful in the diagnosis of OA."	"Controls" only had in vitro MCP-1 testing performed. No blinding. In vitro MCP-1 levels test is not readily available. Data suggest in vitro MCP-1 testing could be a helpful laboratory test to confirm OA due to diisocyanates. This finding has not been corroborated in subsequent research.
Pezzini 1984 Diagnostic Study	6.5	28	Serum IgE to di-issocyanate BY by direct radio-immuno-assay technique (Phadebas PRIST kit)	Specific inhalational challenge testing, skin prick testing	28 workers exposed to Toluene diisocyanate (TDI) and diphenyl-methane diisocyanate (MDI)	Un-known	Specific inhalational challenge bronchial hyper-responsive-ness. IgE levels	Positive IgE test for MDI was 5/6 (83%) and for TDI was 6/22 (27%). Appearance of respiratory symptoms before 6 years of exposure was more frequent in IgE positive group (p = 0.007).	"Our results show a prevalence of specific immuno-logical IgE mediated reactions in subjects who develop asthmatic symptoms after a shorter time of isocyanate exposure and experienced an accidental acute exposure to high concentrations of isocyanate."	Small numbers. Control group with little information provided. Data suggest IgE testing is more reliable for MDI than TDI in patients with symptoms consistent with asthma. Not clear whether Phadebas PRIST kit is commercially available.

Evidence for the Use of Skin Prick Testing

There are 8 high-[65, 141, 185, 210, 211, 227, 228, 232] and 12 moderate-quality[57, 213, 215, 220, 225, 230, 231, 233-237] studies incorporated into this analysis. There are 4 other studies in Appendix 1.[143, 145, 224, 238]

Author/ Year Study Type	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Vandenplas 2001 Diagnostic Study	9.0	45	Natural rubber latex clinical diagnostic testing	Questionnaire, Immunologic testing, SPT, spirometry, NRL challenge, (SIC) and other common asthma inducing present at occupation.	45 with suspected occupational asthma, exposed to airborne NRL	Not specified	Sensitivity, specificity, positive predictive values, negative predictive values	31 with positive SIC results to NRL gloves. Non-specific bronchial responsiveness (%): Sensitivity 90, Specificity 7, PPV 75, NPV 25. SPT (%): Sens. 100, Spec. 21, PPV 74, and NPV 100. Clinical history (%): Sens. 94, Spec. 36, PPV 76, NPV 71.	"[C]ombining the assessment of NSBH and immunologic tests with the open questionnaire is not reliable as an SIC in diagnosing NRL-induced [occupational asthma]."	Evaluated workers' compensation cases. Data suggest combination of clinical history and SPT has greatest sensitivity and specificity compared to SIC. LATEX
Van Kampen 2008 Diagnostic Study	8.5	107	IgE to wheat and rye flour	SIC SPT	Bakers	None	IgE STP SIC	In baker's with OA: IgE to wheat Sn: 87% Sp:68% PPV: 74% NPV: 82% IgE to Rye Sn: 61% Sp: 94% PPV: 95% NPV: 56% SPT to wheat Sn: 68% Sp: 74% PPV: 74% NPV: 68% SPT to rye Sn: 78% Sp: 84% PPV: 91% NPV: 66%	"[B]oth flour specific IgE and SPT with flours, can be used effectively for the prediction of the outcome of specific challenge tests with flours in symptomatic bakers."	Workers were bakers with symptoms of rhinitis, cough, wheezing, and shortness of breath – mean age 40 years. All seeking claims for compensation due to occupational asthma. A positive challenge test was defined as either nasal or bronchial reaction. Data suggest SPT and/or IgE can be used to aid in the diagnosis of bakers' allergy to wheat or rye flours. This data is not specific to just OA, but also included rhinitis symptoms.

										WHEAT AND RYE
van Kampen 2009 Diagnostic Study	8.5	125	SPT to flour	Specific IgE (sIgE) Challenge tests (24 with nebulized aqueous flour solutions, 63 with native flours, 8 nasal challenges)	125 bakers	15 minutes after procedure	Protein in prick test solutions was measured by the Bradford assay	85 (68%) showed sIgE to wheat flour and 83 (66%) sIgE to rye flour	"[B]y increasing the antigen concentration of flour SPT solutions, it is possible to increase sensitivity without substantial loss of specificity."	Similar study as Sander 2004. Data suggest different preparations of flour proteins for skin prick testing need to be standardized and improved. WHEAT AND RYE
Wiszniewska 2011 Diagnostic Study	8.5	151 diagnosed with OA by SIC, 287 had rhinitis symptoms	SPT to flour	SIC Spirometry NSBP Nasal Lavage IgE to flours	Bakers	None	IgE STP Spirometry Symptoms	In baker's with OA: SPT: Sn: 41.7% Sp: 85.9% PPV: 73.3% NPV: 61.4% IgE: Sn: 61.6% Sp: 77.3% PPV: 71.5% NPV: 68.5%	"Results in our study indicate that neither SPTs to occupational allergens nor evaluation of serum allergen-specific IgE alone or combined with nonspecific bronchial hyperreactivity are characterized by sufficient diagnostic accuracy to replace specific inhalational challenge test."	Study included workers with rhinitis and OA. Data suggest that IgE and SPT can be useful in the diagnosis of both occupational asthma and rhinitis in bakers. FLOUR
Park 2001 Diagnostic Study	8.0	151	Serum specific IgE, SPT to reactive dyes	Bronchial provocation testing with methacholine, specific inhalational challenge	42 patients with occupational asthma from reactive dyes,93 asymptomatic factory workers, 16 unexposed controls	None	Skin prick test, IgE testing	SPT: Sens: 76.2% Spec: 91.4% PPV: 80% NPV: 89.5% IgE testing: Sens: 53.7% Spec: 86% PPV: 62.9% NPV: 80.8% Combined:	"SPTs and ELISAs may be valuable tools for screening, diagnosis, and monitoring occupational asthma resulting from exposure to reactive dyes; these two tests might complement each other for such a diagnosis."	Well-defined cases and controls. Co-interventions such as medication use unclear. Bronchial provocation testing with methacholine on all subjects. Specific inhalational challenge testing performed on all with positive methacholine

								Sens: 83.3% NPV 91.7%		challenge testing. Data suggest a combination of SPT and IgE is more sensitive and specific. REACTIVE DYES
Sander 2004 Diagnostic Study	8.0	115	SPT; SDS-PAGE	Bronchial Challenge Test; IgE-Enzyme Allergo Sorbent Test (EAST); Sodium; Dodecyl sulfate-Polyacrylamide Gel electrophoresis (SDS-PAGE)	115 bakers complaining of workplace-related respiratory symptoms	6 hours after challenge test	Protein in prick test solutions measured by ESL protein assay	Specificity above 85% for all tests. 17/40 (43%) patients reacted with wheat SPT extract. Six reacted on all wheat flour extracts and 3/13 (23%) patients with positive rye flour result reacted on all rye flour extracts.	"These data suggest that at present commercial wheat and rye flour SPT solutions differ in protein content and band patterns and fail to detect about 30–60% of patients with a positive allergen challenge."	Skin prick testing material provided by different companies. Data suggest commercially available preparations varied in the protein composition which could affect test results. WHEAT AND RYE, COMMERCIAL EXTRACTS
Koskela 2003 Diagnostic Study	8.0	37	SPT, Bovine dander	Bovine specific inhalational challenge; IgE testing; Histamine; Exhaled NO; Mannitol challenge; Sham inhalational challenge; PEF	37 dairy farmers with suspected occupational asthma to bovine dander	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other test results	11/37 (30%) classified as positive response to bovine dander. Skin prick test (Sensitivity%/ Specificity%/PPV%/ NPV%): (100/50/46/100); IgE (82/100/100/93); Histamine (82/65/50/89); Mannitol (20/94/67/89); exhaled NO (27/77/33/71).	"Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bovine SIC testing."	Data suggest patients with a positive SPT and bIgE testing do not require SIC testing. COW DANDER
Merget 1993 Diagnostic Study	7.0	62	SPTs with non-dialyzed aqueou	Specific inhalational challenge, IgE	42 chemical plant workers referred for pulmonary symptoms, 10	None	Spirometry, IgE levels, and skin prick test results	Positive for 13/42 (31%) participants; Skin prick test: Sn = 100% Sp = 93%	"For enzyme allergy both BPT [bronchial provocation test] and skin prick test	Controls not well described. Data suggest skin prick testing has high sensitivity and

			s enzyme extracts		atopic non-exposed patients, and 10 healthy patients				were appropriate diagnostic tests."	specificity for patients exposed to certain enzymes and can be used in the diagnostic testing of occupational asthma in those patients. CHEMICAL PLANT ENZYMES
Walusiak 2004 Diagnostic Study	6.5	287	SPT to flour	IgE SIC NSBP Symptoms	287 bakers	2 years	SPT IgE SIC Symptoms	25/287 (8.7%) diagnosed with OA by SIC, 23/25 (92%) had positive SPT and IgE testing.	"[T]he results of our study indicate that SPT to common and occupational allergens should be performed in apprentice bakers before starting vocational training."	Baseline testing done during first month of training, meaning there was at least some exposure to work allergens before testing. Average age of worker at start of study 16.2 years. Data suggest SPT and IgE testing are positive in majority of workers with OA to flour. FLOUR
Acero 2003 Diagnostic Study	6.0	12	SPT to latex	IgE NSBP SIC Specific conjunctiva tests Symptoms	12 health care workers	3 years	IgE NSBP SIC Specific conjunctiva tests Symptoms	SIC: 12/12 had positive test SPT: 12/12 had positive test IgE: 2/12 had positive findings	"NRL acts as a common aeroallergen. Minor symptoms often precede occupational asthma. The SIC test was safe in the hands of trained technicians. Occupational asthma due to NRL seems to have a poor prognosis."	Patients were diagnosed as having OA prior to this study either by SIC or serial PEFs. 6/19 patients had anaphylaxis as symptoms. Data suggest that in persons with severe allergy to NRL SIC, SPT, and IgE testing is helpful in diagnosis of allergy. LATEX

Park 1998 Diagnostic Study	5.5	43	SPT to grain dust	All tests used 7 common allergens vs. grain dust (GD) from subjects' workplace. Broncho-provocation, and ELISA questionnaire	N = 43 male animal feed industry workers exposed to grain dust composed of corn, rye, wheat, barley. Of 43, 31 process workers who mixed and carried materials (intermediate exposure group and high exposure group according to exposure intensity measured by dust air sampler); 12/43 office workers classified as low exposure group. Controls (n = 27) never exposed to grain dusts and demonstrated negative skin tests to 50 common inhalant allergens.	Not specified	Common allergens vs. GD in group A, with results compared to that of group B.	34.9% questionnaire respondents complained of lower respiratory symptoms. IgE (GD) positive results in 40% of symptomatic and 11% control (p = 0.02). ELISA: No inhibition noted. Total IgE vs. Specific IgE: insignificant.	"GD can induce an immunologic, IgE-mediated response in exposed workers, which is responsible for their asthmatic symptoms."	Patients selected did not all have symptoms suggestive of asthma. Study had exposure groups but did not mention them in analyses. Data suggest grain dust may be a factor in occupational asthma in workers exposed. GRAIN DUST
Merget 1991	5.5	35	SPT to platinum salts	Lung function, bronchial	35 workers from platinum refineries with	Uncertain	IgE, FEV_1, $FEV_{1\%}$ IVC, sRAW (specific	16/35 (46%) patients had positive reactions to all tests.	"[W]ork related respiratory symptoms are not	Most had been removed completely from exposure, 19

Diagnostic Study				provocation tests	work-related symptoms.		airway resistance), sGaw (specific airway conductance), IVC	22/27 (81%) workers had positive bronchial provocation tests with platinum salt and none of the 9 controls had positive tests. Platinum salt was correlated with skin reactivity ($p<0.0008$; n = 27).	predictive of platinum salt asthma. Negative skin prick tests with hexachloroplatinic acid do not exclude the disease."	had occasional contact. Data suggest SPT may be useful in assessing platinum salt testing, but negative SPTs do not exclude disease. PLATINUM SALTS – not commercially available
Brisman 2003 Diagnostic Study	5.0	89	SPT to flour, alpha-amylase	Whole blood cell count Spirometry	25 asthmatics (determined by questionnaire), 20 bakers with rhinitis, and 44 referent bakers	None	SPT Eosinophils FEV_1, FVC	7/25 asthmatics reported symptoms related to work and 8/20 with rhinitis reported symptoms related to work. Flour SPT positive in 43% of asthmatics or rhinitics vs. 16% of referents.	"[S]ensitization to an occupational allergen, especially flour, is an important, but not the only, mechanism in baker's asthma."	Not all asthmatics were occupational asthma patients. Asthma diagnosed mainly by questionnaire. Data suggest that in bakers with asthma, occupational and non-occupational, there is a larger positive SPT rate to flour proteins. FLOUR and alpha-AMYLASE
Suarthana 2009 Diagnostic Study	4.5	314	SPTs to lab animal allergens	Bronchial Responsive (BR) tests; Methacholine Bronchial Challenge Tests	314 apprentices who had a negative skin reaction to all lab animal (LA) allergens tested at initial visit. LA allergens included rat urine, mouse urine, and rabbit urine and/or rabbit hair.	32 months	4 models – Model 1: questionnaire only, Model 2: questionnaire and SPT, Model 3: questionnaire and BR tests, and Model 4: questionnaire, SPT and BR tests.	LA Allergens: Probability ≥ .10: Sensitivity (89.8%) Specificity (43.0%) PPV (22.6%) NPV (95.8%). Symptoms at work: Probability ≥ 0.10: Sensitivity (82.2%) Specificity (67.7%) PPV (31.4%) NPV (95.5%).	"[W]e developed prognostic models to predict the occurrence of sensitisation to LA allergens and symptoms at work in animal health apprentices. The questionnaire model alone is an easy tool that can give an accurate prediction of the incidence of occupation	Baseline done before exposure to lab animals during training. Data suggest patients with allergic symptoms, positive SPT to common allergens, symptoms of asthma, and bronchial hypersensitivity before exposure are at greater risk for developing sensitization and

									sensitisation and symptoms.”	symptoms to lab animals. LAB ANIMALS
OTHER STUDIES										
Bernstein 2011 Diagnostic Study	9.0	40	SPT – trimellitic anhydride	IgE/IgG Intracutaneous testing	TMA exposed workers Controls	None	IgE levels, SPT results	SPT: Sn 73% Sp 97% PPV 89% NPV 90 SPT negative with intracutaneous testing: Sn 91% Sp 97% PPV 91% NPV 97%	“[U]sing a TMA-HAS skin test reagent can be as sensitive and specific as a sensitive TMA-serum specific IgE immunoassay for detecting TMA-sensitized workers.”	Participants had IgE and IgG testing done prior to study. Used TMA-specific ImmuoCap 1000 Platform. Data suggest SPT useful in detecting TMA sensitized workers. TRI-MELLITIC ANHYDRIDE (not commercially available)
Sharma 2008 Diagnostic Study	7.5	69	SPT-mouse allergens	IgE Nasal Challenge IDT	Laboratory workers	None	Nasal symptoms Ocular symptoms Chest symptoms	SPT: Sn: 67% Sp: 91% PPV: 70% NPV: 79% +LR: 5.2 IgE: Sn: 47% Sp: 91% PPV: 70% NPV: 79% +LR: 11.2	“SPTs perform best in discriminating patients with and without mouse allergy.”	Lab worker mean age 30 years. Length of time exposed not well described. This was not for OA, but for allergy symptoms, 86% had nasal allergy symptoms, 76% had ocular. Data suggest SPT to mouse allergens helpful in diagnosing mouse allergy. MOUSE ALLERGEN

Merget 2000 Diagnostic Study	7.0	265	SPT Platinum salts	None	Workers in platinum process plant	6 years	SPT conversion from negative to positive FEV_1 Symptoms Histamine challenge test with spirometry Atopy Smoking	The two risk factors found that lead to SPT conversion from negative to positive: Exposure level Smoking status	"Pt salts are relevant allergens in catalyst production plants."	6-year prospective cohort with main outcome measure risk factors leading to SPT conversion from negative to positive in exposed populations. PLATINUM SALTS (not commercially available)
Schmid 2009 Diagnostic Study	4.0	132	SPT to mouse and rat danders	IgE Whole body plethsmography NSBP Questionnaire	Laboratory workers	None	SPT IgE Whole body plethsmography NSBP Symptoms	Sensitization rates in workers: Mice 12.7% Rats 16.3%	"In employees with occupational contact with laboratory animal dust, the frequency of complaints was high. The results confirm the necessity of regular medical check-ups for employees with contact with laboratory animal dust."	Main complaints sneezing and runny nose. "Some ocular symptoms and bronchial asthma." SPTs done in 78.8% of participants; IgE testing done in 86.4%. In persons with <1 year of exposure, there were no positive tests. MOUSE AND RAT
Niezborala 1996 Diagnostic Study	4.0	77	SPT Platinum salts	None	Workers in a platinum plant	20 years	SPT conversion Atopy Smoking status Symptoms	18/77 (23%) developed positive SPT and 23/77 (30%) developed symptoms. Incidence of positive SPT and symptoms was highest in first two years. Smoking had a relative risk of conversion on SPT of 5.53.	"The findings confirm that smoking is and that atopy may not be a high risk factor for the development of allergy to complex platinum salts."	Retrospective cohort study done by medical record review. Main outcomes measured were conversion of SPT or development of symptoms in relation to smoking and atopy status. PLATINUM SALTS (not commercially available PST)

Calverley 1995 Prospective Cohort Study	4.0	78	SPT Platinum salts	Symptoms	Workers in platinum refinery	18 months, exam done every 3 months	Symptoms FEV_1 SPT Exposure by air sampling	32/78 (42%) classified as platinum salt sensitive, 22/78 (28%) converted to SPT +, and 10/78 (8%) SPT negative but had symptoms severe enough for removal from work. Smoking increased likelihood of platinum salt sensitivity by 8.0 times. Higher exposure increased PSS by 6.	"Smoking and intensity of exposure were definitely associated with development of PSS. Positive response to platinum salt skin prick test had a 100% positive predictive value for symptoms and signs of PSS if exposure continued."	Prospective cohort. Main outcomes measures were SPT conversion and symptoms during follow-up. Increase in SPT positive conversion and/or symptoms related to higher exposure at work and smoking status reported. PLATINUM SALTS (not commercially available PST)

Evidence for the Use of Specific Inhalational Challenge Testing

There are 4 high-[141, 146, 148, 211] and 16 moderate-quality[53, 71, 150, 151, 213, 242-244, 249, 262, 269, 273-277] studies incorporated into this analysis. There are 12 other studies in Appendix 1.[147, 149, 159, 221, 239-241, 245, 270, 271, 278, 279]

Author/ Year Study Type	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow up	Outcome Measures	Results	Conclusions	Comments
van Kampen 2008 Diagnostic Study	8.5	107	Bronchial, nasal, or workplace-stimulated rye flour challenge	Specific IgE antibodies to wheat and rye flour, skin prick tests vs. aqueous wheat and rye flours	107 (77% male) with reported rhinitis, conjunctivitis, cough, chest tightness, shortness of breath or wheezing. (n = 71, mean age 41 years (71% male) given wheat flour challenge, n	Specific IgE tested at baseline. SPT performed twice with removal of test material after 15 minutes. Challenge performed at baseline.	Sensitivity, specificity, positive predictive values, and negative predictive values at various IgE concentrations, different wheal sizes.	Challenges: Specificity 68% and 62%, PPV 74% and 82%, NPV 82% and 71%, respectively for wheat and rye.	"High concentrations of flour-specific IgE and clearly positive SPT results in symptomatic bakers are good predictors for a positive challenge test. Challenge tests with flours may be avoided in strongly sensitized bakers."	Similar study as Sander 2004. Data suggest challenge testing with flour is helpful in the diagnosis of occupational asthma and the different preparations of flour proteins for skin prick testing need to be standardized and improved.

					= 95 mean age 41 (79% male) given rye flour challenge).					
Koskela 2003 Diagnostic Study	8.0	37	Bovine specific inhalat-ional challenge via dosimetric nebulizer.	1. Skin prick test; 2. IgE testing; 3. Histamine challenge; 4. Exhaled NO measureme nt; 5. Mannitol challenge; 6. Sham inhalational challenge; 7. PEF, twice daily for a week	37 dairy farmers with suspected occupational asthma to bovine dander who were referred for bovine dander specific inhalational challenge testing	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other testing results	*Skin prick test:* Sn = 100% Sp = 50% PPV = 46% NPV = 100% *IgE:* Sn = 82% Sp = 100% PPV = 100% NPV = 93% *Histamine:* Sn = 82% Sp = 65% PPV = 50% NPV = 89% *Mannitol:* Sn = 20% Sp = 94% PPV = 67% NPV = 89% *Exhaled NO:* Sn = 27% Sp = 77% PPV = 33% NPV = 71%	"Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bovine SIC testing."	Patients with suspected occupational asthma by clinical presentation and spirometry were referred for testing. Data suggest patients with a positive SPT and serum specific IgE testing do not require SIC bovine testing.

Munoz 2004 Diagnostic Study	8.0	26	Specific inhalational challenge by pour method	SPT; Total IgE levels; Methacholine challenge testing	8 patients with diagnosed OA due to persulphate salts, 8 patients with asthma with no prior exposure to persulphate salts, 10 healthy patients with no history of asthma.	None	Spirometry after challenge testing	Methacholine testing: 6/8 (75%) of patients with OA had a positive test. 7/8 patients with asthma (88%) had a positive methacholine test. Sensitivity = 100% Specificity = 87.5%	"The procedure described in this study allows patients with bronchial asthma to be distinguished from those with persulphate salt induced OA."	Small numbers. No details on how patients were diagnosed prior to study. 8 patients with asthma did not have exposure to persulphate. Data suggest the pour method is a valid method for SIC with persulphate salt occupational asthma.
Rasanen 1994 Diagnostic Study	8.0	28	Specific inhalational challenge, method not well described. Challenge testing to grains	Methacholine; SPT; IgE; PEFR; Symptoms	16 patients with previous challenge test positive for rhinitis or asthma (worked as farmers and bakery and food industry workers) vs. 12 with seasonal rhinitis with or without suspected occupational exacerbated asthma.	None	Spirometry PEFR Symptoms IgE SPT	SPT: Sn = 74% Sp = 86% RAST: Sn = 89% Sp = 78% BHRT: Sn = 57% Sp = 93% IgE: Sn = 91% Sp = 71%	"On the basis of the present preliminary study, the overall concordance of skin and blood tests with challenge seems to be relatively good in allergic asthma and rhinitis. These tests cannot, however, replace the challenge but serve as additional aids."	Small numbers. All atopic. Some "controls" had workplace exacerbated asthma. Co-interventions not well described. Data suggest skin prick tests, IgE, RAST, and BHRT testing useful but do not replace challenge testing for diagnosing occupational asthma.

Frigas 1984 Diagnostic Study	7.0	13	Bronchial challenge with formaldehyde via Dyna-calibrator, a closed system	Spirometry with placebo challenge	Patients attributing symptoms to formaldehyde exposure(s).	One period of testing	Placebo to all patients, formaldehyde at 0.1 ppm, 1 ppm, or 3ppm for 20 minutes. Spirometry after various levels of exposure to formaldehyde gas.	Adverse events of eye, nose, and throat tightness of the chest but these occurred as frequently with the placebo as with the formaldehyde challenges.	"Testing with a formaldehyde bronchial challenge (3 ppm or less) did not provoke asthma in 13 selected patients with symptoms suggestive of asthma and a history of exposure to formaldehyde gas. Cases of formaldehyde-induce asthma may be rare."	Some participants double-blind and some single-blind. One had decrease in FEV_1 both with formaldehyde and placebo. Data suggest formaldehyde may not induce asthma through sensitizing mechanism. Irritant induced asthma not addressed.
Obtulowicz 1998 Diagnostic Study	7.0	49	Specific inhalational challenge at work, no specific device used. Allergens not defined.	Clinical history consistent with OA. SPT to metals and "professional dust" and totals serum IgE	49 workers in steel and tobacco industries referred for evaluation for OA.	None	Spirometry data	25/49 (51%) patients had a positive inhalational challenge test.	"Bronchial inhalation challenge at work is a very useful diagnostic method in the recognition of occupational asthma. Measurements of small airway obstruction are valuable in the evaluation of inhalation challenge"	Small numbers. Substance used for challenge testing was "professional dust" without explanation. Poor correlation of patch tests to presumed allergens.
Sastre 2003 Diagnostic Study	6.5	22	Specific inhalational challenge with isocyanates in dynamic chamber with an open flask of TDI or nebulized in HDI cases	Methacholine challenge	22 patients with clinical history of diisocyanate-induced asthma	None	Spirometry after and methacholine testing	First round of testing: 13/22 (59%) had positive response; 2nd round of testing: 2/22 (11%) had a negative response. PC_{20}: in 2/9 patients with negative on round 1, PC_{20} fell within the asthmatic range after test.	"PC20 should be systematically assessed before and after SIC with isocyanates. This is especially relevant in the absence of significant changes in FEV1 during SIC to avoid false-negative results."	Small numbers. No controls for non-occupational asthma possibilities. Data suggest PC20 after challenge may help decrease false negatives during testing with isocyanates challenge.

Harries 1980 Diagnostic Study	6.5	37	Specific inhalational challenge to various agents (mainly animal dander) aerosolized.	SPT; IgE	37 workers clinically diagnosed with occupational asthma. All inpatients.	None	Spirometry	24/37 (65%) patients had positive asthma reactions to test antigen. 18/24 (75%) were prick positive for test antigen.	"Until the use of peak flow records is accepted as a discriminating test of occupational asthma, bronchial provocation testing will continue to provide a highly specific but expensive diagnostic tool."	Small numbers. Specific inhalational challenge agent was mixture of 28 allergens. Each patient received placebo challenge. Data suggest specific bronchial provocation testing is gold standard test for diagnosis of high molecular weigh-induced occupational asthma.
Nordman 1985 Diagnostic Study	6.5	230	Bronchial challenge with formaldehyde (controlled exposure)	SPT, spirometry, histamine provocation test, exercise test, serologic tests	230 workers with formaldehyde-induced bronchial asthma	6 1/2 years	Eosinophil count, IgE, FVC, FEV_1, FEV%, PEF	218 had negative reactions to bronchial provocation with formaldehyde; 96 diagnosed with bronchial asthma. Histamine provocation test positive in 71 and negative in 126 of 218 not reacting to formaldehyde.	"The controlled exposure tests demonstrated that concentrations of about 1.2 and 2.5 mg/m3 (1 and 2 ppm) of formaldehyde are enough to trigger the attacks in individuals already sensitized."	Long follow-up time. Data suggest formaldehyde can induce asthma symptoms in some patients with high work exposures.
Moller 1986 Diagnostic Study	6.5	12	Inhalation challenge with toluene diisocyanate (TDI) in chamber with open method	Pulmonary function tests, bronchial challenge test with methacholine, spirometry	12 patients with possible TDI asthma	Uncertain.	FEV1, FVC, (PD_{20})	Five workers showed no significant bronchospasm to TDI challenges at high or low doses, however, 3 of the five had positive methacholine tests.	"In the present study, 12 workers with suspected TDI asthma were evaluated by bronchial challenge to TDI. Seven persons demonstrated sensitivity to low levels of TDI (reactors), confirming isocyanate sensitization."	Small numbers. Addressed removal from work. Several workers with clinical history suggestive of asthma to TDI did not react on SIC. Data suggest SIC may aid in diagnosis of occupational asthma to TDI, but dose and duration of challenge factors that may lead to false negative results.

Walusiak 2004 Diagnostic Study	6.5	64	Specific inhalational challenge to workplace flour by sifting in an open room	Nasal lavage; SPT; IgE; Spirometry	64 bakers with reported symptoms of asthma and or rhinitis at work: A = 17 occupational allergic rhinitis vs. B = 24 both occupational asthma and rhinitis vs. C = 23 atopic asthma without occupational allergy	None	Cellular findings of the nasal lavage. Permeability index of nasal lavage.	A significant decrease in PC_{20} after challenge test observed only in group B ($p<0.001$). Provocation with flour resulted in elevated leukocytes in nasal washing in all groups. Group B had higher elevation than Group C ($p<0.001$). Eosinophils elevated in all groups, but more in A and B when compared to C ($p<0.001$).	"[T]he test does not allow distinguishing subjects with asthma and rhinitis from patients with isolated rhinitis. Therefore, the evaluation of spirometry and non-specific bronchial hyperreactivity is also necessary when diagnosing bakers' respiratory allergy."	Occupational asthma diagnosed with post challenge PC_{20}. Data suggest that nasal lavage alone may determine allergic rhinitis due to flour but does not determine presence of occupational asthma.
Burge 1985 Case Reports	6.0	15	Bronchial Provocation Test done in 6 m3 chamber without air extraction during test	None	15 workers occupational exposure to formaldehyde	24 days	FEV	4/14 (29%) had PC20 values less than 10 mg/ml. 10/14 (71%) had normal bronchial provocation after testing with formaldehyde.	"Irritant reactions to formaldehyde usually occur at concentrations above those likely to occur with home insulation. These concentrations can be reached in industrial situations, particularly when resins containing formaldehyde are overheated."	Small numbers. No placebo. Data suggest formaldehyde may cause irritant asthma during the instillation of home insulation concentrations but not consequently, and that specific inhalation challenge testing may aid in diagnosis.
Vogelmeier 1991 Diagnostic Study	6.0	43	Specific inhalational challenge test to isocyanates in open air chamber	Methacholine challenge test	A = 19 workers with clinical history consistent with occupational asthma vs. B = 14 workers with asthma/no exposure to isocyanates vs. C = 10	None	Methacholine then spirometry.	SIC Positive: A = 13/19 (68%) B = 3/14 (21%) C = 1/10 (10%) Methacholine positive: A = 10/19 (53%) B = 14/14 (100%) C = 0/10 (0%).	"[T]he methacholine test in patients with suspected diisocyanate-induced asthma is only of limited diagnostic value; at least in doubtful cases a diisocyanate challenge should be performed."	Small numbers. There was a 21% and 10% false positive rate on SIC. Data suggest methacholine challenge testing alone is not sufficient to diagnose possible diisocyanate OA.

					healthy workers without asthma					
Mapp 1988 Diagnostic Study	5.5	162	Specific inhalational challenge to isocyanates in open air chamber	Methacholine challenge testing Clinical and occupational history Spirometry SPT IgE to TDI and MDI	162 workers exposed to isocyanates with symptoms suspected to be from asthma	None	Spirometry IgE test results	93/162 (57%) of patients with history consistent with OA had a positive SIC. 15/93 (16.1%) had a FEV_1 lower than 80% predicted. IgE antibodies found in 1 subject.	"In conclusion, isocyanate-asthma is an important cause of occupational respiratory disease...baseline airway responsiveness to methacholine is similar in subjects who developed an immediate, a dual, or a late asthmatic reaction."	Data suggest that clinical diagnosis based on history is only accurate about 50% of the time. SIC is considered the gold standard for diagnosis.
Vanhanen 2000 Diagnostic Study	5.5	11	Specific inhalational challenge to cellulose in open air chamber	Spirometry IgE-RAST SPT	11 workers who were exposed to cellulase with symptoms consistent of allergic rhinitis and or asthma	None	PEF Clinical history	8/11 had no symptoms with 30mg cellulose exposure. 2/8 had no symptoms with 300 mg cellulose exposure.	"The challenge method proved to be a practical means with which to stimulate conditions at the worksite and elicit the specific respiratory symptoms of the patients."	Small numbers. Diagnosis of workplace symptoms not well delineated in differentiating possible other exposures. Data suggest challenge testing may reproduce symptoms in patients with suspected allergy to cellulase.
Lam 1983 Diagnostic Study	5.5	206	Specific inhalational challenge test to plicatic acid using nebulizer	Methacholine (not in all patients). Skin prick test. IgE RAST	206 patients with positive testing to plicatic acid	None	Spirometry results classified as immediate, late or dual reactivity	18/206 (9%) had immediate reaction. 100/206 (49 %) had a dual reaction. 88/206 (43%) had a late reaction. 83 patients had methacholine testing.	"Nonspecific bronchial hyperreactivity is an important factor in determining the type and the severity of asthma reaction induced by inhalation challenge testing in patients with occupational asthma due to western red cedar."	Protocol varied slightly between patient groups. Data suggest late asthmatic reaction is likely an earlier form of occupational asthma compared to immediate or dual reaction to western red cedar.

Schwaiblmair 1997 Diagnostic Study	5.0	55	Specific inhalational challenge to bleach powder in open chamber	SPT. Non-specific bronchial provocation testing with acetylcholine.	38 hairdressers who had symptoms of occupational asthma vs. 17 hairdressers with allergic symptoms at work, but not asthma	None	Spirometry testing; SPT	Skin prick testing was positive to a panel of allergens in 13/54 (24%) of participants. 32/54 (59%) had positive NBPT. 9/46 (22%) had positive results to bleaching powder SIC.	"The acetylcholine test in patients with suspected bleaching-powder-induced asthma is of limited diagnostic value... specific bronchial provocation tests are a useful diagnostic tool for the establishment of a definite diagnosis in suspected cases."	Not all tests performed on all participants. Data suggest some utility in diagnosing persulfate salt occupational asthma in hairdressers by SIC.
Malo 2004 Diagnostic Study	4.0	108/496; 31 with both tests	Closed circuit SIC testing	"Realistic" SIC challenge test	496 with clinical suspicion of occupational asthma and a previously documented positive SIC to occupational agent	None	$FEV_1 \geq 30\%$ after challenge testing	Of 31 patients who had both tests: Closed circuit had 8/31 (26%) change in $FEV_1 \geq 30\%$. "Realistic" had 16/31 (52%) change in $FEV_1 \geq 30\%$.	"More widespread use of the closed-circuit method could potentially result in fewer instances of exaggerated broncho-constriction and greater use of specific inhalation challenges in the confirmation of occupational asthma."	Retrospective study. Question was about two different ways to do SIC. Not all 496 had both tests. Data suggest using the 31 patients exposed to both that closed circuit SIC results in fewer drops of $FEV_1 \geq 30\%$. False negative rate of closed circuit method was 2.2% when compared to "realistic" method.
OTHER STUDIES										
Cote 1990 Diagnostic Study	6.0	48	Asthma symptoms	Spirometry with methacholine challenge	Male workers with diagnosis of occupational asthma to red cedar who stayed in same industry after diagnosis	Minimum one year, average of 6.5 years	Asthma signs and symptoms after continued exposure	10.4% improved; 62.5% were stable; 37.5% worsened. None of the patients completely recovered.	"[Among cedar asthmatics who remained exposed to cedar dust for an average of 6.5 yr, over one-third showed marked deterioration of their asthma symptoms. There is also no way to predict who will deteriorate. A decrease in the amount of exposure to cedar dust does	Patients diagnosed with occupational asthma were followed. Data suggest continued exposure to cedar dust in confirmed asthmatics prevents resolution of symptoms and worsens symptoms in 37.5%.

									not prevent deterioration of asthma. This suggests that the ideal management of cedar asthma is removal from exposure."	
Palczynski 2000 Diagnostic Study	5.0	37	Single blind exposure to phosphate buffered saline, then 7 days later exposure to latex protein. All done by nasal pool method and touching latex with skin.	SPT, Symptom score, RAST results, Spirometry	A = 16 nurses with either rhinitis or asthma related to latex vs. B = 9 nurses with rhinitis or asthma not related to latex vs. C = 6 patients with evidence of atopy vs. D = 6 healthy patients with no evidence of atopy.	None	Symptom score Mediator levels Spirometry Nasal lavage changes in cytogram, protein content, eosinophil cationic protein, and mast-cell tryptase concentration	Allergen challenge produced symptoms of rhinitis in all. Symptoms of rhinitis more severe in group A vs. group D (p = 0.001). Total leukocyte count in nasal washings highest in group A than other groups (p<0.001).	"The nasal challenge test appears to be useful for diagnosing occupational rhinitis in natural rubber latex-sensitized patients."	Small numbers. Nasal challenge testing created some form of response in all patients tested. Used skin prick testing as reference test for reactivity. Data suggest a detailed analysis of nasal lavage washings after nasal challenge test can help diagnose latex allergy patients.

Evidence for the Use of Nitric Oxide Testing

There are 2 high-[304, 305] and 20 moderate-quality[93, 153, 154, 265, 281, 282, 284, 287, 289, 291, 294, 296, 297, 299, 300, 303, 307-310] studies incorporated into this analysis. There are 4 low-quality studies in Appendix 1.[283, 286, 295, 310]

Author/Year Study Type	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusion	Comments
Pedrosa 2010 Diagnostic Study	8.0	115	Exhaled Nitric Oxide (FENO), methacholine inhalation challenge, skin prick test	Broncho-dilator test and spirometry	Patients with asthma-like symptoms with negative bronchodilator tests and normal spirometry measures	None	FeNo, FVC, FEV_1, methacholine levels, and skin prick allergens	Receiver-operating characteristic (ROC) curve and mean area under curve (AUC) was 0.762 (95% CI 0.667-0.857; p = 0.000) for FeNo levels.	"The prevalence of confirmed asthma in our population was 30.4%. The optimal value of FeNO (using NIOX MINO, at a flow rate of 50ml/s) for the diagnosis of asthma was 40 ppb, with a	FeNO measures done with portable analyzer. Age variation 14-68 years. Data suggest FeNO may aid in diagnosis of asthma in patients before bronchial inhalation challenges are done.

									sensitivity of 74% and a specificity of 72.5%."	
Dupont 2003 Diagnostic Study	8.0	240	Exhaled NO	Conventional diagnostic tools	Subjects with symptoms suggestive of obstructive airway disease referred to an asthma outpatient clinic	None	Exhaled NO	Mean exhaled NO level was significantly higher in patients with asthma compared to non-asthmatics (25 ppb, 95% CI 23 to 28 vs. 11 ppb, 95% CI 10 to 12, p<0.001).	"E]xhaled NO might be considered as an additional diagnostic test for asthma, with acceptable levels of sensitivity and specificity. Although an elevation of exhaled NO is not specific for asthma, the measurement of exhaled NO can be used in discrimination asthma from other disease conditions in patients with symptoms suggestive of obstructive airway disease."	Large sample size collected. Study did not include patients taking steroids. No mention of other medications such as NSAIDs. Minimal baseline characteristics given. Data suggest FeNO may useful in the diagnosis of asthma. The exact cutoff level is unclear.
Miedinger 2007 Diagnostic Study	7.5	101	Mannitol Challenge and Methacholine Challenge with BPT	Skin prick test, spirometry, question-naire, and oral exhaled nitric oxide (FeNO)	Firefighter subjects being tested for asthma	Uncertain	FEV_1 and FVC values with spirometry, methacholine, and mannitol challenge tests	Bronchial airway challenge with mannitol (PD_{15}) was more sensitive (92%), specific (97%), PPV (86%), and NPV (98%) when testing for asthma. PD_{20} has a sensitive (78%), specific (94%), PPV (68%), and NPV (96%) when testing for asthma. The only significant difference is FENO >47ppb with sensitivity at 42%.	"Asthma was considerably underdiagnosed in firefighters. The combination of a structured symptom questionnaire with a bronchial challenge test allows to identify patients with asthma and should routinely be used in the assessment of active firefighters and may be of help when evaluating candidates for this profession."	Diagnostic standard for asthma was wheezing plus hyper-responsiveness to bronchial challenge test. All were firefighters. Data suggest asthma is under diagnosed in firefighters. Mannitol challenge testing had highest sensitivity and specificity.

Pérez-de-Llano 2010 Diagnostic Study	7.5	102	Exhaled Nitric Oxide (FENO), Spirometry, broncho-dilator test, methacholine test, and ambulatory peak expiratory flow (PEF)	No comparison tests	Patients with difficult to treat asthma	None	FENO, FVC, FEV_1, airway hyperresponsive-ness, PEFR, and PEF	FeNo levels demonstrated a sensitivity of 87.5% (95% CI 73.9-94.5) and a specificity of 90.6% (95% CI 79.7-95.9).	"Our results demonstrate, for the first time, that FeNO levels might be predictive of response to a stepwise approach in patients with difficult-to-treat asthma."	Patients selected if difficult to control asthma symptoms. Flow rate was 50 ml/s. Used portable device for measurements. Data suggest FENO may help identify which patients with difficult to treat asthma will respond to treatment.
Smith 2004 Diagnostic Study	7.5	47	FENO for asthma diagnosis	Exhaled NO vs. spirometric testing, Fe(NO) measurement, skin allergy testing, broncho-dilator reversibility, hypertonic saline challenge, peak flow measurements, sputum induction (n = 40), oral prednisone	N = 17 mean age of 41.6 years with clinically diagnosed bronchial asthma, symptoms exceeding 6 weeks vs. n = 30 mean age of 31.8 without asthma.	Baseline, 2 weeks, and 4 weeks	Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).	Sensitivity%, specificity%, PPV%, NPV% for: peak flow variation:0, 100, NA,70; peak flow improvement with steroid >15%: 24,100,100,69; FEV_1 <80% predicted: 29,100,100,71; FEV_1 <90%: 35,93,75,72; FEV_1/FVC <70%: 35,100,100,73; FEV_1/FVC <80%: 47,80,57,73; FEV_1 improvement with steroid >15%:12,100,100,66; sputum eosinophils>3%: 86,88,80,92; FeNO>20 ppb: 88,79,70,92.	"[O]ur study confirms the overall superiority of FeNO measurements and induced sputum analysis in the diagnosis of asthma compared with conventional tests. FeNO measurements are quick and easy to perform and may be readily incorporated into routine pulmonary function test procedures. This advance offers the possibility that diagnosis of asthma may be performed more easily and confirmed with much greater confidence than had been possible to this date."	Small numbers. Baseline characteristics different in terms of mean age. Small numbers make conclusions difficult. Data suggest that FeNO and sputum eosinophils may be tests that can be more sensitive and specific than peak flow rate measures or spirometry.

Smith 2005 Diagnostic Study	7.0	97	FeNO	Algorithm based on conventional guidelines	Patients with chronic asthma on inhaled cortico-steroids treated with PCP	12 months	Dose of inhaled corticosteroids, rates of asthma exacerbations	FeNO group: final mean daily dose of fluticasone 370 ug per day. Conventional group: 641 ug per day (p = 0.003). No significant difference in exacerbation.	"With the use of FeNO measurement, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control."	Baseline data minimal in terms of other co-morbidities or symptoms. Exacerbations treated with oral prednisone. Data suggest FeNO may be used to help titrate inhaled fluticasone doses in chronic asthma patients. No mention on function.
Fukuhara 2011 Diagnostic Study	7.0	61	Methacholine test	Pulmonary function tests, blood tests	Outpatients between May 2007 and June 2010 with at least one subjective symptoms of recurrent cough, wheezing or dyspnea.	Uncertain	Comparison of FeNO levels between those with and without asthma. Sensitivity, specificity, positive likelihood, and negative likelihood.	FeNO levels with asthma: 90.1± 4.2 vs. without asthma: 40.1±18.4). Specificity: 89.5%, sensitivity: 78.6%, positive likelihood ratio: 7.46, negative likelihood: 0.24.	"The results of our study suggest that FeNO-based asthma screening criteria proposed in this study can be used to accurately diagnose asthma, particularly in atopic patients, and may be applicable for daily clinical practice."	Small numbers. Used 40 ppb as diagnostic cut-off. No mention of systemic steroid use or other medications. Unsure of duration of symptoms for participants and other co-morbidities. Data suggest FeNO may be helpful in diagnosis of atopic asthma.
Gelb 2006 Diagnostic Study	7.0	87	Total Exhaled Nitric Oxide (FENO)	Spirometry	34 normal subjects, 44 non-smoking, clinically stable asthmatic patients for at least 6 weeks to study initiation.	Not specified	Sensitivity, specificity, positive predictive value, negative predictive value	Using ROC plots for first asthma exacerbation with cut-off point of FEV_1at 76% predicted, sensitivity = 0.91, specificity = 0.50, positive predicted value = 0.65, and negative predictive value = 0.85. Using ROC plots for first asthma exacerbation with cut-off point for FENO at 28 ppb, sensitivity = 0.59, specificity = 0.82, PPV = 0.77, and	"In conclusion, baseline combined measurements of both post-bronchodilator FEV_1 percentage of predicted and FENO in clinically stable, treated, non-smoking patients with asthma may help risk stratify for subsequent exacerbations."	Follow up timing not clear. No blinding done. Co-interventions other than medications and smoking not well described. Data suggest that a combination of FEV_1 <76% and FENO >28 ppb increased the likelihood of an exacerbation requiring medical treatment to 85% over 18 months.

								NPV = 0.87. An abnormal FENO ≥ 28 ppb increased relative risk for exacerbation by 3.4 (χ^2 = 7.34, p = 0.007.		
Lemiere 2010 Diagnostic Study	7.0	41	Exhaled NO (FeNO)	Sputum eosinophil counts.	Subjects undergoing specific inhalation challenges (SIC) for possible occupational asthma.	24 hours	FeNO, FVC, FEV_1, sputum, skin prick tests.	Between baseline and 24 hours after exposure, sputum eosinophil counts and FENO levels were correlated (p = 0.4, p = 0.02; p = 0.4, p = 0.007).	"[B]oth sputum eosinophil counts and FENO were increased in subjects with a positive SIC after exposure to occupational agents, which was not the case in subjects with negative SIC."	Small numbers. Patients diagnosed with OA by SIC. Data suggest FENO is less effective in diagnosing patients with a positive SIC than sputum eosinophil counts.
Miedinger 2010 Diagnostic Study	6.5	284	Mannitol Challenge Methacholine Challenge with BPT	Skin prick test, spirometry, questionnaire, and oral exhaled nitric oxide (FeNO)	Military subjects	January 2007-October 2007	FEV_1 and FVC values with spirometry, methacholine, and mannitol challenge tests	BPT with mannitol and methacholine have similar sensitivity and specificity. Methacholine PD_{20}: sensitivity 43%, specificity 92%, PPV 55%, and NPV 88%. Mannitol PD_{15}: sensitivity 41%, specificity 93%, PPV 55%, and NPV 88%.	"BPT with mannitol has a sensitivity and specificity similar to methacholine for the diagnosis of physician- diagnosed asthma in military conscripts but is less costly to perform without the need to use and maintain a nebulizer."	Physician-based diagnosis of asthma used as gold standard. No explanation for how each person diagnosed with asthma, or how patients without a diagnosis received medical care if any. Recruits age 18-19. Data suggest BPT with mannitol has a similar sensitivity and specificity as methacholine testing.
Kostikas 2008 Diagnostic Study	6.5	219	FeNO measured with a potable nitric oxide analyzer	Patients with respiratory symptoms related to asthma	Students from University of Thessally and Technological Education Institute of Larissa with at least 1 positive answer from European Community	None	FeNO	FeNO higher in those with asthma vs. controls and those with non-specific symptoms, p<0.0001. Predictors of FeNO were diagnoses of asthma (p = 0.002), allergic rhinitis (p<0.001), and	"In conclusion, we report that FeNO measured by a portable analyzer may be used as a screening tool for asthma in a steroid-naïve population of young adults during pollen season. Significant	Small numbers actually tested with FENO. Patients had symptoms of asthma and were diagnosed by a blinded physician based on clinical signs and symptoms. All were University students. No mention of flow rate, gender, height, or

					Respiratory Health Survey II screening questionnaire			currently smoking (p = 0.003). Optimal cut-off point for FENO as diagnostic tool for entire study population was >19 ppb, providing 85.3% specificity (Sp) and 52.4% sensitivity (Se). FeNO performed better in nonsmokers, Sp 84.9% and Se 66.7%, cut-off >19 ppb. FeNO values >25 ppb give Sp >90%; Sp rose to >95% for cut-off of >30 ppb.	confounding factors are allergic rhinitis and current smoking."	recent respiratory infection. Data suggest that FENO is a good diagnostic tool in diagnosing asthma from non-asthma, but it cannot determine the difference between asthma and allergic rhinitis.
Menzies 2007 Diagnostic Study	6.0	151	Exhaled NO (FeNO) using portable device (MINO)	Exhaled NO (FeNo) using laboratory device (NIOX)	N = 101 with asthma, and n = 50 healthy volunteers	None	FeNO, FVC, FEV_1	Receiver-operating characteristics (ROC) and area under the curve (AUC) from both NIOX and MINO differentiating asthma and non-asthma patients was 0.654 (95% CI 0.565-0.744; p = 0.002) and 0.619 (95% CI 0.527-0.711; p = 0.018).	"[F]eNO values deriving using the MINO device are directly comparable with those using the NIOX device."	Patients diagnosed with asthma included using inhaled corticosteroids. Used flow rate 50 ml/s during testing. Did not report smoking status. Data suggest portable exhaled nitric oxide accurately reflects disease activity and correlates spirometry.
Allmers 2000 Diagnostic Study	5.5	9	Exhaled NO	Methacholine challenge test	Subjects with a history of immediate-type allergy to natural rubber latex and of workplace-related asthma when exposed	Follow-up evaluations were made up to 6 hours post exposure, and after 20±22 h (limited by	FEV_1 Exhaled NO	No correlation between a bronchial obstruction after methacholine challenge and bronchial response after specific allergen challenge was found. Decrease of exhaled	"There was no clear relationship between bronchial response, substance-specific IgE antibodies and an increase in exhaled NO levels. However, there was a tendency for subjects with substance-specific	Small numbers. Baseline characteristics similar, but sparse. Data suggest NO may be useful in detecting asthma in a select population. If there is positive IgE testing and a documented bronchial

					to MDI were studied	working hours of lung function laboratory)		NO in 16 of 19 subjects 16-18 hours after methacholine challenge and subsequent bronchodilation using salbutamol; p<0.001. 3/9 participants had a significant decrease in FEV_1 after exposure to MDI (no p-values given).	IgE antibodies and bronchial reaction to develop an increase in exhaled NO concentration."	response, the trend was for increases NO levels.
Berlyne 2000 Diagnostic Study	5.0	131	Fraction of exhaled nitric oxide (FENO)	Spirometry	N = 22 healthy nonatopic subjects, n = 28 healthy atopic subjects, n = 38 asthmatic subjects not taking steroids, n = 35 asthmatic taking steroids, and n = 8 subjects with eosino-philic bronchitis without asthma.	1 day trial	FEV_1, FEV_1/SVC	Significant difference in ENO levels, eosinophil percentages, absolute eosinophil counts ($\times 10^6$/g; p <0.001), macrophage percentages (p = 0.023), and lymphocyte percentages (p = 0.001).	"We conclude that ENO is likely to have limited utility as a surrogate clinical measurement for either the presence or severity of eosinophilic airway inflammation, except in steroid naïve subjects."	Baseline differences in age between groups. Age has been noted to be a significant factor in FENO measurements in younger (<41 years) populations. Other co--interventions such as exposures not documented. Data suggest FENO measures may not be clinically useful in detecting asthma, especially in non-steroid naive patients.
Fortuna 2007 Diagnostic Study	5.0	50	Fraction of exhaled nitric oxide (FENO)	Spirometry	N = 28 non-asthmatic patients vs. n = 22 asthmatic patients	2 con-secutive day study	FEV_1/FVC, FENO, sensitivity, specificity, PPV, NPV. FENO measured at 50 ml/s flow rate for 10 seconds.	Sensitivity was 77%, specificity was 64%, PPV was 62%, and NPV was 78% for FENO of asthmatic and non-asthmatic patients. Sensitivity was 22%, specificity was 100%, PPV was 100%, and NPV was 56% for FEV_1	"The diagnostic accuracy of FENO measurement was superior to that of the standard diagnostic spirometry in patients with symptoms suggestive of asthma. The use of FENO measurement and induced sputum	Small numbers; patients clinically suspected as having asthma. FENO performed first. Baseline characteristics were minimal and did not include many possible influences on FENO. Data suggest FENO under correct

								of asthmatic and non- asthmatic patients.	Eos% together to diagnose asthma in clinical practice is more accurate than spirometry or FENO assessment alone and easier to perform."	conditions may be useful in diagnosing asthma and chronic cough.
Demange 2009 Diagnostic Study	5.0	44	Fractional concen-tration of exhaled nitric oxide (FENO)	Methacholin e bronchial challenge (MBC) test	Subjects were lifeguards at indoor swimming pools	Exams took place between April and June 2006 between 9:00 and 12:00 am, or between 14:00 and 17:00 pm if morning exams not possible.	FENO FCV FEV_1	Median FENO for reactors was 18.9 ppb (11.9 to 36.3 ppb; 59.6 to 219.9% predicted) and 12.5 ppb (8.2 to 17.3 ppb; 44.2 to 96.5% predicted) in non-reactors.	"In conclusion, our results suggest that FENO measurements are potentially useful in detecting workers with AHR considered as a risk factor for the development of symptoms. Using a less than optimal cutoff-point for 'abnormal' FENO, we showed that high FENO values are associated with AHR while low FENO values tended to be associated with normal airway responsiveness."	Small numbers. Included lifeguards with current asthma, not needing corticosteroid treatment, and "not in crisis." Measurements taken at a 50ml/s flow rate. Good baseline comparisons. Data suggest FENO measurements correlate with airway hyper-responsiveness with methacholine challenge in patients with asthma.
Ferrazzoni 2009 Diagnostic Study	5.0	24	Specific inhalation challenge with isocyanate	Sham specific inhalation challenge	Subjects with suspected occupational asthma due to isocyanates (toluene diisocyanate, methylene-diisocyanate, or 1, 6- hexa-methylene diisocyanate). 15 subjects had positive responses to SIC; 24	Examined on 5 consecutiv e days, then follow-up 7 and 30 days after SIC with isocyanat e	FVC FEV Fractional exhaled nitric oxide (FeNO) pH in exhaled breath condensate (EBC)	No significant changes in FeNO in any groups after sham exposure. In SIC-positive group, FeNO increased from 30 minutes to 2 hours (45 ppb to 54 ppb) after isocyanate exposure. FeNO reached maximum between 24 and 48 hours (115 ppb to 118 ppb). FeNO still high after 7 days,	"Our results suggest that FeNO is a useful measurement in the evaluation of patients with occupational asthma, particularly when the causative agent is a low-molecular-weight compound, and the assessment of airway response on specific exposure is necessary for a diagnosis because conventional	Good baseline characteristic comparison. Co-interventions not well controlled. Data suggest FENO is useful in diagnosing asthma related to isocyanates.

					subjects had negative responses to SIC but had workplace exposure.			NS. In SIC-negative and rhinitic group, NS changes in FeNO. EBC pH increased for both SIC-positive and SIC-negative groups after 7 hours after sham exposure. No changes in EBC in pH detected at subsequent time points after isocyanate exposure in any groups.	immunologic tests are not applicable to demonstrate sensitization. The analysis of the time course of FeNO changes after SIC in the laboratory provides the necessary information for an appropriate use of this tool in a natural setting, such as the workplace."	
Jang 2003 Diagnostic Study	5.0	25	Sputum exam; NO metabolites, eosinophils, and eosinophils cationic protein	Peripheral blood measureme nt	N = 15 patients with asthma and in control group vs. n = 10 with no respiratory problems	Unknown	FEV_1, FEV_1/FVC	Higher results in asthmatics than controls for eosinophils and were at higher levels of ECP in blood. FEV_1, FEV_1/FVC negatively correlated with sputum eosinophils, p<0.01. NO metabolites (1220.3±180.2 mol/L vs. 545.6±98.4 mol/L, p<0.01), eosinophils (49.5±5.3% vs. 2.7±0.5%, p<0.01), and higher levels of ECP (1345.1±201.5 g/L vs. 146.5±27.5 g/L, p<0.01) in sputum.	"[T]hese findings suggest that the proportion of eosinophils in sputum have more accurate diagnostic marker of airway inflammation than NO metabolites in sputum and serum in differentiating asthmatic patients from control subjects."	Small numbers. Evaluated metabolites of NO not FENO.
Jang 1999 Diagnostic Study	5.0	23	Fraction of exhaled nitric oxide (FENO)	Spirometry	N = 13 patients with asthma and in control group vs. n = 10 with no respiratory problems	Unknown	FEV_1, FEV_1/FVC	Significant results in asthmatics vs. controls for higher NO metabolites for sputum (1252.5+ 203.3 'moll-' vs. 557.2+ 101.5 mol l-l,	"NO metabolites in induced sputum have a more valuable diagnostic value than those in serum in monitoring airway inflammation in asthma."	Small numbers. Evaluated metabolites of NO not FENO.

								PcO.01) but not in serum.		
Koksal 2003 Diagnostic Study	5.0	63	Nitric oxide (NO)	SO2 on serum TNF-a, IL-1h, IL-6, IL-8, nitrite	N = 40 male workers on farms vs. n = 23 controls, all healthy	Unknown	FEV_1/FVC, and FEV_1	Significant results in nitrates at p<0.0001 for workers than control group.	"These results show that TNF-a, IL-1h, IL-6, IL-8 and nitric oxide may play a role in the pathogenesis of bronchoconstriction in asthma-like syndrome due to the SO2 exposure."	Small numbers. Studied metabolites of NO not FENO.
Olin 2010 Diagnostic Study	4.0	2200	FeNo levels, spiro-metry	No comparison	Subjects from general population	4 years	FeNo, FVC, FEV_1, FEV_1/FVC, and blood tests	49 subjects had onset of wheeze at 4 year follow-up. Of the 49, a significant difference between FeNo levels at baseline and follow-up (p = 0.003) for both >90th and >95th percentile.	"The results indicate that increased FeNo is associated with a two- to three-fold increased risk of developing wheeze."	Did not describe testing method. No control for co-interventions. Data suggest increased FENO can indicate subclinical airway inflammation that may later lead to wheeze in asymptomatic patients.
Moore 2010 Diagnostic Study	4.0	60	Exhaled NO (FeNO)	Methacholine challenge (PD_{20})	Patients with occup-ational asthma	None	Exhaled fractional NO (FeNo), peak expiratory flow (PEF)	Workers with raised FENO levels had significantly higher levels of PD_{20} in the methacholine challenge test compared to those with normal levels (p = 0.035).	"[O]ccupational asthma patients can be divided into two variants by FENO level and that the group with raised FENO has significantly more reactivity in methacholine challenge."	Adjusted for smoking, atopy, and inhaled corticosteroids. All still exposed at work to various agents. FENO measured at 50 ml/s. Data suggest FENO more effective if more inflammatory airway disease.

Appendix III – Low Quality / Supplemental Studies

The following low-quality/supplementary studies were reviewed by the Evidence-based Practice Asthma Panel to be all inclusive, but were not relied upon for purpose of developing this document's guidance because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.[497]

NONSPECIFIC BRONCHIAL PROVOCATION TEST

Author/ Year	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
STUDIES NOT SPECIFIC TO OCCUPATIONAL ASTHMA										
Anderson 2011 MCC vs. mannitol to diagnose asthma Diagnostic Study	N/A	N/A	Mannitol; Methacholine	Exercise test; Physician diagnosis	Various	None	NSBP-Mannitol, methacholine, exercise	NA	"It is likely that both a direct test and an indirect test result may be required in some patients in order to confirm or exclude a diagnosis of asthma with certainty."	Review article. States that Mannitol has a higher specificity for a physician diagnosis of asthma than methacholine.
Decimo 2011 Use of mannitol challenge to diagnose asthma Diagnostic Study	N/A	50	Mannitol	FeNO; Spirometry; Exercise challenge test	Pediatric patients age 9-16 with intermittent allergic bronchial asthma or allergic rhinitis	None			"Mannitol challenge test can be a diagnostic tool more useful than the exercise challenge test to identify BHR in a pediatric population with intermittent allergic asthma or allergic rhinitis because it is better reproducible, quick and easy to perform and well tolerated."	Pediatric population. Not a working population.
Chan-Yeung 1982 MCC vs. SIC	N/A	72	Methacholine	SIC with PA and/or red cedar	Patients with confirmed diagnosis to red cedar	None	Spirometry Immunology NSBP SIC	2 control subjects had a PC_{20} below 25 mg/ml. All had	"Nonspecific bronchial hyperreactivity possibly plays an important role in the	Not truly a diagnostic study. More a measure of bronchial

Diagnostic Study								bronchial hyperreactivity at time of diagnosis, mean PC_{20} 2.5 mg/ml.	pathogenetic mechanism of the disease."	hyperreactivity in patients with already diagnosed red cedar asthma compared to controls. No data on controls. No specificity or sensitivity discussed. Data on removal from work. Data suggest bronchial hyperreactivity plays a role in asthma to red cedar. Not clear if asthma a result of exposure or a pre-existing component that increases chances of developing asthma to red cedar.
Kopferschmitt -Kubler 1998 Use of MCC before and after SIC Diagnostic Study	N/A	11	Non-specific bronchial provocation test	TDI provocation test	11 workers with a clinical history of isocyanate-induced asthma.	Uncertain	FEV_1	9 patients with positive bronchial provocation after TDI challenge had mean FEV_1 fall at PD_{20} (23.5%). Before provocation challenge it was 11.8% with same dose of methacholine ($p<0.01$).	"TDI provocation challenge that induced no fall in FEV1 in isocyanate-sensitive patients led to a slight but significant increase in non-specific BHR."	Small numbers. All diagnosed clinically with TDI-related asthma. On SIC, did not have any positive reactions. Data suggest even with negative SIC a non-specific inhalation challenge may be done to see if increase in hyper-responsiveness indicating a lower level reactivity.
Alvarez 2001	N/A	3	PST; IgE testing; MCC	Oilseed rape extract bronchial	3 non-smoking farmers	3 days	Oilseed rape extract bronchial	10 healthy subjects also skin prick tested	"…[T]he identification of the agent causing OA should always be	Very small numbers. No blinding of

Use of MCC before and after SIC Case reports				provocation test	diagnosed with OA		provocation test compared to the results of the skin prick test and IgE levels	with OSR. Skin prick testing positive in 3 cases, negative in all 10 controls. Metha-choline sensitivity and eosinophils in sputum increased 24 hours after OSR-BRT.	stressed and that allergy to OSR flour should be considered in the investigation of OA among farmers."	evaluators to the skin prick test. No true diagnostic comparison between tests. Data suggest OSR can cause BHR in sensitized patients diagnosed with OA to OSR.
Subiza 1991 MCC vs. SIC Case reports	N/A	11	SPT, IgE testing, precipitin test, bronchial provocation test	Specific inhalational test	One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder and 10 control patients without asthma	Single testing period	Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls	Patient had slight bronchial hyper-responsiveness to methacholine challenge testing. In contrast, patient had an immediate asthmatic response after challenge with the 1:1000 wt/vol dilution of Brazil ginseng extract (Pfaffia paniculata).	"The patient experienced asthma within a few months after starting to package Brazil ginseng-root dust at work with noticeable improvement while she was away from work during vacation…the results of this investigation demonstrate that Brazil ginseng dust is a health hazard as an Ag able to induce asthma."	One participant. Difficult to draw any significance. Patient had a reaction on bronchial provocation test to Brazil ginseng extract.
Histamine										
Dehaut 1983 Diagnostic Study	NA	18	Histamine challenge testing	None	18 clinically stable asthmatics	None	Specific lung conductance, dose-response curves for PC20, threshold concentration, reactivity	PC20 was the most reproducible index.	"In a smaller group of subjects PC20-FEV1 appeared to be more specific than indices using sGL and maximum partial expiratory flow rates in distinguishing normal from asthmatic responses."	No OA. There were a different number of measures done on different patients. No other comparison test used for diagnosis or asthma.

Britton 1986 Comparative Diagnostic Study	NA	24	Histamine challenge testing	None	24 patients with asthma	None	Three different techniques (Crockcroft et al, Yan et al, Mortagy)	Differences in dose response were normally distributed in Yan and Mortagy techniques. No difference in variance between the 3 methods was detected.	"Thus, of the three methods tested, the Yan technique was the simplest. It is fast, convenient, and inexpensive compared to Crockcroft method, and in a clinical setting did not compromise repeatability. These qualities offer potential advantages for clinical and epidemiological use."	No OA. No other comparison test used. This was looking at the different testing options for histamine NSBP testing in people reporting a diagnosis of asthma.
Histamine vs. Methacholine										
James 1997 Diagnostic Study	NA	NA	Histamine	Methacholine	None	None	PD_{20}	Cut-off value 8mg/mL in occupational challenge to define disease: Sn: 76% Sp: 51%	"Testing of airway responsiveness has been proposed in the assessment of occupational asthma, changes in asthma severity and the effects of potential sensitizers or treatments although its value in these settings is not yet fully established."	Review article. Reports there is no gold standard in diagnosing asthma. Not specific to OA in many measures.

SPECIFIC INHALATIONAL CHALLENGE TESTING

Author/Year	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Palczynski 2001 Single-blind clinical	N/A	31	Single blind exposure to 2% glutaralde-hyde and	Skin prick test, IgE evaluation, Spirometry	11 with glutaraldehyde induced asthma, 10 with an asthma	None	Symptom score, mediator levels, spirometry, nasal lavage	In those with GA occupational asthma: Rhinitis, nasal washings of eosinophils, basophils, ECP,	"NLF examination allows us to identify patients with occupational asthma and rhinitis due to GA."	At least 7 days between cross-over testing. Concentration of GA during test was 0.32 mg/m3 (below

crossover trial			saline 0.9% placebo		diagnosis, and 10 healthy individuals		changes in cytogram, protein content, eosinophil cationic protein (ECP), and mast-cell tryptase concentration	and tryptase were higher than after challenge with placebo in same group and then after GA in group with asthma and healthy volunteers (p<0.05).		occupational exposure standards). Cellular findings can also just indicate nasal rhinitis. Data suggest nasal washings can help diagnose work-related asthma in specific inhalational challenge testing procedures.
Vandenplas 1992 Diagnostic Study	N/A	20	Closed circuit SIC testing	History, SPT, spirometry, Challenge room method	20 subjects referred by WC Board or their physicians for evaluation of isocyanate-induced occupational asthma	None	Mean concentration of isocyanates above 20 ppb	Mean variances in isocyanate concentration: Closed circuit method = 6.3. Challenge room = 61.8 (p<0.001). Percentage of total exposure time above 20 ppb reduced from 11.3 to 3.5 % (p<0.001%).	"Specific inhalation challenges are essential to confirm or exclude isocyanate-induced occupational asthma…The closed-circuit method provides more reliable control of exposure levels during challenge test."	Small numbers. Duration of workplace exposure to isocyanates ranged from 0.5 to 36 years. Data suggest closed-circuit method and challenge room method give similar overall results, but there is less variance in isocyanate concentration with closed-circuit method.
Vally 2007 Double-blind, randomized study	N/A	13	Asthmatic response associated with high and low sulphite wine challenge	Spirometry variables, forced expiratory volume (FEV)	N = 7 (6 female, 1 male) aged 26-56 with history of bronchial hyper-responsivenes s within 1 hour of 150 ml of wine	Day 1: 150 mL red, white, or control wines over 5 minutes. Spirometry immediately after, 15/30 min following	Cut-off value determined to be a difference >1 doubling dose of histamine between pre- and post-challenge	Bronchial responsiveness to histamine for high- and low-sulphite wine, respectively (geometric mean): 2.09 mg/mL, 2.45 mg/mL. FEV did not exceed more	"In conclusion, this study had demonstrated that changes in BHR may occur following wine consumption in some wine-sensitive asthmatic patients, in the absence of reductions in FEV.	Small numbers. Baseline characteristics differences. Co-interventions not well described. Data suggest challenge with wine is not helpful in patients complaining of

					consumption vs. n = 1 control patient (male, age 51)	wine. Day 2: ≥48 hours post-initial challenge, if baseline FEV was ≤10% of that of day 1 an identical challenge performed. Day 3: Control challenge, in single blind trial.	BHR. Log (PC20).	than a 15% increase in any subjects.	owever, the lack of an obvious pattern in [BHR changes] suggests that positive responses were not solely related to wine consumption, but resulted from complex interactions…"	wine aggravated asthma symptoms.
Burge 1980 Diagnostic Study	N/A	51	Specific inhalational challenge to soldering flux in a small cubicle with fumes	Histamine provocative test	51 workers in electronics with clinically suspected OA	None	Spirometry and histamine	SIC: Positive in 34/51 (67%) workers. 14/17 workers were negative to histamine challenge test.	"There is reasonable evidence by the three standard criteria that the colcophony is acting as an allergen rather than an irritant in the concentrations encountered at work."	Details not well described. Uncertain of the histamine challenge results in all patients. All patients were in-patients. Testing protocol varied by patient. No control patients. Unable to draw conclusions based on results.
De Zotti 1996 Diagnostic Study	N/A	7	Specific inhalational challenge testing with wood dusts in exposure chamber while sanding	Skin prick tests, Specific IgE	7 wood workers with symptoms consistent with occupational asthma	None	Spirometry, results of SPT and IgE to determine atopy	4/7 (57%) had results consistent with asthma; 3/7 (43%) had results consistent with rhinitis.	"Predisposing factors for wood asthma are unknown but smoking habit, NSBH, and atopy seem to be less important than in asthma caused by high molecular weight substances…The specific provocation tests are particularly useful for	Small numbers. Baseline characteristics are sparse. Data suggest wood dusts may diagnose occupational asthma in furniture makers.

									diagnosing wood rhinitis and asthma…"	
Caron 2010 Diagnostic Study	N/A	44	Specific inhalational challenge by GenaSIC (closed circuit aerosol)	A previous SIC not done with "realistic method"	Subjects with occupational asthma	September 2007 through April 2009	Spirometry and FEV_1 values	No significant changes in spirometry in response to metha-choline. Causal agents are acrylates and isocyanates. Isocyanates: mean 13.98, SD 3.6.	"GenaSIC offers the possibility of reliable and safe exposures to dry particles, formaldehyde and isocyanates in the investigation of OA."	Study was of specific apparatus to deliver substance for specific inhalational challenges. Its main question was whether the machine would be useful. Study did not focus on diagnostic testing results.
Zeiler 2002 Diagnostic Study	N/A	9	Specific inhalational challenge with bovine dander. Using automatic, inhalation-synchron-ized dosimeter	Histamine challenge Skin prick test IgE	Dairy farmers with a clinical history "positive" for occupational asthma to cows	None	Spirometry results after and before histamine, IgE, skin prick test	There was a 275 fold difference in the amount of bovine protein needed for positive test. Histamine challenge was positive for 6/8 (75%).	"Our results support the use of purified major allergens for associating work-related asthma with the exposure to a specific allergen source."	Small numbers. Large variation in concentration of bovine protein needed for positive result. IgE and skin prick test seemed to help, but were less specific. Data suggest bovine protein may be used for specific inhalational challenge testing in dairy farmers.

Lin 1995 Diagnostic Study	N/A	9	Rotahaler device as the delivery method for specific inhalational challenge testing	Spirometry Methacholine challenge testing	9 patients referred for suspected red cedar asthma	None	Spirometry testing results after challenge	Of the 6/9 (66%) of the patients who reacted to plicatic acid, 3/6 (50%) reacted to challenge with red cedar dust delivered by the rotahaler.	"Our pilot study showed that a positive response to challenge with red cedar dust with the rotahaler was diagnostic for red cedar asthma but a negative test cannot rule out the diagnosis."	Small numbers, only 50% of test confirmed cases reacted with rotahaler. Data suggest rotahaler has low sensitivity and needs further testing in larger studies before it can be recommended.
Quirce 1992 Diagnostic Study	N/A	5	Specific inhalational challenge with alpha-amylase and cellulose by nebulizer	Skin prick test IgE REIA Histamine challenge test Methacholine	5 patients suspected of having occupational asthma to flour	None	Spirometry data Laboratory data	5/5 had positive skin prick test. 5/5 had positive IgE, positive methacholine test, and positive response to alpha-amylase. 3/5 (60%) positive response to cellulose on challenge testing.	"[A]lpha-amylase and cellulase behave as potential occupational allergens capable of sensitizing exposed bakers and giving rise to respiratory symptoms by an IgE-mediated mechanism."	Small numbers. No real comparison between diagnostic tests. This was more of a study to see if alpha-amylase and cellulose can cause respiratory symptoms.
Graneek 1987 Diagnostic Study	N/A	9	Specific inhalational challenge to various substances	Histamine provocative test	9 workers in various vocations with different exposures. All inpatient for diagnosis.	None	Spirometry after challenge testing	Histamine responsiveness significantly greater 3 hours after compared to 24 hours ($p<0.05$).	"[A]ttention should be focused not only on the period during and after late asthmatic reactions, but also particularly on the events which precede these reactions."	Small numbers. Study protocol varied between patients. Patients from various occupations. Limitations make it difficult to draw conclusions. Test appeared to cause decrease in FEV_1 in all patients.

Davison 1983 Case Series	N/A	8	Specific inhalational challenge test to castor beans after shaking trays of beans	IgE	5 people suspected of reacting to castor beans (3 Sudanese seamen, 2 lab workers, 3 controls)	None	Spirometry IgE levels	Of 3 patients, none had an immediate reaction, 2/3 (66%) of seamen had a decrease in FEV1. All 3 complained of skin irritations within an hour; 2/3 (66%) developed rhinitis and conjunctivitis.	"RAST inhibition, toxicological and haemagglutination tests suggest that the ricin and deracinated extracts contain distinct allergens."	Small numbers. Does not describe 3 controls. Case series suggests castor beans may cause allergic reactions and possibly occupational asthma.
Mapp 1986 Diagnostic Study	N/A	6	TDI inhalation challenge in an exposure chamber	Methacholine inhalation challenge	6 subjects with a history of sensitivity to TDI and positive results to bronchial challenge to TDI	Uncertain	FEV_1, PD_{20}	All subjects had normal airway responsiveness to methacholine (PD_{20} > 0.7 mg). 8 hours after TDI challenge, airway responsiveness increased significantly ($p<0.01$).	"[A]irway responsiveness is not necessary for the occurrence of toluene diisocyanate-induced asthma."	Small numbers. Baseline comparability different for age and FEV_1. With small numbers and baseline difference, conclusions are difficult to make from this study.

SPECIFIC IMMUNOLOGICAL TESTING

Author/Year	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Subiza 1991 MCC vs. SIC Case reports	N/A	11	Skin prick test, IgE testing, precipitin test, bronchial provo-cation test	Specific inhalational test	One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder and 10 control patients without asthma	Single testing period	Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls	Patient had slight bronchial hyper-responsiveness to methacholine challenge testing. In contrast, the patient had an immediate asthmatic response after challenge with the 1:1000 wt/vol dilution of Brazil ginseng extract	"The patient experienced asthma within a few months after starting to package Brazil ginseng-root dust at work with noticeable improvement while she was away from work during vacation…the results of this investigation demonstrate that Brazil ginseng dust	One participant. Difficult to draw any significance. Patient had a reaction on bronchial provocation test to Brazil ginseng extract.

								(Pfaffia paniculata).	is a health hazard as an Ag able to induce asthma."	
Riccardi 2003 Diagnostic Study	N/A	29	Specific/total IgE to iroko wood dust	Methacholine challenge after avoiding iroko dust exposure, skin prick test, intradermal test, bronchial provocation test, peak expiratory flow w/iroko wood dust	Group A (occ asthma subjects): n = 9 woodworkers with symptoms present after 6 months iroko exposure, Group B (no symptoms to any wood): n = 10 woodworkers, Group C (healthy control): n = 10	Not specified	Spirometry, IgE testing, PEF	PEF (in L/s) (mean±SD): Group A: while off work: 8.44±0.01; working w/iroko: 6.10±0.01; working w/ other wood: 8.31±0.02. Group B: off work: 8.4±0.01; w/iroko: 8.29±0.01; w/other wood: 8.29±0.01. Iroko SPT: all groups showed negative response. IgE (Iroko): all groups negative.	"Our data suggest that the pathogenesis of OA due to iroko could be attributable to the low-molecular-weight compounds of this wood, which could induce immunologic mechanisms other than IgE-mediated immediate hypersensitivity reactions."	Small numbers. Patients were tested without blinding and co-intervention such as concurrent infections not well described. Data suggest occupational asthma to iroko wood dust may be through a mechanism other than IgE.
Howe 1983 Diagnostic Study	N/A	22	RAST IgE to tetra-hydro-phthalic anhy-dride (TCPA)	Inhalation testing, TCPA-HSA, allergen discs, skin prick testing	7 women with respiratory symptoms, 8 volunteers from same factory, and 7 volunteers without TCPA exposure	10 months	IgE	In RAST inhibitions experiments, TCPA-HSA inhibited IgE binding to TCPA-HSA disc. In 7 women with respiratory problems, skin prick reactions occurred with 1.0% and 0.1% TCPA-HSA solutions.	"These results imply that occupational asthma caused by TCPA is an allergic reaction mediated by specific IgE antibody."	Small numbers. Baseline differences existed. Data suggest that TCPA can cause or aggravate asthma symptoms.
Topping 1986 Diagnostic Study	N/A	13	RAST IgE to trime-liitic (TMA), phtlaic (PA) and tetra-hydro-	Other IgE immuno-assays	Workers exposed to acid anhydrides with	None	IgE binding	Antigen binding of the IgE antibody depended both on the acid	"Each anhydride stimulates the formation of a distinct population of antibodies in which the nature of	Did not look at IgE results correlated with clinical presentation. It demonstrates that IgE results need

			phathalic (TCPA) anhydrides		respiratory symptoms			anhydride and the hapten.	the hapten profoundly influences antibody affinity."	to be validated with RAST inhibition for each anhydrides.
Aalto-Korte 2003 Diagnostic Study	N/A	7	IgE- per-sulfates	Skin prick test with ammonium and potassium persulfate salts	138 patients with allergic symptoms. 7 patients tested positive and were analyzed.	Uncertain	IgE	7 patients with positive skin prick were hairdressers; 2 had positive reactions to open application test of both ammonium and potassium persulfate solutions.	"..The mechanism of immediate hypersensitivity to persulfate seems to be IgE-meditated at least in some patients."	Very small numbers; no baseline characteristics provided. Patients did not all have asthma. Data suggest hypersensitivity to persulfates may be IgE mediated.

SKIN PRICK TESTING

Author/Year	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Walusiak 2000 Cohort Study	N/A	452	SPT to wheat flour	None	Apprentice bakers just starting their apprentices	None		3% of examined Polish apprentice bakers were found to have positive skin prick tests to occupational allergens before the onset of occupational exposure.	"In our opinion, the results of SPT should be very carefully examined, when diagnosing occupational allergy, as in some apprentice bakers positive results of SPT to flour allergens are found before vocational training."	Study is preliminary results of cohort study. Average age 16.2 years. "Baseline" SPT done during first month of apprentice work, indicating at least some work exposure before testing was done. WHEAT FLOUR
Subiza 1991 MCC vs. SIC Case reports	N/A	11	Skin prick test, IgE testing, precipitin test, bronchial provo-cation test	Specific inhalational test	One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder	Single testing period	Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls	Patient had slight bronchial hyper-responsiveness to methacholine challenge testing. In contrast, patient had an immediate asthmatic	"The patient experienced asthma within a few months after starting to package Brazil ginseng-root dust at work with noticeable improvement while	One participant. Difficult to draw any significance. Patient had reaction on bronchial provocation test to Brazil ginseng extract.

					and 10 control patients without asthma			response after challenge with the 1:1000 wt/vol dilution of Brazil ginseng extract (Pfaffia paniculata).	she was away from work during vacation…the results of this investigation demonstrate that Brazil ginseng dust is a health hazard as an Ag able to induce asthma."	BRAZILIAN GINSENG ROOT DUST
Alvarez 2001 Case reports	N/A	3	Skin prick test, IgE testing, Metha-choline test	Oilseed extract bronchial provocation test	3 nonsmoking farmers diagnosed with OA	3 days	Oilseed rape extract bronchial provocation test compared to the results of the skin prick test and IgE levels	10 healthy subjects were also skin prick tested with OSR. Skin prick testing positive in al 3 cases, negative in all 10 controls. Methacholine sensitivity and eosinophils in sputum increased 24 hours after OSR-BRT.	"…[T]he identification of the agent causing OA should always be stressed and that allergy to OSR flour should be considered in the investigation of OA among farmers."	Small numbers. No blinding of evaluators to skin prick test. No true diagnostic comparison between tests. Data suggest OSR can cause BHR is sensitized patients diagnosed with OA to OSR. OILSEED RAPE EXTRACT
Park 2002 Diagnostic Study	N/A	4	Skin prick test – porcine extract	Bronchial provocation test	Nurses complaining of asthmatic symptoms when exposed to porcine extract (PPE) powder. Non-smokers.	None	Serum specific IgE antibodies to PPE, α-amylase, lipase.	Significant inhibitions were noted with additions of α-amylase and PPE in a dose-dependent manner, while minimal inhibitions were noted by lipase and D.pteronyssinus antigens.	"[C]ommonly used drug powders, such as PPE, can induce occupational asthma in exposed nurses working in a hospital. Evidence is presented to indicate that –α-amylase included in PPE is a major allergenic component that can induce IgE-mediated broncho constriction."	Small numbers. All nurses with asthma complaints when handling extract. Data suggest porcine extract can cause asthma symptoms. SPT with PPE positive: 4 patients with positive SIC to PPE, but negative in 20 controls. PORCINE EXTRACT (alpha amylase)

NITRIC OXIDE

Author/Year	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Smit 2009 Cross-sectional Study	3.5	425	Exhaled Nitric Oxide (FENO) and endo-toxin levels	None	425 agricultural farmers	None	Exhaled NO, specific immuno-globulin (IgE) antibodies	Exhaled NO levels associated with endotoxin exposure in non-smoking participants (p = 0.02). In non-smoking, non-atopic workers had endotoxins exposure levels and FENO (GMR 1.09; 95% CI 1.05- 1.17; p = 0.006).	"[A] significant exposure-response relationship was found between exposure to endotoxins and exhaled NO in non-smoking, non-atopic agricultural workers."	Used flow rate of 50 ml/s for FENO testing. Baseline characteristics not included. Data suggest endotoxin exposed farmers who are non-smokers and non-atopic can cause a dose-response increase in FENO.
Olin 2004 Diagnostic Study	3.5	246	Exhaled NO (eNO)	Nasal NO (nNo)	246 non-smoking, bleachery and paper-mill workers	None	Exhaled NO, nasal NO, FEV_1, FVC, FEV_1/FVC, and specific IgE	The eNO levels were higher in subjects with asthma compared to those without asthma (22.5 vs. 15.8 ppb; p = 0.0004).	"We found no difference in eNO levels between atopic and non-atopic subjects with no reported asthma or rhinitis. Atopic subjects with asthma or rhinitis had higher eNo levels than those without atopy."	Participants working with bleaching agents in paper mills. Flow rate ~50 ml/s. Data suggest atopy does affect FENO and patients with atopy but without current symptoms are similar to those without atopy.
Lund 2000 Diagnostic Study	3.0	226	Exhaled NO (FeNO)	Nasal NO (nNo)	186 aluminum workers from potroom at a smelter and 40 control subjects from same plant but different area	None	FeNO, FVC, FEV_1	Non-smoking potroom workers with asthma symptoms had higher levels had higher levels of FeNO 21.0 (19.3-41.4) ppb, than those without asthma	"[E]exhaled No concentrations in non-smoking potroom workers were 63% higher than in non-smoking control subjects recruited from the same plant."	All worked for single employer. Co-interventions not well controlled. No mention of FENO testing flow rate. Patients did not have asthma, but exposed to

								symptoms 8.5 (5.9-12.8) ppb ($p<0.001$).		possible irritant at differing levels. Some had respiratory symptoms. Data suggest FENO is elevated in patients exposed to respiratory irritants even without a diagnosis of asthma or abnormal spirometry measures.
Reutman 2009 Diagnostic Study	1.5	43	Exhaled nitric oxide (ENO)	Pulmonary function tests (PFT)	43 nail technicians	None	ENO, cotinine metabolite, FEV_1, FVC	Years worked as a nail technician was significantly related to higher levels of NO ($p<0.05$).	"[J]ob latency and possibly hours of contact with methacrylates have measurable effects on PFT results and inflammation levels (ENO), as did smoking, in a select population of nail technicians....Thes e findings were inconclusive, but do warrant further investigation."	Pilot study. Small numbers. FENO was collected prior to spirometry. Did not include atopy at baseline. Data are difficult to interpret due to study shortcomings. Data suggest working as a nail technician may adversely affect lung function.

MANAGEMENT OF OA WITH INHALED CORTICOSTEROIDS

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
De Marzo 1988 Cross-over clinical trial No mention of industry	NA	N = 9 sensitized to TDI with late asthmatic reactions	Beclomethasone 200ug BID Beclomethasone 1000ug BID Placebo All taken 7 days before TDI inhalational challenge.	FEV_1 four hours after TDI exposure was: Placebo 2.6 +/- 0.17 L 200ug BID 3.3 +/- 0.12 L 1000ug BID 3.5 +/- 0.15 L	"These results suggest that the inhibitory effect of inhaled beclomethasone on TDI-induced late asthmatic reactions and increased responsiveness is dose-dependent."	Small numbers. Data suggest treatment with beclomethasone can be beneficial in employees with OA and TDI exposure.

sponsorship or COI.			Washout period 1 week.			
Marabini 2003 Longitudinal study No mention of industry sponsorship or COI.	NA	N = 10 subjects sensitized to TDI, flour, wood, or cereal	Beclomethasone 1,000 ug Salmeterol 100 ug Salmeterol PRN	No statistically significant differences in any of the morbidity outcomes were found between the beginning of the study and each follow-up time point. No subjects recovered completely.	"…as workers often have to remain exposed to the environmental course of their mild-to-moderate persistent OA, regular treatment with inhaled corticosteroids and long-acting bronchodilators is recommended."	50% drop out rate. Minimal description of inclusion and exclusion criteria. The patients were from different professions, different exposures. No quantifiable data on exposure. Data suggest treatment is beneficial in OA, even with continued exposures.

MANAGEMENT OF OA WITH IMMUNOTHERAPY

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Patriarca 2002 Case-control study No mention of industry sponsorship or COI.	2.0	N = 24 (17 had asthma)	Active group had sublingual SIT with latex extract, treatment was 4 days for desensitization and then a continuous maintenance latex exposure.	Subligual, cutaneous and mucous challenges became negative in 12/12 active patients. They were able to wear latex gloves for 6 hours. No adverse events to treatment reported.	"We believe that our protocol of subligual rush desensitization provides a new important therapeutic approach to latex allergy, without clinically detectable side effects, in our study population."	Asthma status not well described. Minimal baseline information provided. Treatment of "control" group not well described. Data suggest subligual SIT to latex allergy can be beneficial to health care workers and others in allowing continued exposure.
Cistero 2004 Case series	NA	N = 26 with cutaneus latex allergy with some respiratory symptoms	All received SIT subligual therapy	Both glove-use test and rubbing test improved significantly after 10 weeks of treatment $p<0.05$. No change detected for SPTs.	"The long-term effect of the treatment deserves further investigation…Tolerance of sublingual SIT is better than tolerance for injective therapy."	No control or randomization. Asthma not well described.
De jong 1999 Case series	NA	N = 11 with anaphylaxis to bumblebee venom	All received venom immunotherapy (VIT). Maintenance dose reached in 5-8 weeks.	Follow up period was 1.5-5 years. All had decreased skin test reactivity after 1 year of immunotherapy.	"Immunotherapy with bumblebee venom is safe and effective, and is comparable with honeybee	Small numbers. No asthma patients. No control group or alternative treatment group.

					and yellow-jacket venom immunotherapy."	
Leynadier 2000 RCT No mention of industry sponsorship or COI.	NA	N = 17 (9 had asthma) sensitized health care workers to latex	Active group received SIT vs. placebo.	Patients in active group had lower rhinitis score $p<0.05$, conjunctivitis score $p<0.05$, and cutaneous score $p<0.03$. Asthma symptoms not significantly different between groups up to 12 months of treatment.	"Latex-specific immunotherapy may allow sensitized personnel to remain at work, but further trials need to be conducted in a larger number of patients."	Small numbers of asthma patients. There was no benefit after 12 months of therapy in asthma symptoms.
Pereira 2003 Case report	NA	N = 4 all with anaphylaxis reaction to exposure to latex	All 4 patients received SIT with aqueous extract.	A challenge test was performed in 3/4 patients. Two had no reaction to latex gloves, one had rhinoconjunctivitis.	"We consider SIT with latex to be highly affective, safe and well tolerated provided we use this dose of the allergenic extract."	Small numbers. No placebo. Only 1 extract used.
Stern 2000 Case series	NA	N = 2 with systemic reactions to sting (no asthma patients)	Both received SIT.	Improvement with systemic symptoms in both cases	"…immunotherapy with BBV is the only safe therapeutic alternative in bumblebee-allergic patients who cannot avoid exposure."	No asthma patients. Only 2 cases presented.
Grembiale 2000 RCT No mention of industry sponsorship or COI.	NA	N = 44 subjects with history of atopic rhinitis; mean age 19. All had positive skin prick tests for house dust mite, but negative tests for other common aeroallergens.	Specific Immunotherapy (SIT) group (n = 22) received house dust mite allergen extract conjugated with sodium alginate vs. placebo group (n = 22) received 10 mg/ml of histamine phosphate in physiologic saline. Both groups made monthly visits for 2 years.	Methacholine PD_{20} FEV_1 increased 2.88-fold ($p < 0.001$) at 1 year of SIT treatment and 4.1-fold ($p <0.001$) after 2 years compared to pre-treatment values. No difference was found in the placebo group ($p = 0.708$).	"This study suggests that SIT, when administered to carefully selected, monosensitized patients with perennial allergic rhinitis, reduces airway responsiveness in subjects with rhinitis, and may be an appropriate prophylactic treatment for rhinitic patients with hyperreactive airways."	Patients did not have asthma – had allergic rhinitis. No tobacco use. Data suggest specific immunotherapy can be beneficial in patients with perennial allergic rhinitis to Dermatophagoides pteronyssinus.

Appendix IV – References

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