Medical Treatment Guidelines

Occupational / Work-Related Asthma

Effective May 2, 2022

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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 with a focus on a 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 may be considered and given relative weight when the pain has anatomic and physiologic correlation in proportion to the injury.

A.4 Re-Evaluate Treatment
If a given treatment or modality is not producing positive results within a well-defined timeframe, the provider should either modify or discontinue the treatment regime. The provider should evaluate the efficacy of the treatment or modality 2 to 3 weeks after the initial visit and 3 to 4 weeks thereafter. These timeframes may be slightly longer in the context of conditions that are inherently mental health issues, and shorter for other non-musculoskeletal medical conditions (e.g. pulmonary, dermatologic etc.). Recognition that treatment failure is at times attributable to an incorrect diagnosis a failure to respond 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 as timeframes for disease stages:
- Acute – Less than one month
- Subacute - One to three month, 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. It is recognized that treatment 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 and whose subjective symptoms do not correlate with objective signs and tests, reexamination in order to confirm the accuracy of the diagnosis and re-evaluation of the treatment program should be performed. When addressing a clinical issue that is not inherently a mental health issue, assessment for potential barriers to recovery (yellow flags/psychological issues) should be ongoing throughout the care of the patient. At 6-12 weeks, alternate treatment programs, including formal psychological or psychosocial evaluation should be considered. Clinicians must be vigilant for any pre-existing mental health issues or subsequent, consequential mental health issues that may be impacting recovery. For issues that are clearly and inherently mental health issues from the outset (i.e. when it is evident that there is an underlying, work-related, mental health disorder as part of the claim at issue), referral to a mental health provider can and should occur much sooner. Referrals to mental health providers 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, cognition and behavior (when at issue) 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 of imaging procedures and interpretation of results. All diagnostic procedures have characteristic specificities and sensitivities for various diagnoses. Usually, selection of one procedure over others depends upon various factors, which may include: relative diagnostic value; risk/benefit profile of the procedure; availability of technology; a patient’s tolerance; and/or the treating practitioner’s familiarity with the procedure.

When a diagnostic procedure, in conjunction with clinical information, provides sufficient information to establish an accurate diagnosis, a second diagnostic procedure is not required. However, a subsequent diagnostic procedure including a repeat of the original (same) procedure can be performed, when the specialty physician (e.g. physiatrist, sports medicine physician or other appropriate specialist) radiologist or surgeon documents that the initial study was of inadequate quality to make a diagnosis. Therefore, in such circumstances, a repeat or complementary diagnostic procedure is permissible under the MTG.

It is recognized that repeat imaging studies and other tests may be warranted by the clinical course and/or 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/or therapeutic injections when clinically indicated, and post-operatively to follow the healing process. Regarding serial imaging, (including x-rays, but particularly CT scans), it must be recognized that repeat procedures result in an increase in cumulative radiation dose and associated risks.

A given diagnostic imaging procedure may provide the same or distinctive information as
obtained by other procedures. Therefore, prudent choice of procedures(s) for a single diagnostic procedure, a complementary procedure in combination with other procedures(s), or a proper sequential order in multiple procedures will ensure maximum diagnostic accuracy, minimize the likelihood of adverse effect on patients, and promote efficiency by avoiding duplication or redundancy.

A.14 Surgical Interventions
Consideration 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, and other therapeutics 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 procedures listed in section 324.3(1)(a) of Title 12 NYCRR. 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 Psychological/Psychiatric Evaluations
In select patients, mental health evaluations are essential to make, secure or confirm a diagnosis. Of course, the extent and duration of evaluations and/or interventions by mental health professionals may vary, particularly based on whether: the underlying clinical issue in the claim is inherently a mental health issue; or there is a mental health issue that is secondary or consequential to the medical injury or illness that is at issue in the claim in question; or there is a pre-existing, unrelated mental health issue that has been made worse by, or is impeding the recovery from (or both) the medical injury or illness that is at issue in the claim in question.

Tests of psychological function or psychometric testing, when indicated, can be a valuable component of the psychological evaluation in identifying associated psychological, personality and psychosocial issues. Although these instruments may suggest a diagnosis, neither screening nor psychometric tests are capable of making a diagnosis. The diagnosis should only be made after careful analysis of all available data, including from a thorough history and clinical interview.
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: When assessing for a pre-existing, unrelated mental health issue that has been made worse by, or is impeding the recovery from (or both) a work-related, medical injury or illness, then a one-time visit for initial psychiatric/psychological encounter should be sufficient, as care would normally be continued by the prior treating provider. If psychometric testing is indicated by findings in the initial encounter, time for such testing should not exceed an additional three hours of professional time. For conditions in which a mental health issue is a central part of the initial claim, or in which there is a mental health issue that is secondary or consequential to the work-related, medical injury or illness, that is part of the claim in question, then more extensive diagnostic and therapeutic interventions may be clinically indicated, and are discussed in detail in the Medical Treatment Guidelines for such mental health conditions.

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. For all psychological/psychiatric interventions, there must be an assessment and treatment plan with measurable behavioral goals, time frames and specific interventions planned.

- 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 rather to enhance functional recovery.

For PTSD Psychological Intervention:

- Optimum duration three to six months.
- Maximum duration: nine to twelve months.

For select patients, longer supervision and treatment may be required, and if further treatment 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 weeks during the first six months of treatment. For treatment expected to last six to twelve months, such documentation should be provided every four to eight weeks. For long-term treatment beyond twelve months, such documentation should be provided every eight to twelve weeks. All parties should strive for ongoing and continuous communications, in order to facilitate seamless, continuous and uninterrupted 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 and behavioral; (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.

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. An FCE is not indicated early during a treatment regime for any reason including one to support a therapeutic plan.

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.

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 employer’s designee, either in person, by video conference, or by telephone, to obtain information regarding the individual or specific demands of the patient’s pre-injury job. This may include a description of the exertional demands of the job, the need for repetitive activities, load lifting, static or awkward postures, environmental exposures, psychological stressors and other factors that would pose a barrier to re-entry, risk of re-injury or disrupt convalescence. When returning to work at the patient’s previous job tasks or setting is not feasible, given the clinically determined restrictions on the patient’s activities, inquiry should be made about modified duty work settings that align with, the patient’s condition in view of proposed work activities/demands in modified duty jobs. It should be noted, that under certain circumstances, more than one job site evaluation may be indicated.
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, as can video conferences, conducted from the worksite and ideally workstation or work area.

Frequency: one or two contacts
- 1st contact: Patient is in a functional state where the patient can perform some work.
- 2nd contact: 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

Effective date will coincide with the launch of OnBoard: Limited Release

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Chemical</th>
<th>Occupational Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Molecular Weight:</td>
<td>Grains and flours, in particular</td>
<td>Bakers and food processors, dock workers (exposed to</td>
</tr>
<tr>
<td>(Direct sensitizers)</td>
<td>wheat, soya and:</td>
<td>shipping of the materials)</td>
</tr>
<tr>
<td></td>
<td>enzyme additives to these products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal proteins from urine,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dander, fur, hair or saliva</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Latex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Molecular Weight:</td>
<td>Acid anhydrides (plastics, dyes,</td>
<td>Chemical production workers.</td>
</tr>
<tr>
<td></td>
<td>adhesives and resins)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Di-isocyanates (rigid foam, binders,</td>
<td>Cosmetologist</td>
</tr>
<tr>
<td></td>
<td>coatings, elastomers,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and paints)</td>
<td>Refinery workers.</td>
</tr>
<tr>
<td></td>
<td>Platinum salts</td>
<td>Smelters</td>
</tr>
<tr>
<td></td>
<td>Aluminum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cleaning agents</td>
<td>Jewelry/alloy production workers</td>
</tr>
<tr>
<td></td>
<td>Wood dusts</td>
<td>Cleaning services</td>
</tr>
<tr>
<td></td>
<td>Colophony</td>
<td>Sawmill workers/carpenters</td>
</tr>
<tr>
<td></td>
<td>Fluxes</td>
<td>Electronics manufacturing</td>
</tr>
</tbody>
</table>

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:
  o Throat tightness
  o Shortness of breath
o Difficulty with inspiration or expiration
o Harsh breath sounds
o Cough
o Sputum production
o Recurrent bronchitis
o Chest tightness

Duration, onset and frequency of symptoms

• Symptom development including:
  o Aggravation and alleviation of symptoms in relationship to work environment
  o Changes in work environment
  o Changes in symptoms in relation to days worked and not worked (especially improvements on weekends or holidays when not at work)
  o Progression of symptoms
  o 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:
  o Mucous membrane abnormalities
  o Nasal polyps/swelling/discharge
  o Clubbing
  o Anterior-posterior chest diameter

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

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

- Auscultation for:
  o Inspiration to expiration ratio
  o Adventitious breath sounds (crackles, wheeze, rales, rhonchi)
  o 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 (FEV₁) and the ratio of the FEV₁ to the forced vital capacity (FEV₁/FVC ratio) are most useful.

Asthma is confirmed by demonstrating airflow obstruction (e.g., by reduction in both FEV₁/FVC ratio and FEV₁) 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 FEV₁ 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 (FEV₁), expressed in liters and/or as a percentage of predicted values,
- FEV₁ before and after (pre/post) administration of a bronchodilator, usually albuterol (salbutamol),
- Pre/post FEV₁, which is measurement of FEV₁ before and after (pre/post) a work shift, taking into account diurnal variation,
- Ratio of FEV₁ to forced vital capacity (FEV₁/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 (FEF₂₅₋₇₅), 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 FEV₁ or an absolute value increase of at least 200 mL after bronchodilator administration as indicating reversibility of airflow obstruction in FVC or FEV₁ 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 FEV₁ that indicates a 20% fall in FEV₁. 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 FEV₁ is measured and the test is stopped when the FEV₁ has fallen by 20% from baseline or diluent value. The response is usually expressed as a provocative concentration (PC₂₀) producing a 20% fall in forced expiratory volume in 1 second. The presence of asthma is usually defined as a ≥20% fall in the FEV₁ 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 PC₂₀ mg/mL dose.

Recommended - for use in diagnosing asthma if the clinical history is compelling and other tests (spirometry and bronchodilator responsiveness) are not diagnostic.

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 – Bronchoprovocation with methacholine or cold air may be used to establish the diagnosis of asthma, particularly when asthma is suspected and spirometry is normal or near normal. NSBP is not generally recommended if the baseline FEV₁ is <65% of predicted. Absolute contraindications for methacholine challenge testing include:
- severe airflow limitation (FEV₁<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 (FEV₁ <60% predicted or <1.5L;
- unable to perform acceptable-quality spirometry;
- pregnancy;
- nursing mothers; 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, an exposure particularly prevalent in health care settings.

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 FEV1, 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 FEV₁, 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)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Potential Conflict of Interest (COI)</th>
<th>Score (0-11)</th>
<th>Management Topics Evaluated</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung 2014</td>
<td>Guidelines</td>
<td>ERS/ATS Task Force on Severe Asthma</td>
<td>NA</td>
<td>Pharmacological treatment</td>
<td>Treatment of severe asthma relies heavily on the maximal optimal use of corticosteroids and bronchodilators. There is potential for benefits of biological agents.</td>
<td>Recommendations on treatment for severe asthma. No specific mention of OA or WEA.</td>
</tr>
<tr>
<td>Baur 2012</td>
<td>Guidelines</td>
<td>ERS Task Force Report</td>
<td>NA</td>
<td>Reduction of exposure</td>
<td>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.</td>
<td>Specific to OA and WEA. Authors address their recommendations for both diagnosis and treatment of OA and WEA.</td>
</tr>
<tr>
<td>Tarlo 2008</td>
<td>Consensus guideline, literature review document</td>
<td>American College of Chest Physicians Consensus Statement Supported by Schering-Plough Corporation.</td>
<td>NA</td>
<td>Removal from exposure Minimizing exposure Inhaled corticosteroids Other antiinflammatory agents Immunotherapy</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Recommendations</td>
<td>Notes</td>
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<tr>
<td>Beach 2005</td>
<td>Consensus guideline, literature review document</td>
<td>Removal from exposure Reduction of exposure Use of PPE Inhaled Corticosteroids Immunotherapy</td>
<td>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.</td>
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<tr>
<td>Newman 2005</td>
<td>Guidelines for Occupational Asthma</td>
<td>General management of OA</td>
<td>No official recommendations based on literature review. Appears to be mainly consensus recommendations. Not specifically addressing any one type of management.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nicholson 2005</td>
<td>Consensus guideline, literature review document</td>
<td>Removal from exposure Minimizing exposure Medications</td>
<td>Authors follow a grading protocol with recommendations. Recommendations are broad in management sections. No mention of arms/benefits. No level of confidence noted.</td>
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</table>

Reasons: It is most effective when it targets 1 allergen or a few allergens. Immunotherapy is not indicated to treat irritant-induced asthma.

Beach 2005 Consensus guideline, literature review document

Newman 2005 Guidelines for Occupational Asthma
Supported by British Occupational Health Research Foundation (BOHRF)

Nicholson 2005 Consensus guideline, literature review document

FEV<sub>1</sub> 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<sub>20</sub> in patients tested with inhaled corticosteroids. Immunotherapy to wheat flour extract appeared to be safe and resulted in improvement in symptoms and lung function.

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.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Potential Conflict of Interest (COI)</th>
<th>Score (0-11)</th>
<th>Sample Size</th>
<th>Comparison Group</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Malo 1996</td>
<td>RCT-crossover</td>
<td>Supported in part by Glaxo Canada Ltd. No mention of COI.</td>
<td>8.0</td>
<td>N = 44 patients with occupational asthma between ages 20-60 years</td>
<td>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.</td>
<td>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 (±0.32), p &lt;0.001 and -0.88 (±0.2), p &lt;0.001, respectively. Compared to same group during placebo phase: 0.89 (±0.23), p &lt;0.001 and 0.64 (±0.16), p &lt;0.001. FEV₁ and FVC significantly deteriorated in both active-drug and placebo periods.</td>
<td>“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.”</td>
<td>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.</td>
</tr>
<tr>
<td>Maestrelli 1993</td>
<td>RCT</td>
<td>No mention of industry sponsorship or COI.</td>
<td>5.0</td>
<td>N = 15 subjects exposed to TDI in workplace and diagnosed with OA by SIC</td>
<td>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.</td>
<td>10 participants (6 in placebo, 4 in treatment) had no significant fall in FEV₁ at any time after TDI challenge. Severity of reaction to TDI decreased in both groups at 6 months. PD₂₀ FEV₁ increased after 2 months in treatment group (p&lt;0.05).</td>
<td>“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.”</td>
<td>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 FEV₁ decline.</td>
</tr>
<tr>
<td>Mapp 1987</td>
<td>Cross-over clinical trial</td>
<td></td>
<td>6.0</td>
<td>N = 24 sensitized subjects to TDI</td>
<td>Beclomethasone 1 mg BID Theophylline 6.5 mg/kg BID Verapamil 120 mg BID Cromolyn 20 mg QID</td>
<td>After exposure to TDI, subjects treated with placebo, verapamil or cromolyn developed a late or dual</td>
<td>“These results suggest that only high-dose inhaled steroids can completely block TDI-”</td>
<td>Cross over study design, blinding of assessor not described. Baseline characteristics minimal, but...</td>
</tr>
<tr>
<td>No mention of industry sponsorship or COI.</td>
<td>Administered for 7 days</td>
<td>Asthmatic reaction with a decrease in PD$_{20}$ FEV$_1$. Subjects treated with beclomethasone developed no asthmatic reaction or increase in airway responsiveness. Theophylline developed a less severe early and late asthmatic reaction.</td>
<td>Induced late asthmatic reactions.&quot;</td>
<td>Similar. Data suggest that beclomethasone can help treat patients with TDI-related asthma by decreasing hyper-responsiveness of airways.</td>
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</tbody>
</table>
### Management of OA with Immunotherapy

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Potential Conflict of Interest (COI)</th>
<th>Score (0-11)</th>
<th>Sample Size</th>
<th>Comparison Group</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sastre 2003</td>
<td>RCT</td>
<td>No mention of industry sponsorship or COI.</td>
<td>5.5</td>
<td>N = 24 patients allergic to natural rubber latex (NRL), average age 33.8 years</td>
<td>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.</td>
<td>Post-treatment comparison of active group vs. placebo yielded cutaneous tolerance index difference of 8.9 (p &lt; 0.01); reduction in scores for latex use test and rubbing test (p = 0.026 and p = 0.072, respectively).</td>
<td>“…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.”</td>
<td>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.</td>
</tr>
<tr>
<td>Armentia 1990</td>
<td>Case-control study</td>
<td>No mention of industry sponsorship or COI.</td>
<td>4.5</td>
<td>N = 26 patients (16 had active treatment; 10 had placebo)</td>
<td>Injections of what flour extract were done once a week. Treatment was done for 10 or 20 months.</td>
<td>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&lt;0.05). Placebo group had no noticeable changes in testing after 10 months of placebo treatment.</td>
<td>“Our study shows with objective measurements that immuno-therapy with wheat flour results in a significant clinical and immune response in our asthmatic patients.”</td>
<td>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.</td>
</tr>
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</table>

### Studies and Guidelines Addressing Removal/Reduction of Exposures

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Potential Conflict of Interest (COI)</th>
<th>Score (0-11)</th>
<th>Management Topics Evaluated</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banks 1990</td>
<td>Observational study</td>
<td>NA</td>
<td>Reduction of exposure.</td>
<td>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.</td>
<td>Only 6 participants. No comparison to removal from exposure or full continued exposure.</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Methods</td>
<td>Findings</td>
<td>Summary</td>
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<tr>
<td>Beach 2005</td>
<td></td>
<td>N/A</td>
<td>Removal from exposure. Reduction of exposure. Use of PPE. Inhaled Corticosteroids. Immunotherapy.</td>
<td>Less than half of the studies with removal (complete or reduction of exposure) reported improved FEV₁. 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 PD₂₀ in patients tested with inhaled corticosteroids. Immunotherapy to wheat flour extract appeared to be safe and resulted in improvement in symptoms and lung function.</td>
<td>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.</td>
<td></td>
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<tr>
<td>de Groene 2012</td>
<td></td>
<td>NA</td>
<td>Removal from exposure. Reduction of exposure.</td>
<td>Compared to continued exposure, removal from exposure increased the likelihood of reporting absence of symptoms, improved FEV₁ and decreased NSBH. Compared to continued exposure reduced exposure also increased the likelihood of absence of symptoms, but did not affect FEV₁.</td>
<td>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.</td>
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<tr>
<td>Merget 1999</td>
<td></td>
<td>NA</td>
<td>Removal from exposure. Reduction of exposure</td>
<td>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.</td>
<td>Single survey of 83 workers. Authors noted that reduction and removal had similar outcomes in terms of symptoms and FEV₁ values.</td>
<td></td>
</tr>
<tr>
<td>Fishwick 2012</td>
<td></td>
<td>NA</td>
<td>Removal from exposure. Medications</td>
<td>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.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Nicholson 2005</td>
<td></td>
<td>NA</td>
<td>Removal from exposure. Minimizing exposure. Medications.</td>
<td>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.</td>
<td>Followed a grading protocol with recommendations. Recommendations are broad in management sections. No mention of arms/ benefits. No level of confidence noted.</td>
<td></td>
</tr>
<tr>
<td>Paggiaro 1994</td>
<td></td>
<td>NA</td>
<td>Removal from exposure. Reduction of exposure.</td>
<td>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 result in</td>
<td>Looked at several studies of OA due to TDI. Good summary of results. No specific guidelines or level of evidence.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Type</td>
<td>Exposure Management Strategies</td>
<td>Comments</td>
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<tr>
<td>Paggiaro 1984</td>
<td>NA</td>
<td>Observation study</td>
<td>Removal from exposure. Continued exposure.</td>
<td>Following 27 patients over 2 years. 12 were removed/left exposure. Included both employees with and without OA.</td>
<td></td>
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</tr>
<tr>
<td>Vandenplas 2012</td>
<td>NA</td>
<td>Consensus Guideline, literature review</td>
<td>Consequences of persistent exposure. Pharmacological treatment. Immunotherapy. Avoidance of exposure. Reducing exposure through engineering controls. Reducing exposure through PPE.</td>
<td>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.</td>
<td></td>
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<tr>
<td>Vandenplas 2002</td>
<td>NA</td>
<td>Observation study</td>
<td>Removal from exposure. Reduction of exposure.</td>
<td>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.</td>
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</tr>
<tr>
<td>Anees 2006 Retrospective study</td>
<td>NA</td>
<td>Removal from exposure</td>
<td>Mean rate of FEV&lt;sub&gt;1&lt;/sub&gt; decline after removal from exposure was 26.6 ml/year. Mean rate of FEV&lt;sub&gt;1&lt;/sub&gt; decline was not related to duration of symptomatic exposure or smoking. No evidence inhaled corticosteroids after removal from exposure had a major beneficial effect on step-up in FEV&lt;sub&gt;1&lt;/sub&gt;.</td>
<td>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 effects removal from any one causative agent. Various treatments also make determination of treatment effectiveness difficult.</td>
<td></td>
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</table>
Appendix II – Evidence Tables

Evidence for the Use of Peak Expiratory Flow Rates

There are 2 high-quality and 6 moderate-quality studies incorporated into this analysis.

<table>
<thead>
<tr>
<th>Author/Year Study Type</th>
<th>Score</th>
<th>N</th>
<th>Test Used</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrin 1992 Comparative Study</td>
<td>7.5</td>
<td>61</td>
<td>Spirometry both at work and way from work, skin prick test, specific IgE, specific inhalational challenge</td>
<td>Patients with a history suggestive of occupational asthma</td>
<td>4 weeks or more</td>
<td>PEF values</td>
<td>PEF vs. FEV1: Sensitivity of 81% and specificity of 74%.</td>
<td>“[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.”</td>
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<td>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.</td>
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</tr>
<tr>
<td>Park 2009 Controlled Clinical Trial</td>
<td>7.5</td>
<td>76</td>
<td>Serial PEF over 3 weeks</td>
<td>Cross-shift PEF, calculated by taking the pre-shift and post-shift values. Over a 3-week period.</td>
<td>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.</td>
<td>Participants measured their PEF at 2 hour intervals over a 3-week period, including both work days and rest days.</td>
<td>PEF values</td>
<td>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%.</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Impact</td>
<td>Method</td>
<td>Skin prick test (SPT), specific inhalation challenge testing</td>
<td>Uncertain</td>
<td>Sensitivity and specificity of Stenton method</td>
<td>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%.</td>
<td>It does not usually identify the cause of occupation asthma, but can be used to confirm successful relocation as its specificity is high.</td>
<td>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.</td>
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<tr>
<td>Burge 2009</td>
<td>6.5</td>
<td>556</td>
<td>Stenton method</td>
<td>236 records from workers with independently diagnosed occupational asthma and 320 records from controls with asthma</td>
<td>Uncertain</td>
<td>Workday Specificity (WSP), Workday Sensitivity (WSE), Rest day Sensitivity (RSE), and Rest Day Specificity (RSP)</td>
<td>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%.</td>
<td>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.</td>
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</tr>
<tr>
<td>Moore Occup Med 2009:59(6):4 13-7</td>
<td>6.5</td>
<td>311</td>
<td>Serial measurement of peak expiratory flow</td>
<td>Uncertain</td>
<td>FEV1/FVC, sensitivity, specificity</td>
<td>Sensitivity 81.8% for records of 4 weeks duration and 70% for those of 2 weeks duration (specificity 93.8 and 82.4%, respectively).</td>
<td>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.</td>
<td>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 record in serial PEF measurements.</td>
<td></td>
</tr>
<tr>
<td>Anees 2004</td>
<td>5.5</td>
<td>141</td>
<td>Peak expiratory flow</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Outcome Description</td>
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<tr>
<td>Moore Occup Med</td>
<td>2009</td>
<td>67</td>
<td>Serial measurement of peak expiratory flow</td>
<td>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.</td>
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<tr>
<td>Other Studies</td>
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<tr>
<td>Leroyer 1998</td>
<td>1998</td>
<td>20</td>
<td>Peak expiratory flow</td>
<td>PEF: sensitivity = 73%, specificity = 100% Unsupervised FEV₁: Sensitivity = 55%, specificity = 89%</td>
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<tr>
<td>Weytjens 1999</td>
<td>1999</td>
<td>57</td>
<td>Specific inhalational challenge, spirometry</td>
<td>Mean changes in PEF not different from changes in FEV₁ at any time (p = 0.13). 20% fall in PEFc to sensitivity = 92%, specificity = 95%, PPV = 97%.</td>
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</table>

"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.

Small numbers – 55% (11/20) confirmed to have occupational asthma by SIC testing. Data suggest unsupervised FEV₁ not better than unsupervised PEF measures for diagnosing occupational asthma.

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 FEV₁ measures for decreased lung function.
Evidence for the Use of Nonspecific Bronchial Provocation Test

There are 9 high- and 22 moderate-quality studies incorporated into this analysis. There are 9 other studies in Appendix 1.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test Used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunter 2002</td>
<td>Diagnostic, Cross-sectional Study</td>
<td>10.0</td>
<td>110</td>
<td>Spirometry</td>
<td>Methacholine</td>
<td>N = 21 healthy control subjects (no symptoms of asthma and non-smokers) vs. n = 69 with asthma (have FEV₁ values &gt;65%) vs. n = 20 diagnosed with asthma “pseudo-asthma.”</td>
<td>Skin prick test. Peripheral blood eosinophil count. Twice daily PEF.</td>
<td>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</td>
<td>“[T]he methacholine PC20 is the most sensitive marker of mild asthma.”</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Hedman 1998</td>
<td>Diagnostic Study</td>
<td>9.5</td>
<td>230</td>
<td>Rapid methacholine challenge test</td>
<td>Clinical diagnosis with ATS guidelines. PEF Spirometry</td>
<td>Patients referred to clinic due to dyspnea, wheezing or a cough of unknown reasons.</td>
<td>None</td>
<td>Sensitivity, Specificity, Positive Predicted Values, and Negative Predicted Values of MIC based only distribution of PD₁₅ FEV₁, and PD₂₀ FEV₁ in</td>
<td>Sensitivity: PD₁₅ FEV₁ (84%), PD₂₀ FEV₁ (77%) Specificity: PD₁₅ FEV₁ (69%), PD₂₀ FEV₁ (82%) PPVs: PD₁₅ FEV₁ (50%), PD₂₀ FEV₁ (60%) NPVs: PD₁₅ FEV₁ (92%), PD₂₀ FEV₁ (91%)</td>
<td>“The Bayesian analysis approach showed that the present rapid methacholine challenge is as capable as previous methods in distinguishing between normal and asthmatic subjects.”</td>
<td>Patients diagnosed as asthmatics clinically and after spirometry. Data suggest rapid methacholine challenge testing has sensitivity of 77% and specificity of 82% with PD₂₀ FEV₁.</td>
</tr>
<tr>
<td>Study Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Score</td>
<td>N</td>
<td>Diagnostic Test(s)</td>
<td>Clinical Markers</td>
<td>Primary Outcomes</td>
<td>Notes</td>
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<tr>
<td>Di Lorenzo</td>
<td>2007</td>
<td>Diagnostic Study</td>
<td>9.0</td>
<td>115</td>
<td>Methacholine inhalational challenge test</td>
<td>Spirometry, Allergen skin prick testing, Peripheral blood eosinophil testing, serum ECP levels, sputum induction after recovery.</td>
<td>60 patients with mild asthma (Asthma Patients), 30 patients with GERD and asthma-like symptoms (GER Patients), 25 control (Healthy Control Subjects)</td>
<td>None</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio, Maximum PEF A%M, MCh PC&lt;sub&gt;20&lt;/sub&gt;/FEV&lt;sub&gt;1&lt;/sub&gt;, Blood Eosinophils, Serum ECP levels, Induced sputum eosinophils</td>
<td>For primary outcomes: FEV&lt;sub&gt;1&lt;/sub&gt;/FVC ratio (Healthy Control Subjects: 81.3±1.3 vs. Asthma Patients: 76.6±0.4, p&lt;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&lt;0.001; Asthma Patients: 17.4±0.8 vs. GER Patients: 5.6±0.8, p&lt;0.001). “The MCh PC&lt;sub&gt;20&lt;/sub&gt;/FEV&lt;sub&gt;1&lt;/sub&gt; 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.”</td>
<td></td>
</tr>
<tr>
<td>Goldenstein</td>
<td>2001</td>
<td>Diagnostic Study</td>
<td>8.5</td>
<td>121</td>
<td>Methacholine Inhalation Challenge (MIC)</td>
<td>Peak Expiratory Flow Variation (PEFvar), Post-bronchodilator FEV&lt;sub&gt;1&lt;/sub&gt; (post BD FEV&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>At least 7 years old, English speaking, and had recurrent (≥3 months) asthma-like symptoms</td>
<td>3-4 weeks</td>
<td>Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value of MIC, Post-BD FEV&lt;sub&gt;1&lt;/sub&gt;, Best Mean Daily PEFvar, and Best Period PEFvar.</td>
<td>Sensitivity: MIC = 85.71%, Post-BD PEFvar = 53.7%. Specificity: MIC = 100%, Post-BD FEV&lt;sub&gt;1&lt;/sub&gt; = 100%</td>
<td>“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.”</td>
</tr>
<tr>
<td>Cirillo</td>
<td>2006</td>
<td>Cross-sectional Study</td>
<td>7.5</td>
<td>726</td>
<td>Methacholine Inhalation Challenge (MIC)</td>
<td>Spirometry</td>
<td>680 males, 46 females, Navy soldiers referred to Navy Hospital, La Spezia,</td>
<td>Uncertain</td>
<td>Difference (DFF) and the Ratio (RFF) between FEV&lt;sub&gt;1&lt;/sub&gt; and FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>Mean DFF increased significantly in patients with negative (9.0±7.2) to severe</td>
<td>“[I]n the context of a normal FEV&lt;sub&gt;1&lt;/sub&gt; in allergic patients, a DFF &gt; 20 (or an RFF &gt; 1.24) may be considered as an”</td>
</tr>
</tbody>
</table>

**NYS WCB MTG – Occupational / Work-Related Asthma**
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Score</th>
<th>Patients</th>
<th>Methodology</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Diagnostic Study</td>
<td>7.5</td>
<td>123</td>
<td>Skin prick test, blood tests, Spirometry, non-specific bronchial challenge test with methacholine</td>
<td>Yurdakul 2005: 100 patients admitted to asthma outpatient clinic and 23 non-smoking healthy control subjects. Two weeks. 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%). Methacholine 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.</td>
</tr>
<tr>
<td>2009</td>
<td>Diagnostic Study</td>
<td>6.5</td>
<td>155</td>
<td>Spirometry with methacholine challenge, Body plethysmography with methacholine challenge</td>
<td>Nensa 2009: Patients with bronchial asthma undergoing methacholine challenge testing. 1 period of testing. FEV1 and body plethysmographic 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 FEV1 fall of &gt;20% in 50/155 (32%). We 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.</td>
</tr>
<tr>
<td>1988</td>
<td>Histamine vs. Methacholine</td>
<td>5.0</td>
<td>203</td>
<td>Histamine challenge test, Methacholine challenge test</td>
<td>Higgins 1988: 108 random tested non-asthmatics and 95 people who None PD20. More subjects had a measurable PD20 with methacholine. 108 non-asthmatic 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.</td>
</tr>
</tbody>
</table>

*PD20: Potency doubling dose; OA: Occupational Asthma*
Controlled Clinical Trial

reported at least a wheeze in the past year

s = 25 vs. 11, p<0.01; 95 reported with wheeze = 67 vs. 48 p<0.01.

produces more measurements of non-specific bronchial reactivity than histamine, with less unwanted effects.”

“wheeze or asthma” by questionnaire sometime over the past 12 months.

Hypertonic Histamine

Koskela 2005

Diagnostic Study

Hypertonic histamine challenge

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.

FEV₁ and PEF values for challenge tests

Isotonic histamine: At 56%, 100%, & 77%; 1.1 (0.5-2.7) mg/ml; p = 0.047.

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

Hypertonic Histamine Challenge (HHC)

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 hypertonic phosphate aerosol for 2 mins/kg. Challenge continued until FEV ≥20%

Cough/concentration 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Exercise Test</th>
<th>Sensitivity Specificity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>2008</td>
<td>509</td>
<td>Exercise, clinical diagnosis</td>
<td>Age 5-50 years, FEV1 &gt;70% 78% atopic</td>
<td>5 visits</td>
<td>&gt;10% fall in FEV1, Mannitol: 15% fall in FEV1 at ≤ 635 mg cumulative dose or &gt;10% fall in FEV1 between tests; MCC: PC20 &lt;16</td>
<td>Sensitivity/ specificity of mannitol to identify EIB was 59%/65%, for methacholine it was 56%/69%. BHR mild. Mean EIB % fall in FEV1 in subjects positive to exercise 19%, (SD 9.2), mannitol PD15 158 mg (CI: 129, 193), and methacholine PD20 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.</td>
</tr>
<tr>
<td>Not occupationally related. Ages of participants were 5-50 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 bronchoconstriction.</td>
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NYS WCB MTG – Occupational / Work-Related Asthma  50
<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients</th>
<th>Challenge Type</th>
<th>Study Details</th>
<th>N = 10 Healthy Subjects vs. N = 37 Asthmatic Patients</th>
<th>Repeated after 3 and 6 Months of Treatment of Budesonide</th>
<th>FEV₁ values for Mannitol Challenge</th>
<th>Asthmatic Patients coughed more 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&lt;0.0001.</th>
<th>“Coughing during mannitol challenge is associated with asthma and occurs independently of bronchoconstriction … [T]he measurement of the mannitol-provoked coughing may be 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.”</th>
<th>Small numbers. Patients were recently diagnosed and had more cough + sputum than dyspnea + wheeze. Data suggest mannitol more sensitive in demonstrating airway hyperresponsiveness than cold air challenge.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koskela 2004 Diagnostic Study</td>
<td>6.5</td>
<td>47</td>
<td>Mannitol Challenge</td>
<td>Cold Air Challenge, Histamine Challenge, and skin prick test</td>
<td>N = 10 healthy subjects vs. n = 37 asthmatic patients</td>
<td>Repeated after 3 and 6 months of treatment of budesonide</td>
<td>FEV₁ values for Mannitol Challenge</td>
<td>Asthmatic patients coughed more 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&lt;0.0001.</td>
<td>“Coughing during mannitol challenge is associated with asthma and occurs independently of bronchoconstriction … [T]he measurement of the mannitol-provoked coughing may be 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.”</td>
<td>Small numbers. Patients were recently diagnosed and had more cough + sputum than dyspnea + wheeze. Data suggest mannitol more sensitive in demonstrating airway hyperresponsiveness than cold air challenge.</td>
</tr>
<tr>
<td>Miedinger 2010 Diagnostic Study</td>
<td>6.5</td>
<td>284</td>
<td>Mannitol Challenge and Methacholine Challenge with BPT (Bronchial provocation test)</td>
<td>Skin prick test, spirometry, questionnaire, and oral exhaled nitric oxide (FeNO)</td>
<td>Military subjects</td>
<td>January 2007 – October 2007</td>
<td>FEV₁ and FVC values with spirometry, methacholine, and mannitol challenge tests</td>
<td>BPT with mannitol and methacholine have similar sensitivity and specificity. Methacholine PD₂₀: sensitivity 43%, specificity 92%, PPV 55%, and NPV 88%; Mannitol PD₁₅: sensitivity 41%, specificity 93%, PPV 55%, NPV 88%.</td>
<td>“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.”</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>Mannitol</td>
<td>Clinical investigation</td>
<td>Patients with mild to moderate asthma</td>
<td>Intervention Duration</td>
<td>Inhaled Corticosteroid dose</td>
<td>Mannitol challenge testing</td>
<td>Results</td>
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<tr>
<td>Lipworth 2012</td>
<td>Prospective, Randomized Parallel-Group Trial</td>
<td>Mannitol</td>
<td>Clinical investigation. Spirometry PEF FeNO</td>
<td>Patients with mild to moderate asthma</td>
<td>12 months</td>
<td>Inhaled corticosteroid dose. Mannitol challenge testing</td>
<td>“Using mannitol resulted in exposure to a higher dose of ciclesonide, which was associated with equivocal effects on exacerbations without associated adrenal suppression.”</td>
<td>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.</td>
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<tr>
<td>Anderson 1997</td>
<td>Diagnostic Study</td>
<td>Mannitol</td>
<td>Hypertonic saline challenge. Methacholine</td>
<td>43 patients with asthma; 7 healthy controls</td>
<td>None</td>
<td>Challenge testing spirometry</td>
<td>“[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.”</td>
<td>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. FEV1 at baseline ranged from 54.2-129.0 % predicted. Data suggest mannitol challenge is a possible test for asthma in mild to moderate asthmatics.</td>
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**STUDIES TARGETING OCCUPATIONAL ASTHMA**
## Methacholine vs. SIC, symptoms, need for medications, or specific sensitization

<table>
<thead>
<tr>
<th>Study</th>
<th>FEV1</th>
<th>Patients</th>
<th>Challenge</th>
<th>Spirometry</th>
<th>Methacholine</th>
<th>USN</th>
<th>Late reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Munoz 2004</strong></td>
<td>8.0</td>
<td>26</td>
<td>Specific inhalational challenge by pour method</td>
<td>Skin prick test, Total IgE levels, Methacholine Challenge Testing</td>
<td>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</td>
<td>None</td>
<td>PD20, FEV1</td>
</tr>
<tr>
<td><strong>Dellbianca 1996</strong></td>
<td>8.0</td>
<td>40</td>
<td>Ultra-sonically nebulized distilled water</td>
<td>Specific inhalation challenge Methacholine</td>
<td>Patients referred to center because of probable occupational asthma due to low molecular weight chemicals</td>
<td>One period of testing</td>
<td>FEV1 and FCV values during the different tests</td>
</tr>
<tr>
<td><strong>Paggiaro 1986</strong></td>
<td>6.5</td>
<td>114</td>
<td>Challenge test with toluene disocyanate (20 ppb for 15 minutes). Workers classified by reactions to challenge (immediate, late, and dual).</td>
<td>Methacholine challenge test</td>
<td>114 furniture workers with bronchial asthma induced by toluene disocyanate.</td>
<td>8 hours after challenge</td>
<td>PD20, FEV1</td>
</tr>
</tbody>
</table>

**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%

**Ultrasonically nebulized distilled water:** Sensitivity: 65% Specificity: 80%

**Methacholine:** Sensitivity: 75%-90% Specificity: 60%

**Combination of UNDW and methacholine:** Sensitivity: 85% Specificity: 85%

“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. Patients diagnosed by specific inhalation challenge testing, not as well described as other testing. Data suggest combination of methacholine and ultrasonically nebulized distilled water results in higher sensitivity and specificity for occupational asthma.

Data suggest smoking and atopy may affect hyperreactivity reactions with
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Participants</th>
<th>Diagnosis</th>
<th>Testing</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moller 1986</td>
<td>Specific inhalation challenge with toluene diisocyanate (TDI)</td>
<td>12 patients</td>
<td>Uncertain</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, FVC, (PD&lt;sub&gt;20&lt;/sub&gt;)</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Sastre 2003</td>
<td>Specific inhalational challenge with isocyanates</td>
<td>22 patients</td>
<td>None</td>
<td>Spirometry after and methacholine testing</td>
<td>1st round of testing – 13/22 (59%) had positive response. After 2nd round, 2/22 (11%) had negative response PC&lt;sub&gt;20&lt;/sub&gt;: 2/9 with negative on round 1, PC&lt;sub&gt;20&lt;/sub&gt; fell within asthmatic range after test.</td>
<td>Small numbers. No controls for non-occupational asthma possibilities. Data suggest PC&lt;sub&gt;20&lt;/sub&gt; may help decrease false negatives in testing with isocyanates.</td>
</tr>
<tr>
<td>Shirai 2003</td>
<td>Inhalation challenge. Non-specific challenge tests to methacholine</td>
<td>21 patients</td>
<td>None</td>
<td>EGCG; Sensitivity; FEV&lt;sub&gt;1&lt;/sub&gt;; PC&lt;sub&gt;20&lt;/sub&gt;</td>
<td>Skin sensitivity to EGCG had positive correlation with EGCG; PC&lt;sub&gt;20&lt;/sub&gt; (r = 0.760; p = 0.0048), and methacholine PC&lt;sub&gt;20&lt;/sub&gt; had positive correlation with EGCG PC&lt;sub&gt;20&lt;/sub&gt; (r = 0.717, p = 0.0108).</td>
<td>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.</td>
</tr>
<tr>
<td>Cote 1990</td>
<td>Asthma symptoms;Spirometry with</td>
<td>Male workers</td>
<td>Minimum 1 year</td>
<td>Asthma signs and symptoms</td>
<td>10.4% improved, 62.5% were stable,</td>
<td>Among cedar asthmatics who All diagnosed with occupational asthma</td>
</tr>
</tbody>
</table>
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.

**Diagnostic Study**

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogelmeier 1991</td>
<td>6.0</td>
<td>43</td>
</tr>
<tr>
<td>Karol 1994</td>
<td>5.5</td>
<td>63</td>
</tr>
</tbody>
</table>

**Specific inhalational challenge test to isocyanates**

- **Methacholine challenge test**
  - A = 19 workers with clinical history consistent with occupational asthma vs. B = 14 workers with asthma not exposed to isocyanates vs. C = 10 healthy workers without asthma
  - None
  - Methacholine then spirometry
  - A = 13/19 (68%) positive, B = 3/14 (21%) positive, C = 1/10 (10%) positive. Methacholine; A = 10/19 (53%), B = 14/14 (100%), C = 0/10 (0%)

**Methacholine challenge test to TDI**

- 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 (88 vs. 69 IU/ml).

**Methacholine test**

- "[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 were 21% and 10% false positives on testing. Data suggest methacholine testing not sufficient alone to diagnose diisocyanate-induced asthma.

- "[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 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
| 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 patients; 16 atopic non-asthmatics | None | Spirometry in relation to methacholine challenge test. Comparison to previous spirometry | Patients with non-occupational asthma had lower FEV1 than those with occupational asthma (p<0.001). Patients with occupational asthma removed from exposure for a mean of 0.8 years had better lung function than currently exposed group (p<0.02). | “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 bronchial reactivity is the result rather than the predisposing factor in occupational asthma.” |
| 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 | Testing over 2 different days. | IgE levels. ELISA results. Skin prick test. Inhalational challenge testing. | 7/15 (47%) employees with respiratory symptoms had airway hyper-reactiveness to methacholine. 6/15 | “Grain dust can induce an immunologic, IgE-mediated response in exposed workers.” |

Testing protocol varied by patients making a comparison difficult. Baseline characteristics different between groups. Not all had testing to red cedar. Data suggest bronchial hypersensitivity a result of occupational asthma, and removal from exposure improves lung function.
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.

Symptom questionnaire. (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).

Histamine vs. SIC, symptoms, need for medications, or specific sensitization

| Vandenplas 2001 Diagnostic Study | 9.0 | 45 | Natural rubber latex clinical diagnostic testing | Questionnaire Immunologic testing skin prick test. Spirometric lung function tests (PC20 values <16 mg/mL indicative of 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 "Combining 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 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 | No specificity or sensitivity for IgE testing. Data suggest IgE tests more likely positive if exposed to grain dust and have positive symptom questionnaire. |

Vandenplas 2001 Diagnostic Study | 9.0 | 45 | Natural rubber latex clinical diagnostic testing | Questionnaire Immunologic testing skin prick test. Spirometric lung function tests (PC20 values <16 mg/mL indicative of 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 "Combining 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 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 | No specificity or sensitivity for IgE testing. Data suggest IgE tests more likely positive if exposed to grain dust and have positive symptom questionnaire. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Brien 1979 Diagnostic Study</td>
<td>5.0</td>
<td>63 workers</td>
<td>TDI inhalation challenge test and exercise test</td>
<td>FEV₁, FVC, PEFR</td>
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<tr>
<td></td>
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<td></td>
<td>63 workers occupationally exposed to toluene diisocyanate (TDI).</td>
<td>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&lt;0.005) and TDI non-sensitive group (p&lt;0.01).</td>
</tr>
<tr>
<td>Mannitol vs. SIC, symptoms, need for medications, or specific sensitization</td>
<td>Least</td>
<td>37 workers</td>
<td>Inpatient</td>
<td>Patients with suspected occupational asthma by clinical presentation and spirometry. Data suggest patients with positive SPT and bIgE testing do not require SIC testing.</td>
</tr>
<tr>
<td>O’Brien 1979 Diagnostic Study</td>
<td>5.0</td>
<td>63 workers</td>
<td>TDI inhalation challenge test and exercise test</td>
<td>FEV₁, FVC, PEFR</td>
</tr>
</tbody>
</table>

### Bronchial Hyperreactivity

- Bronchial hyper-reactivity with NRL challenge (SIC) and other common asthma inducing present at occupation.

### Responsiveness

- Responsiveness (NSBH) (%): sensitivity was 90, specificity was 7, PPv was 75, and NPV was 25.

### Demonstration of Causal Relationship

- 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.

### Mannitol vs. SIC

- Although is the ‘gold standard’ for the documentation of occupational asthma, the high prevalence of respiratory symptoms and bronchial hyperreactivity in farmers may lead to a very high demand for access to this expensive test... Only asthmatic farmers have greatest sensitivity and specificity vs. SIC for occupational asthma compared to histamine challenge testing.
<table>
<thead>
<tr>
<th>Study</th>
<th>Median</th>
<th>N</th>
<th>Test Methodology</th>
</tr>
</thead>
</table>
| Miedinger 2007        | 7.5    | 101| PEF (twice daily for a week before testing and every 4 hours during testing)                                                                                                                  | PEY = 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% | with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum IgE concentration should be subjected to bs. |
| Lemiere 2012          | 5.0    | 30 | Mannitol and Methacholine Challenge with bronchial provocation test                                                                                                                                         | 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% | “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.” |

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 FEV₁ and FVC values with spirometry, methacholine and mannitol challenge tests  
Bronchial airway challenge with mannitol (PD₁₅) was more sensitive (92%), specific (97%), PPV (86%), and NPV (98%) when testing for asthma.  
“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 impairment/disability and disease activity of workers with a previous diagnosis of OA because this test has the ability to differentiate the |

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 FEV₁ (p = 0.01), higher fraction of exhaled nitric | Patients diagnosed with previous with occupational asthma and removed from work. Various substances included in diagnosis of OA. Baseline characteristics showed baseline FEV₁... |
oxide levels (p = 0.03). subjects according to the severity of airway responsiveness and collection of sputum to be made at the same time.”

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-quality and 12 moderate-quality studies incorporated into this analysis. There are 5 other studies in Appendix 1.

<table>
<thead>
<tr>
<th>Author/Year Study Type</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Molecular Weight Antigens</strong></td>
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<tr>
<td>Van Kampen 2008 Diagnostic Study</td>
<td>8.5</td>
<td>107 bakers</td>
<td>IgE to wheat and rye flour</td>
<td>SIC SPT Symptoms</td>
<td>Bakers</td>
<td>None</td>
<td>IgE STP SIC</td>
<td>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%</td>
<td>“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.”</td>
<td>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.</td>
</tr>
<tr>
<td>Wiszniewska 2011 Diagnostic Study</td>
<td>8.5</td>
<td>151 diagnosed with OA by SIC; 287 had rhinitis symptoms</td>
<td>IgE to flours</td>
<td>SPT SIC Spirometry NSBP Nasal Lavage</td>
<td>Bakers</td>
<td>None</td>
<td>IgE STP Spirometry Symptoms</td>
<td>In bakers’ with OA: SPT Sn: 41.7% Sp: 85.9% PPV: 73.3% NPV: 61.4% IgE Sn: 61.6% Sp: 77.3%</td>
<td>“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-</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Test/Procedure</td>
<td>Subjects</td>
<td>Diagnostic Criteria</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
<td>NPV</td>
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<tr>
<td>Park 2001 Diagnostic Study</td>
<td>2001</td>
<td>Study</td>
<td>Serum specific IgE to reactive dyes; skin prick test</td>
<td>151</td>
<td>Bronchial provocation testing with methacholine, specific inhalational challenge</td>
<td>71.5%</td>
<td>68.5%</td>
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<tr>
<td>Koskela 2003 Diagnostic Study</td>
<td>2003</td>
<td>Study</td>
<td>IgE testing to bovine dander</td>
<td>37</td>
<td>Bovine specific inhalational challenge (bSIC); skin prick test; Histamine challenge exhaled NO measurement Mannitol challenge Sham inhalational challenge; PEF, twice daily for a week</td>
<td>100%</td>
<td>50%</td>
<td>46%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Reactivity are characterized by sufficient diagnostic accuracy to replace specific inhalational challenge test.

“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.

Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum IgE 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 IgE 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 IgE levels do not require SIC bovine testing to diagnose OA.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Primary Exposure</th>
<th>Primary Test</th>
<th>Secondary Test</th>
<th>Symptoms</th>
<th>n</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walusiak</td>
<td>2004</td>
<td>287</td>
<td>IgE to flour</td>
<td>SPT/SIC</td>
<td>NSBP Symptoms</td>
<td>287 bakers</td>
<td>2 years</td>
<td>SPT IgE SIC Symptoms</td>
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<tr>
<td>Park</td>
<td>1991</td>
<td>309</td>
<td>IgE to reactive dyes</td>
<td>Broncho-provocation tests, skin prick tests</td>
<td>78 (25.2%) employees had work-related lower respiratory symptoms associated with or without nasal, skin, or eye symptoms.</td>
<td>None</td>
<td>IgE</td>
<td>25 (8.1%) of 309 demonstrated &gt;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</td>
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<tr>
<td>Tiikkainen</td>
<td>1990</td>
<td>62</td>
<td>IgG to wheat flour</td>
<td>IgE SPT SIC</td>
<td>Bakers with allergic symptoms</td>
<td>None</td>
<td>IgG SIC results Symptoms</td>
<td>36/42 (86%) cases considered to have a wheat flour allergy based on symptoms and</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Test</td>
<td>Antigen</td>
<td>Symptoms</td>
<td>Controls</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Doekes 1999 Diagnostic Study</td>
<td>5.0</td>
<td>IgE to Aspergillus niger derived phytase</td>
<td>Feed plant workers exposed to phytase in an animal feed plant with reported respiratory symptoms. Internal and external controls.</td>
<td>None</td>
<td>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.</td>
<td>“Phytase is a potentially important new occupational allergen causing specific IgE immune responses among exposed workers.”</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Park 1998 Diagnostic Study</td>
<td>5.0</td>
<td>IgE to grain dust</td>
<td>Skin prick test; Broncho-provocation test; SDS-PAGE</td>
<td>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 Testing over 2 different days.</td>
<td>IgE levels ELISA results. Skin prick test. Inhalational challenge testing. Symptom questionnaire</td>
<td>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%)</td>
<td>Grain dust can induce an immunologic, IgE-mediated response in exposed workers.”</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Patients</td>
<td>Methods</td>
<td>Findings</td>
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<tr>
<td>Douglas 1995</td>
<td>4.5</td>
<td>24</td>
<td>IgE levels to salmon, Spirometry, PEF pre and post shift; Symptom questionnaire</td>
<td>Mixed and carried materials (intermediate exposure group and high 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. Smoking had association with IgE test. (p&lt;0.05).</td>
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<tr>
<td>Diagnostic Study</td>
<td>24</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>n</td>
<td>Methodology</td>
<td>Subjects</td>
<td>Results</td>
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<tr>
<td>Crimi 1999 Diagnostic Study</td>
<td>4.5</td>
<td>23</td>
<td>Skin Prick Test, Nasal Challenge Test, Bronchial Challenge Test, Methacholine Challenge Test (REAST)</td>
<td>Non-smoking subjects with mixed allergies (15 females, 8 males)</td>
<td>At least 1 week Asthma diagnosis using methacholine challenge vs. SPT, RAST, nasal challenge, and bronchial challenge IgE density and nasal challenge score (p &lt; 0.0001), bronchial challenge score (p &lt; 0.001), and maximum late FEV fall (p &lt;0.005). Amount of specific IgE and bronchial challenge score (p&lt;0.001). “IgE density as calculated by REAST procedure, ... In rhinitis subjects with multiple 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 responsiveness blunts the predicting value”</td>
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<tr>
<td>Kim 1999 Case Reports</td>
<td>4.5</td>
<td>16</td>
<td>Skin prick test, Airway reversibility, Specific bronchial challenge test</td>
<td>16 citrus farm workers complaining of respiratory symptoms.</td>
<td>Uncertain IgE, FVC, FEV1 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.”</td>
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</tr>
<tr>
<td>Platts-Mills 1987 Diagnostic Study</td>
<td>4.0</td>
<td>179</td>
<td>Reported symptoms, skin prick test</td>
<td>125 lab workers exposed at different levels to rat allergens, 54 pregnant women not exposed</td>
<td>None IgE, IgG, SPT, symptoms of asthma or rhinitis SPT positive in 19/30 of symptomatic and 2/135 asymptomatic employees (p&lt;0.01%). IgE ab to rat antigen 16/30 2/135 (p&lt;0.01%). IgG positive in all 20 employees with “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 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.”</td>
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</table>

Small numbers! 11 asthmatics studied. Diagnosis of asthma was compared against methacholine challenge testing. Data suggest that specific serum IgE expressed as density does not correlate well with the in vivo response in asthmatic subjects.
<table>
<thead>
<tr>
<th>Low Molecular Weight</th>
<th>Budnik 2013 Diagnostic Study</th>
<th>Tee 1998 Diagnostic Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>IgE to MDI by fluorescence enzyme immuno assay detection method (semi-automatic ImmunoCAP100)</td>
<td>RAST IgE to isocyanates</td>
</tr>
<tr>
<td>43</td>
<td>SIC SPT IgG Histamine challenge spirometry Symptoms</td>
<td>SIC PEF Clinical symptoms SPT</td>
</tr>
<tr>
<td></td>
<td>Workers exposed to MDI with presumed OA sent to referral clinic</td>
<td>Patients with clinical symptoms consistent with OA sent to a hospital based clinic</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Varied</td>
</tr>
<tr>
<td></td>
<td>IgE level SIC results Spirometry Symptoms</td>
<td>IgE levels SIC PEF SPT</td>
</tr>
<tr>
<td>10/12 (83%)</td>
<td>4/10 (40%) had positive IgE. No SIC positive patients had negative IgE. 5/10 (50%) had positive SPT. No SIC positive patients had a negative SPT.</td>
<td>58 considered to have OA caused by isocyanates. 46/58 (79%) had positive SIC. Patients with SIC confirmed diagnosis: IgE RAST ≥2: Sn: 28% Sp: 92% IgE RAST ≥3: Sn: 20% Sp: 100%</td>
</tr>
<tr>
<td></td>
<td>“Isocyanate-specific IgE antibodies are not always detectable but their 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.”</td>
<td>“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 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.</td>
</tr>
<tr>
<td>exposure to animals.</td>
<td>Small numbers of positive SIC patients (10). Data suggest IgE antibody testing is 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.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Diagnostic Study</td>
<td>Study</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>-------</td>
</tr>
<tr>
<td>Cartier 1989</td>
<td>Specific inhalational challenge, Skin prick test</td>
<td>Bernstein 2002</td>
</tr>
<tr>
<td>7.5</td>
<td>62</td>
<td>7.0</td>
</tr>
<tr>
<td>IgE and IgG to isocyanates by ELISA</td>
<td>IgE IgG</td>
<td>IgE</td>
</tr>
<tr>
<td>Specific inhalational challenge, Skin prick test</td>
<td>Patients who underwent specific inhalational challenge testing for isocyanates</td>
<td>Patients who underwent specific inhalational challenge testing for isocyanates</td>
</tr>
<tr>
<td>Up to 2 weeks</td>
<td>IgG and IgE levels after testing to isocyanates</td>
<td>Increased specific antibodies: IgE only – 0/62 IgG only – 13/29 (45%), 7/33 (21%) Both IgE and IgG – 8/29 (28%), 1/33 (3%)</td>
</tr>
<tr>
<td>“[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 results of specific inhalation challenges, suggesting an immunologic mechanism is involved.”</td>
<td>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.</td>
<td>“Our results show a prevalence of specific immunological IgE mediated reactions in subjects who develop asthmatic symptoms after a shorter time of isocyanate exposure.”</td>
</tr>
</tbody>
</table>

Cartier 1989: Diagnostic Study

Bernstein 2002: Diagnostic Study

Pezzini 1984: Diagnostic Study

Table: Summary of studies on occupational / work-related asthma.
Evidence for the Use of Skin Prick Testing

There are 8 high-quality (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)

<table>
<thead>
<tr>
<th>Author/Year Study Type</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test Used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandenplaas 2001</td>
<td>9.0</td>
<td>45</td>
<td>Natural rubber latex clinical diagnostic testing</td>
<td>Questionnaire, Immunologic testing, SPT, spirometry, NRL challenge, (SIC) and other common asthma inducing present at occupation.</td>
<td>45 with suspected occupational asthma, exposed to airborne NRL</td>
<td>Not specified</td>
<td>Sensitivity, specificity, positive predictive values, negative predictive values</td>
<td>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.</td>
<td>“[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].”</td>
<td>Evaluated workers’ compensation cases. Data suggest combination of clinical history and SPT has greatest sensitivity and specificity compared to SIC.</td>
</tr>
<tr>
<td>Van Kampen 2008</td>
<td>8.5</td>
<td>107</td>
<td>IgE to wheat and rye flour</td>
<td>SIC SPT</td>
<td>Bakers</td>
<td>None</td>
<td>IgE STP SIC</td>
<td>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%</td>
<td>“[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 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.”</td>
<td>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.</td>
</tr>
</tbody>
</table>

Phadebas PRIST kit is commercially available.
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Subjects</th>
<th>Procedure</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Kampen 2009 Diagnostic Study</td>
<td>2009</td>
<td>125</td>
<td>SPT to flour</td>
<td>Specific IgE (sIgE) Challenge tests (24 with nebulized aqueous flour solutions, 63 with native flours, 8 nasal challenges)</td>
<td>125 bakers</td>
</tr>
<tr>
<td>Wiszniewska 2011 Diagnostic Study</td>
<td>2011</td>
<td>151</td>
<td>SPT to flour</td>
<td>SIC, Spirometry, NSBP, Nasal Lavage</td>
<td>Bakers</td>
</tr>
</tbody>
</table>

**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 asymptomatic bakers.**

“By 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.

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**
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Procedure Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Result Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park 2001 Diagnostic Study</td>
<td>2001</td>
<td>42</td>
<td>Bronchial provocation testing with methacholine, specific inhalational challenge</td>
<td>76.2%</td>
<td>91.4%</td>
<td>80%</td>
<td>89.5%</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93</td>
<td>Skin prick test, IgE testing</td>
<td>53.7%</td>
<td>86%</td>
<td>62.9%</td>
<td>80.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>None</td>
<td>83.3%</td>
<td>91.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 challenge testing. Data suggest a combination of SPT and IgE is more sensitive and specific.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Test/Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sander 2004 Diagnostic Study</td>
<td>8.0</td>
<td>115</td>
<td>SPT; SDS-PAGE&lt;br&gt;Bronchial Challenge Test; IgE-Enzyme Allergo Sorbent Test (EAST); Sodium; Dodecyl sulfate-Polyacrylamide Gel electrophoresis (SDS-PAGE)&lt;br&gt;115 bakers complaining of workplace-related respiratory symptoms</td>
</tr>
<tr>
<td>Koskela 2003 Diagnostic Study</td>
<td>8.0</td>
<td>37</td>
<td>SPT, Bovine dander&lt;br&gt;Bovine specific inhalational challenge; IgE testing; Histamine; Exhaled NO; Mannitol challenge; Sham inhalational challenge; PEF&lt;br&gt;37 dairy farmers with suspected occupational asthma to bovine dander</td>
</tr>
</tbody>
</table>
| Merget 1993 Diagnostic Study | 7.0  | 62       | SPTs with non-dialyzed aqueous enzyme extracts<br>Specific inhalational challenge, IgE<br>42 chemical plant workers referred for pulmonary symptoms, 10 atopic non-exposed patients, and 10 healthy patients | Spirometry, IgE levels, and skin prick test results<br>Positive for 13/42 (31%) participants; Skin prick test: Sn = 100% Sp = 93%<br>“For enzyme allergy both BPT [bronchial provocation test] and skin prick test were appropriate diagnostic tests.”<br>Data suggest skin prick testing has high sensitivity and specificity for patients exposed to certain enzymes and can be used in the diagnostic testing of occupational asthma in those patients.”
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Subjects</th>
<th>Test Material</th>
<th>Test Type</th>
<th>Test Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walusiak 2004</td>
<td>6.5</td>
<td>287</td>
<td>SPT to flour</td>
<td>IgE, SIC, NSBP, Symptoms</td>
<td>287 bakers</td>
<td>2 years</td>
</tr>
<tr>
<td>Acero 2003</td>
<td>6.0</td>
<td>12</td>
<td>SPT to latex</td>
<td>IgE, NSBP, SIC, Specific conjunctiva tests, Symptoms</td>
<td>12 health care workers</td>
<td>3 years</td>
</tr>
<tr>
<td>Park 1998 Diagnostic Study</td>
<td>5.5</td>
<td>43</td>
<td>SPT to grain dust</td>
<td>All tests used 7 common allergens vs. grain dust (GD) from subjects’ workplace. Broncho-provocation, and ELISA questionnaire</td>
<td>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.</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

**GRAIN DUST**
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>SPTs/EOS</th>
<th>Tests and Procedures</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merget 1991 Diagnostic Study</td>
<td>1991</td>
<td>35</td>
<td>SPT to platinum salts</td>
<td>Lung function, bronchial provocation tests 35 workers from platinum refineries with work-related symptoms. Uncertain IgE, FEV1, FEV1%, IVC, sFEV (specific airway resistance), sGaw (specific airway conductance), IVC 16/35 (46%) patients had positive reactions to all tests. 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&lt;0.0008; n = 27). Work related respiratory symptoms are not predictive of platinum salt asthma. Negative skin prick tests with hexachloroplatinic acid do not exclude the disease. Most had been removed completely from exposure, 19 had occasional contact. Data suggest SPT may be useful in assessing platinum salt testing, but negative SPTs do not exclude disease.</td>
<td></td>
</tr>
<tr>
<td>Brisman 2003 Diagnostic Study</td>
<td>2003</td>
<td>89</td>
<td>SPT to flour, alpha-amylase</td>
<td>Whole blood cell count Spirometry 25 asthmatics (determined by questionnaire), 20 bakers with rhinitis, and 44 referent bakers 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. SPT Eosinophils FEV1, 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.</td>
<td>Sensitization 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</td>
</tr>
<tr>
<td>Suarthana 2009 Diagnostic Study</td>
<td>2009</td>
<td>314</td>
<td>SPTs to lab animal allergens</td>
<td>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 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%)</td>
<td>We 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 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</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Participants</td>
<td>Exposure</td>
<td>Test Method</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Bernstein 2011 Diagnostic Study</td>
<td>9.0</td>
<td>40</td>
<td>Laboratory workers</td>
<td>SPT - trimellitic anhydride, IgE/IgG Intracutaneous testing</td>
<td>TMA exposed workers Controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SPT negative with intracutaneous testing: Sn 91%, Sp 97%, PPV 91%, NPV 97%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma 2008 Diagnostic Study</td>
<td>7.5</td>
<td>69</td>
<td>Laboratory workers</td>
<td>SPT - mouse allergens, IgE Nasal Challenge IDT</td>
<td>Laboratory workers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IgE: Sn 47%, Sp 91%, PPV 70%, NPV 79%, +LR: 11.2</td>
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</tbody>
</table>

**Other Studies**

- **Bernstein 2011 Diagnostic Study**
  - SPT - trimellitic anhydride, IgE/IgG Intracutaneous testing
  - TMA exposed workers Controls
  - 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%
  - Using a TMA-HAS skin test reagent can be as sensitive and specific as a sensitive TMA-serum specific IgE immunosassay for detecting TMA-sensitized workers.

- **Sharma 2008 Diagnostic Study**
  - SPT - mouse allergens, IgE Nasal Challenge IDT
  - Laboratory workers
  - 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Methods</th>
<th>Population</th>
<th>Outcome Measure</th>
<th>Risk Factors</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merget 2000 Diagnostic Study</td>
<td>2000</td>
<td>SPT Platinum salts</td>
<td>Workers in platinum process plant</td>
<td>6 years</td>
<td>SPT conversion from negative to positive: FEV&lt;sub&gt;1&lt;/sub&gt; Symptoms Histamine challenge test with spirometry Atopy Smoking</td>
<td>The two risk factors found that lead to SPT conversion from negative to positive: Exposure level Smoking status. &quot;Pt salts are relevant allergens in catalyst production plants.&quot;</td>
</tr>
<tr>
<td>Schmid 2009 Diagnostic Study</td>
<td>2009</td>
<td>SPT to mouse and rat danders</td>
<td>Laboratory workers</td>
<td>None</td>
<td>SPT IgE Whole body plethsmography NSBP Questionnaire</td>
<td>Sensitization rates in workers: Mice 12.7% Rats 16.3% &quot;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.&quot;</td>
</tr>
<tr>
<td>Niezborala 1996 Diagnostic Study</td>
<td>1996</td>
<td>SPT Platinum salts</td>
<td>Workers in a platinum plant</td>
<td>20 years</td>
<td>SPT conversion Atopy Smoking status Symptoms</td>
<td>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. &quot;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.&quot;</td>
</tr>
</tbody>
</table>

MOUSE AND RAT

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.

PLATINUM SALTS (not commercially available)
Calverley 1995
Prospective Cohort Study

<table>
<thead>
<tr>
<th>NYS WCB MTG – Occupational / Work-Related Asthma</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>18 months, exam done every 3 months</td>
</tr>
<tr>
<td>Workers in platinum refinery</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>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.</td>
</tr>
<tr>
<td>“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.”</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

PLATINUM SALTS (not commercially available PST)

Evidence for the Use of Specific Inhalational Challenge Testing

There are 4 high-quality(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)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Kampen 2008</td>
<td>Diagnostic Study</td>
<td>8.5</td>
<td>107</td>
<td>Bronchial, nasal, or workplace-stimulated rye flour challenge</td>
<td>Specific IgE antibodies to wheat and rye flour, skin prick tests vs. aqueous wheat and rye flours</td>
<td>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</td>
<td>Specific IgE tested at baseline. SPT performed twice with removal of test material after 15 minutes. Challenge performed at baseline.</td>
<td>Sensitivity, specificity, positive predictive values, and negative predictive values at various IgE concentrations, different wheal sizes.</td>
<td>Challenges: Specificity 68% and 62%, PPV 74% and 82%, NPV 82% and 71%, respectively for wheat and rye.</td>
<td>“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.”</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>N</td>
<td>Age</td>
<td>Gender</td>
<td>Description</td>
<td></td>
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</tbody>
</table>
| Koskela 2003 | 2003 | 37 | Mean age 41 (79% male) | 37 dairy farmers with suspected occupational asthma to bovine dander who were referred for bovine dander specific inhalational challenge testing vs. other testing results. 

- **Skin prick test**: Sn = 100% Sp = 96% 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 IgE 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.
<table>
<thead>
<tr>
<th>Munoz 2004 Diagnostic Study</th>
<th>8.0</th>
<th>26</th>
<th>Specific inhalational challenge by pour method</th>
<th>SPT; Total IgE levels; Methacholine challenge testing</th>
<th>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.</th>
<th>None</th>
<th>Spirometry after challenge testing</th>
<th>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%</th>
<th>&quot;The procedure described in this study allows patients with bronchial asthma to be distinguished from those with persulphate salt induced OA.&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasanen 1994 Diagnostic Study</td>
<td>8.0</td>
<td>28</td>
<td>Specific inhalational challenge, method not well described. Challenge testing to grains</td>
<td>Methacholine; SPT; IgE; PEFR; Symptoms</td>
<td>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.</td>
<td>None</td>
<td>Spirometry PEFR Symptoms IgE SPT</td>
<td>SPT: Sn = 74% Sp = 86% RAST: Sn = 89% Sp = 78% BHRT: Sn = 57% Sp = 93% IgE: Sn = 91% Sp = 71%</td>
<td>&quot;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.&quot;</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Frigas 1984</th>
<th>7.0</th>
<th>13</th>
<th>Bronchial challenge with formaldehyde via Dynacalibrator, a closed system</th>
<th>Spirometry with placebo challenge</th>
<th>Patients attributing symptoms to formaldehyde exposure(s).</th>
<th>One period of testing</th>
<th>Placebo to all patients. Formaldehyde at 0.1 ppm, 1 ppm, or 3 ppm for 20 minutes. Spirometry after various levels of exposure to formaldehyde gas.</th>
<th>Adverse events of eye, nose, and throat tightness of the chest but these occurred as frequently with the placebo as with the formaldehyde challenges.</th>
<th>“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-induced asthma may be rare.”</th>
<th>Some participants double-blind and some single-blind. One had decrease in FEV1 both with formaldehyde and placebo. Data suggest formaldehyde may not induce asthma through sensitizing mechanism. Irritant induced asthma not addressed. Small numbers. Substance used for challenge testing was “professional dust” without explanation. Poor correlation of patch tests to presumed allergens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtulowicz 1998</td>
<td>7.0</td>
<td>49</td>
<td>Specific inhalational challenge at work, no specific device used. Allergens not defined.</td>
<td>Clinical history consistent with OA. SPT to metals and “professional dust” and total serum IgE</td>
<td>49 workers in steel and tobacco industries referred for evaluation for OA.</td>
<td>None</td>
<td>Spirometry data</td>
<td>25/49 (51%) patients had a positive inhalational challenge test.</td>
<td>“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”</td>
<td>Small numbers. Control for non-occupational asthma possibilities. Data suggest PC20 after challenge may help decrease false negatives during testing with isocyanates.</td>
</tr>
<tr>
<td>Sastre 2003</td>
<td>6.5</td>
<td>22</td>
<td>Specific inhalational challenge with isocyanates in dynamic chamber with an open flask of TDI or nebulized in HDI cases</td>
<td>Methacholine challenge</td>
<td>22 patients with clinical history of diisocyanate-induced asthma</td>
<td>None</td>
<td>Spirometry after and methacholine testing</td>
<td>First round of testing: 13/22 (59%) had positive response; 2nd round of testing: 2/22 (11%) had a negative response. PC&lt;sub&gt;20&lt;/sub&gt;: in 2/9 patients with negative on round 1, PC&lt;sub&gt;20&lt;/sub&gt; fell within the asthmatic range after test.</td>
<td>“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.”</td>
<td>Small numbers. No controls for non-occupational asthma possibilities. Data suggest PC20 after challenge may help decrease false negatives during testing with isocyanates challenge.</td>
</tr>
<tr>
<td>Harries 1980 Diagnostic Study</td>
<td>6.5</td>
<td>37</td>
<td>Specific inhalational challenge to various agents (mainly animal dander) aerosolized.</td>
<td>SPT; IgE</td>
<td>37 workers clinically diagnosed with occupational asthma. All inpatients.</td>
<td>None</td>
<td>Spirometry</td>
<td>24/37 (65%) patients had positive asthma reactions to test antigen. 18/24 (75%) were prick positive for test antigen. <strong>“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.”</strong> 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 weight-induced occupational asthma.</td>
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<tr>
<td>Nordman 1985 Diagnostic Study</td>
<td>6.5</td>
<td>230</td>
<td>Bronchial challenge with formaldehyde (controlled exposure)</td>
<td>SPT, spirometry, histamine provocation test, exercise test, serologic tests</td>
<td>230 workers with formaldehyde-induced bronchial asthma</td>
<td>6 1/2 years</td>
<td>Eosinophil count, IgE, FVC, FEV₁, FEV%, PEF</td>
<td>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. <strong>“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.”</strong> Long follow-up time. Data suggest formaldehyde can induce asthma symptoms in some patients with high work exposures.</td>
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<tr>
<td>Moller 1986 Diagnostic Study</td>
<td>6.5</td>
<td>12</td>
<td>Inhalation challenge with toluene diisocyanate (TDI) in chamber with open method</td>
<td>Pulmonary function tests, bronchial challenge test with methacholine, spirometry</td>
<td>12 patients with possible TDI asthma</td>
<td>Uncertain.</td>
<td>FEV₁, FVC, (PD₂₀)</td>
<td>Five workers showed no significant bronchospasm to TDI challenges at high or low doses, however, 3 of the five had positive methacholine tests. <strong>“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.”</strong> 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.</td>
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<tr>
<td>Reference</td>
<td>Year</td>
<td>N</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Challenges</td>
<td>Controls</td>
<td>Findings</td>
<td>Notes</td>
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<tr>
<td>Walusiak 2004</td>
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<td>64</td>
<td></td>
<td>Specific inhalational challenge to workplace flour by sifting in an open room</td>
<td>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</td>
<td>None</td>
<td>Cellular findings of the nasal lavage. Permeability index of nasal lavage.</td>
<td>A significant decrease in PC20 after challenge test observed only in group B (p&lt;0.001). Provocation with flour resulted in elevated leukocytes in nasal washing in all groups. Group B had higher elevation than Group C (p&lt;0.001). Eosinophils elevated in all groups, but more in A and B when compared to C (p&lt;0.001).</td>
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<tr>
<td>Burge 1985 Case Reports</td>
<td></td>
<td>15</td>
<td></td>
<td>Bronchial Provocation Test done in 6 m³ chamber without air extraction during test</td>
<td>15 workers occupational exposure to formaldehyde</td>
<td>24 days</td>
<td>FEV</td>
<td>4/14 (29%) had PC20 values less than 10 mg/ml. 10/14 (71%) had normal bronchial provocation after testing with formaldehyde.</td>
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<tr>
<td>Vogelmeier 1991 Diagnostic Study</td>
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<td>43</td>
<td></td>
<td>Specific inhalational challenge test to isocyanate s in open air chamber</td>
<td>A = 19 workers with clinical history consistent with occupational asthma vs. B = 14 workers with asthma/no exposure to</td>
<td>None</td>
<td>Methacholine then spirometry.</td>
<td>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%).</td>
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</tbody>
</table>

**Notes:**
- Occupational asthma diagnosed with post challenge PC20. Data suggest that nasal lavage alone may determine allergic rhinitis due to flour but does not determine presence of occupational asthma.
- 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.
- 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Method</th>
<th>Results</th>
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<tbody>
<tr>
<td>Mapp 1988</td>
<td>5.5</td>
<td>162</td>
<td>Specific inhalational challenge to isocyanates in open air chamber</td>
<td>C = 10 healthy workers without asthma vs. C = 10 healthy workers without asthma</td>
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<tr>
<td></td>
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<td>Methacholine challenge testing Clinical and occupational history</td>
<td>Spirometry and methacholine challenge to isocyanates with symptoms suspected to be from asthma</td>
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<td>Spirometry SPT IgE to TDI and MDI</td>
<td>None</td>
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<td>162 workers exposed to isocyanates with symptoms suspected to be from asthma</td>
<td>Spirometry IgE test results</td>
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<td>“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.”</td>
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<tr>
<td>Vanhanen 2000</td>
<td>5.5</td>
<td>11</td>
<td>Specific inhalational challenge to cellulose in open air chamber</td>
<td>Clinical history</td>
</tr>
<tr>
<td></td>
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<td>Spirometry IgE-RAST SPT</td>
<td>None</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>11 workers who were exposed to cellulose with symptoms consistent of allergic rhinitis and or asthma</td>
<td>PEF Clinical history</td>
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<td>“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.”</td>
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<tr>
<td>Lam 1983</td>
<td>5.5</td>
<td>206</td>
<td>Specific inhalational challenge test to plicatic acid using nebulizer</td>
<td>Clinical and occupational history</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Methacholine test (not in all patients). Skin prick test. IgE RAST</td>
<td>Spirometry results classified as immediate, late or dual reactivity</td>
</tr>
<tr>
<td></td>
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<td>206 patients with positive testing to plicatic acid</td>
<td>None</td>
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<td>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.</td>
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<td>“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 compared to immediate or dual reaction.”</td>
</tr>
</tbody>
</table>

Data suggest that clinical diagnosis based on history is only accurate about 50% of the time. SIC is considered the gold standard for diagnosis.

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 cellulose.

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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Patients</th>
<th>Test Type</th>
<th>Method</th>
<th>Spirometry</th>
<th>Skin prick test</th>
<th>FEV₁ ≥30% after challenge testing</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwaibmair 1997</td>
<td>5.0</td>
<td>55</td>
<td>Specific inhalation challenge to bleach powder in open chamber</td>
<td>SPT. Non-specific bronchial provocation testing with acetylcholine</td>
<td>None</td>
<td>Spirometry testing; SPT</td>
<td>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.</td>
<td>occupational asthma due to western red cedar.</td>
<td></td>
</tr>
<tr>
<td>Malo 2004</td>
<td>4.0</td>
<td>108/496; 31 with both tests</td>
<td>Closed circuit SIC challenge test</td>
<td>496 with clinical suspicion of occupational asthma and a previously documented positive SIC to occupational agent</td>
<td>None</td>
<td>FEV₁ ≥30% after challenge testing</td>
<td>Of 31 patients who had both tests: Closed circuit had 8/31 (26%) change in FEV₁ ≥30%. “Realistic” had 16/31 (52%) change in FEV₁ ≥30%.</td>
<td>“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.”</td>
<td></td>
</tr>
<tr>
<td>Cote 1990</td>
<td>6.0</td>
<td>48</td>
<td>Asthma symptoms</td>
<td>Spirometry with methacholine challenge</td>
<td>Male workers with diagnosis of occupational asthma to red cedar who stayed in same industry after diagnosis</td>
<td>Minimum one year, average of 6.5 years</td>
<td>Asthma signs and symptoms after continued exposure</td>
<td>10.4% improved; 62.5% were stable; 37.5% worsened. None of the patients completely recovered.</td>
<td>“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 reaction to western red cedar.”</td>
</tr>
</tbody>
</table>

Other Studies

Cote 1990 Diagnostic Study

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 reaction to western red cedar.”

Not all tests performed on all participants. Data suggest some utility in diagnosing persulfate salt occupational asthma in hairdressers by SIC.

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 FEV₁ ≥30%. False negative rate of closed circuit method was 2.2% when compared to “realistic” method.

Patients diagnosed with occupational asthma were followed. Data suggest continued exposure to cedar dust in confirmed asthmatics prevents resolution of symptoms and...
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\(^{(283, 286, 295, 310)}\).

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test Used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palczynski 2000 Diagnostic Study</td>
<td></td>
<td>5.0</td>
<td>37</td>
<td>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.</td>
<td>SPT, Symptom score, RAST results, Spirometry</td>
<td>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.</td>
<td>None</td>
<td>Symptom score Mediator levels Spirometry Nasal lavage changes in cytogram, protein content, eosinophil cationic protein, and mast-cell tryptase concentration</td>
<td>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&lt;0.001).</td>
<td>“The nasal challenge test appears to be useful for diagnosing occupational rhinitis in natural rubber latex-sensitized patients.”</td>
<td>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.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Diagnostic Tools</td>
<td>Study Population</td>
<td>Diagnostic Measures</td>
<td>Main Findings</td>
<td>Notes</td>
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<tr>
<td>Pedrosa 2010</td>
<td>8.0</td>
<td>Diagnostic Study</td>
<td>Exhaled Nitric Oxide (FENO), methacholine inhalation challenge, skin prick test</td>
<td>Patients with asthma-like symptoms with negative bronchodilator tests and normal spirometry measures</td>
<td>FeNo, FVC, FEV₁, methacholine levels, and skin prick allergens</td>
<td>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.</td>
<td>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 sensitivity of 74% and a specificity of 72.5%. 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.</td>
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<tr>
<td>Dupont 2003</td>
<td>8.0</td>
<td>Diagnostic Study</td>
<td>Exhaled NO</td>
<td>Subjects with symptoms suggestive of obstructive airway disease referred to an asthma outpatient clinic</td>
<td>None</td>
<td>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&lt;0.001).</td>
<td>Exhaled 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.</td>
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<tr>
<td>Miedinger 2007</td>
<td>7.5</td>
<td>Diagnostic Study</td>
<td>Mannitol Challenge and Methacholine Challenge with BPT</td>
<td>Firefighter subjects being tested for asthma</td>
<td>Uncertain</td>
<td>Bronchial airway challenge with mannitol (PD₁₃) was more sensitive (92%), specific (97%), PPV (86%), and NPV (98%) when testing for asthma. PD₂₀ has a sensitive (78%), specific (94%), PPV (68%), and NPV</td>
<td>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 diagnosis 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</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>n</td>
<td>Test Method</td>
<td>No Comparison Tests</td>
<td>Patients with Difficult to Treat Asthma</td>
<td>FeNO, FVC, FEV1, Airway Hyperresponsiveness, PEF, and PEF</td>
<td>Sensitivity% and Predictive Values</td>
<td>Remarks</td>
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<tr>
<td>Pérez-de-Llano 2010 Diagnostic Study</td>
<td>7.5</td>
<td>102</td>
<td>Exhaled Nitric Oxide (FENO), Spirometry, bronchodilator test, methacholine test, and ambulatory peak expiratory flow (PEF)</td>
<td>None</td>
<td>Patients with difficult to treat asthma</td>
<td>None</td>
<td>Sensitivity of 87.5% (95% CI 73.9-94.5) and specificity of 90.6% (95% CI 79.7-95.9).</td>
<td>“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.”</td>
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<tr>
<td>Smith 2004 Diagnostic Study</td>
<td>7.5</td>
<td>47</td>
<td>FENO for asthma diagnosis</td>
<td>Exhaled NO vs. spirometric testing, Fe(NO) measurements, skin allergy testing, bronchodilator reversibility, hypertonic saline challenge, peak flow measurements, sputum induction (n = 40), oral prednisone</td>
<td>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.</td>
<td>Sensitivity%, specificity%, PPV%, NPV% for: peak flow variation: 0, 100, NA, 70; peak flow improvement with steroid &gt;15%: 24,100,100,69; FEV1 &lt;80% predicted: 29,100,100,71; FEV1 &lt;90%: 35,93,75,72; FEV1/FVC &lt;70%: 35,100,100,73; FEV1/FVC &lt;80%: 47,80,57,73; FEV1 improvement with steroid &gt;15%: 12,100,100,66; sputum eosinophils &gt;3%: 86,88,80,92;</td>
<td>“Our 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.”</td>
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</tbody>
</table>

(96%) when testing for asthma. The only significant difference is FENO >47ppb with sensitivity at 42%. assessment of active firefighters and may be of help when evaluating candidates for this profession.”

highest sensitivity and specificity.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Test Type</th>
<th>Study Population</th>
<th>Duration</th>
<th>FeNO &gt; 20 ppb</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith 2005</td>
<td>7.0</td>
<td>97</td>
<td>FeNO</td>
<td>Patients with chronic asthma on inhaled corticosteroids treated with PCP</td>
<td>12 months</td>
<td>88, 79, 70, 92.</td>
<td>“With the use of FeNO measurement, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control.”</td>
<td>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.</td>
</tr>
<tr>
<td>Fukuhara 2011</td>
<td>7.0</td>
<td>61</td>
<td>Methacholine test</td>
<td>Outpatients between May 2007 and June 2010 with at least one subjective symptoms of recurrent cough, wheezing or dyspnea.</td>
<td>Uncertain</td>
<td>FeNO group: 90.1 ± 4.2 vs. without asthma: 40.1 ± 18.4.</td>
<td>“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.”</td>
<td>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.</td>
</tr>
<tr>
<td>Gelb 2006</td>
<td>7.0</td>
<td>87</td>
<td>Spirometry</td>
<td>34 normal subjects, 44 non-smoking, clinically stable asthmatic patients for at least 6 weeks to study initiation.</td>
<td>Not specified</td>
<td>Sensitivity = 0.91, specificity = 0.50, positive predictive value = 0.65, and negative predictive value = 0.85. Using ROC plots for first asthma exacerbation with cut-off point of FEV₁ at 76% predicted.</td>
<td>“In conclusion, baseline combined measurements of both post-bronchodilator FEV₁ percentage of predicted and FENO in clinically stable, treated, non-smoking patients with asthma may help risk stratify for subsequent exacerbations.”</td>
<td>Follow up timing not clear. No blinding done. Co-interventions other than medications and smoking not well described. Data suggest a combination of FEV₁ &lt; 76% and FENO &gt; 28 ppb increased the likelihood of an exacerbation requiring medical treatment to 85% over 18 months.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Study Population</td>
<td>Outcomes</td>
<td></td>
<td></td>
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<tr>
<td>Lemiere 2010 Diagnostic Study</td>
<td>2010</td>
<td>7.0</td>
<td>Exhaled NO (FeNO) Sputum eosinophil counts. Subjects undergoing specific inhalation challenges (SIC) for possible occupational asthma.</td>
<td>24 hours FeNO, FVC, FEV₁, sputum, skin prick tests.</td>
<td>cut-off point for FENO at 28 ppb, sensitivity = 0.59, specificity = 0.82, PPV = 0.77, and NPV = 0.87. An abnormal FENO ≥ 28 ppb increased relative risk for exacerbation by 3.4 (χ² = 7.34, p = 0.007). 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.</td>
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<tr>
<td>Miedinger 2010 Diagnostic Study</td>
<td>2010</td>
<td>6.5</td>
<td>Mannitol Challenge Methacholine Challenge with BPT Skin prick test, spirometry, questionnaires, and oral exhaled nitric oxide (FeNO)</td>
<td>Military subjects January 2007 - October 2007 FEV₁ and FVC values with spirometry, methacholine, and mannitol challenge tests</td>
<td>BPT with mannitol and methacholine have similar sensitivity and specificity. Methacholine PD₂₀: sensitivity 43%, specificity 92%, PPV 55%, and NPV 88%. Mannitol PD₁₅: 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.</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>N</td>
<td>FeNO Measurement</td>
<td>FeNO Data</td>
<td>FeNO Higher in</td>
<td>Cut-Off Point</td>
<td>Study Conclusion</td>
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<tr>
<td>Kostikas 2008</td>
<td>2008</td>
<td>219</td>
<td>FeNO measured with a portable nitric oxide analyzer</td>
<td>Patients with respiratory symptoms related to asthma</td>
<td>Students from University of Thessally and Technological Education Institute of Larissa with at least 1 positive answer from European Community Respiratory Health Survey II screening questionnaire</td>
<td>None</td>
<td>FeNO higher in those with asthma vs. controls and those with non-specific symptoms, p&lt;0.0001. Predictors of FeNO were diagnoses of asthma (p = 0.002), allergic rhinitis (p&lt;0.001), and currently smoking (p = 0.003). Optimal cut-off point for FENO as diagnostic tool for entire study population was &gt;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 &gt;19 ppb. FeNO values &gt;25 ppb give Sp &gt;90%; Sp rose to &gt;95% for cut-off of &gt;30 ppb.</td>
<td>“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 confounding factors are allergic rhinitis and current smoking.”</td>
</tr>
<tr>
<td>Menzies 2007</td>
<td>2007</td>
<td>151</td>
<td>Exhaled NO (FeNO) using portable device (MINO)</td>
<td>Exhaled NO (FeNO) using laboratory device (NIOX)</td>
<td>N = 101 with asthma, and n = 50 healthy volunteers</td>
<td>None</td>
<td>FeNO, FVC, FEV₁ 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</td>
<td>“[F]eNO values deriving using the MINO device are directly comparable with those using the NIOX device.”</td>
</tr>
<tr>
<td>Allmers 2000 Diagnostic Study</td>
<td>5.5</td>
<td>9</td>
<td>Exhaled NO</td>
<td>Methacholine challenge test</td>
<td>Subjects with a history of immediate-type allergy to natural rubber latex and of workplace-related asthma when exposed to MDI were studied</td>
<td>Follow-up evaluations were made up to 6 hours post exposure, and after 20±22 h (limited by working hours of lung function laboratory)</td>
<td>FEV\textsubscript{1} Exhaled NO</td>
<td>No correlation between a bronchial obstruction after methacholine challenge and bronchial response after specific allergen challenge was found. Decrease of exhaled NO in 16 of 19 subjects 16-18 hours after methacholine challenge and subsequent bronchodilation using salbutamol; p&lt;0.001. 3/9 participants had a significant decrease in FEV\textsubscript{1} after exposure to MDI (no p-values given).</td>
</tr>
</tbody>
</table>

<p>| 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 eosinophilic bronchitis | 1 day trial | FEV\textsubscript{1}, FEV\textsubscript{1}/SVC | Significant difference in ENO levels, eosinophil percentages, absolute eosinophil counts (×10\textsuperscript{5}/g; p &lt;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.” | 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 response, the trend was for increases NO levels. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size</th>
<th>Methodology</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortuna 2007 Diagnostic Study</td>
<td>5.0</td>
<td>50</td>
<td>Fraction of exhaled nitric oxide (FENO)</td>
<td>Spirometry, N = 28 non-asthmatic patients vs. n = 22 asthmatic patients</td>
<td>Spirometry: FEV₁/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 FEV₁ of asthmatic and non-asthmatic patients. “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 Eos% together to diagnose asthma in clinical practice is more accurate than spirometry or FENO assessment alone and easier to perform.”</td>
</tr>
<tr>
<td>Demange 2009 Diagnostic Study</td>
<td>5.0</td>
<td>44</td>
<td>Fractional concentration of exhaled nitric oxide (FENO)</td>
<td>Methacholine bronchial challenge (MBC) test, Subjects were lifeguards at indoor swimming pools</td>
<td>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 FEV₁ 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 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 conditions may be useful in diagnosing asthma and chronic cough.”</td>
</tr>
</tbody>
</table>

Small numbers; included lifeguards with current asthma, not needing corticosteroid treatment, and “not in crisis.” Measurements taken at a 50 ml/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

Specific inhalation challenge with isocyanate

Sham specific inhalation challenge

Subjects with suspected occupational asthma due to isocyanates (toluene diisocyanate, methylene-diisocyanate, or 1, 6- hexamethylene diisocyanate). 15 subjects had positive responses to SIC; 24 subjects had negative responses to SIC but had workplace exposure. Examined on 5 consecutive days, then follow-up 7 and 30 days after SIC with isocyanate exposure.

FVC FEV1 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, 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.

“[T]hese findings suggest that the proportion of eosinophils in sputum have more accurate diagnostic marker of normal airway responsiveness.”

Good baseline characteristic comparison. Co-interventions not well controlled. Data suggest FENO is useful in diagnosing asthma related to isocyanates.

Jang 2003 Diagnostic Study

Sputum exam; NO metabolites, eosinophils, and eosinophils

Peripheral blood measurement

N = 15 patients with asthma and in control group vs. n = 10 with unknown

FEV1, FEV1/FVC

Higher results in asthmatics than controls for eosinophils and were at higher levels of ECP in blood. FEV1,

“[T]hese findings 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 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.”

Small numbers. Evaluated metabolites of NO not FENO.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jang 1999</td>
<td>5.0</td>
<td>23</td>
<td>Fraction of exhaled nitric oxide (FENO)</td>
<td>Spirometry, N = 13 patients with asthma and in control group vs. n = 10 with no respiratory problems</td>
<td>FEV₁/FVC negatively correlated with sputum eosinophils, p&lt;0.01. NO metabolites (1220.3±180.2 mol/L vs. 545.6±98.4 mol/L, p&lt;0.01), eosinophils (49.5±5.3% vs. 2.7±0.5%, p&lt;0.01), and higher levels of ECP (1345.1±201.5 g/L vs. 146.5±27.5 g/L, p&lt;0.01) in sputum.</td>
</tr>
<tr>
<td>Koksal 2003</td>
<td>5.0</td>
<td>63</td>
<td>Nitric oxide (NO)</td>
<td>SO2 on serum TNF-α, IL-1h, IL-6, IL-8, nitrite, N = 40 male workers on farms vs. n = 23 controls, all healthy</td>
<td>Significant results in asthmatics vs. controls for higher NO metabolites for sputum (1252.5+203.3 μmol·L⁻¹ vs. 557.2+101.5 μmol·L⁻¹, p&lt;0.01) but not in serum.</td>
</tr>
<tr>
<td>Olin 2010</td>
<td>4.0</td>
<td>220</td>
<td>FeNo levels, spirometry</td>
<td>Subjects from general population</td>
<td>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 airway inflammation than NO metabolites in sputum and serum in differentiating asthmatic patients from control subjects.</td>
</tr>
</tbody>
</table>

*Note: Small numbers. Evaluated metabolites of NO not FENO.*

**Diagnostic Study**

- **Jang 1999**
  - Fraction of exhaled nitric oxide (FENO)
  - Spirometry
  - N = 13 patients with asthma and in control group vs. n = 10 with no respiratory problems
  - FEV₁/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.

- **Koksal 2003**
  - Nitric oxide (NO)
  - SO2 on serum TNF-α, IL-1h, IL-6, IL-8, nitrite
  - N = 40 male workers on farms vs. n = 23 controls, all healthy
  - Significant results in asthmatics vs. controls for higher NO metabolites for sputum (1252.5+203.3 μmol·L⁻¹ vs. 557.2+101.5 μmol·L⁻¹, p<0.01) but not in serum.

- **Olin 2010**
  - FeNo levels, spirometry
  - Subjects from general population
  - 4 years
  - 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 airway inflammation than NO metabolites in sputum and serum in differentiating asthmatic patients from control subjects.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cut-off</th>
<th>Subjects</th>
<th>Test Parameters</th>
<th>Controls</th>
<th>Test Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore 2010 Diagnostic Study</td>
<td>4.0</td>
<td>60</td>
<td>Exhaled NO (FeNO), peak expiratory flow (PEF)</td>
<td>None</td>
<td>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).</td>
<td>&quot;[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.&quot; 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.</td>
</tr>
</tbody>
</table>

Both >90th and >95th percentile.
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

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test Used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2011</td>
<td>N/A</td>
<td>N/A</td>
<td>Mannitol; Methacholine</td>
<td>Exercise test; Physician diagnosis</td>
<td>Various</td>
<td>None</td>
<td>NSBP-Mannitol, methacholine, exercise</td>
<td>NA</td>
<td>“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.”</td>
<td>Review article. States that Mannitol has a higher specificity for a physician diagnosis of asthma than methacholine.</td>
</tr>
<tr>
<td>Decimo 2011</td>
<td>N/A</td>
<td>50</td>
<td>Mannitol</td>
<td>FeNO; Spirometry; Exercise challenge test</td>
<td>Pediatric patients age 9-16 with intermittent allergic bronchial asthma or allergic rhinitis</td>
<td>None</td>
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<td></td>
<td>“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.”</td>
<td>Pediatric population. Not a working population.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>N/A</td>
<td>Methacholine</td>
<td>SIC with PA and/or red cedar</td>
<td>Patients with confirmed diagnosis to red cedar</td>
<td>Spirometry</td>
<td>Immunology</td>
<td>NSBP</td>
<td>SIC</td>
<td>2 control subjects had a PC&lt;sub&gt;20&lt;/sub&gt; below 25 mg/ml. All had bronchial hyperreactivity at time of diagnosis, mean PC&lt;sub&gt;20&lt;/sub&gt; 2.5 mg/ml.</td>
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<tr>
<td>Chan-Yeung 1982</td>
<td>MCC vs. SIC Diagnostic Study</td>
<td>N/A</td>
<td>72</td>
<td>Methacholine</td>
<td>SIC with PA and/or red cedar</td>
<td>Patients with confirmed diagnosis to red cedar</td>
<td>None</td>
<td>Spirometry</td>
<td>Immunology</td>
<td>NSBP</td>
</tr>
<tr>
<td>Kopferschmitt - Kubler 1998</td>
<td>Use of MCC before and after SIC Diagnostic Study</td>
<td>N/A</td>
<td>11</td>
<td>Non-specific bronchial provocation test</td>
<td>TDI provocation test</td>
<td>11 workers with a clinical history of isocyanate-induced asthma.</td>
<td>Uncertain</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>9 patients with positive bronchial provocation after TDI challenge had mean FEV&lt;sub&gt;1&lt;/sub&gt; fall at PD&lt;sub&gt;20&lt;/sub&gt; (23.5%). Before provocation challenge it was 11.8% with same dose of methacholine (p&lt;0.01).</td>
<td>&quot;TDI provocation challenge that induced no fall in FEV&lt;sub&gt;1&lt;/sub&gt; in isocyanate-sensitive patients led to a slight but significant increase in non-specific BHR.&quot;</td>
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</table>

Not truly a diagnostic study. More a measure of bronchial 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Subjects</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez 2001</td>
<td>Use of MCC before and after SIC</td>
<td>N/A</td>
<td>PST; IgE testing; MCC Oilseed rape extract bronchial provocation test</td>
<td>3 non-smoking 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 also skin prick tested 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. “…[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.”</td>
</tr>
<tr>
<td>Subiza 1991</td>
<td>MCC vs. SIC</td>
<td>N/A</td>
<td>SPT, IgE testing, precipitin test, bronchial provocation test Specific inhalational test</td>
<td>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</td>
</tr>
<tr>
<td>Histamine</td>
<td>Dehaut 1983</td>
<td>NA</td>
<td>Histamine challenge testing</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td># of Patients</td>
<td>Challenge</td>
<td>Patients</td>
<td>Test Type</td>
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<td>-----------------------------------------</td>
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</tr>
<tr>
<td>Britton 1986 (Comparative Diagnostic Study)</td>
<td>24</td>
<td>Histamine</td>
<td>None</td>
<td>24 patients with asthma</td>
</tr>
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</tbody>
</table>

**Histamine vs. Methacholine**

<table>
<thead>
<tr>
<th>Study</th>
<th># of Patients</th>
<th>Challenge</th>
<th>Patients</th>
<th>Test Type</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>James 1997 (Diagnostic Study)</td>
<td>NA</td>
<td>Histamine</td>
<td>None</td>
<td>None</td>
<td>PD&lt;sub&gt;20&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methacholine</td>
<td>None</td>
<td>None</td>
<td>Cut-off value 8mg/mL in occupational challenge to define disease: Sn: 76% Sp: 51%</td>
</tr>
<tr>
<td></td>
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<td>&quot;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.&quot;</td>
</tr>
<tr>
<td></td>
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<td>review article. Reports there is no gold standard in diagnosing asthma. Not specific to OA in many measures.</td>
</tr>
</tbody>
</table>

**SPECIFIC INHALATIONAL CHALLENGE TESTING**
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Score</th>
<th>N</th>
<th>Test used</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palczynski 2001</td>
<td>N/A</td>
<td>31</td>
<td>Single blind exposure to 2% glutaraldehyde and saline 0.9% placebo</td>
<td>Skin prick test, IgE evaluation, Spirometry</td>
<td>None</td>
<td>Symptom score, mediator levels, spirometry, nasal lavage changes in cytogram, protein content, eosinophil cationic protein (ECP), and mast-cell tryptase concentration</td>
<td>In those with GA occupational asthma: Rhinitis, nasal washings of eosinophils, basophils, ECP, and tryptase were higher than after challenge with placebo in same group and then after GA in group with asthma and healthy volunteers (p&lt;0.05).</td>
<td>&quot;NLF examination allows us to identify patients with occupational asthma and rhinitis due to GA.&quot;</td>
<td>At least 7 days between cross-over testing. Concentration of GA during test was 0.32 mg/m3 (below 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.</td>
</tr>
<tr>
<td>Vandenplas 1992</td>
<td>N/A</td>
<td>20</td>
<td>Closed circuit SIC testing</td>
<td>20 subjects referred by WC Board or their physicians for evaluation of isocyanate-induced occupational asthma</td>
<td>None</td>
<td>Mean concentration of isocyanates above 20 ppb</td>
<td>Mean variances in isocyanate concentration: Closed circuit method = 6.3. Challenge room = 61.8 (p&lt;0.001). Percentage of total exposure time above 20 ppb reduced from 11.3 to 3.5 % (p&lt;0.001%).</td>
<td>&quot;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.&quot;</td>
<td>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.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Design/Method</td>
<td>Outcome Measure</td>
<td>Results/Findings</td>
<td></td>
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<tr>
<td>Vally 2007</td>
<td>N/A</td>
<td>13</td>
<td>Asthmatic response associated with high and low sulphite wine challenge</td>
<td>N = 7 (6 female, 1 male) aged 26-56 with history of bronchial hyper-responsiveness within 1 hour of 150 ml of wine consumption vs. n = 1 control patient (male, age 51) Day 1: 150 mL red, white, or control wines over 5 minutes. Spirometry immediately after, 15/30 min following 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. Cut-off value determined to be a difference &gt;1 doubling dose of histamine between pre- and post-challenge BHR. Log (PC20). 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 than a 15% increase in any subjects. &quot;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. However, 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…&quot; Small numbers. Baseline characteristics differences. Co-interventions not well described. Data suggest challenge with wine is not helpful in patients complaining of wine aggravated asthma symptoms.</td>
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<tr>
<td>Burge 1980</td>
<td>N/A</td>
<td>51</td>
<td>Specific inhalational challenge to soldering flux in a small cubicle with fumes</td>
<td>Spirometry 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. &quot;There is reasonable evidence by the three standard criteria that the colophony is acting as an allergen rather than an irritant in the concentrations encountered at work.&quot; 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.</td>
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<tr>
<td>Study</td>
<td>N/A</td>
<td>7</td>
<td>Specific inhalational challenge testing with wood dusts in exposure chamber while sanding</td>
<td>Skin prick tests, Specific IgE for woodworkers with symptoms consistent with occupational asthma</td>
<td>None</td>
<td>Spirometry, results of SPT and IgE to determine atopy</td>
<td>4/7 (57%) had results consistent with asthma; 3/7 (43%) had results consistent with rhinitis.</td>
<td>&quot;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 diagnosing wood rhinitis and asthma...&quot;</td>
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<tr>
<td>Caron 2010</td>
<td>N/A</td>
<td>44</td>
<td>Specific inhalational challenge by GenaSIC (closed circuit aerosol)</td>
<td>A previous SIC not done with &quot;realistic method&quot;</td>
<td>Subjects with occupational asthma</td>
<td>Spirometry and FEV1 values</td>
<td>No significant changes in spirometry in response to metha-choline. Causal agents are acrylates and isocyanates. Isocyanates: mean 13.98, SD 3.6.</td>
<td>&quot;GenaSIC offers the possibility of reliable and safe exposures to dry particles, formaldehyde and isocyanates in the investigation of OA.&quot;</td>
<td></td>
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</table>

Small numbers. Baseline characteristics are sparse. Data suggest wood dusts may diagnose occupational asthma in furniture makers.
<table>
<thead>
<tr>
<th>Zeiler 2002</th>
<th>N/A</th>
<th>9</th>
<th>Specific inhalational challenge with bovine dander. Using automatic, inhalation-synchronized dosimeter</th>
<th>Histamine challenge Skin prick test IgE</th>
<th>Dairy farmers with a clinical history “positive” for occupational asthma to cows</th>
<th>None</th>
<th>Spirometry results after and before histamine, IgE, skin prick test</th>
<th>There was a 275 fold difference in the amount of bovine protein needed for positive test. Histamine challenge was positive for 6/8 (75%).</th>
<th>“Our results support the use of purified major allergens for associating work-related asthma with the exposure to a specific allergen source.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 1995</td>
<td>N/A</td>
<td>9</td>
<td>Rotahaler device as the delivery method for specific inhalational challenge testing</td>
<td>Spirometry Methacholine challenge testing</td>
<td>9 patients referred for suspected red cedar asthma</td>
<td>None</td>
<td>Spirometry testing results after challenge</td>
<td>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.</td>
<td>“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.”</td>
</tr>
<tr>
<td>Quirce 1992</td>
<td>N/A</td>
<td>5</td>
<td>Specific inhalational challenge with alpha-amylase and cellulose by nebulizer</td>
<td>Skin prick test IgE REIA Histamine challenge test Methacholine</td>
<td>5 patients suspected of having occupational asthma to flour</td>
<td>None</td>
<td>Spirometry data Laboratory data</td>
<td>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.</td>
<td>“[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.”</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Score (0-11)</td>
<td>N</td>
<td>Test used</td>
<td>Population</td>
<td>Length of Follow-up</td>
<td>Outcome Measures</td>
<td>Results</td>
<td>Conclusions</td>
<td>Comments</td>
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<tr>
<td>Graneek 1987 Diagnostic Study</td>
<td>N/A</td>
<td>9</td>
<td>Specific inhalational challenge to various substances</td>
<td>9 workers in various vocations with different exposures. All inpatient for diagnosis.</td>
<td>None</td>
<td>Spirometry after challenge testing</td>
<td>Histamine responsiveness significantly greater 3 hours after compared to 24 hours (p&lt;0.05).</td>
<td>&quot;[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.&quot;</td>
<td>Small numbers. Study protocol varied between patients. Patients from various occupations. Limitations make it difficult to draw conclusions. Test appeared to cause decrease in FEV₁ in all patients.</td>
</tr>
<tr>
<td>Davison 1983 Case Series</td>
<td>N/A</td>
<td>8</td>
<td>Specific inhalational challenge test to castor beans after shaking trays of beans</td>
<td>IgE</td>
<td>5 people suspected of reacting to castor beans (3 Sudanese seamen, 2 lab workers, 3 controls)</td>
<td>None</td>
<td>Spirometry IgE levels</td>
<td>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.</td>
<td>&quot;RAST inhibition, toxicological and haemagglutination tests suggest that the ricin and deracinated extracts contain distinct allergens.&quot;</td>
</tr>
<tr>
<td>Mapp 1986 Diagnostic Study</td>
<td>N/A</td>
<td>6</td>
<td>TDI inhalation challenge in an exposure chamber</td>
<td>Methacholine inhalation challenge</td>
<td>6 subjects with a history of sensitivity to TDI and positive results to bronchial challenge to TDI</td>
<td>Uncertain</td>
<td>FEV₁, PD₂₀</td>
<td>All subjects had normal airway responsiveness to methacholine (PD₂₀ &gt; 0.7 mg). 8 hours after TDI challenge, airway responsiveness increased significantly (p&lt;0.01).</td>
<td>&quot;[A]irway responsiveness is not necessary for the occurrence of toluene disocyanate-induced asthma.&quot;</td>
</tr>
<tr>
<td>Subiza 1991 MCC vs. SIC Case reports</td>
<td>N/A</td>
<td>11</td>
<td>Skin prick test, IgE testing, precipitin test, bronchial provocation test</td>
<td>Specific inhalational test</td>
<td>One patient who developed symptoms of asthma after exposure to <em>Pfaffia paniculata</em> root powder and 10 control patients without asthma</td>
<td>Single testing period</td>
<td>Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls</td>
<td>Patient had slight bronchial hypersensitivity 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 (<em>Pfaffia paniculata</em>).</td>
<td>“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.”</td>
</tr>
<tr>
<td>Riccardi 2003 Diagnostic Study</td>
<td>N/A</td>
<td>29</td>
<td>Specific/total IgE to iroko wood dust</td>
<td>Methacholine challenge after avoiding iroko dust exposure, skin prick test, intradermal test, bronchial provocation test, peak expiratory flow w/iroko wood dust</td>
<td>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</td>
<td>Not specified</td>
<td>Spirometry, IgE testing, PEF</td>
<td>PEF (in L/s) (mean±SD): Group A: while off work: 8.4±0.01; working w/iroko: 6.10±0.01; working w/o other wood: 8.31±0.02. Group B: off work: 8.4±0.01; w/iroko: 8.29±0.01; w/o other wood: 8.29±0.01. Iroko SPT: all groups showed negative response. IgE (Iroko): all groups negative.</td>
<td>“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.”</td>
</tr>
<tr>
<td>Howe 1983 Diagnostic Study</td>
<td>N/A</td>
<td>22</td>
<td>RAST IgE to tetra-hydrophthalic</td>
<td>Inhalation testing,</td>
<td>7 women with respiratory symptoms, 8 volunteers</td>
<td>10 months</td>
<td>IgE</td>
<td>In RAST inhibitions experiments, TCPA-HSA</td>
<td>“These results imply that occupational asthma caused by</td>
</tr>
</tbody>
</table>
TCPA (anhydride) is an allergic reaction mediated by specific IgE antibody. Topping 1986 Diagnostic Study suggests that TCPA can cause or aggravate asthma symptoms. TCPA-HSA, allergen discs, skin prick testing from same factory, and 7 volunteers without TCPA exposure 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. In 7 women with respiratory problems, skin prick reactions occurred with 1.0% and 0.1% TCPA-HSA solutions. 7% positive test results correlated with clinical presentation. It demonstrates that IgE results need to be validated with RAST inhibition for each anhydrides. Did not look at IgE results correlated with clinical presentation. It demonstrates that IgE results need to be validated with RAST inhibition for each anhydrides. 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

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
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<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walusiak 2000 Cohort Study</td>
<td>N/A</td>
<td>452</td>
<td>SPT to wheat flour</td>
<td>None</td>
<td>Apprentice bakers just starting their apprentices</td>
<td>None</td>
<td>3% of examined Polish apprentice bakers were found to have positive skin prick</td>
<td>&quot;In our opinion, the results of SPT should be very carefully examined, when diagnosing&quot;</td>
<td>Study is preliminary results of cohort study. Average age 16.2 years. &quot;Baseline&quot;</td>
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</tr>
</tbody>
</table>
### Subiza 1991

<table>
<thead>
<tr>
<th>MCC vs. SIC</th>
<th>Case reports</th>
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</thead>
<tbody>
<tr>
<td>Skin prick test, IgE testing, precipitin test, bronchial provocation test</td>
<td>Skin prick test, IgE testing, bronchial provocation test in 1 case vs. controls</td>
</tr>
<tr>
<td>Specific inhalational test</td>
<td>Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls</td>
</tr>
<tr>
<td>One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder and 10 control patients without asthma</td>
<td>Patient had slight bronchial hyperresponsiveness 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).</td>
</tr>
<tr>
<td>Single testing period</td>
<td>“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.”</td>
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</table>

### Alvarez 2001

<table>
<thead>
<tr>
<th>Case reports</th>
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<tbody>
<tr>
<td>Skin prick test, IgE testing, Methacholine test</td>
</tr>
<tr>
<td>Oilseed rape extract bronchial provocation test</td>
</tr>
<tr>
<td>3 nonsmoking farmers diagnosed with OA</td>
</tr>
<tr>
<td>3 days</td>
</tr>
</tbody>
</table>

#### Tests to occupational allergens before the onset of occupational exposure.

- **SPT done during first month of apprentice work, indicating at least some work exposure before testing was done.**

#### Occupational allergy, as in some apprentice bakers positive results of SPT to flour allergens are found before vocational training.”

#### Wheat Flour

- **One participant.**
  - Difficult to draw any significance.
  - Patient had reaction on bronchial provocation test to Brazil ginseng extract.

#### Brazilian Ginseng Root Dust

- **Small numbers.**
  - No blinding of evaluators to skin prick test. No true diagnostic comparison between tests.
  - Data suggest OSR can cause BHR in sensitized patients diagnosed with OA to OSR.

#### Oilseed Rape Extract

- **N/A**
  - 3 days
  - Skin prick test, IgE testing, Methacholine test
  - 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 all 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.”**
Commonly 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 allergic component that can induce IgE-mediated bronchoconstriction.

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)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Score (0-11)</th>
<th>N</th>
<th>Test Used</th>
<th>Comparison Test</th>
<th>Population</th>
<th>Length of Follow-up</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smit 2009</td>
<td>3.5</td>
<td>425</td>
<td>Exhaled Nitric Oxide (FENO) and endotoxin levels</td>
<td>None</td>
<td>425 agricultural farmers</td>
<td>None</td>
<td>Exhaled NO, specific immunoglobulin (IgE) antibodies</td>
<td>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).</td>
<td>“[A] significant exposure-response relationship was found between exposure to endotoxins and exhaled NO in non-smoking, non-atopic agricultural workers.”</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>FEV₁</td>
<td>Subjects</td>
<td>Variables Measured</td>
<td>Findings</td>
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<tr>
<td>Olin 2004</td>
<td>3.5</td>
<td>246</td>
<td>Exhaled NO, nasal NO</td>
<td>None</td>
<td>The eNO levels were higher in subjects with asthma compared to those without asthma (22.5 vs. 15.8 ppb; p = 0.0004).</td>
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<tr>
<td>Lund 2000</td>
<td>3.0</td>
<td>226</td>
<td>Exhaled NO, nasal NO</td>
<td>None</td>
<td>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 symptoms 8.5 (5.9-12.8) ppb (p&lt;0.001).</td>
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</table>

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.

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 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.
### Exhaled nitric oxide (ENO)

<table>
<thead>
<tr>
<th>Reutman 2009</th>
<th>Diagnostic Study</th>
<th>1.5</th>
<th>43</th>
<th>Exhaled nitric oxide (ENO)</th>
<th>Pulmonary function tests (PFT)</th>
<th>43 nail technicians</th>
<th>None</th>
<th>ENO, cotinine metabolite, FEV₁, FVC</th>
<th>Years worked as a nail technician was significantly related to higher levels of NO (p&lt;0.05).</th>
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</thead>
</table>

"Job 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....These 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

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Potential Conflict of Interest (COI)</th>
<th>Score (0-11)</th>
<th>Sample Size</th>
<th>Comparison Group</th>
<th>Results</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Marzo 1988</td>
<td>Cross-over clinical trial</td>
<td>No mention of industry sponsorship or COI.</td>
<td>NA</td>
<td>N = 9</td>
<td>Beclomethasone 200ug BID</td>
<td>FEV₁ 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</td>
<td>&quot;These results suggest that the inhibitory effect of inhaled beclomethasone on TDI-induced late asthmatic reactions and increased responsiveness is dose-dependent.&quot;</td>
<td>Small numbers. Data suggest treatment with beclomethasone can be beneficial in employees with OA and TDI exposure.</td>
</tr>
<tr>
<td>Marabini 2003</td>
<td>Longitudinal study</td>
<td>No mention of industry sponsorship or COI.</td>
<td>NA</td>
<td>N = 10</td>
<td>Beclomethasone 1,000 ug Salmeterol 100 ug Salmeterol PRN</td>
<td>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.</td>
<td>&quot;...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.&quot;</td>
<td>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.</td>
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## MANAGEMENT OF OA WITH IMMUNOTHERAPY

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<tr>
<td>Patriarca 2002</td>
<td>Case-control study</td>
<td>No mention of industry sponsorship or COI.</td>
<td>2.0</td>
<td>N = 24 (17 had asthma)</td>
<td>Active group had sublingual SIT with latex extract. Treatment was 4 days for desensitization and then a continuous maintenance latex exposure.</td>
<td>Sublingual, 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.</td>
<td>“We believe that our protocol of sublingual rush desensitization provides a new important therapeutic approach to latex allergy, without clinically detectable side effects, in our study population.”</td>
<td>Asthma status not well described. Minimal baseline information provided. Treatment of “control” group not well described. Data suggest sublingual SIT to latex allergy can be beneficial to health care workers and others in allowing continued exposure.</td>
</tr>
<tr>
<td>Cistero 2004</td>
<td>Case series</td>
<td>NA</td>
<td>NA</td>
<td>N = 26 with cutaneous latex allergy with some respiratory symptoms</td>
<td>All received SIT sublingual therapy</td>
<td>Both glove-use test and rubbing test improved significantly after 10 weeks of treatment p&lt;0.05. No change detected for SPTs.</td>
<td>“The long-term effect of the treatment deserves further investigation…Tolerance of sublingual SIT is better than tolerance for injective therapy.”</td>
<td>No control or randomization. Asthma not well described.</td>
</tr>
<tr>
<td>De jong 1999</td>
<td>Case series</td>
<td>NA</td>
<td>NA</td>
<td>N = 11 with anaphylaxis to bumblebee venom</td>
<td>All received venom immunotherapy (VIT). Maintenance dose reached in 5-8 weeks.</td>
<td>Follow up period was 1.5-5 years. All had decreased skin test reactivity after 1 year of immunotherapy.</td>
<td>“Immunotherapy with bumblebee venom is safe and effective, and is comparable with honeybee and yellow-jacket venom immunotherapy.”</td>
<td>Small numbers. No asthma patients. No control group or alternative treatment group.</td>
</tr>
<tr>
<td>Leynadier 2000</td>
<td>RCT</td>
<td>No mention of industry sponsorship or COI.</td>
<td>NA</td>
<td>N = 17 (9 had asthma) sensitized health care workers to latex</td>
<td>Active group received SIT vs. placebo.</td>
<td>Patients in active group had lower rhinitis score p&lt;0.05, conjunctivitis score p&lt;0.05, and cutaneous score p&lt;0.03. Asthma symptoms not significantly different between groups up to 12 months of treatment.</td>
<td>“Latex-specific immunotherapy may allow sensitized personnel to remain at work, but further trials need to be conducted in a larger number of patients.”</td>
<td>Small numbers of asthma patients. There was no benefit after 12 months of therapy in asthma symptoms.</td>
</tr>
<tr>
<td>Pereira 2003</td>
<td>Case report</td>
<td>NA</td>
<td>NA</td>
<td>N = 4 all with anaphylaxis reaction to</td>
<td>All 4 patients received SIT with aqueous extract.</td>
<td>A challenge test was performed in 3/4 patients. Two had no</td>
<td>“We consider SIT with latex to be highly affective, safe and well tolerated provided”</td>
<td>Small numbers. No placebo. Only 1 extract used.</td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>N</td>
<td>Description</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Stern 2000 Case series</td>
<td>Case series</td>
<td>NA</td>
<td>Exposure to latex reaction to latex gloves, one had rhinoconjunctivitis.</td>
<td>&quot;...immunotherapy with BBV is the only safe therapeutic alternative in bumblebee-allergic patients who cannot avoid exposure.&quot;</td>
<td>No asthma patients. Only 2 cases presented.</td>
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<td>Grembiale 2000 RCT</td>
<td>RCT</td>
<td>NA</td>
<td>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.</td>
<td>Methacholine PD&lt;sub&gt;20&lt;/sub&gt; FEV&lt;sub&gt;1&lt;/sub&gt; increased 2.88-fold (p &lt; 0.001) at 1 year of SIT treatment and 4.1-fold (p &lt;0.001) after 2 years compared to pre-treatment values. No difference was found in the placebo group (p = 0.708).</td>
<td>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.</td>
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</table>
Appendix IV – References


DRAFT – For Discussion Purposes Only


310. Reutm


DRAFT – For Discussion Purposes Only


385. National Institute for Occupational Safety and Health. Work-related Lung Disease Surveillance System (eWorld). Work-related asthma: ten most frequently reported agent categories associated with cases of work-related asthma, 1993-2006. Available at: http://www2a.cdc.gov/drds/worldrepor/data/FigureTableDetails.asp?FigureTableID=2607&GroupRefNumber=F09-01. 2012.


