MEDICAL TREATMENT UTILIZATION SCHEDULE (MTUS)

OCCUPATIONAL/WORK-RELATED ASTHMA GUIDELINE

OCTOBER 2015

AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

CONTRIBUTORS TO THE OCCUPATIONAL/WORK-RELATED ASTHMA GUIDELINE

Editor-in-Chief:
Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Assistant Editors:
Jeremy J. Biggs, MD, MSPH
Matthew A. Hughes, MD, MPH, FACOEM

Evidence-based Practice Asthma Panel Chairs:
Athena T. Jolly, MD, MPH, FACOEM
Julia E. Klees, MD, MPH, FACOEM

Evidence-based Practice Asthma Panel Members:
Bruce K. Bohnker, MD, MPH, FACOEM
Tee L. Guidotti, MD, MPH, FACOEM
Philip Harber, MD, MPH, FACOEM, FCCP
Mark H. Hyman, MD, FACP, FAADEP
Howard M. Kipen, MD, MPH, FACOEM
Karin A. Pacheco, MD, MSPH

Methodology Committee Consultant:
Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Managing Editors:
Production: Marianne Dreger, MA
Research: Julie A. Ording, MPH

This Chapter of the Medical Treatment Utilization Schedule is based on American College of Occupational and Environmental Medicine (ACOEM) Occupational Practice Guidelines published and copyrighted by the Reed Group Ltd.

Research Conducted By:
Jeremy J. Biggs, MD, MSPH
Matthew A. Hughes, MD, MPH, FACOEM
Matthew S. Thiese, PhD, MSPH
Ulrike Ott, PhDc, MSPH
Atim C. Effiong, MPH
Leslie M. Cepeda-Echeverria
Tessa Langley
Deborah G. Passey, MS
William Caughey, MS
Kylee Fon Tokita, BS
Riann Robbins, BS
Alzina Koric, MPP
Jeremiah L. Dortch, BS

Specialty Society and Society Representative Listing:
ACOEM acknowledges the following organizations and their representatives who served as reviewers of the Occupational/Work-related Asthma Guideline. Their contributions are greatly appreciated. By listing the following individuals or organizations, it does not infer that these individuals or organizations support or endorse the Occupational/Work-related Asthma Guideline developed by ACOEM.

American College of Chest Physicians
Diego J. Maselli, MD, FCCP

American Thoracic Society
Lisa Maier, MD, MSPH, FCCP

Other External Reviewers:
Theodore Lytras, MD, MPH
Mary C. Townsend, DrPH

These panel members represent expertise in occupational medicine, internal medicine, preventive medicine, pulmonary medicine, allergy and immunology, toxicology, aerospace medicine, and epidemiology. As required for quality guidelines (Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines and Appraisal of Guidelines for Research and Evaluation (AGREE)), a detailed application process captured conflicts of interest.

TABLE OF CONTENTS

IMPACT

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.[1-5] Increased airway responsiveness to a variety of stimuli is typical. Work-related asthma (WRA) includes both occupational asthma (OA, asthma of occupational origin) 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.[6-12]

Occupational asthma has become the most common form of occupational lung disease in many industrialized countries, with approximately 10 to 15% of all prevalent cases of adult asthma attributed to occupational factors.[6-9, 11, 13, 14] The percentage of new onset adult asthma attributable to occupational causes is considered to be much higher, up to a third of all cases.[15, 16] The frequency of work-exacerbated asthma, defined as preexisting reactive airways disease that is made temporarily or permanently worse due to occupational exposures, is known to be much higher than new-onset occupational asthma.[17]

The diagnosis of occupational asthma is a specialty-level function and is usually done by physicians who have special training and expertise in occupational lung disease and workplace exposures. If the treating physician does not have this specialized expertise, prompt referral is advised.

WORK-RELATED ASTHMA

Work-related asthma (WRA) presents with symptoms of asthma that began or became worse at work, usually in the context of exposure to a new chemical or environmental change. The symptoms may occur during or after work hours. The specific respiratory symptoms in WRA patients are the same as in non-WRA patients, which requires a high level of suspicion and incorporation of work history in the evaluation of all cases of adult-onset asthma. They include cough, wheeze, shortness of breath, and chest tightness, with physiological evidence of reversible/variable airway obstruction and/or hyperresponsiveness.[3, 6, 7]

Occupational asthma (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 or OA without latency. OA without latency is less common and is believed to represent between 5 and 15 percent of all OA cases.[1] OA with latency is observed in all instances of immunologically mediated asthma. 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. OA without latency can occur after a single exposure to irritant gas, fumes, or chemicals, such as nitrogen oxide, ammonia, and chloride.[1, 18] This was originally classified as reactive airways dysfunction syndrome (RADS).[18] RADS is an overused diagnosis and often confused with irritant-induced occupational asthma and WEA. RADS should be reserved for new onset reactive airways associated with a single incident. It classically relies on a single high-level (non-routine) exposure to an inhaled irritant.

Brooks and other authors have suggested modification of these criteria to include a role for multiple cumulative irritant insults or even for an allergic diathesis along with the irritant exposure that would result in new onset workplace asthma that would involve latency. It has been reported that low-level irritant-induced occupational asthma with latency is clinically indistinguishable from sensitization-induced asthma.[19] However, clear-cut guidelines beyond Brooks 1985 have not been established for such irritant induced asthma.[20, 21] WEA is the activation of preexistent asthma or bronchia hyper-responsiveness by many factors such as temperature, exercise, dust, or low level irritants.[17, 22]

Prevalence estimates of asthma and WRA have been assessed in small cohort and cross-sectional studies. Studies of workplaces with exposures to specific substances reported prevalences of asthma or OA ranging from 3% to 54%.[1, 2, 23, 24] More than 200 agents have been reported to cause WRA, based on epidemiological and/or clinic evidence. Asthmagens (sensitizing antigens resulting in asthma) are often classified into categories based on their molecular weight, with high molecular weight defined as ≥5,000 daltons versus low molecular weight <5,000 daltons. Molecular weights are believed to be important in the mechanisms of action in the development of OA.[1])

The predisposing factors for developing WRA are not well known. Atopy is the primary established risk factor for occupational asthma, operating largely with respect to high molecular weight antigens such as animal proteins. It has been proposed that human leukocyte antigen class-2 (HLA class II) alleles can be a risk factor for the development of WRA resulting from low-molecular weight agents.[12, 25, 26] However, HLA typing is not routinely performed for asthma clinically and has no demonstrated value in individual diagnosis.

Medical management and compensation decisions require a thorough assessment of suspected OA. OA may be mistaken for non-occupational asthma unless a detailed history, including occupational history, and appropriate medical tests are performed to support an association with work.[27]

SUMMARY OF RECOMMENDATIONS

Summary Table: Recommendations and Evidence

Table 1 summarizes the recommendations from the Evidence-based Practice Asthma Panel for diagnostic testing for occupational asthma. Table 2 summarizes the recommendations for management of occupational asthma. The recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles when higher quality evidence was unavailable or inconsistent. **The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, prior testing or treatment, and contraindications that are elaborated in more detail for each test or treatment in the body of this *Guideline* in using these recommendations in clinical practice or medical management.** These recommendations are not simple "yes/no" criteria, and the evidence supporting them is in nearly all circumstances developed from typical patients, not unusual situations or exceptions.

Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient-Recommended (Consensus-based), "I" Level
- Insufficient-No Recommendation (Consensus-based), "I" Level
- Insufficient-Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Table 1. Summary of Recommendations for Diagnostic Testing for Occupational Asthma

TEST	RECOMMENDATION(S)
Spirometry	Spirometry testing is an essential component in the evaluation and management of patients with possible work-related asthma.
Peak Expiratory Flow Rates	Serial peak expiratory flow measurements as an initial evaluation method for diagnosing work-related asthma, in patients already diagnosed with asthma by other methods **– Moderately Recommended, Evidence (B)**
Nonspecific Bronchial Provocation	Nonspecific bronchial provocation test (e.g., methacholine) for use in diagnosing asthma, if the clinical history is compelling, and other tests (spirometry and bronchodilator responsiveness) are unhelpful – **Strongly Recommended, Evidence (A)**

Test	Nonspecific bronchial provocation test (e.g., methacholine) for use in diagnosing work-related asthma, as other steps are required to establish the work-relatedness of the asthma – **Moderately Recommended, Evidence (B)** Mannitol bronchial provocation test for use in diagnosing work-related asthma, and other steps are required to establish the work-relatedness of the asthma – **Recommended, Evidence (C)**
Specific Immunological Testing	Specific immunological testing (IgE) for workers with symptoms consistent with occupational asthma to certain high molecular weight specific allergens and when standardized antigens and assay protocols exist – **Strongly Recommended, Evidence (A)** Specific immunological testing (IgG) as a diagnostic tool for select workers with symptoms consistent with occupational asthma to high molecular weight specific allergens – **Not Recommended, Evidence (C)** Specific immunological testing (IgE) for workers with symptoms consistent with occupational asthma to low molecular weight specific allergens due to low sensitivity and specificity and lack of method validation – **Not Recommended, Insufficient Evidence (I)**
Skin Prick Testing	Skin prick testing for high molecular weight allergens for select workers with symptoms consistent with occupational asthma to specific allergens and where validated, commercial skin testing extracts are available – **Strongly Recommended, Evidence (A)** Skin prick testing for low molecular weight allergens for select workers with symptoms consistent with occupational asthma to specific allergens, and where skin testing extracts are available – **Moderately Recommended, Evidence (B)** Skin prick testing for allergens not covered above – **Not Recommended, Insufficient Evidence (I)**
Specific Inhalation Challenge Testing	Specific inhalation challenge testing 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 – **Recommended, Evidence (C)**
Nitric Oxide	Nitric oxide testing for the diagnosis of occupational asthma, as it cannot differentiate between, e.g., occupational asthma and other eosinophilic lung inflammatory conditions – **Not Recommended, Insufficient Evidence (I)** Exhaled nitric oxide testing for establishing a diagnosis of asthma when more objective evidence is needed such as in litigated cases – **Recommended, Evidence (C)** Exhaled nitric oxide testing for selective use in monitoring airway inflammation in patients with moderate and severe asthma – **Moderately Recommended, Evidence (B)**
Nasal Lavage	Nasal lavage fluid analysis after challenge with the allergen for the diagnosis of occupational asthma – **Not Recommended, Insufficient Evidence (I)** Nasal lavage for select workers with symptoms consistent with occupational airways allergy to specific allergens – **Recommended, Evidence (C)**

Table 2. Summary of Recommendations for Management of Occupational Asthma

Recommended	Not Recommended
Patients, physicians, and employers be informed that persistence of exposure to the causal agent is likely to result in deterioration of asthma symptoms and airway obstruction (I) Patients and their physicians be aware that complete avoidance of exposure is associated with the highest probability of improvement, but may not lead to a complete	Reduction of exposure as a strategy for certain low molecular weight asthmagens (diisocyanates). (I) As an alternative to complete elimination of exposure, continued low level exposure with use of personal protective equipment has been associated with adverse health outcomes including reports of death. Reducing exposure to the causal agent as a strategy

recovery from asthma (I) For irritant-induced asthma, exposure reduction to the lowest levels possible and careful medical monitoring should be performed to ensure early identification of worsening asthma (I) Pharmacological treatment of work-related asthma follows general recommendations for asthma (C). Current American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations for treatment of severe asthma should be followed. Immunotherapy may be considered in settings where occupational asthma due to a specific high molecular weight (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 (I)	in the management of sensitizer-induced asthma, as available evidence indicates that most asthma will worsen in continued exposure. (I) However, it is recognized that some workers will insist on remaining in their jobs for social, economic, and professional reasons, despite counseling on the adverse health consequences. Continued exposure, even at low levels, may result in worsening asthma. If such patients remain in exposure, documentation of the recommendation regarding removal is RECOMMENDED (I). Required close and careful medical monitoring of such patients is RECOMMENDED (I) in order to ensure early identification of worsening asthma. Reducing exposure to the causal agent in addition to providing immunotherapy and other asthma management, where applicable, may be RECOMMENDED (I), and will depend on the asthmagen, level of exposure, severity of asthma (see Table 5), and the clinical judgment of the physician. Use of respiratory protective devices as a safe approach for managing asthma, especially in the long-term and in patients with severe asthma (I) Anti-asthma medications as a reasonable alternative to environmental interventions such as exposure reduction or medical removal. (I)

CLASSIFICATION OF WORK-RELATED ASTHMA

WORK-RELATED ASTHMA

Occupational/work-related asthma may be classified as follows:

1. Exacerbation of pre-existing asthma (WEA)
    a. Irritant Gases
    b. Allergens
    c. Other (e.g., environmental tobacco smoke, exercise ,other irritants)
2. New Onset Asthma
    a. Without sensitization
        i. Endotoxin (Byssinosis from cotton dust)[i]
        ii. Cholinesterase inhibitors (pesticide exposure)
        iii. Inflammatory response (chlorine, ammonia)
        iv. Irritant induced:
            1. Acute irritant exposure (RADS)
            2. Low level irritant exposure with latency)[ii]
            3. Cold –induced (non-specific)
            4. (Nonspecific)
    b. With sensitization
        i. High molecular weight compounds – IgE mediated (complete allergens: animal, plant, bacterial)

[i] In the early stage when there is reversible airflow constriction and before it becomes a fixed obstruction.
[ii] New onset asthma due to low level irritant exposure has been described but is not widely accepted in the absence of pre-existing airway hyperreactivity.

ii. Low-molecular weight compounds
    1. IgE-mediated (platinum, antibiotics)
    2. Uncertain mechanism (isocyanates, amines, acid anhydrides, plicatic acid)

Table 3. Types of Work-related Asthma

Nomenclature	Term	Defining Features
Sensitizer-induced occupational asthma (OA)	Occupational asthma with latency of allergic or presumed immunological mechanism (not necessarily IgE)	Immunological/hypersensitivity component and diagnostic tests include measures of specific sensitization (e.g. skin prick test, serum specific IgE, circulating IgC against the antigen or skin sensitization).
Irritant-induced occupational asthma (OA)	Occupational asthma without latency	No allergic component and worker is not "sensitized" to an agent; rather, the agent causes inflammatory responses through irritant mechanisms.
Work-exacerbated or work-aggravated asthma (WEA)	Work-exacerbated or aggravated asthma (no latency period)	Worker has prior or concurrent history of asthma not induced by that workplace. The worker is not sensitized to an agent at work, but is irritated by a "non-massive" exposure (e.g. cold, exercise, non-sensitizing dust, fumes, or sprays) that provokes an asthmatic reaction.

Adapted from the American College of Chest Physicians (ACCP).

There are many occupations and exposures that have been associated with allergic occupational asthma. A list of common occupations and exposures is provided in Malo & Chan-Yeung 2009 (available at: http://www.jacionline.org/article/S0091-6749(08)01671-0/pdf).

ETIOLOGY

More than 300 natural and synthetic chemicals have been implicated in causing WRA. This section highlights a few commonly encountered chemicals causing "asthma with latency" (a term that suggests a process that does not provoke a response on first contact, which implies that sensitization may be the mechanism) that are seen in the occupational setting. More extensive lists of agents and occupations are available (e.g., "Agents Causing Occupational Asthma with Latency" in Malo & Chan-Yeung 2009: http://www.jacionline.org/article/S0091-6749(08)01671-0/pdf; Toxnet: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB; Centers for Disease Control and Prevention: http://www.cdc.gov/niosh//topics/; Agency for Toxic Substances and Disease Registry: http://www.atsdr.cdc.gov/; and Haz-Map: http://hazmap.nlm.nih.gov/index.php).

When referring to etiologic chemicals, these substances are often divided between high molecular weight (HMW and low molecular weight (LMW) agents. The former include proteins and polysaccharides of plant or animal origin (>5-10 kD) while the latter are low-molecular-weight chemicals (e.g., isocyanates, trimellitic anhydride, formaldehyde. This distinction is utilized to draw attention to typical mechanisms of pathogenesis. In particular, HMW agents can serve as a direct sensitizing antigen, leading to classic IgE mediated immune response. LMW compounds act as haptens, binding to existing proteins in the body and producing an IgE response. These mechanisms lead to asthma after a latency period. Typical HMW IgE mediated examples would be flour or laboratory animal proteins, while acid anhydrides and metals would be LMW examples.

However, there are LMW antigens that cause asthma without an IgE mechanism being currently identified. Immune mediation is thought to exist as the patients still present with a latency period. Examples include the di-isocyanates – toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI) – and formaldehyde and cleaning agents. Even with immunologic mechanisms present, there may be

non-immune pathways operating. This has been seen with TDI as well as Western Red Cedar due to the latter containing plicatic acid.

Specific HMW Chemicals:

- Grains and flours, in particular wheat and soya, have been among the most commonly described products. This is due not only to the flour product itself, but at times due to bug infestation into the material as well as additives including enzymes. Bakers and food processors would be a risk group, as well as dock workers exposed to shipping of the materials.
- Animal proteins are a HMW asthma precipitant that comes from the dander, fur, hair, saliva or urine. Animal urine protein is probably the most potent immunizing source in this group. Workers at risk for this would include farmers, veterinarians, and laboratory researchers or their assistants.
- Much attention has focused on the HMW latex exposure. This natural product (derived from the rubber tree) not only causes WRA, but also contact dermatitis. This latter condition is seen most commonly in health care workers. Environmental control in the form of avoiding latex gloves has helped diminish the burden of this condition.

Specific LMW Dhemicals:

- Acid anhydrides are a large group of LMW compounds including phthalic anhydride, trimellitic anhydride, maleic anhydride and tetrachlorophthalic anhydride. Products manufactured include plastics, dyes, adhesives and resins, with workers involved in production as being at risk for WRA. Exposed workers with a history of cigarette use are at particular risk.
- Platinum salts and aluminum can produce symptoms in workers exposed in jewelry and alloy production. Exposed workers with a history of cigarettes are at particular risk.
- Di-isocyanates have been identified as the most common cause of LMW WRA. The commonly used di-isocyanates in industries are TDI, MDI, hexamethylene di-isocyanate (HDI), and prepolymers of MDI and HDI. They all have in common N=C=O groups that are highly reactive and explain their sensitizing properties. The reported prevalence of di-isocyanate induced asthma has varied but may have been reduced in recent years due to better preventive measures.[28] These chemicals have properties to form polymers giving rise to polyurethane. They are used across a wide variety of industries in the production of flexible and rigid foam, binders, coatings, elastomers, and paints.

OTHER AIRWAYS ASSOCIATED DYSFUNCTION DISORDERS

While asthma is the principal occupational airways disorder in working adults, other conditions should be considered as part of the differential diagnosis. These may include fixed airway obstruction, upper airway abnormalities, laryngeal disorders and cardiac diseases.

These specific respiratory disorders should be considered in the differential diagnosis:

- Asthmatic bronchitis. This is an inflammatory disorder of airways that can have a hypersensitivity or an irritant component or both; bronchiectasis may also be present.
- Hypersensitivity pneumonitis. Predominantly an interstitial disease, HP often has an airways component, especially acutely.
- Chronic obstructive pulmonary disease (COPD). This disorder is characterized by a fixed obstruction to airflow with or without a reversible component. It may be associated with smoking, and manifested by emphysema or bronchitis,[29] or dust (such as silica, coal, or asbestos) exposure.[30]
- Allergic rhinitis and atopy. Persons with allergies often experience wheezing and reversible airflow obstruction during exacerbations of their allergies as a secondary symptom, especially during acute allergic reactions and respiratory tract infections.

- Bronchiolitis and other obstructive airways diseases in adults, such as constrictive bronchiolitis and during progression to bronchiolitis obliterans.
- Eosinophilic pneumonias. A family of disorders presenting as asthma but characterized by a hyperimmune response involving eosinophils. This family includes allergic bronchopulmonary aspergillosis (ABPA) and Loeffler's disease.
- Upper airway obstruction in adults may be confused with asthma and stridor may be confused with wheezing. Acute upper airway obstruction, such as that occurring with epiglottitis and anaphylaxis, is a medical emergency and is unlikely to be confused with asthma. Chronic partial upper airway obstruction may be seen in tumors, sarcoidosis, vocal cord paralysis, vocal cord papilloma and a variety of rare conditions (such as retropharyngeal abscess) unlikely to be confusing in practice.[31]

DIAGNOSIS OF WORK-RELATED ASTHMA

SYMPTOMS AND SIGNS IN 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.[32]

Cough requires special attention. It has been found to be the single most troublesome complaint for patients with stable, chronic asthma, which may also be true for other airway conditions.[33] Many cases of asthma do not show wheezing and have cough as the predominant symptom[34] as do most cases of bronchiolitis.

COMPLICATIONS AND COMORBID CONDITIONS RELEVANT TO WORK

People with asthma often experience complicating conditions and symptoms that are not primary parts of the diagnosis and are usually not the endpoints for treatment but affect daily life and work. These conditions and symptoms may occur in the context of work-related asthma and may therefore, be considered to be additional outcomes arising from directly work. They are also common conditions accompanying asthma that are not work-related that affect fitness for duty and that may occur with work capacity and job performance.[35] These complicating symptoms do not necessarily change with improvement in asthma status or with treatment. These complications may affect speech and voice, alertness and cognitive acuity, and risk for sleep apnea and should be considered in assessing fitness for duty and in impairment evaluation.

- *Coughing spells*. These may be disruptive in the workplace and are sometimes associated with acute rhinitis and susceptibility to fragrances and capsaicin.
- *Voice changes and unreliability*. There are many reasons why asthma affects the voice: breathlessness, vocal cord edema due to inhaled corticosteroids, concurrent allergies, and "paradoxical vocal fold motion dysfunction" (VCD). VCD also occurs in other respiratory conditions, but is more common in asthma.[36-38] Patients with asthma and similar airway problems may have difficulty in any job requiring them to use their voice to communicate.
- *Irritability, loss of concentration and restlessness*. This may be due to distraction, given that cough, mild choking sensations, and breathing issues interfere with close concentration and fine work.
- *Musculoskeletal symptoms*. Chronic coughing and altered trunk mechanics may be associated with chest (thoracic cage) pain and low back pain.
- *Leg pain*. Some asthma medications (including formoterol – Foradil®) may cause restless leg syndrome, or alter tissue levels of potassium, magnesium and other elements that can cause muscle cramps.

- *Eye problems*. Abnormalities in the stability of tear film may accompany nasal inflammation and airways disorders.[39] Cough and increased intrathoracic pressure may raise pressure levels in the eye, causing small blood vessels to become engorged and even to break.
- *Sleep disorders, fatigue, and cognitive deficits*. These connected conditions are associated with night-time asthma and disturbed sleep patterns, not just time awake at night due to wheezing, shortness of breath, leg pain, and, especially, cough. The result is a substantial decrease in performance in any task requiring mental processing, short-term memory, and sustained attention, even when asthma is treated.[40, 41] There has long been strong evidence that RADS also affects the upper airway.[42] It may occur as obstructive sleep apnea because of dysfunction of the upper airway – a feature of Reactive Upper-Airways Dysfunction Syndrome (RUDS) – or it may reflect reactive airways and cough during the night. The relationship between obstructive and central (brain-driven) sleep apnea also appears to be closer than has been previously believed and predominantly central apnea may account for some cases. Further, sleep apnea itself, apart from obesity, with which it is confounded, substantially raises the risk of a variety of serious complications, including heart attacks and stroke.[43]
- *Depression*. This is common to all chronic diseases and is known to occur in asthma. Sleep deprivation may aggravate it in asthma and bronchitis.[44]
- *Gastro-esophageal reflux disease (GERD)*. GERD often coexists with asthma and may be associated with it, although both diseases are also common alone.[45] GERD, phlegm-producing cough, and a heightened cough reflex may predispose the patient with asthma to choking and gagging.[46, 47]

These symptoms and signs cluster in five sets of related conditions, which have been given broad rubrics of *panic-fear*, *airways obstruction*, *hyperventilation*, *fatigue*, and *irritability*. Within these categories, symptoms and signs tend to track one another; that is, within a cluster, symptoms have been observed to appear together rather than separately.[48]

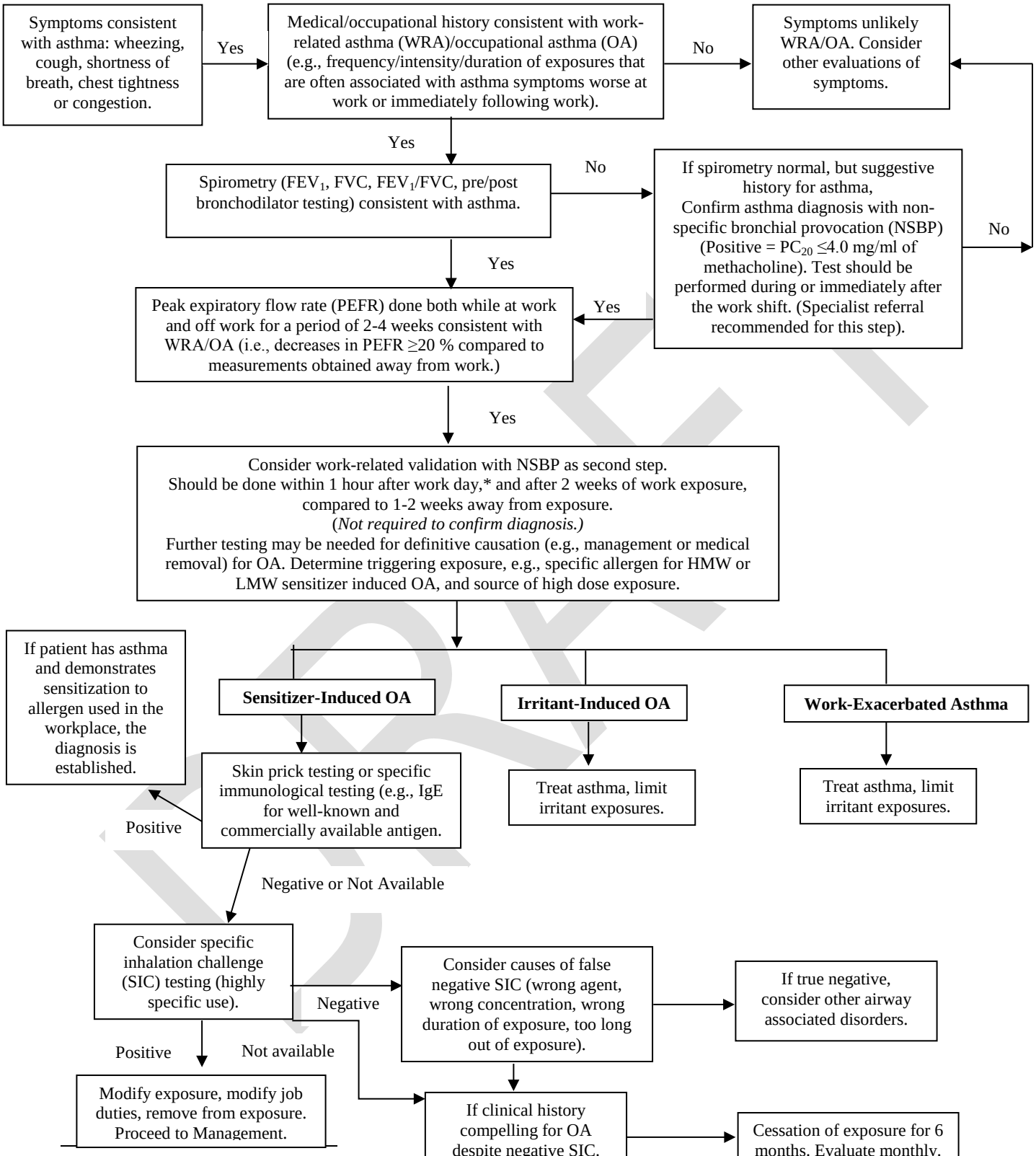
DIAGNOSTIC ASSESSMENT OF OCCUPATIONAL ASTHMA

In this guideline, we emphasize pulmonary evidence-based evaluations. See MTUS General Approach to Initial Assessment and Documentation for an overview of occupational evaluations, including the history and physical examination. More 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 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.[9]

The algorithm below is a consensus-based recommendation from the Evidence-based Practice Asthma Panel for the diagnostic evaluation of an individual with suspected occupational asthma.

Algorithm 1 – Diagnostic Evaluation of Occupational Asthma with Continuing Exposure[iii]



[iii] In the absence of ongoing suspect exposure, the relationship between the suspect agent can only be confirmed with SIC, this may be the only absolute indication for performing a specific bronchial provocation challenge with a diisocyanate and is justified if the result will have an impact on future health and economic outcomes.

*This step can be omitted if NSBP already completed.

MEDICAL HISTORY

Taking a thorough medical history is the first step when suspecting occupational lung disease. The history should include three components: 1) current and previous respiratory symptoms; 2) an occupational history that includes a detailed exposure history; and 3) focused questions linking the symptoms to the workplace, in space, time, and latency from first exposure. The ultimate goals of a structured investigation are to assist in determining causation, implementing treatment, and intervening to prevent disease in other exposed workers.[49]

The patient should be queried regarding childhood respiratory symptoms, as well as colds, bronchitis, pneumonia, hay fever, sinus problems or allergies. Evidence for atopic disease should be sought (e.g., asthma, hay fever, and eczema).[50] Ask about the length and severity of these illnesses, medication history, and whether emergency department treatment or hospitalization was required. Some studies show that atopy increases the risk of WRA or sensitization for certain asthmagens including enzymes, isocyanates, animals, bakery allergens, dyes, green coffee, castor bean, certain shellfish, and acid anhydrides.[51] While family history is important in asthma incidence, the same family history does not reliably predict occupational lung disease in exposed workers.[52]

A history of asthma symptoms arising during a period of employment, especially with improvement on the weekends or holidays is suggestive of WRA. However, more evidence is needed to verify that the symptoms are due to asthma, and that the asthma is related to workplace exposures.[27]

Although the probability of WRA from history alone is not high, a typical history consistent with WRA can lead to a pretest probability as high as 70% before diagnostic tests are conducted.[7] Cote, et. al., reported that a history suggestive of western red cedar asthma had a diagnostic specificity of 45%.[53] In contrast, Malo et al., reported that 76% of referred clinical patients reported improvement in respiratory symptoms while away from work but were subsequently found to have no objective evidence of WRA.[49] Taken together, the clinical history is believed to be more reliable for excluding than confirming the diagnosis of WRA.[9] For OA without latency, frequently resulting from accidents or other non-routine workplace conditions, the history is often the primary source of information to establish that a highly offensive atmosphere was present. In this section, we will use the words inflammatory or irritating interchangeably.

INTERVIEW QUESTIONS

Larger employers often have the benefit of workplace surveillance programs, medical staff on location, accessible spirometry, and general knowledge of the chemicals used in the work environment. This may allow a more focused history than the general recommendations below. Symptoms of occupational asthma include episodic wheezing, chest tightness, cough, dyspnea, or recurrent attacks of bronchitis with cough and sputum production. The history[iv] should include the following questions:

1. **What are your symptoms?**
   - What are your symptoms of concern? Do you have cough, shortness of breath, or wheezing?
   - When did these symptoms first occur? Was there an event that precipitated the symptoms?
   - When did these symptoms first occur relative to the beginning of your work in that location?
   - How frequently have symptoms occurred?
   - Do they get worse at any particular time of day or night?
   - If yes indicate below the patterns of the symptoms:
     - Do these symptoms ever begin immediately after starting work (less than 1 hour)?
     - Do these symptoms begin hours after starting work?
     - Do these symptoms continue or start while at home?

[iv]History for asthma does not replace the OSHA questionnaire when required by regulations. See OSHA Respiratory Questionnaire Appendix C to Sec. 1910.134: OSHA Respirator Medical Evaluation Questionnaire.

- Do they improve when you are away from work such as on weekends, nighttime (off-shift) or holidays or vacations?

- Are your symptoms constant or intermittent? What makes them worse or better?
- Has the pattern of your symptoms changed over time? How?
- Is there a seasonal pattern to your symptoms? What time of year are they the worst?
- Are the symptoms associated with any substance or process at work?
- How frequent and severe are your symptoms? Have your pulmonary symptoms included throat tightness, difficulty with inspiration or expiration, harsh sounds, cough, or sputum production?
- Did any emergency room or physician visit document lung function?
- Do you have a history of pre-existing asthma, (in particular childhood asthma which can recur in adults), including prior frequency of symptoms, treatment with asthma medication and response to medications?
- Do you have a history of allergy or has anyone mentioned the word atopy to you?
- Do you have symptoms of allergic rhinitis and/or conjunctivitis that are worse with work?
- Did the symptoms begin after a one-time, high-level workplace inhalation exposure to an irritant gas, fume, smoke or vapor?
- How does medication use affect the symptoms? Do you use prescribed medications, over-the-counter medications and/or complementary/alternative preparations? Do you use pulmonary and non-pulmonary medications? Are you taking an angiotensin converting enzyme inhibitor? Beta-blocker?
- Do others at work have the same symptoms you have?

2. **How did your condition develop?**
   PAST:
- Have you had previous similar episodes before your current job?
- What kind of treatment did you receive for these symptoms in the past?
- Who was your physician?
- Were the treatments effective?
  CAUSE:
- What do you think caused the problem?
- How do you think it is related to work?

OCCUPATIONS AND ACTIVITIES:
- What do you do for work?
- Current occupation and specific work activities including shift, hours, duration, and days worked per week. (Patients working 6 days a week or more may not have enough time away from work to symptomatically improve.)
- Any past work history including specific activities, especially if there is a history of similar symptoms?
- What chemicals or substances including gas, fumes, vapors, dusts, or aerosols do you work with? What about at home?
- What is the work area's room size, specific ventilation, other co-worker reports, exhaust hoods, remodeling, and recent change in processes? Are there Material Safety Data Sheets (MSDSs) and industrial hygiene reports available?
- Were there changes in work processes in the period preceding the onset of symptoms? Symptoms of asthma that develop or worsen after a worker starts a new job or after new materials are introduced on a job are suggestive. (A substantial period – from months to years – can elapse between initial exposure and development of symptoms.)
- Was there an unusual work exposure before the onset of initial asthma symptoms?
- Do you have any protective equipment at work, such as masks or respirators? How often do you use them? Are they required?

- Do you have a second job (moonlighting)?

NON-OCCUPATIONAL ACTIVITIES:

- What is your home environment including any hobbies, crafts, pets, family members who work with chemicals, family members who smoke, living near an industrial plant, or living near congested traffic area?[54]
- What are your leisure activities (e.g., woodworking, gardening, welding, etc.)?

3. **How do these symptoms limit you?**
   - Are there any activities that you can no longer perform?
   - Do you feel more short of breath during exercise?
   - Do you feel more short of breath when doing normal daily activities?
   - How long have your activities been limited?
4. **Do you have other medical problems?**
   - Do you have headaches, fatigue, malaise, weight loss, appetite changes, fever, physical abilities and exercise intolerance?
   - Do you have any autoimmune, infectious, or metabolic diseases?
   - Do you have any allergies?
   - Do you have any other respiratory diseases or conditions?
   - Do you smoke? Does someone else in your environment smoke?
   - Do you use other drugs, including marijuana?
   - Do you have diabetes or HIV?
   - Have you ever had cancer?
5. **What are your expectations regarding your return to work and disability from this health problem?**
6. **What are your concerns about the potential for further injury to your lungs?**
7. **How do you like your job, your supervisor, and co-workers? What is your relationship with your co-workers and supervisor and how do they treat you?**
8. **What do you hope to accomplish during this visit?**[13]

Standardized Questionnaires

There have been general articles and questionnaires used to document occupational illness.[55, 56] Similarly, authors have suggested questions targeting work-related pulmonary conditions.[57, 58] Questionnaire adequacy measures have shown instruments that are reliable, valid and correlate with testing.[59-63] Reliability should be considered as reproducibility of response and validity is a measure of how well the instrument measures the intended target. Ultimately, there have been investigations looking at correlations between history and diagnosis of occupational lung disease.[64] Malo, et al., examined the accuracy of the medical history in 162 workers referred for evaluation of occupational asthma, using specific inhalation challenge to confirm the diagnosis. They reported a positive predictive value of 46% and negative predictive value of 83%. In a study by Baur, et al., who used methacholine testing and specific bronchoprovocation challenge, the predictive value of the medical history was 90% with a negative history and 30% with a positive history. Vandenplas, et al., reported a specificity of 14% and sensitivity of 87% in natural latex workers when compared to specific inhalational challenge testing for diagnosis of OA.[65]

All instruments have limitations that will miss true cases of occupational asthma.[49, 66] The American Thoracic Society Division of Lung Diseases (ATS-DLD) instrument[67] is the most widely used questionnaire for pulmonary symptoms and disease that is validated in the literature.

Family History
A family history of atopic diseases may help identify individuals with greater susceptibility to occupational asthma with latency, particularly for occupational asthma to high molecular weight agents. However, it is important to note that many workers with occupational asthma will have no family history of atopy, and conversely, many workers with an atopic history without occupational asthma. A history of similar symptoms in other household and family members may also help identify non-occupational causes of asthma, such as home and hobby exposures.

Occupational History
The physician should obtain an accurate and detailed history of current and prior occupations. All possible occupational exposures should be identified, especially those that are known to induce airflow obstruction (e.g., animal and plant proteins, organic dusts, proteolytic enzymes, specific chemicals such as isocyanates and anhydrides, noxious fumes, metals and drugs). Both routine and episodic tasks are potential exposures and should be evaluated.

The physician should also attempt to quantify the exposure. The intensity (duration and concentration), frequency, duration, and peak concentrations of the exposures are all important to document if possible.[68] A detailed history of current exposure status is important. Lam, et al., reported a significant improvement in spirometry results after a mean of 0.8 years after removal from exposure in patients with occupational asthma.[69]

EXPOSURE ASSESSMENT

Respiratory injury is dependent upon both the site of toxin deposition and the type of cell and structure damaged. The concentration and chemical properties (pH, water solubility, reactivity) of the substance involved are relevant, as they affect the site of deposition. The degree to which a given inhalational exposure results in disease not only reflects the intensity, duration, and type of exposure, but also varies based on host factors such as genetic susceptibility, comorbid conditions, and lifestyle factors and habits (e.g., cigarette smoking). The presence of work-related pulmonary conditions should include assessment of whether representative measurable environmental determinations exist, to ascertain whether there has been sufficient exposure to affect the lungs.[70] However, measurable environmental determinations are not routinely performed in most workplaces, and when performed, represent a brief snapshot of selected exposures that may or may not reflect the relevant work exposures.

Information on work exposures may be obtained from MSDSs, industrial hygiene data, employer records, and union health and safety personnel information.[9] 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.[71]

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). In particular, the group's biological exposure indices and threshold limit values are more frequently evaluated and

updated than those occupational exposure levels (OELs) from the Occupational Safety and Health Administration (OSHA), the Mine Safety and Health Administration (MSHA), and the permissible exposure limits (PELs) defined by the National Institute for Occupational Safety and Health (NIOSH). OELs are set primarily to provide a means for standardized hazard assessment of a material, communicate a relatively safe target concentration relative to time interval which can be verified quantitatively, and to provide a target control approach to ensure that workers are not overexposed.

For workplace risk assessment, the *NIOSH Pocket Guide to Chemical Hazards* [(72)] provides a concise summary of toxicologic information. Most inhaled particles with a diameter of greater than 3 µm are deposited along the airways of the upper and lower respiratory tract. Smaller particles may penetrate the alveolar region, but the physical characteristics, total mass and chemistry of the particle and airway structure and airflow must be considered.[(73)] Water soluble gases, vapors and aerosols are usually deposited in the upper airway, while water insoluble substances affect the lower airways or lung parenchyma. Extremes of pH also are associated with severity of injury. Of importance in evaluation of respirable exposures is the distance of the worker from the source. The area tested should usually be within 2 feet of the worker's mouth and nose.[(74)] The probability of exposure is evaluated by considering: 1) the presence, form and biological availability of potential hazards; 2) confounding exposure factors in the workplace or the patient's medical and occupational history that may account for other exposure potential and experience; 3) non-worker controlled factors such as materials used, ventilation, hazard control, and physical barriers; 4) the worker's use of employer-selected personal protective equipment (i.e., respirators, gloves) and training in appropriate work practices; and 5) the presence or absence of illness in co-workers with similar exposure potential.[(75)]

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. The majority of the U.S. population is skin-test-positive to at least one environmental allergen.[(76)] It is difficult to determine the relative contribution of work-related and non-work-related factors to the genesis of symptoms in people with multiple risk factors or exposures.

Smoking History
The greatest threat to personal lung health is from tobacco inhalation.[(5, 77)] Although it is customary to quantify tobacco use in terms of pack-years, the variation in cigarette type and inhalational habits does not permit more than an approximation for potential lung injury.[(78)] Cigarette smoking is a recognized risk factor for common airway diseases with the unusual exception of diisocyanate asthma.[(51)] The smoking history should quantify the packs per day and the years smoked. Cigarette smoking may have an additive effect to airways obstruction from other causes, it may superimpose additional symptoms, or it may lead to misdiagnosis if the condition is apportioned disproportionately to smoking. Cigarette smoking may condition or modify the response to some antigens but this is not known at this time and cannot be assumed.[(9, 50)] Regardless of the history, a physical examination and diagnostic testing should be conducted as indicated.

Physical Examination
The art of physical examination traces its modern roots to the introduction of the stethoscope by Laennec in 1821. Standard textbooks provide guidance on pulmonary examination.[(79, 80)] In general, an occupational pulmonary physical examination should include elements of the following:

- Inspection for stigmata of pulmonary disease as well as potential etiologies including mucous membrane abnormalities, nasal polyps/swelling, clubbing, nasal flaring, nasal crease line, accessory muscle use, AP diameter;
- Palpation primarily for chest wall abnormalities, tracheal deviation or tactile fremitus;

- Percussion for resonance to identify aeration, diaphragm level, suggestion for fluid interface or consolidation;
- Auscultation for inspiration to expiration ratio, breath sounds including crackles, wheeze and bronchi;
- Cardiac examination; and
- Dermal examination.[81]

However, a shift has occurred in medicine where physical diagnosis is often measured against a technologic gold standard for the presence or absence of disease. Thus, a useful measure of an examination would be the likelihood of a finding causing a change in the probability of a disease. Numerically the likelihood ratio is equal to the probability of a finding in patients with a disease/probability of a finding in patients without a disease. For example, it is often taught that the crackles of fibrosis are late and fine whereas those of COPD are early and coarse. Yet, this assumption has never been rigorously tested. On the other hand, diagnostic pneumonia findings have been subjected to numerous studies and are incorporated in both diagnosis and prognosis.[82-84]

Formal spirometry testing and interpretation is covered elsewhere. Many clinicians will utilize simple clinical tests as part of their "physical examination." This includes obtaining a simple pulse oximetry reading and/or having the patient walk in the hallway to identify desaturation.

DIAGNOSTIC TESTING

SPIROMETRY TESTING

Use of Spirometry in WRA

Spirometry testing is an essential component in the evaluation and management of persons with possible work-related asthma.[85-91] 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).

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 (e.g., a worker experiencing chronic or intermittent cough, chest tightness, wheezing or dyspnea, occurring at the workplace or developing over several hours following the end of a work shift or awakening from sleep, which may or may not be obviously associated with the same location, product, process, or activity, or change in asthma medication use pattern).[85, 92-94] Spirometry with bronchodilator is an essential test for the evaluation of pulmonary function and would be performed in most cases whether or not occupational asthma is under consideration. Evidence for the utility of spirometric testing in the diagnosis and management of general asthma is summarized in other evidence-based guidelines.[94, 95]

Spirometry is also included in other more specialized tests discussed later in this document. These include measurement of airway reactivity (e.g., methacholine, mannitol, or histamine challenge) and specific inhalation challenge (SIC). Variability of airflow obstruction fundamentally distinguishes asthma from other obstructive disorders. Comparison of spirometry results before and after administration of a bronchodilator and variability of results when repeated over many days are effective and simple methods of assessing such variability.

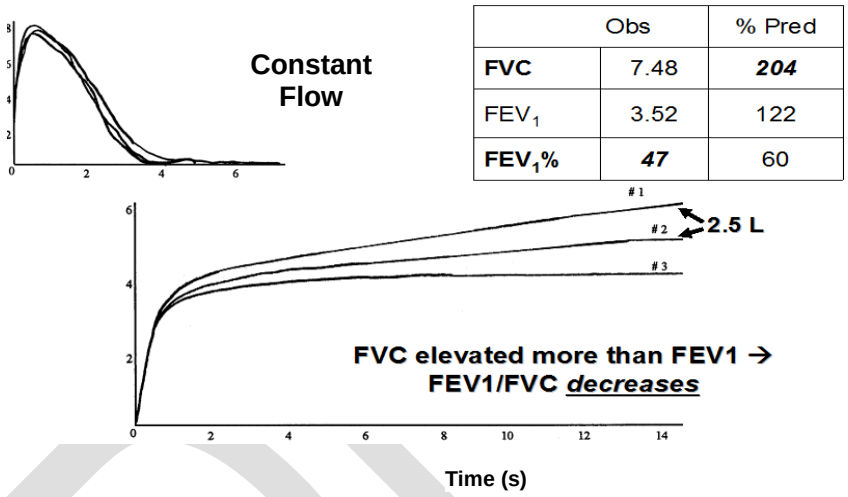
When considering WRA, spirometry with bronchodilator is used primarily to document and quantify airflow obstruction. For this purpose, the forced expiratory volume in one second (FEV_1) and the ratio of the FEV_1 to the forced vital capacity (FEV_1/FVC ratio) are most useful. The average flow rate during the midportion of the expiratory maneuver ($FEF_{25-75\%}$) may occasionally be useful.

Asthma is confirmed by demonstrating airflow obstruction (e.g., by reduction in both FEV_1/FVC ratio and FEV_1) or by a positive metacholine challenge. Methacholine challenge testing is a specific test for airways reactivity in which FEV_1 is used as the test outcome, but it cannot clarify the work relationship or the particular antigen involved in work-related asthma. 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.

Methods

Accurate results depend upon use of proper equipment, proper test performance, and qualified interpretation. Considerations for spirometry quality assurance are not specific for WRA, and several excellent reviews are available.[95-97] OSHA has also recently issued guidance on best practices for occupational spirometry testing.[98] ACOEM has emphasized the critical role of obtaining accurate data. The figures below illustrate common pitfalls.

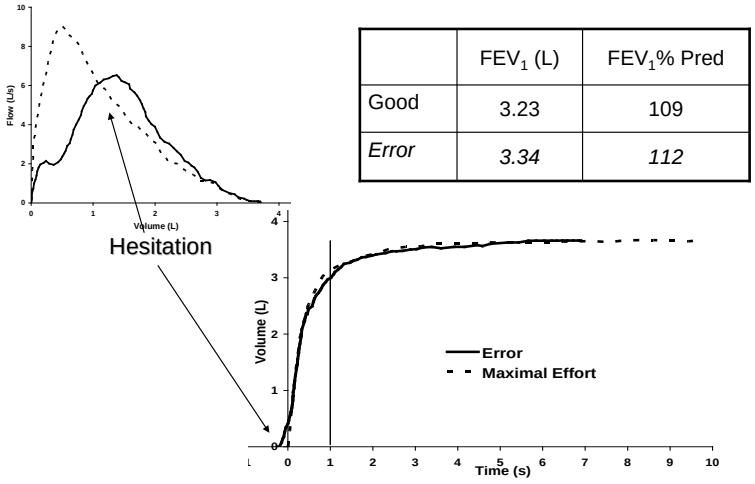
Figure 1. Error: Inconsistent Zero-Flow Errors Causing Flows to be *Over*-Recorded



DELETE THIS TEST. This spirometer's zero-flow reference point was set at different incorrect levels before the first two maneuvers, causing the volume-time curves (bottom figure) to be splayed apart. FVC is more increased than FEV_1, falsely *reducing* the FEV_1/FVC and probably leading to an erroneous "obstructive impairment" pattern. Block sensor when the spirometer is zeroed and hold sensor still during subject testing to avoid this problem.

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med*. 2011;53(5):569-84.

Figure 2. Error: Excessive Hesitation (solid curves)

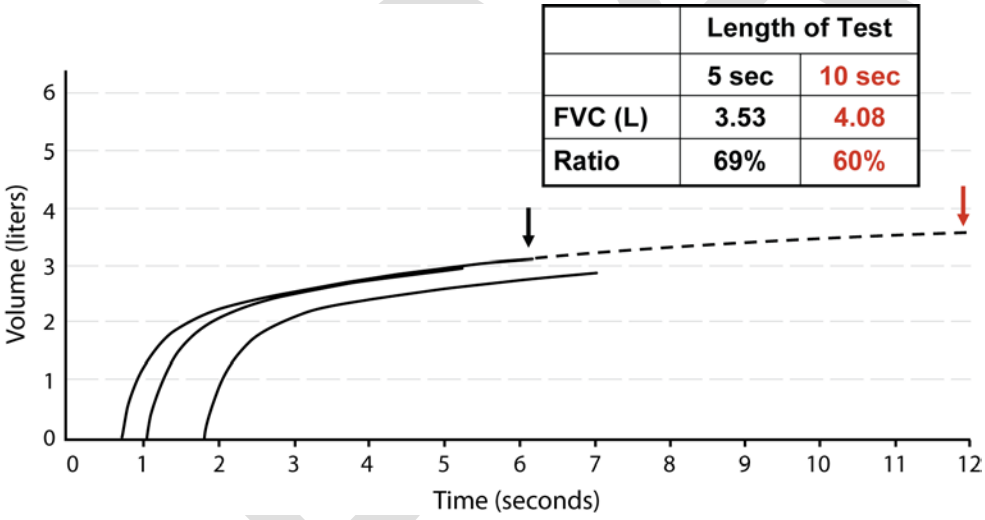


	FEV_1 (L)	FEV_1% Pred
Good	3.23	109
Error	*3.34*	*112*

DELETE THIS TEST. Since the worker's initial blast is delayed, the peak of the flow-volume curve (top figure) is displaced to the right, and a gradually climbing tail is seen at the start of the volume-time curve (bottom figure). Coach the worker: "BLAST out as soon as you are ready."

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med*. 2011;53(5):569-84.

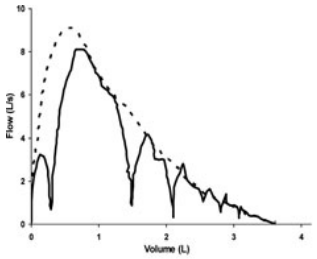
Figure 3. Error: Early Termination (solid curves)



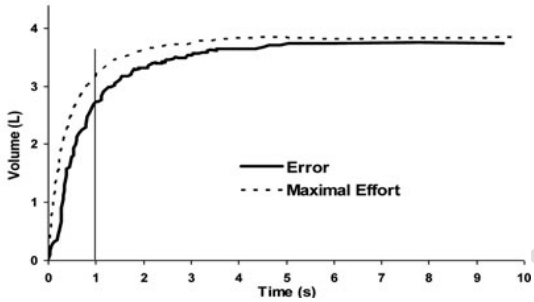
When an expiration stops before the volume-time curve flattens into a 1-second plateau, the FVC may not be fully recorded. An incompletely recorded FVC will falsely *increase* the FEV_1/FVC and may cause the spirometer interpretation to be "normal" even when airways obstruction is present. The solid lines show the curves that were terminated early. The dashed line shows the increase in "FVC" that would have occurred with only 5 more seconds of expiration. The more accurate FEV_1/FVC recorded after 10 seconds would trigger a correct interpretation of "airways obstruction." (Note that no more than one maneuver should be recorded for longer than 15 seconds.) Coach "Keep blowing until I tell you to stop."

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med*. 2011;53(5):569-84.

Figure 4. Cough in First Second—Invalid Test (Must be Deleted)



	FEV_1	% Pred
Maximal	3.23	109
Error	*2.95*	*99*



Cough in the first second produces steep interruptions in the flow-volume curve and subtle steps in the first second of the volume-time curve. Coughs often reduce the FEV1. Try offering a drink of water to solve this problem.

Townsend MC, Occupational and Environmental Lung Disorder Committee. ACOEM Guidance Statement: Spirometry in the occupational health setting – 2011 update. *J Occup Environ Med*. 2011;53(5):569-84.

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 (usually albuterol, known internationally as salbutamol, a short-acting $beta_2$-receptor adrenergic agonist).

The American Thoracic Society (ATS) defines a 12% improvement in the FEV_1 or an absolute value increase of at least 200 mL after bronchodilator administration as indicating reversibility of airflow obstruction in FVC or FEV_1 values.[6, 27, 90, 94, 95, 99-101] 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.

Spirometry is difficult for some patients to perform, and irreproducible results may make interpretation difficult.[102] (Allen 09) Using spirometers that show large real-time graphical displays, testing should be performed by a technician who has completed NIOSH-approved spirometry course.[98] Up to eight maneuvers may be attempted (beyond which most subjects tire) to produce three acceptable tracings, and the difference between the highest and second highest FVCs and FEV_1s should be within 0.15 of each other to achieve consistent "repeatable" results. The highest values of FVC and FEV_1 are used to summarize the patient's lung function, regardless of whether they are drawn from the same or different curves. Inability to perform reproducible tracings is often due to failure to cooperate or poor effort because, properly performed, spirometry achieves a physiological limit on flow that is beyond voluntary manipulation. A small number of subjects will not be capable of producing reproducible tracings due to behavioral problems, poor neuromuscular coordination, or very low lung function. Such subjects often have a poor prognosis for survival and for future disease, even if their pulmonary function are within or close to the normal range.[102-104] The American Thoracic Society and European Respiratory Society (ATS/ERS) have published 4 statements since 1979 on how to conduct spirometry tests and 2

statements since 1991 on how to interpret results.[95, 105] Since 2000, ACOEM has published three comprehensive spirometry statements on conducting and interpreting tests – most recently in 2011.[96] These statements emphasize the importance of performing and interpreting the results correctly.

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.[106] Failure to demonstrate reversible airway obstruction on a single test day does not exclude the diagnosis of asthma or of airways reactivity in general.[92, 94]

Important caveats to consider:

- Failure to demonstrate reversible airway obstruction on a single test day does not exclude asthma.
- Serial measurements can be used with clinical correlation to track progression and variability under different conditions and exposures, with the understanding that improvement in the measurements does not always correlate well with an improvement in the disease.
- Because asthma is characterized by variability, airflow obstruction is an indicator of status at any one time and does not necessarily reflect trends over time, but can indicate worsening of disease if it is much worse than a previous FEV_1 measurement.
- Therefore, its main value is in demonstrating variability (e.g., ruling out irreversible obstruction).[27, 85, 94, 95, 99, 107]

The measurements of greatest utility in spirometry for the evaluation of airways disease are[97, 99]:

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

Variability in appropriate spirometry measures in testing separated in time (days) or in response to bronchodilators (most accurately for FEV_1) indicates asthma. Fixed airways obstruction is present when volumes are unchanged, within limits of the test.

While FEF_{25-75} is a measure of airflow through smaller airways, structures that are commonly and disproportionately affected by cigarette smoking, FEF_{25-75} tends to vary far more than the FEV_1 both within and between healthy individuals, and so it is difficult to interpret abnormality of this flow rate in individual patients. When early emphysema is present, airflow in small airways is disproportionately reduced and is less variable than in asthma, but standards for this interpretation have not been established. Since 1991, ATS has discouraged using the FEF_{25-25} to diagnose small airways disease in individual patients when the FEV_1 and FEV_1/FVC are in the normal range.

Spirometry with bronchodilator is not invasive, has few adverse effects and is low to moderate cost and high in yield for complications and other respiratory problems. Its value comes in correlation with clinical information and observation. Spirometry with bronchodilator is thus recommended as an integral part of the evaluation of work-related asthma.

PEAK EXPIRATORY FLOW RATES (PEFR)

Peak expiratory flow rates (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.[108]

The use of PEFR is common in the diagnostic investigation of asthma including work-related asthma and occupational asthma. PEFR is most readily performed via a hand-held peak flow meter providing air flow measurement in liters/minute, and must be performed by the patient outside of a medical setting to be useful in evaluation of occupational asthma.[109-111] Thus, 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.

Recommendation: Peak Expiratory Flow Rates – Serial Measures

Serial peak expiratory flow measurements are moderately recommended as an initial evaluation method for diagnosing 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. A meter that can store the measurements should be used when possible.[7, 81, 112-114]

Strength of Evidence **– Moderately Recommended, Evidence (B)**
Level of Confidence – High

Performed – 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.[115] 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.[115] The optimal frequency and duration of serial PEFR has not been agreed upon. Generally, workers are instructed to record PEFR every 2-3 hours for 4 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.[1, 3, 7, 9, 108, 111] 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 4 weeks, including a period of at least 2 weeks away from suspect exposure is recommended, although longer periods increase the value of the test.[109-111] 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 2 hours while awake.

There are several interpretive methods for analysis of serial PEFR data. Values must be plotted with the average reading for time of day for work and off-work periods. Analysis may be performed visually by an expert, although there is a degree of intraexpert and interexpert variability.[116] Two alternative methods include difference in diurnal variability (maximum-minimum/maximum value x 100) and differences in mean PEF between work and non-work days. The difference between mean PEFR on rest days and mean PEFR on work days has been recommended as the best index for differentiating workers with occupational asthma from those with nonoccupational asthma by Anees, et al. They proposed a value of >16 1/minute as the most sensitive index to differentiate subjects with occupational asthma from healthy individuals and non-occupational asthmatics.[110]

Indications – To assist in screening patients with a history consistent with WRA.[9, 110, 114] There have been concerns over the reliability of self-reported peak flow measurements. One study found that self-recorded PEFRs were concordant with less than half of electronically stored measurements.[117] Although other investigators have reported better concordance,[118] these findings emphasize the importance of careful monitoring and daily supervision of workers during performance of serial PEFR measurements. 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).[119-124]

Harms – None.

Benefits – Can provide moderately objective evidence of relationship between work and asthma worsening.

Advantages and Limitations – PEFR is heavily dependent upon the worker's efforts, including reliable performance of a forced expiratory maneuver, accurate recording of the results, and assumes worker honesty in performing and recording the test results.[1, 3, 90, 107] In a study of 17 subjects blinded to simultaneous recording by the peak flow meter, only 55% of the records were completed accurately by the participants.[6] Quirce, et al., reported that 23% of PEF readings were inaccurate and 23% of the readings were invented, although these did not tend to change interpretation of work-relatedness.[117] PEF measures cannot differentiate between OA and work exacerbated asthma.[7]

Rationale for Recommendation
There are 4 moderate-quality studies that support the use of PEFR as an investigational tool for the diagnosis of OA and work-related asthma.[109, 111, 114, 122] Three studies performed compared PEFR readings to FEV_1/FVC measurements over a 4 week period in workers with a diagnosis of OA, concluding that serial PEFR measurements over a 4-week period including a period away from the workplace was moderately sensitive and specific. There is a suggested "minimum data criterion" of greater than or equal to four readings per day for more than two weeks that should be met before analysis of the data.[109, 111, 114] Another study demonstrated similar results over a shorter period of time with the use of a specific analysis tool.[121, 122] There is evidence that both supervised and unsupervised PEFR methods are acceptable, and thus no recommendation for or against a particular method is made, and is left to the discretion of the treating physician for each particular patient.[107, 125] There is one high-quality study demonstrating poor sensitivity with a cross-shift technique.[113] PEFR is non-invasive and is low cost. 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 are relatively inexpensive, have a low risk of adverse events, and may add information on airway resistance both at work and at home and are thus recommended. This recommendation is downgraded from strongly recommended to moderately recommended due to the technical challenges and the ability to manipulate the results.

Evidence for the Use of Peak Expiratory Flow Rates

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

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

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

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

NONSPECIFIC BRONCHIAL PROVOCATION TEST

Establishing the diagnosis of occupational asthma must start with the confirmation of the presence of asthma. Bronchoprovocation with methacholine, histamine, cold air, mannitol, 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.[17, 126] Methacholine is preferred to histamine because it is associated with fewer side effects, and lung function measurements are more reproducible.[127] 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.[126, 128] These stimuli are thought to evoke airflow limitation predominately by an effect on airway smooth muscle, although the mechanisms preceding this effect differ. Persistence of bronchial hyperresponsiveness out of the workplace is more likely in those with longer duration of symptoms and exposure than in workers with early diagnosis and removal. 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.

1. *Recommendation: Nonspecific Bronchial Provocation Test*
   Nonspecific bronchial provocation test (e.g., methacholine) is strongly recommended for use in diagnosing asthma if the clinical history is compelling and other tests (spirometry and bronchodilator responsiveness) are unhelpful.

   Strength of Evidence **– Strongly Recommended, Evidence (A)**
   Level of Confidence **–** High

2. *Recommendation: Nonspecific Bronchial Provocation Test*
   Nonspecific bronchial provocation test (e.g., methacholine) is moderately recommended for use in diagnosing work-related asthma as other steps are required to establish the work-relatedness of the asthma.

   Strength of Evidence **– Moderately Recommended, Evidence (B)**
   Level of Confidence **–** High

3. *Recommendation: Mannitol Bronchial Provocation Test*
   Mannitol bronchial provocation test is recommended for use in diagnosing work-related asthma; other steps are required to establish the work-relatedness of the asthma.

   Strength of Evidence **– Recommended, Evidence (C)**
   Level of Confidence **–** Moderate

Performed – Testing location should be experienced and technicians properly trained on performance of spirometry.[127] There are two methods for inhaling aqueous solutions of pharmacologic stimuli: 1) the 2-minute tidal breathing protocol; and 2) 5-breath dosimeter protocol.[126, 127, 129, 130] The method of performing nonspecific bronchial provocation tests is to first measure baseline lung function and to calculate a target FEV_1 that indicates a 20% fall in FEV_1. Inhalation of a placebo or diluent (0.9% NaCl) is optional. Inhalation of the bronchoconstrictor agent methacholine typically starts at a concentration of 0.031 to 0.0625 mg/mL, and then increases by doubling or quadrupling concentrations up to 16, 25, or 32 mg/mL, depending on the protocol. Following each inhalation, the FEV_1 is measured and the test is stopped when the FEV_1 has fallen by 20% from baseline or diluent value. The response is usually expressed as a provocative concentration (PC_{20}) producing a 20% fall in forced expiratory volume in 1 second. The presence of asthma is usually defined as a ≥20% fall in the FEV_1 at a methacholine dose of 4 mg/mL or below.[69, 131-135] Methacholine 4-16 mg/ml is considered borderline full categorization of bronchial responsiveness based on methacholine PC_{20} mg/mL dose.[v]

[v] According to ATS *Guidelines for Methacholine and Exercise Challenge Testing –1999*, the categories of bronchial responsiveness by methacholine dose (PC20 mg/mL) are as follows:

Mannitol testing is performed via inhalation of increasing doses of dry mannitol powder in capsules, up to 160 mg. The test is considered positive if the cumulative dose of mannitol inducing a 15% decrease in FEV_1 is 635 mg or less. The dosing is sequential, starting at 5 mg, and increasing to 10, 20, 40, 80, and 160 mg doses. The 160 mg dose may be repeated two additional times for a cumulative possible dose of 635 mg.[136-139]

Criteria and Standards for Use – Bronchial challenge testing should be done according to the 1999 ATS statement and the 1993 European Respiratory Society statement.[85, 139]

Indications/Contraindications – To establish the diagnosis of asthma and to aid in the diagnosis of work- related asthma. NSBP is not generally recommended if the baseline FEV_1 is <65% of predicted.[1, 5] Absolute contraindications for methacholine challenge testing include:

- severe airflow limitation (FEV_1<50% predicted or <1.0L), heart attack, or stroke in previous 3 months;
- uncontrolled hypertension (systolic BP>200 or diastolic BP>100); and
- known aortic aneurysm.[127]

Relative contraindications include:

- moderate airflow limitation (FEV_1 <60% predicted or <1.5L;
- unable to perform acceptable-quality spirometry;
- pregnancy;
- nursing mothers; and
- current use of cholinesterase inhibitor medication (for myasthenia gravis).[127] (ATS 00)

Harms – Bronchoconstriction, transient symptoms of wheezing, cough, mild dyspnea, and chest tightness, with smaller risk for dizziness and headaches post-test.

Benefits – Accurate diagnosis of asthma.

Advantages and Limitations – Testing for airway hyperresponsiveness is relatively objective and due to its accessibility, it is used regularly in clinical practice. It is limited in differentiating occupational asthma from non-occupational asthma without additional history, testing, and information. Methacholine challenge testing is more useful in excluding a diagnosis of asthma than in establishing a diagnosis because its negative predictive power is greater than its positive predictive power.[127] Bronchial hyperresponsiveness with methacholine challenge testing may also be seen in conditions other than asthma, including smoking-induced chronic airway obstruction, congestive heart failure, cystic fibrosis, bronchitis, and allergic rhinitis.[127]

Rationale for Recommendations

Many high- and moderate-quality studies have evaluated the diagnostic utility of nonspecific bronchial challenge testing in comparison to other studies including specific inhalational challenge testing, peak expiratory flow meters, and immunological testing to establish the diagnosis of work-related asthma.[53, 69, 85, 134, 135, 140-162] In one study of dairy farmers, the sensitivity of methacholine challenge compared to bovine inhalational challenge in diagnosing occupational asthma was reported as 82%, and specificity of

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- >16 is normal bronchial responsiveness;
- 4.0-16 is borderline BHR;
- 1.0-4.0 is mild BHR (positive test); and
- <1.0 is moderate to severe BHR.

Before using this categorization, the following must be true: baseline airway obstruction is absent; spirometry quality is good; and there is substantial postchallenge FEV1 in response to bronchodilator.

65%.[141] Another study comparing specific inhalational challenge to nonspecific bronchial challenge testing reported a sensitivity of 57% and a specificity of 93% for occupational asthma.[148]

Methacholine and histamine challenges are reported to be more reliable than other nonspecific bronchial provocation tests.[135, 160] Overall, methacholine challenge testing has been reported to have a sensitivity level of around 95% in the diagnosis of asthma.[92] A major caveat is that nonspecific bronchial provocation testing is not capable of reliably differentiating between occupational and non-occupational asthma.[64, 133] The temporal relationship of nonspecific bronchial hyperreactivity (NSBHR) with exposure is important[163] and the test should be performed either during or immediately after the work shift if possible. The authors considered a two-fold increase in the PC20 FEV_1 after removal of exposure to be significant.

Methacholine challenge tests do not always remain positive after a diagnosis of occupational asthma or work-related asthma, as methacholine reactivity may wane out of exposure. In a case report, a worker with asthma secondary to toluene diisocyanate (TDI) lost his reactivity to methacholine after 2 months of removal from exposure.[164] Other studies of workers with occupational asthma to TDI,[165] cobalt,[166] and reactive dyes[167] have demonstrated persistent bronchial hyper-responsiveness in some from 5 to 13 years out of exposure. Those with asthma from HMW agents may also demonstrate persistent airways hyperresponsiveness.[168] Workers were more likely to lose their methacholine responsiveness with early diagnosis and early removal from exposure after onset of asthma. Those who became asymptomatic out of exposure were more likely to revert to normal bronchial reactivity than those who reported ongoing asthma symptoms.[128]

Compared to specific inhalational challenges, bronchoprovocation is less hazardous, lower cost, easier to perform, more readily available, and can be completed in less time. Therefore, it is recommended for the diagnosis of asthma, and work-related asthma, particularly when the baseline spirometry is normal yet there is sufficient index of clinical suspicion.

Although most bronchoprovocation agents cause a fall in the FEV_1 by triggering bronchial smooth muscle contraction, different agents act through different pathways to achieve this effect. Methacholine acts as a non-selective muscarinic agonist on receptors on bronchial smooth muscle, whereas histamine acts through stimulation of H1 receptors on bronchial smooth muscle, or indirectly through stimulation of vagal parasympathetic reflex bronchoconstriction. Cold air leads to respiratory heat and water loss with transient hyperosmolarity in the respiratory mucosa, triggering mediator release from eosinophils or mast cells that cause the airways to narrow. Mannitol likely triggers the release of inflammatory and/or bronchospastic mediators, causing the smooth muscle of the airway to contract and resulting in airway narrowing. The exercise challenge is thought to cause inflammatory cells to release mediators such as leukotrienes, prostaglandins, and histamine that secondarily provoke airway smooth muscle constriction and a measurable fall in the FEV_1.

Evidence for the Use of Nonspecific Bronchial Provocation Test

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

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

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

					periodic first visit.			responses to BHR testing (p<0.001).	of the existence of moderate-to-severe BHR. Of course, these indexes are 'soft data' and must be used as first approximation only."	compared to FEV1 can help predict a positive response to methacholine challenge testing.
Yurdakul 2005 Diagnostic Study	7.5	123	Skin prick test, blood tests	Spirometry, non-specific bronchial challenge test with methacholine.	100 patients admitted to asthma outpatient clinic and 23 non-smoking healthy control subjects.	Two weeks	Spirometry, PEF monitoring, methacholine, aeroallergens, total IgE, and eosinophil count.	Methacholine challenge test had highest sensitivity (96.5%) vs. other tests. Specificity (78.4%) of methacholine lower than total IgE (84.6%), reversibility test (95%), and PEFR variability (81.8%).	"[M]ethacholine airway responsiveness is the most valuable diagnostic tool for asthma. In addition, there is significant correlation between methacholine airway responsiveness and some patient symptoms."	Good description of study. Larger study population, though not occupational asthma. Data suggest methacholine challenge testing helpful in diagnosis of asthma.
Nensa 2009 Diagnostic Study	6.5	155	Spirometry with methacholine challenge	Body plethysmo-graphy with methacholine challenge	Patients with bronchial asthma undergoing methacholine challenge testing	1 period of testing	FEV_1 and body plethysmo-graphic data	Body plethysmography showed a positive MCH challenge test based on sReff in 113/155 (75%) participants. Spirometry showed a positive MCH challenge test based on FEV_1 fall of >20% in 50/155 (32%)	"[W]e would recommend sReff and sGaw as the reliable parameters for classification of AHR. Additional investigations on healthy subjects and patients with asthma and COPD should be performed to compare sensitivity and specificity of body plethysmography and forced spirometry for MCH-challenge tests."	Not specific to occupational asthma. Included patients with chronic cough. No specificity or sensitivity calculated. Data suggest body plethysmography is abnormal more often with a methacholine challenge vs. spirometry in healthy patients, those with chronic cough, and those with bronchial asthma.
Histamine vs. Methacholine										
Higgins 1988 Controlled Clinical Trial	5.0	203	Histamine challenge test	Methacholine challenge test	108 random tested non-asthmatics and 95 people who reported at least a wheeze	None	PD_{20}	More subjects had a measurable PD_{20} with methacholine. 108 non-asthmatics = 25 vs. 11, p<0.01; 95	"We have shown that when used in an epidemiological study methacholine produces more measurements of	No OA. No real diagnosis of asthma in 95 people who had reported a "wheeze or asthma" by questionnaire

					in the past year			reported with wheeze = 67 vs. 48 p<0.01.	non-specific bronchial reactivity than histamine, with less unwanted effects."	sometime over the past 12 months.
Hypertonic Histamine										
Koskela 2005 Diagnostic Study	6.0	47	Hypertonic histamine challenge	Skin prick test, Challenge solution of hypertonic saline, isotonic histamine, and hypertonic histamine	N = 15 healthy subjects vs. n = 16 asthmatic subjects (steroid-naïve) vs. n = 16 asthmatic subjects (with steroid treatment)	Healthy subjects between April and August. Asthmatic subjects between Septemb er and April.	FEV_1 and PEF values for challenge tests	Isotonic histamine: At 56%, 100%, & 77%; 1.1 (0.5-2.7) vs. Hypertonic histamine: at 81%, 100%, and 90%; 0.5(0.2-1.2) mg/ml; p = 0.047. Results as stated are not interpretable.	"[T]he diagnostic accuracy of histamine challenge can be improved by using a hypertonic challenge solution. Hypertonic histamine challenge may also be more capable to detect the effects of inhaled corticosteroid treatment than the conventional, isotonic histamine challenge."	Small numbers in each group. Baseline differences in age and smoking. Co-interventions not well described besides smoking and inhaled steroids. Data suggest in steroid naive patients, hypertonic histamine challenge is more sensitive than isotonic histamine.
Purokivi 2008 Diagnostic Study	5.0	138	Hypertonic Histamine Challenge (HHC)	HHC provocation based asthma diagnosis vs. FEV diagnosis	N = 30 clinically diagnosed asthmatics, n = 26 healthy control subjects, n = 82 non-asthmatic symptomatic subjects	Ultrasoun d nebulizer at 0.44-0.48 mL/min output with hyper-tonic phospate aerosol for 2 mins/kg. Challenge continued until FEV ≥20% from baseline.	Cough/con-centration ratio (CCR) in mg/mL, coughing frequency (CF), ROC curves, Area under curve (AUC) values, used to assess sensitivity, specificity, and accuracy.	CCR (asthmatics): 302 (166-562) mg/mL, CCR (symptomatic controls): 29.5 (20-43.7); p<0.001. CF>0.5 % (healthy controls): 6.31 (3.47-11.5) Asthmatic subjects vs. healthy controls = disparity of 80% sensitivity, 96% specificity. Diagnostic accuracy: p<0.001.	"[T]he cough response to hyperosmolar airway challenges can be utilized in the differential diagnosis of asthma. Since this response is independent of patient cooperation, it may be especially useful among subjects who cannot perform spirometry in a reliable manner."	Baseline characteristics minimal, but similar. Co-interventions and medications not well described. Data suggest calculation of coughing vs. concentration of histamine during histamine challenge test may be useful in diagnosing asthma and other lung diseases vs. healthy patients.
Mannitol										

Anderson 2009 Diagnostic Study	8.5	509	Mannitol, Methacholine	Exercise, clinical diagnosis	Age 5-50 years. FEV_1 >70% 78% atopic Clinically suspected to have exercised induced broncho-constriction	5 visits	Exercise test: $\geq$10% fall in FEV_1 Mannitol: 15% fall in FEV_1 at $\leq$ 635 mg cumulative dose or >10% fall in FEV_1 between tests; MCC: PC_{20} <16	Sensitivity/ specificity of mannitol to identify EIB was 59%/65%, for methacholine it was 56%/69%. BHR mild. Mean EIB % fall in FEV_1 in subjects positive to exercise 19%, (SD 9.2), mannitol PD_{15} 158 mg (CI: 129, 193), and methacholine PC_{20} 2.1 mg/ml (CI: 1.7, 2.6). Prevalence of BHR same: exercise (43.5%), mannitol (44.8%), methacholine (41.6%) with test agreement between 62-69%. Sensitivity and specificity for clinician diagnosis of asthma 56%/73% for mannitol, 51%/75% for methacholine. Sensitivity increased to 73% and 72% for mannitol and methacholine when 2 exercise tests were positive.	"In this group with normal FEV1, mild symptoms, and mild BHR, the sensitivity and specificity for both mannitol and methacholine to identify EIB and a clinician diagnosis of asthma were equivalent, but lower than previously documented in well-defined populations."	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 broncho-constriction.
Koskela 2004 Diagnostic Study	6.5	47	Mannitol Challenge	Cold Air Challenge, Histamine Challenge, and skin prick test	N = 10 healthy subjects vs. n = 37 asthmatic patients	Repeated after 3 and 6 months of treatment of	FEV_1 values for Mannitol Challenge	Asthmatic patients coughed mere during the Mannitol Challenge than healthy subjects. Cough-to-dose	"Coughing during mannitol challenge is associated with asthma and occurs independently of bronchoconstriction	Small numbers. Patients were recently diagnosed and had more cough + sputum than dyspnea + wheeze.

						budeso-nide		ratio (CDR) is 8.3 coughs per 100mg [95% CI, 0.4 to 3.0]; p<0.0001.	… [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."	Data suggest mannitol more sensitive in demonstrating airway hyperresponsivenes s than cold air challenge.
Miedinger 2010 Diagnostic Study	6.5	284	Mannitol Challenge and Methacholin e Challenge with BPT (Bronchial provocation test)	Skin prick test, spirometry, questionnaire , and oral exhaled nitric oxide (FeNO)	Military subjects	January 2007 – October 2007	FEV_1 and FVC values with spirometry, methacholine, and mannitol challenge tests	BPT with mannitol and methacholine have similar sensitivity and specificity. Methacholine PD_{20}: sensitivity 43%, specificity 92%, PPV 55%, and NPV 88% Mannitol PD_{15}: sensitivity 41%, specificity 93%, PPV 55%, NPV 88%.	"BPT with mannitol has a sensitivity and specificity similar to methacholine for the diagnosis of physician-diagnosed asthma in military conscripts but is less costly to perform without the need to use and maintain a nebulizer."	Physician diagnosed asthma as "gold standard." Recruits ages 18-19 so many may not have seen MD. Data suggest BPT with mannitol has similar sensitivity and specificity as methacholine testing.

Lipworth 2012 Prospective, Randomized Parallel-Group Trial	6.0	157	Mannitol	Clinical investigation. Spirometry PEF FeNO	Patients with mild to moderate asthma	12 months	Inhaled corticosteroid dose. Mannitol challenge testing		"Using mannitol resulted in exposure to a higher dose of ciclesonide, which was associated with equivocal effects on exacerbations without associated adrenal suppression."	Good baseline characteristics given. Randomized trial. Study of general population with asthma. Question was for control of asthma using Mannitol testing, not diagnosis of asthma. Data suggest mannitol testing can be used to help titrate medication in mild to moderate asthma but in this study resulted in a higher dose of steroid use compared to clinical judgment with no significant difference in clinical outcomes.
Anderson 1997 Diagnostic Study	5.5	50	Mannitol	Hypertonic saline challenge. Methacholine	43 patients with asthma; 7 healthy controls	None	Challenge testing spirometry		"[T[his study clearly demonstrate that a dry powder preparation of mannitol…can provoke airway narrowing in asthmatic subjects who are sensitive to a wet aerosol preparation of 4.5% NaCl and methacholine."	Methacholine (considered gold standard) performed on 25/43 (58%) cases. All cases had hypertonic saline testing performed; 7 controls did not have methacholine or hypertonic saline testing. FEV_1 at baseline ranged from 54.2-129.0 % predicted. Data suggest mannitol challenge is a possible test for asthma in mild to moderate asthmatics.

STUDIES TARGETING OCCUPATIONAL ASTHMA										
Methacholine vs. SIC, symptoms, need for medications, or specific sensitization										
Munoz 2004 Diagnostic Study	8.0	26	Specific inhalational challenge by pour method	Skin prick test, Total IgE levels, Methacholine Challenge Testing	8 patients with diagnosed OA due to persulphate salts vs. 8 with asthma and no prior exposure to persulphate salts vs. 0 healthy patients with no history of asthma	None	Spirometry after challenge testing	*Methacholine testing*: 6/8 (75%) of patients with OA had positive test. 7/8 patients with asthma (88%) had positive methacholine test. *Pour test*: Sensitivity = 100% Specificity = 87.5%	"The procedure described in this study allows patients with bronchial asthma to be distinguished from those with persulphate salt induced OA."	Small numbers. No details on how they determined the 8 patients with asthma did not have exposure to persulphate salts. Data suggest methacholine testing is a valid test for patients with persulphate salt induced OA.
Dellabianca 1996 Diagnostic Study	8.0	40	Ultra-sonically nebulized distilled water	Specific inhalation challenge Methacholine	Patients referred to center because of probable occupational asthma due to low molecular weight chemicals	One period of testing	FEV_1 and FCV values during the different tests	*Ultrasonically nebulized distilled water*: Sensitivity: 65% Specificity: 80% *Methacholine*: Sensitivity: 75%-90% Specificity: 60% *Combination of UNDW and methacholine*: Sensitivity: 85% Specificity: 85%	"[I]n the assessment of low molecular weight chemical-induced asthma diagnosed with the specific challenge as the "gold standard," UNDW challenge proves more specific than methacholine for occupational asthma, but is considerably less sensitive."	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.
Paggiaro 1986 Diagnostic Study	6.5	114	Challenge test with toluene diisocyanate (20 ppb for 15 minutes). Workers classified by reactions to challenge (immediate, late, and	Methacholine challenge test	114 furniture workers with bronchial asthma induced by toluene diisocyanate.	8 hours after challenge	PD_{20}, FEV_1	Late reactions in non-smoking subjects was significantly greater than the other two groups (immediate and dual) ($p<0.01$).	"[A]sthmatic subjects sensitive to toluene diisocyannateose with a dual reaction at the time of diagnosis have a greater degree of airway obstruction and more evident non-specific bronchial hyper-	All had prior diagnosis of TDI asthma. Non-specific inhalational challenge test done differently on different participants making conclusions difficult. Data suggest smoking and atopy may affect hyperreactivity

			dual).						responsiveness."	reactions with specific inhalational challenge testing.
Moller 1986 Diagnostic Study	6.5	12	Inhalation challenge with toluene diisocyanate (TDI)	Pulmonary function tests (PFT), bronchial challenge test with methacholine , Spirometry	12 patients with possible TDI asthma.	Uncertain	FEV_1, FVC, (PD_{20})	5 workers showed no significant bronchospasm to TDI challenges at high or low doses; but 3/5 had positive methacholine tests. 8 of 12 had serologic measurements of specific IgE to TDI-HSA, MDI-HSA, or HDI-HSA.	"In the present study, 12 workers with suspected TDI asthma were evaluated by bronchial challenge to TDI. Seven persons demonstrated sensitivity to low levels of TDI (reactors), confirming isocyanate sensitization."	Small numbers. Addressed removal from work. Co-interventions not well described. Several workers with clinical history suggestive of asthma to TDI did not react on SIC. Data suggest methacholine test is nonspecific enough that 60% of patients negative to SIC still positive to NSBP testing.
Sastre 2003 Diagnostic Study	6.5	22	Specific inhalational challenge with isocyanates	Methacholine challenge	22 patients with a clinical history of di-isocyanate induced asthma	None	Spirometry after and methacholine testing	1st round of testing – 13/22 (59%) had positive response. After 2nd round, 2/22 (11%) had negative response PC_{20}: 2/9 with negative on round 1, PC_{20} fell within asthmatic range after test.	"PC20 should be systematically assessed before and after isocyanates. This is especially relevant in the absence of significant changes in FEV1 during."	Small numbers. No controls for non-occupational asthma possibilities. Data suggest PC20 may help decrease false negatives in testing with isocyanates.
Shirai 2003 Diagnostic Study	6.5	21	Inhalation challenge. Non-specific challenge tests to metha-choline	Immuno-logical assessment	Patients suspected of having green tea induced asthma on basis of a suggestive clinical history (had worked at different green tea factories).	None	EGCg; Sensitivity; FEV_1; PC_{20}	Skin sensitivity to EGCg had positive correlation with EGCg; PC_{20} (r = 0.760; p = 0.0048), and methacholine PC_{20} had positive correlation with EGCg PC20 (r = 0.717, p = 0.0108).	"[B]ronchial responsiveness to EGCg can be highly satisfactorily predicted by skin sensitivity to EGCg and bronchial responsiveness to methacholine."	Small numbers. Data suggest use of skin prick testing in conjunction with methacholine challenge test may aid in diagnosis of green tea related asthma with methacholine challenge test.
Cote 1990	6.0	48	Asthma symptoms;	Spirometry with	Male workers with diagnosis	Minimum 1 year,	Asthma signs and symptoms	10.4% improved, 62.5% were stable,	"[A]mong cedar asthmatics who	All diagnosed with occupational asthma

Diagnostic Study			requirement for anti-asthma medications	methacholine challenge	of occupational asthma to red cedar who stayed in same industry after diagnosis.	average of 6.5 years	after continued exposure	37.5% worsened. None of the patients completely recovered.	remained exposed to cedar dust for an average of 6.5 yr, over one-third showed marked deterioration of their asthma symptoms. There is also no way to predict who will deteriorate. A decrease in the amount of exposure to cedar dust does not prevent deterioration of asthma. This suggests that the ideal management of cedar asthma is removal from exposure."	by testing then followed forward. Data suggest continued exposure to cedar dust in confirmed asthmatics prevents resolution of symptoms and worsens symptoms in 37.5%. MCC test used to monitor course of asthma.
Vogelmeier 1991 Diagnostic Study	6.0	43	Specific inhalational challenge test to isocyanates	Methacholine challenge test	A = 19 workers clinical history consistent with occupational asthma vs. B = 14 workers 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%)	"[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.
Karol 1994 Diagnostic Study	5.5	63	Methacholine challenge test	SIC IgE to TDI	63 patients exposed to TDI with symptoms consistent with occupational asthma	None	Methacholine challenge testing SIC IgE levels	No difference in geometric mean of serum IgE level for responders and non-responders at (68 vs. 69 IU/ml).	"[O]ccupational history was not a good indicator of current sensitivity to TDI. Methacholine responsiveness was a good predictor of response to TDI. TDI-specific antibodies of both	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

									the IgE and IgG classes, assessed with well characterized haptenated serum albumin conjugates, were found in only a few individuals… suggest that the early-onset response might reflect an IgE-mediated mechanism, whereas the mechanism of the late onset response is yet uncertain."	methacholine and having symptoms consistent with TDI asthma more likely to have positive result with SIC to TDI.
Lam 1979 Diagnostic Study	5.5	193	Methacholine testing	Skin prick testing.	86 patients with OA – 33 nonatopic healthy volunteers; 30 non-occupational asthma patients; 17 chronic bronchitis patients; 16 atopic non-asthmatics	None	Spirometry in relation to methacholine challenge test. Comparison to previous spirometry	Patients with non-occupational asthma had lower FEV_1 than those with occupational asthma ($p<0.001$). Patients with occupational asthma removed from exposure for a mean of 0.8 years 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."	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.
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-responsiveness to methacholine. 6/15	"[G]rain dust can induce an immunologic, IgE-mediated response in exposed workers."	Differing tests protocols as symptoms determined testing protocol. Cases defined by possible exposure and results

					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. ($p<0.05$).		of symptoms questionnaire. No specificity or sensitivity for IgE testing. Data suggest IgE tests more likely positive if exposed to grain dust and have positive symptom questionnaire.
Histamine vs. SIC, symptoms, need for medications, or specific sensitization										
Vandenplas 2001 Diagnostic Study	9.0	45	Natural rubber latex clinical diagnostic testing	Question-naire Immunologic testing skin prick test. Spirometric lung function tests (PC20 values <16 mg/mL indicative of	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	"[C]ombining the assessment of NSBH and immunologic tests with the open questionnaire is not reliable as an SIC in diagnosing NRL-induced [occupational asthma] among subjects referred to	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

				bronchial hyper-responsive-ness) with NRL challenge (SIC) and other common asthma inducing present at occupation.				responsiveness (NSBH) (%): sensitivity was 90, specificity was 7, PPv was 75, and NPV was 25.	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."	have greatest sensitivity and specificity vs. SIC for occupational asthma compared to histamine challenge testing.
O'Brien 1979 Diagnostic Study	5.0	63	TDI inhalation challenge test	Histamine inhalation test and exercise test	63 workers occupationally exposed to toluene di-isocyanate (TDI).	Uncertain	FEV_1, FVC, PEFR	Differences in histamine inhalation tests between TDI highly sensitive with asthmatic reactions to concentrations of 0.001 ppm and TDI non-sensitive groups with reactions to concentrations of 0.001-0.02 ppm ($p<0.005$) and TDI non-sensitive group ($p<0.01$).	"[S]ubjects giving asthmatic reactions to TDI tests, seventeen out of thirty-one (55%) had increased histamine reactivity and eighteen out of twenty-nine (62%) had exercise-induced asthma."	Not all received same testing protocols making comparisons difficult. No mention of co-intervention. Data suggest TDI may induce asthma and spirometry, histamine inhalational testing, and specific inhalation challenge testing all aid in diagnosis of asthma.
Mannitol vs. SIC, symptoms, need for medications, or specific sensitization										
Koskela 2003 Diagnostic Study	8.0	37	Skin prick test, IgE testing, Histamine challenge, Exhaled NO measure-ment, Mannitol challenge, sham inhalational challenge,	Bovine specific inhalational challenge	37 dairy farmers with suspected occupational asthma to bovine dander who were referred for bovine dander specific inhalational challenge testing	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other testing results	11/37 (30%) classified as positive response to b. *Skin prick test:* r = 065 (p = 0.0001) Sn = 100% Sp = 50% PPV = 46% NPV = 100% *IgE:* Sn = 82%	"[A]lthough is the 'gold standard' for the documentation of occupational asthma, the high prevalence of respiratory symptoms and bronchial hyper reactivity in farmers may lead to a very high demand for access to this	Patients with suspected occupational asthma by clinical presentation and spirometry. Data suggest patients with positive SPT and bIgE testing do not require SIC testing.

			PEF(twice daily for a week before testing and every 4 hours during testing)					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%	expensive test… Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bs."	
Miedinger 2007 Diagnostic Study	7.5	101	Mannitol Challenge and Metha-choline Challenge with bronchial provo-cation test	Skin prick test, spirometry, questionnaire, and oral exhaled nitric oxide (FeNO)	101 firefighter subjects being tested for asthma. Diagnostic standard for asthma wheezing plus hyper-responsiveness to bronchial challenge testing.	Uncertain	FEV_1 and FVC values with spirometry, methacholine and mannitol challenge tests	Bronchial airway challenge with mannitol (PD_{15}) was more sensitive (92%), specific (97%), PPV (86%), and NPV (98%) when testing for asthma.	"Asthma was considerably underdiagnosed in firefighters. The combination of a structured symptom questionnaire with a bronchial challenge test allows to identify patients with asthma and should routinely be used in the assessment of active firefighters and may be of help when evaluating candidates for this profession."	All firefighters. Data suggest asthma under diagnosed in firefighters. Mannitol challenge testing had highest sensitivity and specificity.
Lemiere 2012 Diagnostic Study	5.0	30	Mannitol Metha-choline FeNO Sputum	Historic diagnosis of OA by SIC	30 patients previously diagnosed with OA to different substances. Removed from exposure.	None	Spirometry FeNO Sputum cell	50% were never smokers. 9/30 (30%) had positive mannitol test. 13/30 (43%) had PC20 <4. Positive mannitol had lower	"[T]he mannitol BPT is a useful test for assessing the impairment/ disability and disease activity of workers with a previous diagnosis of	Patients diagnosed previous with occupational asthma and removed from work. Various substances included in diagnosis of OA.

								FEV_1 ($p = 0.01$), higher fraction of exhaled nitric oxide levels ($p = 0.03$).	OA because this test has the ability to differentiate the subjects according to the severity of airway responsive-ness and collection of sputum to be made at the same time."	Baseline characteristics showed baseline FEV_1 as 95.9-101.8 of predicted for all participants. Data suggest mannitol is not as sensitive as methacholine but may be more specific.

SPECIFIC IMMUNOLOGICAL TESTING

Specific immunological testing to suspected allergens is commonly used to aid in the diagnosis of allergic rhinitis and occupational asthma.[141, 162, 182-189] These tests are performed to evaluate type I (IgE) hypersensitivity reactions to specific allergens,[143, 162] 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. For more information on skin testing, see section below. Three methods of detecting serum IgE antibodies have been employed to assess antigenicity to occupational antigens: 1) RAST; 2) ELISA; and 3) ImmunoCAP. This guideline, in addition to basing the recommendations on the available literature that has compared and validated a particular method, will also take into consideration the commercial availability of these assays.

The sensitizing agents known to induce occupational asthma are traditionally divided into high molecular weight (HMW) and low molecular weight (LWM) antigens. The allergens and extracts are better characterized and available for HMW antigens, and much less so for LMW antigens.

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. Once sensitization has occurred, subsequently inhaled allergens bind and cross-link allergen-specific IgE present on the surface of mast cells and basophils. This cell surface perturbation triggers these cells to release an array of allergic and inflammatory mediators that give rise to the asthmatic response.[186] Examples of HMW asthmagens include:

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

Such proteins are considered complete allergens, capable of causing the elaboration of specific IgE antibodies. Also, for the most part, commercial validated assays exist for most common HMW allergens; therefore, recommendations will be made for the class as a whole.

Low Molecular Weight Agents

Low molecular weight (LMW) agents that induce occupational asthma are incomplete antigens or haptens that 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.

Specific IgE to the hapten-protein conjugate (frequently human serum albumin) is detectable in some but not all cases of asthma, and sensitivity varies with each agent. Several reasons have been proposed. Unlike the HMW agents that are complete antigens, low molecular weight chemicals may couple variably to a protein to form a complete hapten-protein complex. The process may form new and unique antigenic determinants that are not shared by different affected workers. Waning of the immune response since last

exposure, and the lack of standardization of laboratory assays are additional factors that make testing difficult.[190-192] Thus, interpretation of testing results must include consideration of the sensitivity and specificity of the test for the suspected agent. For example, specific IgE antibodies have been detected to anhydride acids, trimellitic and tetrahydrophthalic anhydrides[193, 194] but not to maleic anhydride.[195] Although the allergic reaction to platinum salts is considered to be type 1 IgE mediated, there is no commercially available radioimmunoassay and the detection of specific IgE antibodies to complex (unconjugated) halide platinum salts by skin-prick test is considered more sensitive. Specific IgE antibodies to colophony and diisocyanates, two important causes of low molecular weight occupational asthma, are poorly characterized. No reliable method of antibody detection for colophony-fume asthma has been established.[196] For asthma induced by diisocyanates, the presence of specific IgE antibodies to a diisocyanate-human serum albumin (HSA) conjugate is relatively insensitive, being found in less than half of clinically confirmed cases of diisocyanate related OA.[197, 198] Investigators who have evaluated the sensitivity and specificity of diisocyanate specific IgE to diagnose occupational asthma have demonstrated an association with diisocyanate asthma, but inadequate sensitivity to be used as screening tools.[198, 199] This difficulty may in part be caused by the variability of serologic methods used in the various studies,[200] and in part because different antigens are formed from these highly reactive chemicals that can differ between individuals and types of exposure. Thus, no one particular antigen has been identified for all cases of diisocyanate-induced asthma.

The lack of assay standardization is an important drawback to the detection of LMW IgE antibodies, as most studies have reported results using in house assays that are not commercially available.[200] In addition, there is no consensus in conjugate preparation, although vapor hapten-albumin conjugates have been reported as having greater sensitivity.[200] Finally, the method of making the asthma diagnosis has varied between studies, causing difficulty in interpreting the sensitivity and specificity of serologic results.[201]

The role of specific IgG is also unclear.[196, 200] Studies that have investigated high molecular weight IgG antibodies among laboratory workers and bakers have found a correlation with exposure intensity, but not a significant relationship with allergic symptom.[202, 203] IgG4, a subtype of IgG, may be associated with the development of tolerance rather than allergy. Several studies have found that specific IgG responses to diisocyanate/HSA conjugates are also generally associated with exposure[200, 204, 205] and not disease.

Recommendations: High Molecular Weight Specific Antigens

1. *Recommendation: IgE Specific Immunological Testing for High Molecular Weight Specific Antigens* **Specific immunological testing (IgE) is strongly recommended for workers with symptoms consistent with occupational asthma to certain high molecular weight specific allergens and when standardized antigens and assay protocols exist**. The specificity and sensitivity of the allergens should have been evaluated in quality studies using validated test methods that are commercially available. 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.

   Strength of Evidence **– Strongly Recommended, Evidence (A)**
   Level of Confidence **–** High

2. *Recommendation: IgG Specific Immunological Testing for High Molecular Weight Specific Antigens* **Specific immunological testing (IgG) is not recommended as a diagnostic tool for select workers with symptoms consistent with occupational asthma to high molecular weight**

specific allergens. It can be used for a marker of exposure to certain allergens, but in and of itself does not diagnose disease.

Strength of Evidence **– Not Recommended, Evidence (C)**
Level of Confidence **–** High

Recommendation: Low Molecular Weight Specific Antigens

3. *Recommendation: IgE Specific Immunological Testing for Low Molecular Weight Specific Antigens* **Specific immunological testing (IgE) is not recommended for workers with symptoms consistent with occupational asthma to low molecular weight specific allergens due to low sensitivity and specificity and lack of method validation.**

Strength of Evidence **– Not Recommended, Insufficient Evidence (I)**
Level of Confidence **–** Moderate

According to the Practice Parameters of the American Academy of Allergy, Asthma & Immunology, specific allergens need documented evaluation in quality studies with reported specificity and sensitivity and using standardized antigens and assay protocols. In addition, they need to be commercially available before they can be considered reliable for routine evaluation of workers. This is not the case for LMW test antigens, which are usually prepared and evaluated in individual research laboratories and are not in general commercially available. A more detailed rationale for the recommendations follows below:

Performance – The assay should improve on disease prediction by demonstrating high sensitivity and specificity. Methods for testing antibodies need to be standardized, with established population norms to guide interpretation of results. Each assay needs to be performed according to the manufactures recommendations following a proper protocol for testing.[206] 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.[206, 207] If no studies have been conducted for the agent(s), no recommendation is made.

Harms – None.

Benefits – Non-invasive relatively inexpensive method of establishing sensitization to suspect agent.

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.[197, 208] There are unique challenges with such testing for work-related asthma. The reported half-life for specific IgE in serum, the time available for specific immunological testing, is approximately 7 hours. In tissue, it has varied from a short half-life of approximately two days[184] to 5.8-6.7 months.[197] Specificity and sensitivity differ by allergen and time since exposure.[141-143, 162, 183, 185, 194, 197, 208, 209] Without accurate exposure data including time since exposure, a negative specific IgE may lead to a misdiagnosis and false conclusions about the disease. There is documented cross-reactivity between different isocyanates, which may confound the determination of causation in some cases.[197, 203] Different laboratories and commercial tests have not been validated with proper homogenous controls.[3, 208] This variability creates difficulty in creating overall recommendations for immunological testing.

Rationale for Recommendations

High Molecular Weight Agents:

Wiszniewska, et al., reported a sensitivity of 61.6%, specificity of 77.3%, PPV 71.5%, NPV 68.5% in workers with baker's asthma to wheat flour.[210] Van Kampen 2008 reported sensitivity of 61-87%, specificity of 68-94%, PPV 74-95%, NPV 56-82% in workers with baker's asthma to wheat/rye flour.[211] Another study evaluating IgE to bovine dander reported sensitivity of 82%, specificity of 100%, PPV 100%, and NPV 89%.[141] A moderate-quality study reported smoking and generalized atopy also were independently significantly associated with positive IgE to grain dust ($p<0.05$).[162] Platts-Mills, et al., reported IgE was more specific in workers exposed to rats with symptoms of asthma and rhinitis than IgG was.[198] IgG levels were reported to show evidence of exposure to wheat flour, but did not have a correlation with allergic symptoms in bakers.[202] IgE levels were also elevated in workers with self-reported respiratory symptoms compared to controls in a feed plant.[212] Other studies also reported positive IgE to HMW allergens in patients diagnosed with OA by SIC.[213]

Low Molecular Weight Agents:
Park, et al., evaluated IgE levels in patients with work-related asthma to reactive dyes.[214] The authors reported a sensitivity of 53.7%, specificity 86.0%, PPV 62.9% and NPV of 80.8%. For diisocyanates, Lushniak, et al., reported a small study where IgG was a marker of exposure, but not of occupational asthma in a group of workers exposed to MDI.[203] Bernstein, et al., reported a sensitivity of IgE to isocyanates of 21% and a specificity of 89%.[142] Tee, et al., reported IgE related to diisocyanate exposure as highly specific, at 91-100% in patients investigated for occupational asthma and confirmed with specific inhalational challenge testing, but a sensitivity of 19-28%. Therefore, it is a useful test if it is positive, but a negative test is less informative.[197] Budnik, et al., reported no false positive results with IgE or SPT testing in patients exposed to MDI with asthma confirmed by positive specific inhalational challenge testing.[200]

Evidence for the Use of Specific Immunological Testing

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

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

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

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

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

					(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.			(p<0.05).		
Douglas 1995 Diagnostic Study	4.5	24	IgE levels to salmon	Spirometry, PEF pre and post shift; Symptom questionnaire	24 patients with occup-ational asthma in automated salmon processing, in group of 291 employees	One period of testing	IgE antibody production	Associations with increasing symptom severity: IgE levels: (p<0.001); IgG levels: (p = 0.037). Occupational asthma higher in workers who smoked compared to non-smokers (p<0.001).	"We have shown an 8.2% prevalence of occupational asthma caused by exposure to respirable aerosols containing salmon-serum antigens generated by processing machinery."	No specific inhalational challenge to confirm diagnosis. Data suggest salmon proteins may increase asthma type symptoms in workers exposed after as little as 2 weeks. Smoking increased risk of developing occupational asthma.
Crimi 1999	4.5	23	Reverse	Skin Prick	Non-smoking	At least 1	Asthma	IgE density and	"IgE density as	Small numbersl 11

Diagnostic Study			Allergo-Sorbent Test (REAST)	Test, Nasal Challenge Test, Bronchial Challenge Test, Methacholine Challenge Test (MIC)	subjects with mixed allergies (15 females, 8 males)	week	diagnosis using methacholine challenge vs. SPT, RAST, nasal challenge, and bronchial challenge	nasal challenge score ($p < 0.0001$), bronchial challenge score ($p < 0.001$), and maximum late FEV fall ($p < 0.005$). Amount of specific IgE and bronchial challenge score ($p<0.001$).	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 responsive-ness blunts the predicting value"	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.
Kim 1999 Case Reports	4.5	16	IgE to citrus red mite (CRM)	Skin prick test, Airway reversibility, Specific bronchial challenge test	16 citrus farm workers complaining of respiratory symptoms.	Uncertain	IgE, FVC, FEV_1	All patients had strong reactions to the skin prick test of CRM extract. 62.5% of patients had isolated positive reactions to CRM.	"CRM-derived allergens may be important factors in the development of both occupational rhinitis and asthma in farmers cultivating citrus fruits."	Skin prick testing and IgE testing performed on all participants. Data suggest allergic reactions can occur to citrus red mite and occupational asthma may also occur but further testing is needed.
Platts-Mills 1987 Diagnostic Study	4.0	179	IgE and IgG to rat allergens	Reported symptoms, skin prick test	125 lab workers exposed at different levels to rat allergens, 54 pregnant women not exposed	None	IgE, IgG, SPT, symptoms of asthma or rhinitis	SPT positive in 19/30 of symptomatic and 2/135 asymptomatic employees ($p<0.01\%$). IgE ab to rat antigen 16/30 2/135 ($p<0.01\%$). IgG positive in all 20 employees with positive IgE but also in 30% of asymptomatic employees.	"The correlation between IgE ab and positive skin test to rat urine strongly supports the view that this is the major allergen of rat urine…the incidence of IgG antibodies to this protein correlates with exposure to animals."	No good baseline data on cases versus controls. Asthma diagnosis was done by employee report. Data suggest IgG is a marker of ever being exposed to rat allergens. IgE is more of a marker of having symptoms associated with rat exposures.

Low Molecular Weight										
Budnik 2013 Diagnostic Study	8.0	43	IgE to MDI by fluor-escence enzyme immune assay detection method (semi-automatic ImmunoCAP100)	SIC SPT IgG Histamine challenge spirometry Symptoms	Workers exposed to MDI with presumed OA sent to referral clinic	None	IgE level SIC results Spirometry Symptoms	10/12 (83%) had positive SIC. 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.	"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."	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.
Tee 1998 Diagnostic Study	8.0	101	RAST IgE to isocya-nates	SIC PEF Clinical symptoms SPT	Patients with clinical symptoms consistent with OA sent to a hospital based clinic	Varied	IgE levels SIC PEF SPT	58 considered to have OA caused by isocyanates. 46/58 (79%) had positive SIC. Patients with SIC confirmed diagnosis: IgE RAST $\geq$2: Sn: 28% Sp: 92% IgE RAST $\geq$3: Sn: 20% Sp: 100%	"IgE to isocyanates is a more specific than sensitive index of occupational asthma. With a RAST score of 3 or greater, it is wholly specific and therefore diagnostic of isocyanate-induced asthma. The sensitivity of specific IgE measurement is highest when blood is taken less than 30 days from last exposure, which is consistent with the observed half-life."	SIC done on 70/101 (69%) of workers. Some of the diagnoses made by retro-spective review of symptoms. Cross-reactivity of IgE was seen. Data suggest RAST IgE testing within 30 days of exposure can aid in diagnosis of OA. Methods for immunological analysis of isocyanates Ag was RAST which is not commercially available for isocyanates.
Cartier 1989	7.5	62	IgE and IgG to	Specific inhalational	Patients who underwent	Up to 2 weeks	IgG and IgE levels after	Increased specific	"[T]he levels of specific IgG to the	All patients had SIC testing and then were

Diagnostic Study			isocyanates by ELISA	challenge, Skin prick test	specific inhalational challenge testing for isocyanates		testing to isocyanates.	antibodies: IgE only – 0/62 IgG only – 13/29 (45%), 7/33 (21%) Both IgE and IgG – 8/29 (28%), 1/33 (3%)	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."	tested for IgE and IgG levels. Data suggest IgG levels are better correlated than IgE with IgE, which suggests an immunologic mechanism.
Bernstein 2002 Diagnostic Study	7.0	75	IgE testing to di-isocyanates by ELISA	In vitro MCP-1 production testing Methacholine challenge testing SIC to a diisocyanate encountered in workplace (TDI, MDI or HDI)	54 diisocyanate-exposed workers who had prior histories consistent with OA, 9 non-asthmatics, 12 asthmatics with no diisocyanate exposure	One period of testing	In vitro MCP-1 levels	In vitro MCP-1: Sn = 79% Sp = 100% IgE: Sn = 21% Sp = 89%	"[A] strong association between diisocyanate antigen enhancement of MCP-1 and DA suggest that further investigation and validation of cellular immunoassays could enable development of more sensitive and specific diagnostic tests that could be useful in the diagnosis of OA."	"Controls" only had in vitro MCP-1 testing performed. No blinding. In vitro MCP-1 levels test is not readily available. Data suggest in vitro MCP-1 testing could be a helpful laboratory test to confirm OA due to diisocyanates. This finding has not been corroborated in subsequent research.
Pezzini 1984 Diagnostic Study	6.5	28	Serum IgE to di-issocyanate BY by direct radio-immuno-assay technique (Phadebas PRIST kit)	Specific inhalational challenge testing, skin prick testing	28 workers exposed to Toluene diisocyanate (TDI) and diphenyl-methane diisocyanate (MDI)	Un-known	Specific inhalational challenge bronchial hyper-responsive-ness. IgE levels	Positive IgE test for MDI was 5/6 (83%) and for TDI was 6/22 (27%). Appearance of respiratory symptoms before 6 years of exposure was more frequent in IgE positive group (p = 0.007).	"Our results show a prevalence of specific immuno-logical IgE mediated reactions in subjects who develop asthmatic symptoms after a shorter time of isocyanate exposure and experienced an accidental acute exposure to	Small numbers. Control group with little information provided. Data suggest IgE testing is more reliable for MDI than TDI in patients with symptoms consistent with asthma. Not clear whether Phadebas PRIST kit is commercially available.

									high concentrations of isocyanate."	

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). Prick testing involves introducing a needle into the upper layers of the skin through a drop of allergen extract and gently lifting up the epidermis. Intracutaneous (intradermal) testing involves injecting a small amount of allergen (0.01-0.02 mL) into the dermis. 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. Testing is most often performed with various allergens placed on the skin of the volar forearm or the back.[145, 215, 216] Although the back is more reactive, the difference is minimal. Prick testing methods are the preferred initial technique for detecting the presence of IgE. They correlate better with clinical sensitivity and are more specific but less sensitive than intradermal testing.[217] 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.[218] Many studies have demonstrated that the prick skin test response correlates much better with clinical allergy.[219]

Skin prick testing has been used to assess allergy to asthmagens in various types of patients and occupational settings.[57, 69, 185, 214-216, 218, 220-224] This systematic review will synthesize the skin prick testing literature as it directly relates to other diagnostic methods for occupational asthma, but will not incorporate the entirety of allergic skin testing for common allergens.[222] Not all allergens have the same level of investigative studies to validate skin prick testing as an authoritative diagnostic test. 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.[219]

1. *Recommendation: Skin Prick Testing to High Molecular Weight Allergens*
   Skin prick testing is strongly recommended for high molecular weight allergens 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.

   Strength of Evidence **– Strongly Recommended, Evidence (A)**
   Level of Confidence – High

2. *Recommendation: Skin Prick Testing to Low Molecular Weight Allergens*
   Skin prick testing is moderately recommended for low molecular weight allergens 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.

   Strength of Evidence **– Moderately Recommended, Evidence (B)**
   Level of Confidence **–** Moderate

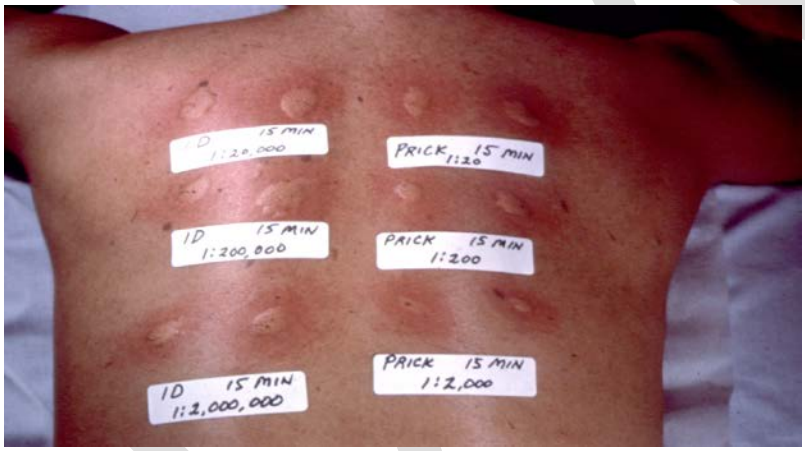
3. *Recommendation: Skin Prick Testing to Other Allergens Not Covered Above*

Skin prick testing is 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.[210, 225] Skin prick testing is also not recommended if suspected cause is non-allergenic.

Strength of Evidence **– Not Recommended, Insufficient Evidence (I)**
Level of Confidence – High

Performed – 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)[226] Skin tests should be performed with 1.0 mg/ml histamine dihydrochloride as the preferred positive control and normal saline or 0.5% glycerin-saline as the negative control.[185, 219, 223, 227] Histamine control tests should be read 15 minutes after application to determine their peak reactivity. Concurrent use of antihistamines, H2 antagonists, tricyclic antidepressants and other medications impair histamine responsiveness and may reduce the size of the skin test response or suppress it altogether. Several physiologic factors may affect interpretation of skin test results, including skin pigmentation and endogenous cortisol. Different devices used for skin testing result in variable degrees of trauma imparted to the skin, and may thereby produce different sizes of positive reactions. Thus, consistent criteria are needed to rate a positive reaction produced by different skin test devices. Positive tests are often defined as a mean diameter of wheal larger by 2-3 mm more than the negative control and/or an erythematous reaction larger than 10-21 mm.[141, 185, 223, 227] Skin tests should not be performed at skin sites with active dermatitis. Adequate equipment to treat anaphylaxis must be available, although this is very rare with prick skin testing.[226]

Figure 5. Percutaneous Allergy Skin Test Results: Measuring the Wheal and Flare



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Each individual extract is often prepared differently and this process should be well understood by the practitioner. Frequently, a dilute preparation of an extract that is appropriate for skin prick testing is not commercially available and must be prepared by the practitioner. The stability and potency of allergen extracts are important issues that affect skin test results. Allergen extracts deteriorate with time, accelerated by dilution and higher temperatures, and lead to smaller or absent skin test responses. Some extracts such as molds contain proteases that degrade other extracts if mixed together. Expiration dates should be checked on a regular basis. Cross-contamination or bacterial contamination should be prevented, and all extracts should be stored under cold (4°C) to ensure stability.

Indications – Prick skin testing should be performed with allergens that have acceptable sensitivity, specificity, positive predictive value, and negative predictive value.[227, 228] 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.

Benefits – Minimally invasive, inexpensive and has few adverse events.

Advantages and Limitations – Skin prick testing is minimally invasive, has few adverse events, is moderately inexpensive and is recommended for specific cases where the allergen extracts have known sensitivity, specificity and those results are reliable. 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.[229]

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.[222] However, there are 20 high- or moderate-quality studies that provide results of skin prick testing compared to specific inhalational challenge testing for the diagnosis of occupational asthma.[141, 143, 145, 185, 208, 215, 220] For patients with occupational asthma related to enzymes used in baking and pharmaceuticals confirmed by specific inhalational challenge testing, the sensitivity of skin prick testing was 100% and specificity was 93%.[211, 215, 227, 228] Wiszniewska, et al., reported a sensitivity of 42%, specificity of 86%, PPV 73%, NPV 61% for skin testing in workers with baker's asthma to wheat flour.[210] In workers exposed to reactive dyes, the sensitivity of skin prick testing was 76% and the specificity was 91% for occupational asthma.[185] In a study of platinum salt workers, SPT was used to confirm sensitization in individuals with work-related asthma.[225, 230, 231]

Evidence for the Use of Skin Prick Testing

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

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

								SPT to rye Sn: 78% Sp: 84% PPV: 91% NPV: 66%		wheat or rye flours. This data is not specific to just OA, but also included rhinitis symptoms. WHEAT AND RYE
van Kampen 2009 Diagnostic Study	8.5	125	SPT to flour	Specific IgE (sIgE) Challenge tests (24 with nebulized aqueous flour solutions, 63 with native flours, 8 nasal challenges)	125 bakers	15 minutes after procedure	Protein in prick test solutions was measured by the Bradford assay	85 (68%) showed sIgE to wheat flour and 83 (66%) sIgE to rye flour	"[B]y increasing the antigen concentration of flour SPT solutions, it is possible to increase sensitivity without substantial loss of specificity."	Similar study as Sander 2004. Data suggest different preparations of flour proteins for skin prick testing need to be standardized and improved. WHEAT AND RYE
Wiszniewska 2011 Diagnostic Study	8.5	151 diagnosed with OA by SIC, 287 had rhinitis symptoms	SPT to flour	SIC Spirometry NSBP Nasal Lavage IgE to flours	Bakers	None	IgE STP Spirometry Symptoms	In baker's with OA: SPT: Sn: 41.7% Sp: 85.9% PPV: 73.3% NPV: 61.4% IgE: Sn: 61.6% Sp: 77.3% PPV: 71.5% NPV: 68.5%	"Results in our study indicate that neither SPTs to occupational allergens nor evaluation of serum allergen-specific IgE alone or combined with nonspecific bronchial hyperreactivity are characterized by sufficient diagnostic accuracy to replace specific inhalational challenge test."	Study included workers with rhinitis and OA. Data suggest that IgE and SPT can be useful in the diagnosis of both occupational asthma and rhinitis in bakers. FLOUR
Park 2001 Diagnostic Study	8.0	151	Serum specific IgE, SPT to reactive dyes	Bronchial provocation testing with methacholine, specific inhalational	42 patients with occupational asthma from reactive dyes,93	None	Skin prick test, IgE testing	SPT: Sens: 76.2% Spec: 91.4% PPV: 80% NPV: 89.5%	"SPTs and ELISAs may be valuable tools for screening, diagnosis, and monitoring occupational	Well-defined cases and controls. Co-interventions such as medication use unclear. Bronchial provocation testing

				challenge	asymptomatic factory workers, 16 unexposed controls			IgE testing: Sens: 53.7% Spec: 86% PPV: 62.9% NPV: 80.8% Combined: Sens: 83.3% NPV 91.7%	asthma resulting from exposure to reactive dyes; these two tests might complement each other for such a diagnosis."	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. REACTIVE DYES
Sander 2004 Diagnostic Study	8.0	115	SPT; SDS-PAGE	Bronchial Challenge Test; IgE-Enzyme Allergo Sorbent Test (EAST); Sodium; Dodecyl sulfate-Polyacrylamide Gel electrophoresis (SDS-PAGE)	115 bakers complaining of workplace-related respiratory symptoms	6 hours after challenge test	Protein in prick test solutions measured by ESL protein assay	Specificity above 85% for all tests. 17/40 (43%) patients reacted with wheat SPT extract. Six reacted on all wheat flour extracts and 3/13 (23%) patients with positive rye flour result reacted on all rye flour extracts.	"These data suggest that at present commercial wheat and rye flour SPT solutions differ in protein content and band patterns and fail to detect about 30–60% of patients with a positive allergen challenge."	Skin prick testing material provided by different companies. Data suggest commercially available preparations varied in the protein composition which could affect test results. WHEAT AND RYE, COMMERCIAL EXTRACTS
Koskela 2003 Diagnostic Study	8.0	37	SPT, Bovine dander	Bovine specific inhalational challenge; IgE testing; Histamine; Exhaled NO; Mannitol challenge; Sham inhalational challenge; PEF	37 dairy farmers with suspected occupational asthma to bovine dander	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other test results	11/37 (30%) classified as positive response to bovine dander. Skin prick test (Sensitivity%/ Specificity%/PPV%/ NPV%): (100/50/46/100); IgE (82/100/100/93); Histamine (82/65/50/89); Mannitol (20/94/67/89);	"Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bovine SIC testing."	Data suggest patients with a positive SPT and bIgE testing do not require SIC testing. COW DANDER

								exhaled NO (27/77/33/71).		
Merget 1993 Diagnostic Study	7.0	62	SPTs with non-dialyzed aqueous enzyme extracts	Specific inhalational challenge, IgE	42 chemical plant workers referred for pulmonary symptoms, 10 atopic non-exposed patients, and 10 healthy patients	None	Spirometry, IgE levels, and skin prick test results	Positive for 13/42 (31%) participants; Skin prick test: Sn = 100% Sp = 93%	"For enzyme allergy both BPT [bronchial provocation test] and skin prick test were appropriate diagnostic tests."	Controls not well described. 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. CHEMICAL PLANT ENZYMES
Walusiak 2004 Diagnostic Study	6.5	287	SPT to flour	IgE SIC NSBP Symptoms	287 bakers	2 years	SPT IgE SIC Symptoms	25/287 (8.7%) diagnosed with OA by SIC, 23/25 (92%) had positive SPT and IgE testing.	"[T]he results of our study indicate that SPT to common and occupational allergens should be performed in apprentice bakers before starting vocational training."	Baseline testing done during first month of training, meaning there was at least some exposure to work allergens before testing. Average age of worker at start of study 16.2 years. Data suggest SPT and IgE testing are positive in majority of workers with OA to flour. FLOUR
Acero 2003 Diagnostic Study	6.0	12	SPT to latex	IgE NSBP SIC Specific conjunctiva tests Symptoms	12 health care workers	3 years	IgE NSBP SIC Specific conjunctiva tests Symptoms	SIC: 12/12 had positive test SPT: 12/12 had positive test IgE: 2/12 had	"NRL acts as a common aeroallergen. Minor symptoms often precede occupational asthma. The SIC	Patients were diagnosed as having OA prior to this study either by SIC or serial PEFs. 6/19 patients had anaphylaxis as

								positive findings	test was safe in the hands of trained technicians. Occupational asthma due to NRL seems to have a poor prognosis."	symptoms. Data suggest that in persons with severe allergy to NRL SIC, SPT, and IgE testing is helpful in diagnosis of allergy. LATEX
Park 1998 Diagnostic Study	5.5	43	SPT to grain dust	All tests used 7 common allergens vs. grain dust (GD) from subjects' workplace. Broncho-provocation, and ELISA questionnaire	N = 43 male animal feed industry workers exposed to grain dust composed of corn, rye, wheat, barley. Of 43, 31 process workers who mixed and carried materials (intermediate exposure group and high exposure group according to exposure intensity measured by dust air sampler); 12/43 office workers classified as low exposure group. Controls (n = 27) never exposed to	Not specified	Common allergens vs. GD in group A, with results compared to that of group B.	34.9% questionnaire respondents complained of lower respiratory symptoms. IgE (GD) positive results in 40% of symptomatic and 11% control (p = 0.02). ELISA: No inhibition noted. Total IgE vs. Specific IgE: insignificant.	"GD can induce an immunologic, IgE-mediated response in exposed workers, which is responsible for their asthmatic symptoms."	Patients selected did not all have symptoms suggestive of asthma. Study had exposure groups but did not mention them in analyses. Data suggest grain dust may be a factor in occupational asthma in workers exposed. GRAIN DUST

					grain dusts and demonstrated negative skin tests to 50 common inhalant allergens.					
Merget 1991 Diagnostic Study	5.5	35	SPT to platinum salts	Lung function, bronchial provocation tests	35 workers from platinum refineries with work-related symptoms.	Uncertain	IgE, FEV_1, $FEV_{1\%}$ IVC, sRAW (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 ($p<0.0008$; $n = 27$).	"[W]ork 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. PLATINUM SALTS – not commercially available
Brisman 2003 Diagnostic Study	5.0	89	SPT to flour, alpha-amylase	Whole blood cell count Spirometry	25 asthmatics (determined by questionnaire), 20 bakers with rhinitis, and 44 referent bakers	None	SPT Eosinophils FEV_1, FVC	7/25 asthmatics reported symptoms related to work and 8/20 with rhinitis reported symptoms related to work. Flour SPT positive in 43% of asthmatics or rhinitics vs. 16% of referents.	"[S]ensitization to an occupational allergen, especially flour, is an important, but not the only, mechanism in baker's asthma."	Not all asthmatics were occupational asthma patients. Asthma diagnosed mainly by questionnaire. Data suggest that in bakers with asthma, occupational and non-occupational, there is a larger positive SPT rate to flour proteins. FLOUR and alpha-AMYLASE

Suarthana 2009 Diagnostic Study	4.5	314	SPTs to lab animal allergens	Bronchial Responsive (BR) tests; Methacholine Bronchial Challenge Tests	314 apprentices who had a negative skin reaction to all lab animal (LA) allergens tested at initial visit. LA allergens included rat urine, mouse urine, and rabbit urine and/or rabbit hair.	32 months	4 models – Model 1: questionnaire only, Model 2: questionnaire and SPT, Model 3: questionnaire and BR tests, and Model 4: questionnaire, SPT and BR tests.	LA Allergens: Probability ≥ .10: Sensitivity (89.8%) Specificity (43.0%) PPV (22.6%) NPV (95.8%). Symptoms at work: Probability ≥ 0.10: Sensitivity (82.2%) Specificity (67.7%) PPV (31.4%) NPV (95.5%).	"[W]e developed prognostic models to predict the occurrence of sensitisation to LA allergens and symptoms at work in animal health apprentices. The questionnaire model alone is an easy tool that can give an accurate prediction of the incidence of occupation sensitisation and symptoms."	Baseline done before exposure to lab animals during training. Data suggest patients with allergic symptoms, positive SPT to common allergens, symptoms of asthma, and bronchial hypersensitivity before exposure are at greater risk for developing sensitization and symptoms to lab animals. LAB ANIMALS
OTHER STUDIES										
Bernstein 2011 Diagnostic Study	9.0	40	SPT – trimellitic anhydride	IgE/IgG Intracutaneous testing	TMA exposed workers Controls	None	IgE levels, SPT results	SPT: Sn 73% Sp 97% PPV 89% NPV 90 SPT negative with intracutaneous testing: Sn 91% Sp 97% PPV 91% NPV 97%	"[U]sing a TMA-HAS skin test reagent can be as sensitive and specific as a sensitive TMA-serum specific IgE immunoassay for detecting TMA-sensitized workers."	Participants had IgE and IgG testing done prior to study. Used TMA-specific ImmuoCap 1000 Platform. Data suggest SPT useful in detecting TMA sensitized workers. TRI-MELLITIC ANHYDRIDE (not commercially available)

Sharma 2008 Diagnostic Study	7.5	69	SPT-mouse allergens	IgE Nasal Challenge IDT	Laboratory workers	None	Nasal symptoms Ocular symptoms Chest symptoms	SPT: Sn: 67% Sp: 91% PPV: 70% NPV: 79% +LR: 5.2 IgE: Sn: 47% Sp: 91% PPV: 70% NPV: 79% +LR: 11.2	"SPTs perform best in discriminating patients with and without mouse allergy."	Lab worker mean age 30 years. Length of time exposed not well described. This was not for OA, but for allergy symptoms, 86% had nasal allergy symptoms, 76% had ocular. Data suggest SPT to mouse allergens helpful in diagnosing mouse allergy. MOUSE ALLERGEN
Merget 2000 Diagnostic Study	7.0	265	SPT Platinum salts	None	Workers in platinum process plant	6 years	SPT conversion from negative to positive FEV_1 Symptoms Histamine challenge test with spirometry Atopy Smoking	The two risk factors found that lead to SPT conversion from negative to positive: Exposure level Smoking status	"Pt salts are relevant allergens in catalyst production plants."	6-year prospective cohort with main outcome measure risk factors leading to SPT conversion from negative to positive in exposed populations. PLATINUM SALTS (not commercially available)
Schmid 2009 Diagnostic Study	4.0	132	SPT to mouse and rat danders	IgE Whole body plethsmography NSBP Questionnaire	Laboratory workers	None	SPT IgE Whole body plethsmography NSBP Symptoms	Sensitization rates in workers: Mice 12.7% Rats 16.3%	"In employees with occupational contact with laboratory animal dust, the frequency of complaints was high. The results confirm the necessity of regular medical check-ups for employees with contact with laboratory animal dust."	Main complaints sneezing and runny nose. "Some ocular symptoms and bronchial asthma." SPTs done in 78.8% of participants; IgE testing done in 86.4%. In persons with <1 year of exposure, there were no positive tests. MOUSE AND RAT

Niezborala 1996 Diagnostic Study	4.0	77	SPT Platinum salts	None	Workers in a platinum plant	20 years	SPT conversion Atopy Smoking status Symptoms	18/77 (23%) developed positive SPT and 23/77 (30%) developed symptoms. Incidence of positive SPT and symptoms was highest in first two years. Smoking had a relative risk of conversion on SPT of 5.53.	"The findings confirm that smoking is and that atopy may not be a high risk factor for the development of allergy to complex platinum salts."	Retrospective cohort study done by medical record review. Main outcomes measured were conversion of SPT or development of symptoms in relation to smoking and atopy status. PLATINUM SALTS (not commercially available PST)
Calverley 1995 Prospective Cohort Study	4.0	78	SPT Platinum salts	Symptoms	Workers in platinum refinery	18 months, exam done every 3 months	Symptoms FEV_1 SPT Exposure by air sampling	32/78 (42%) classified as platinum salt sensitive, 22/78 (28%) converted to SPT +, and 10/78 (8%) SPT negative but had symptoms severe enough for removal from work. Smoking increased likelihood of platinum salt sensitivity by 8.0 times. Higher exposure increased PSS by 6.	"Smoking and intensity of exposure were definitely associated with development of PSS. Positive response to platinum salt skin prick test had a 100% positive predictive value for symptoms and signs of PSS if exposure continued."	Prospective cohort. Main outcomes measures were SPT conversion and symptoms during follow-up. Increase in SPT positive conversion and/or symptoms related to higher exposure at work and smoking status reported. PLATINUM SALTS (not commercially available PST)

SPECIFIC INHALATIONAL CHALLENGE TESTING

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 considered the ultimate "gold standard" for diagnosing sensitizer-induced occupational asthma, used when other methods have failed to establish the diagnosis;[3, 7, 9, 12, 90, 108, 158, 159, 184, 187, 189, 239-249] or a reference standard as there is no other definitive diagnostic test.[1] False negative results have been described if the wrong agent or dose challenge has been utilized or the sensitivity to an agent has decreased after long removal from exposure. However, this has been reported as a rare occurrence.[250]

There are certain limitations to its use. The challenge system and equipment needed for generation of safe levels of exposure during specific inhalation challenge testing are complex and expensive.[3, 6, 7, 11, 27] Significant problems include limited availability of test facilities and infrequent though potentially serious adverse effects.[251, 252] There is little standardization in the method for generation and measurement of inhalation challenge material. Methods for performing diisocyanate challenges have varied from small open air rooms where the worker performs the task suspected of causing symptoms, to a closed circuit apparatus that generates vapor by blowing humidified air over the chemical contained in a flask residing in a silicon bath.[146, 245] This technique offers distinct advantages over challenge rooms, in which wide variations in ambient diisocyanate concentrations may result in exposures above the TLVs. Due to better control of diisocyanate exposures, this method will trigger less exaggerated bronchoconstriction.[71] Although adverse effects are less frequent than in the uncontrolled work challenge to diisocyanates,[251, 253-255] the safer closed circuit method is performed in few centers and is unavailable for most patients suspected of having diisocyanate or other sensitizer-induced asthma.

Recommendation: Specific Inhalational Challenge Testing

Specific inhalation challenge testing is 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. For this reason, the recommendation is at level "C" despite the table of evidence, see below for full rationale.

Strength of Evidence **– Recommended, Evidence (C)**
Level of Confidence **–** Moderate

Performance – 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 training.[51] 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.[7] Patients should stop using short-acting beta 2-agonist agents 8 hours before testing and longer acting medications 24 hours before testing.[114] Positive responses, defined as a 20% fall in the FEV_1, may present in an immediate pattern (within 30 minutes of the exposure), is typical for HMW agents; a delayed pattern (2-8 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.[256] Full method and criteria for positivity of specific inhalation challenges with diisocyanates may be further reviewed in this reference.[257]

Indications – Most patients with suspected sensitizer-induced OA do not require this test, as their OA can be diagnosed with less invasive means.[7, 244] The indications for SIC include: 1) evaluation of a worker who has left the workplace and is unable or unwilling to return to work utilizing serial measurements of lung function; 2) initial documentation of a new cause of occupational asthma; 3) identification of a specific causative agent when there is work exposure to multiple substances;[7, 249] or 4) 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.[258]

Harms – Excessive bronchoconstriction and exacerbation of asthma; infrequently systemic and anaphylactic reactions.[258]

Benefits – Accurate diagnosis facilitates management of OA.

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.[259, 260] A specific bronchial challenge test should not be used for the sole purpose of settling medico legal issues.[199] Limitations to the validity of the SIC include: 1) the challenge exposure does not replicate the work exposure; 2) the OA is caused by a mixture of agents, and not one single agent; 3) the worker has been out of exposure for too long, and has lost immediate reactivity to the agent; 4) the patient has unstable asthma with variations in airflow independent of exposure.

Rationale for Recommendation

There are numerous high- and moderate-quality studies evaluating the use of specific inhalational challenge testing as a confirmatory test for the diagnosis of occupational asthma.[8, 49, 53, 64, 113, 114, 125, 141, 146-152, 175, 187, 199, 213, 221, 240-243, 249, 261-272] Specific inhalational challenge testing is expensive, time consuming, requires specialized sophisticated equipment, and has a considerably higher potential for adverse events than other diagnostic testing. While there are strongly supportive research studies that have been published suggesting level (A) recommendation, the major limitations and complications warrant downgrading to a recommended (C). SIC is recommended only for highly select cases, particularly where assurance of an accurate diagnosis is important.[185]

Evidence for the Use of Specific Inhalational Challenge Testing

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

Author/ Year Study Type	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow up	Outcome Measures	Results	Conclusions	Comments
van Kampen 2008 Diagnostic Study	8.5	107	Bronchial, nasal, or workplace-stimulated rye flour challenge	Specific IgE antibodies to wheat and rye flour, skin prick tests vs. aqueous wheat and rye flours	107 (77% male) with reported rhinitis, conjunctivitis, cough, chest tightness, shortness of breath or wheezing. (n = 71, mean age 41 years (71% male) given wheat flour challenge, n = 95 mean age 41 (79% male) given rye flour challenge).	Specific IgE tested at baseline. SPT performed twice with removal of test material after 15 minutes. Challenge performed at baseline.	Sensitivity, specificity, positive predictive values, and negative predictive values at various IgE concentrations, different wheal sizes.	Challenges: Specificity 68% and 62%, PPV 74% and 82%, NPV 82% and 71%, respectively for wheat and rye.	"High concentrations of flour-specific IgE and clearly positive SPT results in symptomatic bakers are good predictors for a positive challenge test. Challenge tests with flours may be avoided in strongly sensitized bakers."	Similar study as Sander 2004. Data suggest challenge testing with flour is helpful in the diagnosis of occupational asthma and the different preparations of flour proteins for skin prick testing need to be standardized and improved.
Koskela 2003 Diagnostic Study	8.0	37	Bovine specific inhalat-ional challenge via dosimetric nebulizer.	1. Skin prick test; 2. IgE testing; 3. Histamine challenge; 4. Exhaled NO measurement; 5. Mannitol challenge; 6. Sham inhalational challenge; 7. PEF, twice daily for a	37 dairy farmers with suspected occupational asthma to bovine dander who were referred for bovine dander specific inhalational challenge testing	5 or 6 days inpatient	Bovine dander specific inhalational challenge testing vs. other testing results	*Skin prick test:* Sn = 100% Sp = 50% PPV = 46% NPV = 100% *IgE:* Sn = 82% Sp = 100% PPV = 100% NPV = 93% *Histamine:* Sn = 82% Sp = 65% PPV = 50%	"Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal >3mm in size with a <5 IU/L serum bIgE concentration should be subjected to bovine SIC testing."	Patients with suspected occupational asthma by clinical presentation and spirometry were referred for testing. Data suggest patients with a positive SPT and serum specific IgE testing do not require SIC bovine testing.

				week				NPV = 89% *Mannitol:* Sn = 20% Sp = 94% PPV = 67% NPV = 89% *Exhaled NO:* Sn = 27% Sp = 77% PPV = 33% NPV = 71%		
Munoz 2004 Diagnostic Study	8.0	26	Specific inhalational challenge by pour method	SPT; Total IgE levels; Methacholine challenge testing	8 patients with diagnosed OA due to persulphate salts, 8 patients with asthma with no prior exposure to persulphate salts, 10 healthy patients with no history of asthma.	None	Spirometry after challenge testing	Methacholine testing: 6/8 (75%) of patients with OA had a positive test. 7/8 patients with asthma (88%) had a positive methacholine test. Sensitivity = 100% Specificity = 87.5%	"The procedure described in this study allows patients with bronchial asthma to be distinguished from those with persulphate salt induced OA."	Small numbers. No details on how patients were diagnosed prior to study. 8 patients with asthma did not have exposure to persulphate. Data suggest the pour method is a valid method for SIC with persulphate salt occupational asthma.
Rasanen 1994 Diagnostic Study	8.0	28	Specific inhalational challenge, method not well described. Challenge testing to grains	Methacholine; SPT; IgE; PEFR; Symptoms	16 patients with previous challenge test positive for rhinitis or asthma (worked as farmers and bakery and food industry workers) vs. 12 with seasonal rhinitis with or without	None	Spirometry PEFR Symptoms IgE SPT	SPT: Sn = 74% Sp = 86% RAST: Sn = 89% Sp = 78% BHRT: Sn = 57% Sp = 93% IgE: Sn = 91% Sp = 71%	"On the basis of the present preliminary study, the overall concordance of skin and blood tests with challenge seems to be relatively good in allergic asthma and rhinitis. These tests cannot, however, replace the challenge but serve as additional aids."	Small numbers. All atopic. Some "controls" had workplace exacerbated asthma. Co-interventions not well described. Data suggest skin prick tests, IgE, RAST, and BHRT testing useful but do not replace challenge testing for diagnosing occupational asthma.

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

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

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

					with asthma/no exposure to isocyanates vs. C = 10 healthy workers without asthma			C = 0/10 (0%).	challenge should be performed."	diisocyanate OA.
Mapp 1988 Diagnostic Study	5.5	162	Specific inhalational challenge to isocyanates in open air chamber	Methacholine challenge testing Clinical and occupational history Spirometry SPT IgE to TDI and MDI	162 workers exposed to isocyanates with symptoms suspected to be from asthma	None	Spirometry IgE test results	93/162 (57%) of patients with history consistent with OA had a positive SIC. 15/93 (16.1%) had a FEV_1 lower than 80% predicted. IgE antibodies found in 1 subject.	"In conclusion, isocyanate-asthma is an important cause of occupational respiratory disease...baseline airway responsiveness to methacholine is similar in subjects who developed an immediate, a dual, or a late asthmatic reaction."	Data suggest that clinical diagnosis based on history is only accurate about 50% of the time. SIC is considered the gold standard for diagnosis.
Vanhanen 2000 Diagnostic Study	5.5	11	Specific inhalational challenge to cellulose in open air chamber	Spirometry IgE-RAST SPT	11 workers who were exposed to cellulase with symptoms consistent of allergic rhinitis and or asthma	None	PEF Clinical history	8/11 had no symptoms with 30mg cellulose exposure. 2/8 had no symptoms with 300 mg cellulose exposure.	"The challenge method proved to be a practical means with which to stimulate conditions at the worksite and elicit the specific respiratory symptoms of the patients."	Small numbers. Diagnosis of workplace symptoms not well delineated in differentiating possible other exposures. Data suggest challenge testing may reproduce symptoms in patients with suspected allergy to cellulase.
Lam 1983 Diagnostic Study	5.5	206	Specific inhalational challenge test to plicatic acid using nebulizer	Methacholine (not in all patients). Skin prick test. IgE RAST	206 patients with positive testing to plicatic acid	None	Spirometry results classified as immediate, late or dual reactivity	18/206 (9%) had immediate reaction. 100/206 (49 %) had a dual reaction. 88/206 (43%) had a late reaction. 83 patients had	"Nonspecific bronchial hyperreactivity is an important factor in determining the type and the severity of asthma reaction	Protocol varied slightly between patient groups. Data suggest late asthmatic reaction is likely an earlier form of occupational

								methacholine testing.	induced by inhalation challenge testing in patients with occupational asthma due to western red cedar."	asthma compared to immediate or dual reaction to western red cedar.
Schwaibl mair 1997 Diagnostic Study	5.0	55	Specific inhalational challenge to bleach powder in open chamber	SPT. Non-specific bronchial provocation testing with acetylcholine.	38 hairdressers who had symptoms of occupational asthma vs. 17 hairdressers with allergic symptoms at work, but not asthma	None	Spirometry testing; SPT	Skin prick testing was positive to a panel of allergens in 13/54 (24%) of participants. 32/54 (59%) had positive NBPT. 9/46 (22%) had positive results to bleaching powder SIC.	"The acetylcholine test in patients with suspected bleaching-powder-induced asthma is of limited diagnostic value... specific bronchial provocation tests are a useful diagnostic tool for the establishment of a definite diagnosis in suspected cases."	Not all tests performed on all participants. Data suggest some utility in diagnosing persulfate salt occupational asthma in hairdressers by SIC.
Malo 2004 Diagnostic Study	4.0	108/496; 31 with both tests	Closed circuit SIC testing	"Realistic" SIC challenge test	496 with clinical suspicion of occupational asthma and a previously documented positive SIC to occupational agent	None	$FEV_1 \geq 30\%$ after challenge testing	Of 31 patients who had both tests: Closed circuit had 8/31 (26%) change in $FEV_1 \geq 30\%$. "Realistic" had 16/31 (52%) change in $FEV_1 \geq 30\%$.	"More widespread use of the closed-circuit method could potentially result in fewer instances of exaggerated broncho-constriction and greater use of specific inhalation challenges in the confirmation of occupational asthma."	Retrospective study. Question was about two different ways to do SIC. Not all 496 had both tests. Data suggest using the 31 patients exposed to both that closed circuit SIC results in fewer drops of $FEV_1 \geq 30\%$. False negative rate of closed circuit method was 2.2% when compared to "realistic" method.
OTHER STUDIES										
Cote 1990 Diagnostic Study	6.0	48	Asthma symptoms	Spirometry with methacholine challenge	Male workers with diagnosis of occupational asthma to red cedar who stayed in	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	Patients diagnosed with occupational asthma were followed. Data suggest continued exposure to cedar dust in confirmed

					same industry after diagnosis				deterioration of their asthma symptoms. There is also no way to predict who will deteriorate. A decrease in the amount of exposure to cedar dust does not prevent deterioration of asthma. This suggests that the ideal management of cedar asthma is removal from exposure."	asthmatics prevents resolution of symptoms and worsens symptoms in 37.5%.
Palczynski 2000 Diagnostic Study	5.0	37	Single blind exposure to phosphate buffered saline, then 7 days later exposure to latex protein. All done by nasal pool method and touching latex with skin.	SPT, Symptom score, RAST results, Spirometry	A = 16 nurses with either rhinitis or asthma related to latex vs. B = 9 nurses with rhinitis or asthma not related to latex vs. C = 6 patients with evidence of atopy vs. D = 6 healthy patients with no evidence of atopy.	None	Symptom score Mediator levels Spirometry Nasal lavage changes in cytogram, protein content, eosinophil cationic protein, and mast-cell tryptase concentration	Allergen challenge produced symptoms of rhinitis in all. Symptoms of rhinitis more severe in group A vs. group D ($p = 0.001$). Total leukocyte count in nasal washings highest in group A than other groups ($p<0.001$).	"The nasal challenge test appears to be useful for diagnosing occupational rhinitis in natural rubber latex-sensitized patients."	Small numbers. Nasal challenge testing created some form of response in all patients tested. Used skin prick testing as reference test for reactivity. Data suggest a detailed analysis of nasal lavage washings after nasal challenge test can help diagnose latex allergy patients.

NITRIC OXIDE (FRACTIONAL EXHALED NITRIC OXIDE, FENO)

Nitric oxide (NO) is recognized as a biological mediator in humans.[280] Measurement of total exhaled nitric oxide (FENO) is a test used for detection of endogenous inflammatory signals in childhood and adult asthmatics.[265, 281-287] FENO is acknowledged to assess pathological rather than physiological changes in asthma.[288] Increased nitric oxide in asthmatic airways is associated with up-regulation of inducible nitric oxide synthase as well as nitrite protonation in the acid environment of inflamed airways. 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.[282] FENO is reportedly directly related to eosinophil activity suggesting other conditions such as eosinophilic bronchiolitis will affect FENO independent of asthma status.[280, 288-291] 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.[288, 292-295] These factors, if not well described or controlled for, may make comparisons from one diagnostic study to another difficult.[288] A more complete list of factors which may influence FENO follows, although there is not always agreement between studies as to the direction of change. Conditions in which FENO may be increased include allergic rhinitis and eczema (atopy), cough, chronic bronchitis, COPD, airway viral illness, a nitrate-rich diet, systemic sclerosis, and exercise induced bronchoconstriction.[280] Reductions (or reductions mixed with studies showing no change) in FENO have been reported for alcohol use, altitude, congestive heart failure, obesity, pulmonary hypertension, and spirometry.[280] Smoking (active, passive, and cessation), caffeine, and cystic fibrosis have been reported to show both increases and decreases.[280]

1. *Recommendation: Exhaled Nitric Oxide Testing for Diagnosis of Occupational Asthma*
   Nitric oxide testing is not recommended for the diagnosis of occupational asthma, as it cannot differentiate between e.g., occupational asthma and other eosinophilic lung inflammatory conditions.

   Strength of Evidence **– Not Recommended, Insufficient Evidence (I)**
   Level of Confidence **–** High

2. *Recommendation: Exhaled Nitric Oxide Testing for Diagnosis of Asthma*
   Exhaled nitric oxide testing is recommended for establishing a diagnosis of asthma when more objective evidence is needed such as in litigated cases.

   Strength of Evidence **– Recommended, Evidence (C)**
   Level of Confidence **–** High

3. *Recommendation: Exhaled Nitric Oxide Testing for Selective Monitoring of Asthma*
   Exhaled nitric oxide testing is moderately recommended for selective use in monitoring airway inflammation in patients with moderate and severe asthma.[284, 296, 297]

   Strength of Evidence **– Moderately Recommended, Evidence (B)**
   Level of Confidence – Moderate

   Performed – 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 physiology of the nitric oxide testing is well understood both by the examiner and the clinician interpreting the test. There are several inflammatory phenotypes in asthma and determination of the subtype is important in understanding the results and usefulness of FENO as a test.[280]

   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.[280]

Indications – Monitoring airway inflammation. It may be of assistance in corroborating a diagnosis in patients with moderate to severe asthma when more objective measures are needed. It should not be used during acute asthma exacerbations.[298] FENO is reported to be more accurate in patients with more inflammatory airway disease and therefore, more effective in some patients than others.[280, 284, 296] Normative values are still being developed.[288, 292, 299-301] One review article opined that a single diagnostic measurement of 35 ppb or greater in a symptomatic individual should be considered clinically significant.[288] ATS recommends that FeNO values greater than 50ppb be used to indicate that eosinophilic inflammation is present.[280] Exhaled nitric oxide may also be used for sequential measurements to monitor asthma control. Studies suggest that a change of 20% in the value between visits is clinically significant.[280, 288, 302] Optimum flow rates have been reported to be 50 ml/s.[288]

Timing and Frequency of Testing – When changing therapy, it is recommended that FENO be measured every 2-4 weeks while the treatment plan is being modified and finalized.

Harms – None.

Benefits – Provides an objective index of airway inflammation that is minimally effort-dependent.

Advantages and Limitations – FENO is noninvasive and has been reported to be moderately effective in the monitoring of asthma.[303, 304]

Rationale for Recommendations
The limitation of FENO in the diagnosis of asthma includes the heterogeneity of asthma causes and subtypes. While eosinophilic airway inflammation is common, it is not always the process in asthma (i.e., neutrophilic airway inflammation). Similarly, in patients already treated with steroids, the test may be falsely negative.[280] Thus, the importance of FENO lies in its potential to identify steroid responsiveness rather than the diagnosis of asthma.[280, 288, 296, 297] However, in certain circumstances, such as in litigation, where effort on spirometry can be in question, FENO can be used to support the diagnosis of asthma where more objective evidence is needed.[280]

The sensitivity and specificity of FENO have not been sufficiently assessed for the diagnosis of occupational asthma. There are not any occupational allergens that have had investigational studies performed regarding FENO with determination of acceptable sensitivity, specificity, positive predictive value, and negative predictive value. However, there are multiple moderate and a few high-quality studies of FENO for testing a variety of non-occupational asthmatic patients ranging from potentially mild cases to refractory asthmatic cases. One moderate-quality study assessed steroid naïve patients and reported a sensitivity of 85% and a specificity of 90% for the diagnosis of asthma.[305] Another study reported sensitivity of 88%.[93] A study of steroid naïve patients reported a sensitivity of 72.2% and specificity of 70.6% for the diagnosis of asthma compared to spirometry.[306] Fortuna, et al., reported a sensitivity of 77%, specificity of 64% in asthma patients.[307] Kostikas 2008 reported a sensitivity of 52% and specificity of 85% when comparing young patients diagnosed with asthma to all other patients.[294] Another study concluded that FENO is not likely to be beneficial in clinical measurement except in steroid-naïve patients.[289] Demange, et al., reported a sensitivity of 80% and specificity of 42% in detecting patients with airway hyper-responsiveness confirmed by methacholine challenge testing.[299]

FENO is not invasive, has few adverse effects but is moderate to high cost when used repeatedly. It is recommended for select use in moderate to severe asthma for monitoring response to asthma treatments. It is believed that controlling asthma will decrease lung inflammation therefore, decreasing the FENO levels with repeated testing.

Evidence for the Use of Nitric Oxide Testing

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

Author/Year Study Type	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusion	Comments
Pedrosa 2010 Diagnostic Study	8.0	115	Exhaled Nitric Oxide (FENO), methacholine inhalation challenge, skin prick test	Broncho-dilator test and spirometry	Patients with asthma-like symptoms with negative bronchodilator tests and normal spirometry measures	None	FeNo, FVC, FEV_1, methacholine levels, and skin prick allergens	Receiver-operating characteristic (ROC) curve and mean area under curve (AUC) was 0.762 (95% CI 0.667-0.857; p = 0.000) for FeNo levels.	"The prevalence of confirmed asthma in our population was 30.4%. The optimal value of FeNO (using NIOX MINO, at a flow rate of 50ml/s) for the diagnosis of asthma was 40 ppb, with a 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.
Dupont 2003 Diagnostic Study	8.0	240	Exhaled NO	Conventional diagnostic tools	Subjects with symptoms suggestive of obstructive airway disease referred to an asthma outpatient clinic	None	Exhaled NO	Mean exhaled NO level was significantly higher in patients with asthma compared to non-asthmatics (25 ppb, 95% CI 23 to 28 vs. 11 ppb, 95% CI 10 to 12, p<0.001).	"E]xhaled NO might be considered as an additional diagnostic test for asthma, with acceptable levels of sensitivity and specificity. Although an elevation of exhaled NO is not specific for asthma, the measurement of exhaled NO can be used in discrimination asthma from other disease conditions in patients with symptoms suggestive of obstructive airway disease."	Large sample size collected. Study did not include patients taking steroids. No mention of other medications such as NSAIDs. Minimal baseline characteristics given. Data suggest FeNO may useful in the diagnosis of asthma. The exact cutoff level is unclear.

Miedinger 2007 Diagnostic Study	7.5	101	Mannitol Challenge and Methacholine Challenge with BPT	Skin prick test, spirometry, question-naire, and oral exhaled nitric oxide (FeNO)	Firefighter subjects being tested for asthma	Uncertain	FEV_1 and FVC values with spirometry, methacholine, and mannitol challenge tests	Bronchial airway challenge with mannitol (PD_{15}) was more sensitive (92%), specific (97%), PPV (86%), and NPV (98%) when testing for asthma. PD_{20} has a sensitive (78%), specific (94%), PPV (68%), and NPV (96%) when testing for asthma. The only significant difference is FENO >47ppb with sensitivity at 42%.	"Asthma was considerably underdiagnosed in firefighters. The combination of a structured symptom questionnaire with a bronchial challenge test allows to identify patients with asthma and should routinely be used in the assessment of active firefighters and may be of help when evaluating candidates for this profession."	Diagnostic standard for asthma was wheezing plus hyper-responsiveness to bronchial challenge test. All were firefighters. Data suggest asthma is under diagnosed in firefighters. Mannitol challenge testing had highest sensitivity and specificity.
Pérez-de-Llano 2010 Diagnostic Study	7.5	102	Exhaled Nitric Oxide (FENO), Spirometry, broncho-dilator test, methacholine test, and ambulatory peak expiratory flow (PEF)	No comparison tests	Patients with difficult to treat asthma	None	FENO, FVC, FEV_1, airway hyperresponsive-ness, PEFR, and PEF	FeNo levels demonstrated a sensitivity of 87.5% (95% CI 73.9-94.5) and a specificity of 90.6% (95% CI 79.7-95.9).	"Our results demonstrate, for the first time, that FeNO levels might be predictive of response to a stepwise approach in patients with difficult-to-treat asthma."	Patients selected if difficult to control asthma symptoms. Flow rate was 50 ml/s. Used portable device for measurements. Data suggest FENO may help identify which patients with difficult to treat asthma will respond to treatment.
Smith 2004 Diagnostic Study	7.5	47	FENO for asthma diagnosis	Exhaled NO vs. spirometric testing, Fe(NO) measurement, skin allergy testing, broncho-dilator reversibility,	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	Baseline, 2 weeks, and 4 weeks	Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively).	Sensitivity%, specificity%, PPV%, NPV% for: peak flow variation:0, 100, NA,70; peak flow improvement with steroid >15%: 24,100,100,69; FEV_1 <80% predicted: 29,100,100,71; FEV_1 <90%:	"[O]ur study confirms the overall superiority of FeNO measurements and induced sputum analysis in the diagnosis of asthma compared with conventional tests. FeNO measurements are quick and easy to perform and may be	Small numbers. Baseline characteristics different in terms of mean age. Small numbers make conclusions difficult. Data suggest that FeNO and sputum eosinophils may be tests that can be more sensitive and

				hypertonic saline challenge, peak flow measurements, sputum induction (n = 40), oral prednisone	asthma.			35,93,75,72; FEV_1/FVC <70%: 35,100,100,73; FEV_1/FVC <80%: 47,80,57,73; FEV_1 improvement with steroid >15%:12,100,100,66; sputum eosinophils>3%: 86,88,80,92; FeNO>20 ppb: 88,79,70,92.	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."	specific than peak flow rate measures or spirometry.
Smith 2005 Diagnostic Study	7.0	97	FeNO	Algorithm based on conventional guidelines	Patients with chronic asthma on inhaled cortico-steroids treated with PCP	12 months	Dose of inhaled corticosteroids, rates of asthma exacerbations	FeNO group: final mean daily dose of fluticasone 370 ug per day. Conventional group: 641 ug per day (p = 0.003). No significant difference in exacerbation.	"With the use of FeNO measurement, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control."	Baseline data minimal in terms of other co-morbidities or symptoms. Exacerbations treated with oral prednisone. Data suggest FeNO may be used to help titrate inhaled fluticasone doses in chronic asthma patients. No mention on function.
Fukuhara 2011 Diagnostic Study	7.0	61	Methacholine test	Pulmonary function tests, blood tests	Outpatients between May 2007 and June 2010 with at least one subjective symptoms of recurrent cough, wheezing or dyspnea.	Uncertain	Comparison of FeNO levels between those with and without asthma. Sensitivity, specificity, positive likelihood, and negative likelihood.	FeNO levels with asthma: 90.1± 4.2 vs. without asthma: 40.1±18.4). Specificity: 89.5%, sensitivity: 78.6%, positive likelihood ratio: 7.46, negative likelihood: 0.24.	"The results of our study suggest that FeNO-based asthma screening criteria proposed in this study can be used to accurately diagnose asthma, particularly in atopic patients, and may be applicable for daily clinical practice."	Small numbers. Used 40 ppb as diagnostic cut-off. No mention of systemic steroid use or other medications. Unsure of duration of symptoms for participants and other co-morbidities. Data suggest FeNO may be helpful in diagnosis of atopic asthma.

Gelb 2006 Diagnostic Study	7.0	87	Total Exhaled Nitric Oxide (FENO)	Spirometry	34 normal subjects, 44 non-smoking, clinically stable asthmatic patients for at least 6 weeks to study initiation.	Not specified	Sensitivity, specificity, positive predictive value, negative predictive value	Using ROC plots for first asthma exacerbation with cut-off point of FEV_1at 76% predicted, sensitivity = 0.91, specificity = 0.50, positive predicted value = 0.65, and negative predictive value = 0.85. Using ROC plots for first asthma exacerbation with cut-off point for FENO at 28 ppb, sensitivity = 0.59, specificity = 0.82, PPV = 0.77, and NPV = 0.87. An abnormal FENO ≥ 28 ppb increased relative risk for exacerbation by 3.4 ($\chi^2 = 7.34$, p = 0.007.	"In conclusion, baseline combined measurements of both post-bronchodilator FEV_1 percentage of predicted and FENO in clinically stable, treated, non-smoking patients with asthma may help risk stratify for subsequent exacerbations."	Follow up timing not clear. No blinding done. Co-interventions other than medications and smoking not well described. Data suggest that a combination of FEV_1 <76% and FENO >28 ppb increased the likelihood of an exacerbation requiring medical treatment to 85% over 18 months.
Lemiere 2010 Diagnostic Study	7.0	41	Exhaled NO (FeNO)	Sputum eosinophil counts.	Subjects undergoing specific inhalation challenges (SIC) for possible occupational asthma.	24 hours	FeNO, FVC, FEV_1, sputum, skin prick tests.	Between baseline and 24 hours after exposure, sputum eosinophil counts and FENO levels were correlated (p = 0.4, p = 0.02; p = 0.4, p = 0.007).	"[B]oth sputum eosinophil counts and FENO were increased in subjects with a positive SIC after exposure to occupational agents, which was not the case in subjects with negative SIC."	Small numbers. Patients diagnosed with OA by SIC. Data suggest FENO is less effective in diagnosing patients with a positive SIC than sputum eosinophil counts.
Miedinger 2010 Diagnostic Study	6.5	284	Mannitol Challenge Methacholin e Challenge with BPT	Skin prick test, spirometry, questionnair e, and oral exhaled nitric oxide	Military subjects	January 2007-October 2007	FEV_1 and FVC values with spirometry, methacholine, and mannitol challenge tests	BPT with mannitol and methacholine have similar sensitivity and specificity. Methacholine PD_{20}: sensitivity 43%,	"BPT with mannitol has a sensitivity and specificity similar to methacholine for the diagnosis of physician- diagnosed asthma in military	Physician-based diagnosis of asthma used as gold standard. No explanation for how each person diagnosed with

				(FeNO)				specificity 92%, PPV 55%, and NPV 88%. Mannitol PD_{15}: sensitivity 41%, specificity 93%, PPV 55%, and NPV 88%.	conscripts but is less costly to perform without the need to use and maintain a nebulizer."	asthma, or how patients without a diagnosis received medical care if any. Recruits age 18-19. Data suggest BPT with mannitol has a similar sensitivity and specificity as methacholine testing.
Kostikas 2008 Diagnostic Study	6.5	219	FeNO measured with a potable nitric oxide analyzer	Patients with respiratory symptoms related to asthma	Students from University of Thessally and Technological Education Institute of Larissa with at least 1 positive answer from European Community Respiratory Health Survey II screening questionnaire	None	FeNO	FeNO higher in those with asthma vs. controls and those with non-specific symptoms, p<0.0001. Predictors of FeNO were diagnoses of asthma (p = 0.002), allergic rhinitis (p<0.001), and currently smoking (p = 0.003). Optimal cut-off point for FENO as diagnostic tool for entire study population was >19 ppb, providing 85.3% specificity (Sp) and 52.4% sensitivity (Se). FeNO performed better in nonsmokers, Sp 84.9% and Se 66.7%, cut-off >19 ppb. FeNO values >25 ppb give Sp >90%; Sp rose to >95% for cut-off of >30 ppb.	"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."	Small numbers actually tested with FENO. Patients had symptoms of asthma and were diagnosed by a blinded physician based on clinical signs and symptoms. All were University students. No mention of flow rate, gender, height, or recent respiratory infection. Data suggest that FENO is a good diagnostic tool in diagnosing asthma from non-asthma, but it cannot determine the difference between asthma and allergic rhinitis.

Menzies 2007 Diagnostic Study	6.0	151	Exhaled NO (FeNO) using portable device (MINO)	Exhaled NO (FeNo) using laboratory device (NIOX)	N = 101 with asthma, and n = 50 healthy volunteers	None	FeNO, FVC, FEV_1	Receiver-operating characteristics (ROC) and area under the curve (AUC) from both NIOX and MINO differentiating asthma and non-asthma patients was 0.654 (95% CI 0.565-0.744; p = 0.002) and 0.619 (95% CI 0.527-0.711; p = 0.018).	"[F]eNO values deriving using the MINO device are directly comparable with those using the NIOX device."	Patients diagnosed with asthma included using inhaled corticosteroids. Used flow rate 50 ml/s during testing. Did not report smoking status. Data suggest portable exhaled nitric oxide accurately reflects disease activity and correlates spirometry.
Allmers 2000 Diagnostic Study	5.5	9	Exhaled NO	Methacholine challenge test	Subjects with a history of immediate-type allergy to natural rubber latex and of workplace-related asthma when exposed to MDI were studied	Follow-up evaluations were made up to 6 hours post exposure, and after 20±22 h (limited by working hours of lung function laboratory)	FEV_1 Exhaled NO	No correlation between a bronchial obstruction after methacholine challenge and bronchial response after specific allergen challenge was found. Decrease of exhaled NO in 16 of 19 subjects 16-18 hours after methacholine challenge and subsequent bronchodilation using salbutamol; p<0.001. 3/9 participants had a significant decrease in FEV_1 after exposure to MDI (no p-values given).	"There was no clear relationship between bronchial response, substance-specific IgE antibodies and an increase in exhaled NO levels. However, there was a tendency for subjects with substance-specific IgE antibodies and bronchial reaction to develop an increase in exhaled NO concentration."	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.

Berlyne 2000 Diagnostic Study	5.0	131	Fraction of exhaled nitric oxide (FENO)	Spirometry	N = 22 healthy nonatopic subjects, n = 28 healthy atopic subjects, n = 38 asthmatic subjects not taking steroids, n = 35 asthmatic taking steroids, and n = 8 subjects with eosino-philic bronchitis without asthma.	1 day trial	FEV_1, FEV_1/SVC	Significant difference in ENO levels, eosinophil percentages, absolute eosinophil counts ($\times 10^6$/g; p <0.001), macrophage percentages (p = 0.023), and lymphocyte percentages (p = 0.001).	"We conclude that ENO is likely to have limited utility as a surrogate clinical measurement for either the presence or severity of eosinophilic airway inflammation, except in steroid naïve subjects."	Baseline differences in age between groups. Age has been noted to be a significant factor in FENO measurements in younger (<41 years) populations. Other co--interventions such as exposures not documented. Data suggest FENO measures may not be clinically useful in detecting asthma, especially in non-steroid naive patients.
Fortuna 2007 Diagnostic Study	5.0	50	Fraction of exhaled nitric oxide (FENO)	Spirometry	N = 28 non-asthmatic patients vs. n = 22 asthmatic patients	2 con-secutive day study	FEV_1/FVC, FENO, sensitivity, specificity, PPV, NPV. FENO measured at 50 ml/s flow rate for 10 seconds.	Sensitivity was 77%, specificity was 64%, PPV was 62%, and NPV was 78% for FENO of asthmatic and non-asthmatic patients. Sensitivity was 22%, specificity was 100%, PPV was 100%, and NPV was 56% for FEV_1 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."	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.

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

								after 7 hours after sham exposure. No changes in EBC in pH detected at subsequent time points after isocyanate exposure in any groups.	the laboratory provides the necessary information for an appropriate use of this tool in a natural setting, such as the workplace."	
Jang 2003 Diagnostic Study	5.0	25	Sputum exam; NO metabolites, eosinophils, and eosinophils cationic protein	Peripheral blood measurement	N = 15 patients with asthma and in control group vs. n = 10 with no respiratory problems	Unknown	FEV_1, FEV_1/FVC	Higher results in asthmatics than controls for eosinophils and were at higher levels of ECP in blood. FEV_1, FEV_1/FVC negatively correlated with sputum eosinophils, p<0.01. NO metabolites (1220.3±180.2 mol/L vs. 545.6±98.4 mol/L, p<0.01), eosinophils (49.5±5.3% vs. 2.7±0.5%, p<0.01), and higher levels of ECP (1345.1±201.5 g/L vs. 146.5±27.5 g/L, p<0.01) in sputum.	"[T]hese findings suggest that the proportion of eosinophils in sputum have more accurate diagnostic marker of airway inflammation than NO metabolites in sputum and serum in differentiating asthmatic patients from control subjects."	Small numbers. Evaluated metabolites of NO not FENO.
Jang 1999 Diagnostic Study	5.0	23	Fraction of exhaled nitric oxide (FENO)	Spirometry	N = 13 patients with asthma and in control group vs. n = 10 with no respiratory problems	Unknown	FEV_1, FEV_1/FVC	Significant results in asthmatics vs. controls for higher NO metabolites for sputum (1252.5+ 203.3 'moll-' vs. 557.2+ 101.5 mol l-l, PcO.01) but not in serum.	"NO metabolites in induced sputum have a more valuable diagnostic value than those in serum in monitoring airway inflammation in asthma."	Small numbers. Evaluated metabolites of NO not FENO.

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

NASAL LAVAGE

Nasal lavage, following nasal provocation testing, is used to assess occupational airway sensitization and allergic reactions.[311-314] In nasal lavage, the cellular and biochemical findings in the nasal lavage fluid are analyzed for evidence of allergic reaction, including **changes** in the percentage of eosinophils, neutrophils, eosinophilic cationic protein (ECP), mast-cell tryptase, etc. before and after nasal provocation testing. The technique may differentiate allergic from non-allergic reactions, but does not distinguish allergic manifestations of rhinitis from asthma.

1. *Recommendation: Nasal Lavage Fluid Testing for Diagnosis of Occupational Asthma*
   Nasal lavage fluid analysis after challenge with the allergen is not recommended for the diagnosis of occupational asthma.

   Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
   Level of Confidence – Moderate

2. *Recommendation: Nasal Lavage Fluid Testing for Specific Allergen Testing and Monitoring of Symptomatic Workers*
   Nasal lavage is recommended for select workers with symptoms consistent with occupational airways allergy to specific allergens. Those specific allergens should have been evaluated in quality studies with reported specificity and sensitivity.

   Strength of Evidence – **Recommended, Evidence (C)**
   Level of Confidence **–** Moderate

   Performed – Testing location needs to be experienced and properly trained in technique and have cell analyzation capabilities.

   Criteria and Standards for Use – The use of nasal lavage in clinical practice is still limited due to great interindividual variability and the lack of a standardized and validated method. Inflammatory cells, protein content and mediators can be measured in nasal lavage washings, but normative values have not been established. The types of mediators measured are not standardized but frequently include eosinophil cationic protein and mast-cell tryptase. Nasal secretions can be collected and weighed for quantifying the secretory activity, especially after allergen challenges.

   Indications – To be used for allergens that have had investigational studies performed with acceptable sensitivity, specificity, positive predictive value, and negative predictive value. Allergens having met these criteria are animal allergens,[315] flour,[213, 264] chloramines,[261] latex,[262] and glutaraldehyde.[221] Garbage workers have also been studied.[267]

   Timing and Frequency of Testing – The timing and frequency of testing has not been established. Nasal lavage is more useful in situations where subjects serve as their own controls as it occurs during nasal provocation testing or exposure at the workplace.

   Harms – Minimal discomfort and minimal risk of coughing due to fluid aspiration.

   Benefits – Sampling of relevant tissue for demonstration of specific allergic response.

   Advantages and Limitations – Nasal lavage fluid testing is minimally invasive, has low adverse events, and may be high cost depending on frequency of testing. The test results do not diagnose occupational asthma but may indicate occupational airway allergy.

Rationale for Recommendations

There are seven moderate-quality studies that evaluated nasal lavage fluid in comparison to spirometry, skin prick testing, IgE testing and peak expiratory flow rates.[213, 221, 261, 262, 264, 267, 315] Studies have reported significant increases in eosinophils, basophils, cytokines, and eosinophil cationic protein in

patients with occupational allergies after challenge testing. They have also reported decreased spirometric FEV_1 values. These findings may assist with the diagnosis of occupational asthma; however, they cannot provide definitive evidence to confirm a suspected diagnosis. It is recommended for select, specific cases where there is known sensitivity, specificity and those results are reliable.

Evidence for the Use of Nasal Lavage

There are 8 moderate-quality studies incorporated into this analysis.[213, 221, 261, 262, 264, 267, 268, 315]

Author/ Year Study Type	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Palczynski 2001 Clinical, Crossover, Single-Blind Trial	6.5	31	Single blind exposure to 2% glutaralde-hyde and saline 0.9% placebo	Skin prick test IgE evaluation Spirometry	11 with glutaraldehyde induced asthma vs. 10 with asthma diagnosis vs. 10 healthy individuals	None	Symptom score, mediator levels, spirometry, nasal lavage changes in cytogram protein content, eosinophil cationic protein, and mast-cell tryptase concentration	In patients with GA occupational asthma: rhinitis, nasal washings of eosinophils, basophils, ECP concentration, and tryptase levels significantly higher than after challenge with placebo in same group and then after GA in group with asthma and healthy volunteers. ($p<0.05$).	"The result of the present study indicated the relevance of changes in NLF and spirometry due to specific inhalatory challenge. NLF examination allows us to identify patients with occupational asthma and rhinitis due to GA."	At least 7 days between cross-over testing. Concentration of GA during test 0.32 mg/m3 (below occupational exposure standards). Cellular findings can also just indicate nasal rhinitis. Data suggest nasal washings may help diagnose work-related asthma in specific inhalational challenge testing procedures.
Walusiak 2004 Clinical, Single-Blind, Crossover Trial	6.5	64	Specific inhalation challenge. Nasal lavage	SPT, IgE, Spirometry	64 bakers with reported symptoms of asthma and or rhinitis at work. A = 17 had occupational allergic rhinitis, B = 24 had both occupational asthma and rhinitis, C = 23 had atopic asthma without occupational allergy.	None	Cellular findings of nasal lavage, permeability index of nasal lavage	A significant decrease in PC_{20} after challenge test observed only in Group B ($p<0.001$). Provocation with flour resulted in elevated leukocytes in nasal washing in all groups. Group B had higher elevation than Group C ($p<0.001$). Eosinophils elevated in all groups, but more in groups A and B when compared to C ($p<0.001$).	"The results indicate the applicability of the 'nasal pool' technique as a simple diagnostic procedure in flour-induced airway allergy. However, the test does not allow to distinguish subjects with asthma and rhinitis from patients with isolated rhinitis. Therefore, the evaluation of spirometry and non-specific bronchial hyperreactivity is also necessary when diagnosing bakers' respiratory allergy."	Criteria for diagnosis of occupational asthma unclear. Nasal lavage for allergy to substance and not asthma. Data suggest nasal lavage may help determine if there is an allergic reaction in patients, not if there is a diagnosis of occupational asthma.

Krakowiak 2003 Diagnostic Study	6.0	47	Nasal lavage testing with lab animal protein	Spirometry Skin prick test IgE	25 lab workers diagnosed with occupational asthma vs. 22 atopic asthmatics without a diagnosis of occupational asthma to animals	None	Nasal challenge fluid, Spirometry, IgE, and skin prick testing	In 25 patients with occupational asthma, all had increased eosinophils and basophils in nasal lavage fluid compared to atopic controls with asthma ($p<0.05$). 8/25 (32%) had elevated IgE levels. 13/25 (52%) had positive skin prick testing	"Eosinophils and basophils are the predominant cells in NALF of patients with occupational airway allergy after a challenge with laboratory animal allergens. The inflammatory reaction constantly occurs after specific challenge and its intensity is related to the total symptom score and expiratory nasal resistance in occupational allergics."	Not well described how diagnosis of occupational asthma was obtained. Data suggest nasal lavage fluid testing may be used for diagnosing occupational airway allergy.
Palczynski 2003 Clinical, Single-blind Trial	5.5	19	Single blind exposure to 0.9% saline, then at least 7 days later allergen challenge with 2% CLT. Nasal lavage performe d	Skin prick test; Total IgE; Symptom score	6 health care workers with history of asthma or rhinitis related to chloramines T (CLT) exposure with positive SPT to CLT vs. 7 atopic patients with perennial respiratory symptoms, asthma and rhinitis and positive SPT to CLT vs. 6 healthy women with negative SPT to CLT	24 hours	Nasal challenge test in diagnostics of respiratory allergy to chloramine T.	Inhalation challenge with CLT induced late asthmatic reactions in 2 patients sensitized to CLT, with decrease in FEV_1 ≥20%. Placebo provocation in subjects in all groups, as well as CLT challenge in controls, without significant changes in symptoms score or nasal washings. Increased nasal lavage fluid from patients with chloramine T respiratory allergy when compared to both controls.	"The results indicate the applicability of the 'nasal pool' technique as a diagnostic procedure in chloramine T-induced airway allergy."	Small numbers. No calculation of sensitivity, specificity, number needed to test. Positive nasal lavage can also just indicate nasal rhinitis. Data suggest nasal pool technique is a possible diagnostic test for chloramine occupational asthma patients.
Palczynski 2000 Clinical, Single-blind Crossover Trial	5.0	37	Single blind exposure to phosphat e buffered saline,	SPT, Symptom score, RAST results, Spirometry	A = 16 nurses with rhinitis or asthma related to latex, B = 9 nurses rhinitis or asthma not related to latex,	None	Symptom score, mediator levels, Spirometry, nasal lavage changes in cytogram,	The allergen challenge produced symptoms of rhinitis in all subjects. Symptoms of rhinitis more severe in group A vs. group D (p =	"The nasal challenge test appears to be useful for diagnosing occupational rhinitis in natural rubber latex-sensitized patients."	Small numbers. Nasal challenge testing created some form of response in all patients tested. Skin prick reference test for diagnosing reactivity.

			then 7 days later exposure to latex protein		C = 6 patients evidence of atopy, D = 6 healthy patients no evidence of atopy		protein content, eosinophil cationic protein, and mast-cell tryptase concentration	0.001). Total leukocyte count in nasal washings was higher in group A than all other groups ($p<0.001$).		No calculations of sensitivity or specificity. Data suggest detailed analysis of nasal lavage washings after nasal challenge test may help diagnose latex allergy patients.
Gorski 1998 Controlled, Single-Blind, Clinical Trial	4.5	140	Single blind exposure to nasal challenge test. First to placebo. At least 7 days later, challenged with flour.	SPT, Spirometry, Histamine challenge testing on some participants	100 atopic patients with suspected allergy to flour vs. 20 atopic patients with no allergy to flour vs. 20 healthy subjects	None	Nasal challenge testing on cellular changes, mucosal/vascular permeability and mediator levels induced by specific and nonspecific nasal provocation.	Nasal challenge testing with allergen produced symptoms of rhinitis in 70/100 patients with occupational allergy. Concentrations of eosinophil cationic protein, tryptase levels, eosinophils, and basophils increased in occupational allergy patients compared to baseline ($p<0.05$).	"The nasal challenge test appears to be a very useful and safe tool for diagnosing occupational allergy."	Patients were not diagnosed with specific inhalational challenge testing. Comparison statistics used in same group compared to baseline instead of across groups. Data suggest that nasal challenge can provoke symptoms more often in patients with an allergy to the specific antigen.
Sigsgaard 2000 Clinical, Double-Blind, Crossover Trial	4.5	10	Nasal lavage Cytokine measures Cysteinyl leuko-trienes Acoustic rhinometry	Spirometry, SPT	5 garbage workers with occupational airway symptoms (at least 4 of the following: wheeze, chest tightness, dyspnea, bronchial hyper-sensitiveness) and peak expiratory flow variability >20% on working days vs. 5 garbage workers without any airway	1 period of testing	SPT, pulmonary function testing, acoustic rhinometry, nasal lavage, cytokine measurements, cysteinyl leukotrienes	8/10 smokers. No positive SPTs. No decrease in lung function on PFT. LPS had I NS increased inflammatory response in nasal mucosa 6/10 vs, GLU 0/10 ($p = 0.057$). Significant increase in cytokines after LPS exposure ($p<0.05$). Only difference between groups was greater PMNs in nasal lavage at 6 hours postexposure to LPS ($p<0.05$) in those without OAL.	"The authors found significantly less polymorphonucleates in nasal lavage from workers with occupational asthma-like symptoms compared to healthy recycling workers after exposure to LPS indicating a possible difference in the first line defense between the two groups."	Small study. Participants blinded to exposure medium. Data suggest different response with nasal PMNs between patients with suspected occupational asthma to refuse compared to those without occupational asthma.

					symptoms					
OTHER STUDIES										
Obata 1999 Diagnostic Study	7.0	17	Sputum eosinophils; Exhaled NO	Specific inhalational challenge testing; Skin prick test	17 patients referred for suspected OA to red cedar	None	Sputum cell count, Exhaled NO	9/17 (53%) responders to challenge. Of responders, there was a significant increase in number of sputum eosinophil after testing ($p<0.05$).	"[T]he late asthmatic reaction induced by plicatic acid in patients with western red cedar asthma is associated with an increase in sputum eosinophils."	Small numbers. Data suggest increased sputum eosinophils may be a clinical test to help identify occupational asthma after exposure to allergen.

PREVENTION AND EXPOSURE CONTROL

It has been stated that "all work related asthma is potentially preventable through a tiered strategy of primary, secondary and tertiary prevention."[7] Workplace exposure is considered primary prevention and consists of engineering controls, administrative controls, and personal protective equipment (PPE). 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.[316] 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.[317]

Exposure limits have been set by various bodies such as the American Conference of Governmental Industrial Hygienists (ACGIH) and the German MAK Commission. Control of exposure can be achieved by different control measures and a hierarchical strategy is commonly applied (see Table 4).[316]

Table 4. Hierarchy of Control Measures for Airborne Contaminants in the Work Environment in Order of Priority and Preference

Elimination • Total substitution of agent • Different process • Layout changes to work environment • Adjust work practices: automation, robotization, remote control
Reduction • Partial substitution of agent, change of form • Adjustment to process, preventive maintenance, specialized appliance • Good housekeeping in work environment • Work practices: correct work procedures, training/instruction, motivation, supervision
Isolation • Enclosure segregation • Changes to working environment: glove box, safety cabinet, segregation, high-exposure departments • Ensure enclosure of process hazards
Ventilation • Local exhaust, ventilation, push/pull ventilation • Changes to work environment: dilution ventilation, air douches, air curtains • Work practices: portable jets, low-volume, high-velocity tools
Exposure Avoidance • Changes to work environment: booths for operators • Work practices: shorter shifts, fewer people, adjustment of work schedules
Personal Protection • Work practices: respiratory protection, gloves, clothing

Adapted from Heederik D, Henneberger PK, Redlich CA. Primary prevention: exposure reduction, skin exposure and respiratory protection. *Eur Respir Rev*. 2012;21(124):112-24.

Substitution of an agent, for instance, can include substitution of enzymes with strong sensitizing potential by less strong sensitizing enzymes, or a change to a process that does not require the use of enzymes at all. When substitution is not possible, exposure reduction is the next best approach. Engineering controls can include isolation and enclosure to prevent inhalation of any possible irritants, or substituting a new agent that is less sensitizing.[1] Exposure reduction can be achieved by reducing the source strength (i.e., amount or concentration emitted), modifying the formulation of the active ingredient (e.g., liquid or granule instead of powder), changing the process, or by improving general hygiene (good housekeeping). Other options are isolation of the source (enclosure or segregation), ventilation, avoidance of exposure, and use of PPE. Administrative controls can include limiting time in certain areas of the plant to decrease the amount of exposure and use PPE and respirators. Often, optimal exposure

reduction strategies consist of a combination of technical and organizational measures. In practice, exposure reduction relies on a combination of different interventions.[316]

The relationship between the level of exposure to allergens and the occurrence of sensitization or work-related asthma has been studied for detergent enzymes,[318-323] baking operations,[324-330] wood dusts,[331] platinum salts,[225, 231] laboratory animals,[198, 332-335] anhydrides,[336, 337] diisocyanates,[338-340] and shellfish.[341, 342] Exposure response relationships indicate that implementation of primary preventive measures in the workplace that result in a reduction of exposure should also lead to a reduction in sensitization rate. However, the effect of exposure reduction measures has not been frequently studied in practice. Thus, relatively little is known about the effectiveness and efficacy of many possible exposure reduction measures.

The most convincing example of the beneficial effects of an exposure intervention is exposure to latex allergens. For natural rubber latex (NRL), a meta-analysis is available reviewing several studies that explored differences in exposure levels between health care workers using powdered and non-powdered gloves.[343] The most powerful study investigating the use of non-powdered gloves, which was associated with lower exposure, was a longitudinal case crossover intervention. Substitution of powdered latex gloves with low-protein, powder-free NRL gloves or latex-free gloves greatly reduces NRL aeroallergens, NRL sensitization and NRL asthma in health care workers. None of the individual studies fulfilled strict criteria for good-quality intervention studies, i.e., they were observational studies without a randomized design. However, taken together, these studies support assertions that substitution of NRL greatly reduces NRL sensitization and asthma.

Fewer studies are available for asthma-inducing agents other than NRL. A modest increase in use of control measures and proper work practices has included the use of local exhaust ventilation and decreased use of compressed air. Studies have been undertaken with interventions comprising combinations of different preventive dust control measures, as well as education and PPE, for laboratory animals,[344, 345] detergent enzymes,[319, 346] anhydrides,[347] diisocyanates,[348] and baking operations.[93, 349]

Skin exposure to certain occupational asthma inducing agents may increase the risk of occupational asthma, despite the limited epidemiological studies to date primarily regarding diisocyanate exposure. The contribution of skin exposure to asthma risk probably varies greatly with different allergenic exposures, work processes and settings, as well as other factors than can alter skin barrier function. Elimination of exposure, the preferred approach to preventing occupational asthma, reduces all routes of exposure, including skin exposure. Concern that skin exposure to chemical allergens and even possibly to HMW protein allergens may increase asthma risk has arisen based on several lines of “evidence,” including clinical experience and case reports, animal studies, and limited epidemiological findings.[23, 350, 351] Indirect exposure by others to work areas where asthmagens are in use is also of concern.[352]

Use of PPE, particularly respirators, is considered less effective than eliminating or minimizing exposures at the source or in the environment.[353] 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. Such comprehensive exposure control systems that include the use of respirators have been implemented for workers exposed to laboratory animals,[345, 354-356] dusts and fumes in aluminum production,[357] diisocyanates,[358] and disinfectants.[7, 359] Although success at prevention has been reported, it is not possible to determine the contribution made by respirators alone.

Statements from professional organizations have addressed use of respirators for primary prevention of work-related asthma. An expert panel convened by the American College of Chest Physicians (ACCP)

produced a publication on the diagnosis and management of work-related asthma.[7] This document advises primary prevention by controlling exposures to known workplace sensitizers and irritants, briefly citing a variety of methods, including respirators. The British Occupational Health Research Foundation (BOHRF) also developed guidelines for occupational asthma.[51] Similar to the ACCP document, the BOHRF guidelines emphasize reducing airborne exposures to occupational asthma agents. The advice specific to respiratory protective equipment (RPE) was: "use of RPE reduces the incidence of, but does not completely prevent, occupational asthma."[51] The European Respiratory Society has recently reviewed the topic and concluded that there is little direct evidence that use of respirators is effective for the primary prevention of occupational asthma. Elimination or minimization of exposures was considered to be more effective.[316]

There are a few studies that directly test whether respirator use is associated with a decline in the onset of occupational asthma. In one study, automobile body shop employees who applied paints containing diisocyanates were approximately one-third as likely to have occupational asthma symptoms if they used a positive pressure respirator. However, a relatively small number of participants used this respirator and the finding was not statistically significant.[360] A second study provided evidence that inconsistent use of respiratory protection might have negative consequences. Specifically, diisocyanate-exposed workers at a wood products plant were at greater risk for new-onset asthma-like symptoms if they removed their respirators even briefly ($p = 0.05$).[350] A more direct investigation of the value of respiratory protection for primary prevention was conducted among workers who were manufacturing an epoxy resin utilizing hexahydrophthalic anhydride (HHPA).[361] Study participants were offered a choice of three different respirators: a disposable dust and mist respirator, a half-face organic vapor respirator, or a full-face organic vapor respirator. The highest annual incidence for asthma over the 7 years of follow-up was 2%, compared to approximately 10% that was observed in employees before the introduction of respirators. There was no statistically significant difference between respirators, but none of the workers who wore the full-face respirators developed occupational asthma, even those who worked in high-exposure jobs.

MEDICAL SURVEILLANCE

Medical surveillance is the systematic collection and analysis of health data from defined populations for the purpose of prevention and is considered secondary prevention by preventing advanced disease in exposed workers. There are generally three stages in the process: 1) data collection and analysis; 2) preventive interventions; and 3) evaluation. Medical surveillance is **not** the detailed diagnoses of an individual patient, epidemiologic research, individual case reporting, data collection without prevention benefit, or a substitute for exposure control. It is not hazard surveillance, in which exposure and processes are measured, nor is it biomonitoring, which in the context of occupational asthma, is used to assess exposure to a few specific occupational asthmagens.

While engineering controls are the ideal solution for exposure control and primary prevention, they are often not possible due to technology, lack of substitutions, or cost. If there is any possibility of exposures to occupational asthmagens, a medical surveillance program is appropriate.[7] Additionally, medical surveillance has been found beneficial by identifying work processes associated with incidence of occupational asthma.[352] Multiple surveillance methods for occupational asthma have been utilized, and the methods have varied by setting. The goal is to include all potentially exposed workers in a health surveillance program that can be effective for secondary prevention, the early identification of occupational asthma before permanent impairment occurs. A diagnosis of occupational asthma (i.e., asthma caused by work) should not be made on the basis of history alone, but be supported by physiological and immunological investigations of proven diagnostic benefit.[7, 51, 362] Following a validated diagnosis of occupational asthma, physicians should recommend early avoidance of further exposure, because this offers the best chance of complete recovery. If appropriate and timely interventions are not taken, the prognosis of occupational asthma is poor, with only approximately one-third of workers achieving full symptomatic recovery.

Medical surveillance methods for early detection of occupational asthma in worker groups known to have sensitizer exposure in the workplace most frequently use a health questionnaire, spirometry, peak expiratory flow monitoring and, for specific asthmagens, antibody and skin prick testing, as recommended elsewhere in this guideline. The focus is to detect "possible" cases and then engage in diagnostic confirmation or exclusion by means of definitive clinical testing. The medical surveillance program may primarily be based on questionnaires but should also include lung function tests to document the temporal change in respiratory function and also identify non-symptomatic workers with respiratory changes consistent with a diagnosis of asthma. If there are positive findings, the individual should be referred to a physician having competence in assessment of occupational asthma so that the evaluation may proceed rapidly to confirm a diagnosis of occupational asthma before worker relocation. The process of objective confirmation of a diagnosis of occupational asthma should proceed immediately and rapidly on reasonable suspicion that occupational asthma may have developed.[51, 362]

Surveillance questionnaire items found to be most useful in identifying subjects with occupational asthma in surveillance programs were job title and duration of work under the same job title, and identification of products causing symptoms in order to define a process or a product responsible for the respiratory symptoms. The nature and timing of symptoms in relation to work, interval between onset of exposure at work and onset of symptoms, and the status of respiratory symptoms on working days as compared with days away from work (including weekends and vacations) is key. Persistence and timing of symptoms should be evaluated, including if they disappear or change.[62, 363]

Questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for work-related asthma. Questionnaire items that distinguish occupational asthma confirmed by specific inhalation challenge from non-occupational asthma or symptoms not resulting from asthma were sensitive but non-specific and were more useful for high molecular weight agents than low molecular weight agents. Questionnaire alone would have found all individuals referred for further diagnostic evaluation (i.e., no spirometry benefit).[364, 365] A change in questionnaire responses over time should lead to assessment of the interval between onset of symptoms and current questionnaire and interval between last occupational exposure and current questionnaire. Questionnaires need as much technical attention and skill as PFTs regarding content items, wording, and cultural relevance. They can be delivered on paper, on-line, assisted, interviewer and are subject to interpretation by the examiner, especially when reviewing sequential questionnaires over time.[366]

Timing of the surveillance should be at least pre-placement, periodic (with the interval defined by consideration of the history of incidence in reported cases) and upon concern post exposure or onset of significant respiratory illness. Beyond a good questionnaire, occupational asthma medical surveillance frequently includes spirometry. Antibody and skin prick testing may be part of the surveillance scheme for specific asthmagens, if the asthmagens meet criteria for use. Review by a well-qualified objective physician, with experience in the evaluation of occupational asthma is important. Questionnaire answers suggestive of occupational asthma, and significant decrement in FEV_1 and FVC beyond that predicted by age indicates that a confirmatory assessment be performed to confirm not only a diagnosis of asthma but also to establish whether temporal changes in pulmonary function correlate with symptoms in the workplace. The confirmatory assessment is essentially to diagnose or exclude the diagnosis of occupational asthma, and recommended methods are as noted in the diagnosis section of this guideline. Serial peak expiratory flow monitoring may be used as part of the initial stages of the confirmatory assessment while the worker is in the workplace to objectively document correlation of loss of airflow with symptoms.[367-375]

The early detection of cases of occupational asthma should focus primarily on respiratory symptoms and any temporal relationship with work, as opposed to reliance upon spirometry. It requires a coordinated approach between occupational health, primary care and secondary health care. There should be as few steps as possible between symptom detection and final diagnosis to diminish loss of initially identified

cases to follow-up.[376] Use of a two-step screening process, identifying work-related symptoms and presence of sensitization in general[377, 378] or sensitization to work-related high molecular weight allergens,[379] is the most efficient approach to identify potential cases of high molecular weight occupational asthma. For example, a strategy identifying bakers with sensitization to a work-related asthmagen (positive serological test against wheat flour or fungal a-amylase) and also reporting upper respiratory symptoms was the most effective strategy at identifying early stage baker's asthma, reducing exposures and improving outcomes.[379] In another study of workers exposed to laboratory animal allergens, a two-step prediction rule based on work-related symptom reports, and positive skin prick tests indicating atopy, was able to accurately identify those workers to be subsequently evaluated by skin testing to lab animal allergens.[377, 378]

One-time screening, as in cross-sectional studies, misses cases due to the low prevalence of occupational asthma, healthy worker effect, and selection bias (those affected select out of employment). But routine surveillance may underestimate cases without ongoing participation.[380] Case loss is minimized by longitudinal study and follow-up as long as inception cohort is stable and no workers are lost to follow-up.[381, 382] However, cases detected by one-time screening had less severe asthma than cases from pre-screening era, in cases confirmed by specific inhalation challenge, and had a better outcome at time of diagnosis and 2 years later.[383]

State and federal surveillance programs such as NIOSH Sentinel Event Notification System for Occupational Risks (SENSOR) have limits as most cases are reported "without objective evidence" of asthma such as spirometry, serial peak expiratory or methacholine challenge being impractical, specific inhalation challenge being infeasible or unavailable. State reports of occupational asthma are mainly from health care providers and are affected by practice variability.[384] State reporting requirements are variable, and are often ignored. Voluntary physician reporting is frequently unreliable, unrepresentative, and not effective in prevention.[385, 386]

A decline in the number of workers' compensation occupational asthma cases due to isocyanates has been noted in Ontario after surveillance for diisocyanates was introduced. Occupational asthma from all causes was diagnosed earlier and indicators of severity of asthma were also milder. Although engineering and industrial hygiene measures may have contributed to these changes, the findings indicated a beneficial contribution from the medical surveillance program for workers exposed to diisocyanates. However, the reduction in the number of cases could not be directly attributed to the performance of medical surveillance alone.[27]

MANAGEMENT OF OCCUPATIONAL ASTHMA (OA)

The medical management of occupational asthma and outcome of interventions following a confirmed diagnosis of OA may depend on several factors, including the worker's age and the causative agent. Early diagnosis and early avoidance of further exposure, either by relocation of the worker or substitution of the hazard, offer the best chance of complete recovery. Patients with sensitizer-induced OA should be removed from further exposure to the causative agent in addition to providing other asthma management.[7] 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 health surveillance to demonstrate the absence of worsening of disease.[51, 387] Determining the most effective treatment for OA requires having precise information on the effect of different management options on clinical, physiological, and socioeconomic outcomes. However, the evidence that can be derived from current data has been limited by methodological weaknesses.[388] There are very few articles that meet the methodologic quality of a randomized controlled trial or prospective cohort study, thus the recommendations regarding management of occupational asthma are made on the basis of consensus due to insufficient evidence.

1. *Recommendation: Management of Asthma (Persistence of Exposure)*
   It is recommended that patients, physicians, and employers be informed that persistence of exposure to the causal agent is likely to result in a deterioration of asthma symptoms and airway obstruction.

   Strength of Evidence – **Recommended, Insufficient Evidence (I)**
   L*evel of Confidence* – High

2. *Recommendation: Management of Asthma (Avoidance of Exposure)*
   It is recommended that patients and their physicians be aware that complete avoidance of exposure is associated with the highest probability of improvement, but may not lead to a complete recovery from asthma.

   Strength of Evidence – **Recommended, Insufficient Evidence (I)**
   Level of Confidence – High

3. *Recommendation: Management of Sensitizer-induced Asthma (Reduction of Exposure to Low Molecular Weight Asthmagens)*
   Reduction of exposure is not recommended as a strategy for certain low molecular weight asthmagens (diisocyanates). As an alternative to complete elimination of exposure, continued low level exposure with use of personal protective equipment has been associated with adverse health outcomes and including reports of death.

   Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
   Level of Confidence – Moderate

4. *Recommendation: Management of Sensitizer-induced Asthma (Reduction of Exposure)*
   Reducing exposure to the causal agent is NOT RECOMMENDED (I) as a strategy in the management of sensitizer-induced asthma, as available evidence indicates that many asthma cases will worsen in continued exposure. However, it is recognized that some workers will insist on remaining in their jobs for social, economic, and professional reasons, despite counseling on the adverse health consequences. Continued exposure, even at low levels, may result in worsening asthma. If such patients remain in exposure, documentation of the recommendation regarding removal is RECOMMENDED (I). Required close and careful medical monitoring of such patients is RECOMMENDED (I) in order to ensure early identification of worsening asthma. Reducing exposure to the causal agent in addition to providing immunotherapy and other asthma management, where applicable, may be RECOMMENDED (I), and will depend on the asthmagen, level of exposure, severity of asthma (see Table 5), and the clinical judgment of the physician.

   Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
   Level of Confidence – Moderate

5. *Recommendation: Management of Irritant-induced Asthma (Reduction of Exposure)*
   For irritant-induced asthma, it is recommended that exposure reduction to the lowest levels possible and careful medical monitoring should be performed to ensure early identification of worsening asthma.

   Strength of Evidence – **Recommended, Insufficient Evidence (I)**
   Level of Confidence – Moderate

Table 5. Medical Removal Considerations

Workplace Exposure*	Severe OA**	Moderately Severe OA	Low Severity OA

Low	Remove	Remove. Selectively consider low exposure, with monthly surveillance with symptom questionnaire and spirometry. Remove if progression.	Remove or reduce exposure; frequent surveillance with symptom questionnaire and spirometry. Remove if progression of disease.
Medium	Remove	Remove	Remove or reduce exposure; frequent surveillance with symptom questionnaire and spirometry. Remove if progression of disease.
High	Remove	Remove	Removal is the best option as exposure predicts progression.

*Workplace exposure is defined as follows:

- Low exposure: when regular airborne exposure to the causative agent is not expected.
- Moderate exposure: when airborne exposures at or below the level of the occupational exposure limit (OEL) of the causative agent are expected.
- High exposure: when airborne exposures above the level of the occupational exposure limit (OEL) of the causative agent are expected.
- The occupational exposure limit (OEL) selected should be a recent, scientifically reviewed, widely-used guideline designed for use by industrial hygienists in making decisions regarding safe levels of exposure to various chemical substances and physical agents found in the workplace, such as the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs®).

**Severity is defined as per severity of asthma and asthma control, as defined in the Global Initiative for Asthma Guidelines.[389]

- Severe OA: having abnormal FEV_1 (<70%) and requiring use of high-dose inhaled corticosteroids and long-acting inhaled beta-agonists for symptom control.
- Moderately Severe OA: having abnormal FEV_1 (<70%) and symptoms that are well-controlled with low dose inhaled corticosteroids and long-acting inhaled beta-agonists.
- Low Severity OA: having normal FEV1 and symptom control by as needed beta-agonist rescue or with low-intensity controller treatment such as low dose inhaled corticosteroids, leukotriene receptor antagonists or chromones.

6. *Recommendation: Management of Asthma (Respiratory Protective Devices)*
   The use of respiratory protective devices is not recommended as a safe approach for managing asthma, especially in the long-term and in patients with severe asthma.

   Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
   Level of Confidence – High

7. *Recommendation: Management of Asthma (Anti-asthma Medications)*
   Anti-asthma medications are not recommended as a reasonable alternative to environmental interventions such as exposure reduction or medical removal.

   Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
   Level of Confidence – High

8. *Recommendation: Management of Asthma (Pharmacological Treatment)*
   It is recommended that the pharmacological treatment of work-related asthma follow general recommendations for asthma. The current ATS/ERS recommendations for treatment of severe asthma should be followed.

   Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – Moderate

9. *Recommendation: Management of Asthma (Immunotherapy)*
   It is recommended that immunotherapy may be considered 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.

   Strength of Evidence – **Recommended, Insufficient Evidence (I)**
   Level of Confidence – Moderate

MANAGEMENT OF IRRITANT-INDUCED OA

After acute inhalation of a respiratory irritant, acute airway responses should be assessed early and may require supplemental oxygen, bronchodilators, and corticosteroids. Although there is little objective evidence for the effectiveness for systemic corticosteroid therapy, this is often used for treatment in the hope of limiting airway inflammation.[390] In individuals with subsequent irritant-induced asthma or WEA, optimizing asthma treatment and reducing the exposure to relevant workplace triggers has been recommended.[7] If not successful, change to a workplace with fewer triggers is suggested in order to control asthma. Limited data exist on the effect of the cessation of exposure in patients with irritant-induced OA. One report of three patients with repetitive exposure to irritants at work suggested a benefit for removal from the exposure.[391] Improvement in symptoms, though not always NSBHR was found in aluminum potroom workers after cessation of exposure.[392, 393] Unlike workers with sensitizer-induced OA, workers with irritant-induced OA may be able to continue in their usual jobs if the risk of a similar high-level exposure to the inciting irritant substance is diminished via engineering controls and similar means are employed to prevent subsequent WEA, including the appropriate use of respiratory protective devices. The rationale for this approach is based on the unproven assumption that irritant-induced airway inflammation in patients with irritant-induced OA will diminish with a reduction of exposure that is analogous to what may occur in patients with occupational or tobacco smoke-related chronic bronchitis with a reduction in exposure.[7]

MANAGEMENT OF WEA

The literature on the natural history and management of patients with WEA is limited, and the factors that predict outcome are not well defined. The few studies completed to date have significant methodologic weaknesses and evaluated different treatment or preventive strategies in WEA patients.[7] 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 nonwork 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.[17] When a WEA case 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.[394] Workers with work-exacerbated asthma had reduced airway inflammation and improved quality of life after the implementation of smoke-free environment legislation.[395]

MANAGEMENT OF SENSITIZER-INDUCED OA

Following the diagnosis of sensitizer-induced OA, management decisions can be complex. For example, while complete avoidance of the sensitizer may be advisable, alternative employment is often not available or feasible, symptoms may initially be mild, and therapy may alleviate symptoms sufficiently to

consider continued employment. This section summarizes the evidence available for the management of sensitizer-induced OA.

PHARMACOLOGIC TREATMENT OF WRA

The pharmacologic treatment of OA and WEA does not differ from the treatment of asthma that is not work related.[7] It relies on a stepwise approach according to the severity of asthma and asthma control, as defined in the Global Initiative for Asthma Guidelines.[389, 396] Treatment for patients with a diagnosis of severe asthma has been recommended by the ATS/ERS but the recommendations did not exclude nor specifically address OA or WEA.[397] The physician and the patient should discuss and create a written "asthma action plan." Pharmacological management of patients with asthma should occur in conjunction with recommendations to avoid exposure to the causative agent.[51, 362] However, there is currently insufficient evidence that treatment with inhaled corticosteroids and long-acting b2-agonists is able to prevent the long-term deterioration of asthma in subjects who remain exposed to the agent causing occupational asthma.[388] The methodological quality of the studies is low, the sample sizes are small, and dissimilar populations and interventions have precluded meta-analytic synthesis.[7]

There are very few studies that have specifically examined pharmacologic treatment in the management of OA. The effectiveness of anti-asthma medications in patients who remain exposed to the causal agent has not been specifically addressed in some of the previously published guidelines[7, 51] or in the Agency for Healthcare Research and Quality (AHRQ) systematic review.[1] The AHRQ review identified 10 controlled clinical trials specifically involving patients with sensitizer-induced OA, of which several were short-term trials examining acute effects on the response to SIC. There was no significant deterioration in any of the asthma outcomes compared with baseline values in 10 subjects with occupational asthma due to various agents who were treated with inhaled corticosteroids and long-acting b2-agonists over a 3-year period.[398] In contrast, another study reported that the decline in FEV_1 before removal from exposure to agents causing occupational asthma was not affected by the use of inhaled corticosteroids.[399] A pilot study used treatment with leukotriene inhibitors.[400]

Asthma Treatment Guidelines (by Others)[1, 7, 51, 397, 401, 402]

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Management Topics Evaluated	Results	Comments
Chung 2014 Guidelines ERS/ATS Task Force on Severe Asthma	NA	Pharmacological treatment	Treatment of severe asthma relies heavily on the maximal optimal use of corticosteroids and bronchodilators. There is potential for benefits of biological agents.	Recommendations on treatment for severe asthma. No specific mention of OA or WEA.
Baur 2012 Guidelines ERS Task Force Report	NA	Reduction of exposure Removal from exposure Personal respiratory equipment Pharmacological treatment	Reported insufficient evidence that treatment with inhaled corticosteroids and long-acting beta 2-agonists is able to prevent long-term deterioration of asthma is subjects who remain exposed to the agent causing occupational asthma.	Specific to OA and WEA. Authors address their recommendations for both diagnosis and treatment of OA and WEA.
Tarlo 2008 Consensus guideline, literature review document American	NA	Removal from exposure Minimizing exposure Inhaled corticosteroids Other antiinflammatory agents Immunotherapy	Removal from work is beneficial in relation to both symptoms and pulmonary function. There is limited evidence that minimizing exposure is a safe, or appropriate method of management. It seems beneficial to initiate early treatment an early treatment with	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

College of Chest Physicians Consensus Statement Supported by Schering-Plough Corporation.			inhaled corticosteroids in subjects with sensitizer-induced OA in addition to removal from exposure. Evidence of other anti-inflammatory agents is weak. Immunotherapy may be an effective management option when a commercial extract is available and the causative agent cannot be completely avoided for economic, professional, or other reasons. It is most effective when it targets 1 allergen or a few allergens. Immunotherapy is not indicated to treat irritant-induced asthma.	evidence noted. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Beach 2005 Consensus guideline, literature review document Sponsored by Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.	NA	Removal from exposure Reduction of exposure Use of PPE Inhaled Corticosteroids Immunotherapy	Less than half of the studies with removal (complete or reduction of exposure) reported improved FEV_1. 14/15 studies reported removal resulted in decreased hyper-responsiveness on NSBP testing. The majority of studies reported improved symptoms after removal from exposure and reduction of exposure. Use of PPE also reported reduction of symptoms, but did not eliminate symptoms. Studies reported improved PD_{20} in patients tested with inhaled corticosteroids. Immunotherapy to wheat flour extract appeared to be safe and resulted in improvement in symptoms and lung function.	Good summary details of studies included. No level of evidence provided for statements. No level of confidence provided. Authors noted small numbers in most treatment/management studies and that most corticosteroid agent studies reported efficacy but these were done primarily with di-isocyanate induced OA. Concluded that workers with OA often require medication treatment long after diagnosis, but no clear trend was identified based on LMW versus HMW asthmagen division.
Newman 2005 Guidelines for Occupational Asthma Supported by British Occupational Health Research Foundation (BOHRF)	NA	General management of OA	Occupational asthma should be diagnosed early and treated appropriately.	No official recommendations based on literature review. Appears to be mainly consensus recommendations. Not specifically addressing any one type of management.
Nicholson 2005 Consensus guideline, literature review document Commissioned by BOHRF	NA	Removal from exposure Minimizing exposure Medications	Employees should avoid further exposure to causative agents in the workplace. Physicians treating patients with OA should follow published guidelines for the medical management of OA.	Authors follow a grading protocol with recommendations. Recommendations are broad in management sections. No mention of arms/benefits. No level of confidence noted.

Inhaled Corticosteroids

It may be beneficial to initiate an early treatment with inhaled corticosteroids in subjects with sensitizer-induced OA in addition to removal from exposure,[7] although there is insufficient evidence to support systematic treatment with high-dose inhaled corticosteroids.[388] The AHRQ systematic review[1] noted that after treatment with steroids, most of the available studies documented an improvement in asthma

symptoms and NSBHR, and an increase in mean FEV_1, although only a few reported complete resolution of symptoms in the majority of the subjects. Two randomized controlled trials assessed the effects of systematic treatment with inhaled corticosteroids in addition to cessation of exposure. Treatment with beclomethasone dipropionate (1 mg twice daily for 5 months) was associated with reduced NSBHR.[403] Beclomethasone dipropionate (1 mg daily) was associated with a significant, though minimal, improvement in symptoms, peak expiratory flow and quality of life but no change in specific responsiveness to the causative agent (diisocyanates).[404]

Evidence for the Use of Inhaled Corticosteroids
There is 1 high-[404] and 2 moderate-quality RCTs/crossover studies incorporated into this analysis.[403, 405] There are 2 other studies[398, 406] in Appendix 1.

Management of OA with Inhaled Corticosteroids

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

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

MANAGEMENT OF SENSITIZER-INDUCED OA BY IMMUNOTHERAPY

Immunotherapy is a possible treatment option for patients with sensitizer-induced OA, but there is limited evidence to support its efficacy except under selected circumstances.[407] Immunotherapy could be considered in settings where OA 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.[7] There is a lack of evidence-based information on the effectiveness and adverse effects of specific immunotherapy with high molecular weight occupational allergens.[388] Immunotherapy for high molecular weight antigens should be most effective when it targets one allergen or a few allergens in the workplace that are linked clinically to disease, and it may have less effect when the worker is also sensitized to environmental allergens not included in the extract. Immunotherapy for OA due to LMW chemicals is untested because of concerns about toxicity and the unclear role of IgE-associated sensitization. Immunotherapy may be given by the standard subcutaneous route, where there is ample published literature for some non-occupational allergens, or by the sublingual route, for which there is less information about efficacy especially with occupational allergens.[7] Systemic reactions to immunotherapy are less frequent with the sublingual approach.[408]

There have been a limited number of studies of immunotherapy with HMW allergens of potential occupational relevance. These include natural rubber latex (NRL) for health care workers, venom from stinging insects for beekeepers, wheat for bakers, and grass or ragweed pollen for outdoor workers. Subcutaneous immunotherapy for exposure to NRL has been shown to be effective in reducing workplace symptoms, specific skin reactivity, and medication use,[409, 410] but has not yet been shown to improve the clinical course of OA.[173, 411] These studies documented an improvement in rhinoconjunctivitis symptoms and a reduction in skin reactivity to latex, but there was no clear improvement in asthma outcomes. In addition, latex immunotherapy resulted in frequent systemic adverse reactions. Sublingual NRL immunotherapy has similar effects,[412] but anaphylaxis occurred with higher doses.[413]

Specific occupations have characteristic challenges that may affect management. Hymenoptera venom allergy is an occupational hazard of beekeepers and other outdoor workers. Immunotherapy is highly effective and is indicated for those with sensitizer-induced OA associated with severe anaphylaxis[414-418] who are at risk for future stings. A placebo-controlled, double-blind trial of subcutaneous immunotherapy with a flour extract in 30 bakers with occupational asthma demonstrated that the treated patients showed a significant decrease in subjective symptoms, NSBHR to methacholine, and skin sensitivity and specific immunoglobulin (Ig)E to wheat flour without any adverse reactions.[419, 420] A later study demonstrated diminished symptoms and drug use in a cohort of bakers after similar treatment.[421] No studies have evaluated the efficacy of immunotherapy for laboratory animal allergy in animal workers (e.g., researchers and veterinarians), compared to the many studies for pet allergy. In non-occupational environmental settings, immunotherapy has been shown to prevent progression from rhinitis to asthma, and thus has the potential ability to alter the natural history of the disease.[422-424] Immunotherapy is not indicated to treat irritant-induced asthma.

Evidence for the Use of Immunotherapy

There are 2 moderate-quality studies incorporated into this analysis.[173, 420] There is 1 low-quality[412] and 6 other studies[409, 411, 413, 416, 417, 422] in Appendix 1.

Management of OA with Immunotherapy

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

MEDICAL REMOVAL

Once a diagnosis of OA is confirmed, the patient should be advised (preferably verbally and in writing) 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.[51, 387] Persistence of exposure to the agent causing occupational asthma is more likely to be associated with the persistence of asthma and NSBHR, and an accelerated decline in FEV_1, compared with complete avoidance of exposure.[388] The systematic review conducted by the AHRQ concluded that workers with occupational asthma who remain exposed to the causal agent continue to experience stable or worsened asthma symptoms and tend to show a decrease in FEV_1 over time, as well as an increase in NSBHR.[1] The consequences of persistent exposure were not specifically examined in the clinical practice guidelines issued by the British Occupational Health Research Foundation (BOHRF)[51] and the American College of Chest Physicians (ACCP).[7]

Exposure Control as Treatment

As stated in a recent Cochrane review regarding workplace interventions for the treatment of OA, "There is very low-quality evidence that removal from exposure improves asthma symptoms and lung function compared with continued exposure. Reducing exposure also improves symptoms, but seems not as effective as complete removal. However, removal from exposure is associated with an increased risk of unemployment, whereas reduction of exposure is not. The clinical benefit of removal from exposure or exposure reduction should be balanced against the increased risk of unemployment."[425] However, there is some case report and small cohort study literature that supports removal or reduction of exposure to the causative agent. Exposure reduction and/or removal has been recommended by others, including BOHRF,[51] ACCP,[7] and the European Respiratory Society (ERS).[388]

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have no further exposure to the causative agent.[128, 246, 247, 358, 426-433] The consequences of persistent exposure to the causal agent are more frequent persistence of symptoms and decline in pulmonary function.[118, 426, 427, 429, 434-436] Asthma symptoms persist in almost all patients who remain exposed, while one-third of those who avoided exposure recover from their asthma.[388] Persistence of exposure was associated with a decrease in forced expiratory volume in 1 sec (FEV_1)[118, 434] and an increase in NSBHR[434] compared with cessation of exposure. Changes in FEV_1 have been investigated according to cessation or persistence of exposure to the sensitizing agent. Patients with occupational asthma caused by red cedar dust who continued to be exposed had a more rapid decline in FEV_1 than those who were removed.[437] The rate of decline in FEV_1 before and after removal from exposure in individuals with occupational asthma (87% of the cohort due to LMW agents) was significantly greater before than after cessation of exposure. The rate of decline after removal from exposure is similar to that observed in healthy adults.[399]

Redeployment to a low-exposure area is not always effective. Reduction of exposure to the causal agent can lead to improvement or resolution of symptoms and NSBHR, although the limited available evidence indicates that this approach is less beneficial than cessation of exposure.[388, 430, 438, 439] The AHRQ systematic review[1] analyzed the outcome of symptoms,[246, 247, 392, 426, 427, 440-444] asthma medications,[246, 247, 426, 440, 441, 445] FEV_1, and NSBHR[246, 247, 426, 440] after the reduction of exposure in studies published up to 2004. The review concluded that the data documented some improvement in asthma symptoms; no clear pattern of changes in medication use; an improvement in FEV_1 over time in less than half of the studies; and provided insufficient data (improvement in one of three studies) to draw conclusions about the changes in NSBHR. The guidelines of the BOHRF and ACCP stated that reduction of exposure "is not always effective"[51] and that "there is little evidence for using this approach."[7] If workers are redeployed, exposure should be minimized to as low as possible by means of worker relocation. Relocated workers should have increased health surveillance to demonstrate the absence of worsening of disease.[362]

The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to avoidance of exposure.[426, 429, 430, 446-449] A meta-analysis[450] regarding asthma outcomes (i.e., improvement, recovery, and worsening of asthma symptoms and NSBHR) compared subjects who reduced exposure to the causal agent with those who completely avoided exposure. The most commonly identified causal agents, in seven out of 10 publications, were LMW agents, including isocyanates,[358, 426, 451] colophony,[246, 247] red cedar dust,[434] platinum salts,[427] and persulfate salts.[452] Two studies involved a single HMW agent, NRL,[440, 453] and one study evaluated patients with occupational asthma caused by various agents, of which 90% were LMW agents.[435] The meta-analysis of pooled data showed that a reduction of exposure was associated with a lower likelihood of improvement and recovery of asthma symptoms and a higher risk of worsening of the symptoms and NSBHR compared with complete avoidance of exposure.[450]

Patients should be informed of the possible adverse health effects of continuing exposure to themselves and to co-workers should they not permit necessary workplace investigations. Communicating with the workplace is useful, but requires the patient's written consent.[387] Employers and their health and safety personnel should ensure that measures are taken to ensure that workers diagnosed as having occupational asthma avoid further exposure to its cause in the workplace.

Respiratory personal protective equipment (RPPE) can result in an improvement – but not complete elimination – of respiratory symptoms and airway obstruction in the short term.[51, 388] Studies investigating the effectiveness of RPPE in those with OA are limited to small studies in provocation chambers or limited case reports. Air-fed helmet respirators may improve or prevent symptoms in some but not all workers who continue to be exposed to the causative agent.[358, 454-459] Use of RPPE led to a significant reduction in respiratory symptoms and changes in functional parameters during short-term exposures, but failed to provide complete protection. There was no protective effect in workers with more severe asthma or in those who used RPPE irregularly.[458] The proportion of workers with occupational asthma induced by red cedar dust who used a twin-cartridge respirator and remained exposed to the causal agent was significantly higher among the group with stable asthma than among the group with a deterioration of asthma.[53] None of these studies provide information on practical issues (e.g., compliance) that could result from the long-term use of RPPE. Individuals with asthma might have difficulty adapting to a dual cartridge half-face mask respirator due to increased inspiratory resistance resulting in increased respiratory cycle time.[460]

An exception is isocyanate-induced OA. This requires removal from exposure, as there have been reported deaths in patients on medication and using respiratory protection.[254, 461-465] Studies have found that "continued TDI exposure has been associated with increasingly persistent and severe respiratory symptoms.[340, 358, 426, 466] Several early investigators described a progression of symptoms with decreasing exposure-response intervals and increasing severity of bronchospasm.[467, 468] In addition, a significant decline in FEV_1 was observed among subjects with TDI-induced asthma who remained on the job (average duration 27 months), whereas a modest improvement in FEV_1 was observed among those who left.[466] Similar results were reported in another study.[358] There have been several cases of fatal bronchospasm reported in persons diagnosed with or believed to have had TDI-induced asthma at the time of an exposure incident.[462, 469] The earlier case report pertained to an automobile refinisher with TDI-induced asthma, who continued working with a two-component PUR paint and subsequently died during a severe asthma attack 6 years later.[462] This person had used a bronchodilator and steroids for asthma control and reported using a respirator to reduce exposure.

Evidence for Removal/Reduction of Exposures

There are 11 other studies incorporated into this analysis.[1, 7, 51, 387, 388, 399, 425, 427, 440, 441, 466, 470] None of these studies met the criteria for high- or moderate-quality studies, but are incorporated into this section (not Appendix 1) for the reader's ease of review.

Studies and Guidelines Addressing Removal/Reduction of Exposures

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Management Topics Evaluated	Results	Comments
Banks 1990 Observational study	NA	Reduction of exposure.	Workers with reduced but continued exposure to TDI had continued symptoms of OA. Serial evaluations of participants showed no improvement in bronchial methacholine testing and some showed 15% decline.	Only 6 participants. No comparison to removal from exposure or full continued exposure.
Beach 2005 Consensus Guideline, literature review document Sponsered by Agency for Healthcare Research and Quality. U.S. Department of Health and Human Services.	N/A	Removal from exposure. Reduction of exposure. Use of PPE. Inhaled Corticosteroids. Immunotherapy.	Less than half of the studies with removal (complete or reduction of exposure) reported improved FEV_1. 14/15 studies reported removal resulted in decreased hyper-responsiveness on NSBP testing. The majority of studies reported improved symptoms after removal from exposure and reduction of exposure. Use of PPE also reported reduction of symptoms, but did not eliminate symptoms. Studies reported improved PD_{20} in patients tested with inhaled corticosteroids. Immunotherapy to wheat flour extract appeared to be safe and resulted in improvement in symptoms and lung function.	Good summary details of studies included. No level of evidence provided for statements. No level of confidence provided. Authors noted small numbers in most treatment/management studies and that most corticosteroid agent studies reported efficacy but these were done primarily with di-isocyanate induced OA. Concluded that workers with OA often require medication treatment long after diagnosis, but no clear trend was identified based on LMW vs. HMW asthmagen division.
de Groene 2012 Cochrane Review	NA	Removal from exposure. Reduction of exposure.	Compared to continued exposure, removal from exposure increased the likelihood of reporting absence of symptoms, improved FEV_1 and decreased NSBH. Compared to continued exposure reduced exposure also increased the likelihood of absence of symptoms, but did not affect FEV_1.	Good summary study findings in paper. Used statistics in order to develop conclusions. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Merget 1999 Observational study	NA	Removal from exposure. Reduction of exposure	For the majority of subjects with OA due to platinum salts transfer to low exposure areas may not be associated with a more unfavorable outcome as compared with complete removal from exposure sources.	Single survey of 83 workers. Authors noted that reduction and removal had similar outcomes in terms of symptoms and FEV_1 values.
Fishwick 2012 Consensus Guideline, literature review document British Thoracic Society.	NA	Removal from exposure. Medications	The patient should be advised that the prognosis is improved by early and complete removal from exposure. The pharmacological management of OA does not differ from the management of asthma that is not work related.	Minimal references. No grading of articles. No summary table of recommendations, no level of evidence noted. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Nicholson 2005 Consensus Guideline, literature review document	NA	Removal from exposure. Minimizing exposure. Medications.	Employees should avoid further exposure to causative agents in the workplace. Physicians treating patients with OA should follow published guidelines for the medical management of OA.	Followed a grading protocol with recommendations. Recommendations are broad in management sections. No mention of arms/ benefits. No level of confidence

Commissioned by British Occupational Health Research Foundation.				noted.
Paggiaro 1994 Study summary document	NA	Removal from exposure. Reduction of exposure.	Removal from occupational exposure is associated with recovery of asthma in about 50% of subjects. Delay in diagnosis, in the removal from occupational exposure and in drug treatment may result in persistent chronic dysregulation of airway tone and in progressive deterioration of lung function.	Looked at several studies of OA due to TDI. Good summary of results. No specific guidelines or level of evidence.
Paggiaro 1984 Observational study	NA	Removal from exposure. Continued exposure.	Stopping occupational exposure to TDI frequently did not produce an improvement of the TDI bronchial asthma, and persistence of the occupational exposure causes a more rapid decline in the respiratory function.	Followed 27 patients over 2 years. 12 were removed/left exposure. Included both employees with and without OA.
Tarlo 2008 Consensus Guideline, literature review document. American College of Chest Physicians Consensus Standard Sponsored by Schering-Plough Corporation.	NA	Removal from exposure Minimizing exposure Inhaled corticosteroids Other antiinflammatory agents Immunotherapy	Removal from work is beneficial in relation to both symptoms and pulmonary function. There is limited evidence that minimizing exposure is a safe, or appropriate method of management. It seems beneficial to initiate early treatment an early treatment with inhaled corticosteroids in subjects with sensitizer-induced OA in addition to removal from exposure. Evidence of other antiinflammatory agents is weak. Immunotherapy may be an effective management option when a commercial extract is available and the causative agent cannot be completely avoided for economic, professional, or other reasons. It is most effective when it targets one allergen or a few allergens. Immunotherapy is not indicated to treat irritant-induced asthma.	A thorough look at the available evidence with good overall organization. Addressed several issues in relation to diagnosis and treatment of OA and WEA. Noted limitations in the literature. No summary table of recommendations, no level of evidence noted. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Vandenplas 2012 Consensus Guideline, literature review Task Force was funded by the ERS. No COI stated.	NA	Consequences of persistent exposure. Pharmacological treatment. Immunotherapy. Avoidance of exposure. Reducing exposure through engineering controls. Reducing exposure through PPE.	Asthma symptoms persisted in 93% of subjects who remained exposed and 66.3% in subjects removed from exposure. Some evidence of inhaled corticosteroids benefit. Immunotherapy had evidence showing improvement in asthma control in patients with flour and latex allergy. Studies reported decline in FEV_1 after removal was similar in healthy adults. 7/10 reviewed studies were LMW antigens. Reducing exposure was associated with a lower level of improvement when compared to complete removal. Use of PPE lead to a significant reduction in symptoms, but failed to provide complete protection.	Good summary tables provided of studies that were included in the statements. Addressed several issues in relation to diagnosis and treatment of OA and WEA. Noted limitations in the literature. No summary table of recommendations. No level of confidence noted. No mention of harms/benefits. No grading of articles presented.
Vandenplas 2002	NA	Removal from exposure.	Reduction of exposure to latex should be considered a reasonably safe alternative that is	Single study design. Total of 36 subjects followed for 56 months (range 12-92).

Observational study		Reduction of exposure.	associated with fewer socioeconomic consequences than removal from exposure.	Noted decreased symptoms and improved PC(20) values in both removal and reduction to exposure groups. Removal groups had more work-related disability and loss of income compared to reduction.
Anees 2006 Retrospective study	NA	Removal from exposure	Mean rate of FEV_1 decline after removal from exposure was 26.6 ml/year. Mean rate of FEV_1 decline was not related to duration of symptomatic exposure or smoking. No evidence inhaled corticosteroids after removal from exposure had a major beneficial effect on step-up in FEV_1.	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.

OUTCOME

Prognosis of OA

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 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.[7] Evidence supports the view that OA may become a chronic condition, similar to non-OA, and may require similar prolonged medical management.[51, 387]

The symptoms and functional impairment of OA caused by various agents may persist for many years after avoidance of further exposure to the causative agent.[128, 175, 250, 276, 358, 392, 426, 434, 436, 440, 447, 451, 466, 471-479] Improvement or resolution of symptoms or of preventing deterioration is more likely in workers who have:

1) no further exposure to the causative agent,[128, 246, 247, 358, 426-429, 431-433]

2) relatively normal lung function at the time of diagnosis,[128, 426, 436, 447, 448, 479, 480] and

3) shorter duration of symptoms prior to diagnosis.[128, 358, 426, 429, 430, 446, 448, 449, 479]

The AHRQ review of sensitizer-induced OA demonstrated continued improvement of lung function, often requiring follow-up durations of more than 2 years.[1] Prolonged follow-up has also been required to demonstrate improvement in nonspecific airway responsiveness. However, complete avoidance of exposure to the causal agent results in symptom recovery and resolution of NSBHR in less than one-third of affected workers.[388] A systematic review of the outcome of sensitizer-induced OA reported a pooled estimate of symptomatic recovery of 32%, within a median duration of follow-up of 31 months. The pooled prevalence of persisting nonspecific bronchial hyperresponsiveness was 73% and was significantly greater for those with OA from HMW agents compared with those with OA from LMW agents.[481] More recent studies published subsequently to the review by Rachiotis yielded similar estimated rates of symptomatic recovery and persistence of NSBHR.[106, 165, 167, 168, 482, 483]

Improvement in NSBHR can continue for years after cessation of exposure, but the rate of improvement is steeper during the first 2.5 years.[484] A determinant of improvement in NSBHR at follow-up has been found to be the severity of NSBHR at diagnosis.[439] Induced sputum analysis has demonstrated that failure to improve NSBHR after cessation of exposure was associated with persistent airway inflammation,[480, 485] but inflammation and airway remodelling may be present in subjects who have recovered from symptoms and NSBHR.[106, 486] The long-term outcomes of acute irritant-induced asthma are thought to be no different.[487] However, a cohort study of pulp mill workers found that irritant peak exposure during gassing episodes was a strong predictor of changing work due to respiratory problems, even after adjustment for asthma, chronic bronchitis, and chronic rhinitis.[488]

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 followed up at a specialist center while risks of continuing exposure to allergen remain. The recommended follow-up is every 3 months for 1 year, and then every 6 months thereafter. Patients with confirmed OA who have left work, or who have no ongoing asthmagen exposure risk, should be followed up for a minimum of 3 years at a specialist center.[51, 387] Patients with a diagnosis of OA should be followed with pulmonary function testing and nonspecific airway responsiveness testing (if available), unless asthma has cleared, regardless of their continued exposure status.[7]

Employment Outcome

The risk of unemployment may[489] or may not,[490, 491] be higher than in other adult asthmatics and may fall with increasing time from diagnosis.[446] Approximately one- third of workers with OA are unemployed up to six years after diagnosis.[118, 440, 446, 478, 489-493] Workers with OA suffer financially.[23, 118, 440, 489, 491, 492] Systems that incorporate retraining may be more effective than those that do not.[492, 494]

One prospective study compared asthma severity, disease-related costs and work-derived income after cessation or persistence of exposure to various agents causing occupational asthma. Noticeably, the investigators did not clearly distinguish the persistence of exposure to the same conditions at work from a reduction of exposure to the causal agent, since 43% of the subjects with persistent exposure actually had intermittent or lower exposure.[428] When compared with persistence of exposure to causal agents, complete avoidance resulted in a significant decrease in asthma severity and health care expenses, but also in work-derived income.[428] Two publications reported on the socioeconomic outcomes of workers with occupational asthma caused by colophony[246, 247] and NRL gloves. These studies revealed that the rate of unemployment was significantly higher among those who avoided exposure compared with those who reduced exposure. Among workers with latex-induced occupational asthma,[440] a "major" loss of income was more frequently reported by subjects who ceased exposure to latex than by those who remained exposed to reduced levels of latex. A recent case review found that continued employment in the same job 6 months after diagnosis of OA could not be predicted by FEV_1, gender, age, occupational status, exposure antigen, smoking habits, or duration of symptoms before diagnosis; only atopy was a prognostic factor.[495]

Pulmonary rehabilitation may be effective even in the complex settings of occupational respiratory diseases, including asthma, providing sustained improvement of functional capacity, and reducing health care utilization.[496] No studies have made direct comparisons between different systems of rehabilitation.[51]

Specialty Care (When do you refer to a pulmonary or allergy specialist?)
The National Heart, Lung, and Blood Institute (NHLBI) has established the following guidelines for referral of adult patients to a medical specialist in asthma:[5]

- Patient has had a life-threatening asthma exacerbation.
- Patient is not meeting the goals of asthma therapy after 3-6 months of treatment. An earlier referral or consultation is appropriate if the physician concludes that the patient is unresponsive to therapy.
- Signs and symptoms are atypical suggesting an alternative diagnosis.
- Other conditions complicate asthma or its diagnosis (e.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis, vocal cord dysfunction, gastroesophageal reflux disease, and COPD).
- Additional diagnostic testing is indicated (e.g., allergy skin testing, rhinoscopy, complete pulmonary function studies, provocative challenge, bronchoscopy).
- Patient requires additional education and guidance on complications of therapy, problems with adherence, or allergen avoidance.
- Patient is being considered for immunotherapy.
- Patients that require more intense therapy in the stepwise algorithm for the management of asthma as per the NHLBI guidelines (NHLBI: Step 4 care or higher or step 3 for children 0-4 years of age. Consider referral if patient requires step 3 care or step 2 for children 0-4 years of age.)
- Patient has required more than two bursts of oral corticosteroids in 1 year or has an exacerbation requiring hospitalization.
- Patient requires confirmation of a history that suggests that an occupational or environmental inhalant or ingested substance is provoking or contributing to asthma.
- Depending on the complexities of diagnosis, treatment, or the intervention required in the work environment, it may be appropriate in some cases for the specialist to manage the patient over a period of time or to co-manage with the primary care physician.
- In addition, patients who have significant psychiatric, psychosocial, or family problems that interfere with their asthma therapy may need referral to an appropriate mental health professional

for counseling or treatment. These problems have been shown to interfere with a patient's ability to adhere to treatment.

In general, cases of reversible airways obstruction suspected of work-related asthma should be referred to a specialist in occupational medicine in the following situations:

- The triggering condition or antigen is unknown and the patient continues to work in the environment.
- The worker is planning a return to work or change in jobs or assignment and requires counseling on future risk, accommodation, and fitness for duty.
- The pulmonary specialist in the case is unfamiliar with occupational exposures and the workplace.

APPENDIX 1: LOW-QUALITY/SUPPLEMENTARY STUDIES

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

NONSPECIFIC BRONCHIAL PROVOCATION TEST

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

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

							the skin prick test and IgE levels	in all 10 controls. Metha-choline sensitivity and eosinophils in sputum increased 24 hours after OSR-BRT.	OA among farmers."	between tests. Data suggest OSR can cause BHR in sensitized patients diagnosed with OA to OSR.
Subiza 1991 MCC vs. SIC Case reports	N/A	11	SPT, IgE testing, precipitin test, bronchial provocation test	Specific inhalational test	One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder and 10 control patients without asthma	Single testing period	Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls	Patient had slight bronchial hyper-responsiveness to methacholine challenge testing. In contrast, patient had an immediate asthmatic response after challenge with the 1:1000 wt/vol dilution of Brazil ginseng extract (Pfaffia paniculata).	"The patient experienced asthma within a few months after starting to package Brazil ginseng-root dust at work with noticeable improvement while she was away from work during vacation…the results of this investigation demonstrate that Brazil ginseng dust is a health hazard as an Ag able to induce asthma."	One participant. Difficult to draw any significance. Patient had a reaction on bronchial provocation test to Brazil ginseng extract.
Histamine										
Dehaut 1983 Diagnostic Study	NA	18	Histamine challenge testing	None	18 clinically stable asthmatics	None	Specific lung conductance, dose-response curves for PC20, threshold concentration, reactivity	PC20 was the most reproducible index.	"In a smaller group of subjects PC20-FEV1 appeared to be more specific than indices using sGL and maximum partial expiratory flow rates in distinguishing normal from asthmatic responses."	No OA. There were a different number of measures done on different patients. No other comparison test used for diagnosis or asthma.
Britton 1986 Comparative Diagnostic Study	NA	24	Histamine challenge testing	None	24 patients with asthma	None	Three different techniques (Crockcroft et al, Yan et al,	Differences in dose response were normally distributed in Yan and Mortagy	"Thus, of the three methods tested, the Yan technique was the simplest. It is fast, convenient,	No OA. No other comparison test used. This was looking at the different testing

							Mortagy)	techniques. No difference in variance between the 3 methods was detected.	and inexpensive compared to Crockcroft method, and in a clinical setting did not compromise repeatability. These qualities offer potential advantages for clinical and epidemiological use."	options for histamine NSBP testing in people reporting a diagnosis of asthma.
Histamine vs. Methacholine										
James 1997 Diagnostic Study	NA	NA	Histamine	Methacholine	None	None	PD_{20}	Cut-off value 8mg/mL in occupational challenge to define disease: Sn: 76% Sp: 51%	"Testing of airway responsiveness has been proposed in the assessment of occupational asthma, changes in asthma severity and the effects of potential sensitizers or treatments although its value in these settings is not yet fully established."	Review article. Reports there is no gold standard in diagnosing asthma. Not specific to OA in many measures.

SPECIFIC INHALATIONAL CHALLENGE TESTING

Author/Year	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Palczynski 2001 Single-blind clinical crossover trial	N/A	31	Single blind exposure to 2% glutaralde-hyde and saline 0.9% placebo	Skin prick test, IgE evaluation, Spirometry	11 with glutaraldehyde induced asthma, 10 with an asthma diagnosis, and 10 healthy individuals	None	Symptom score, mediator levels, spirometry, nasal lavage changes in cytogram, protein content, eosinophil	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	"NLF examination allows us to identify patients with occupational asthma and rhinitis due to GA."	At least 7 days between cross-over testing. Concentration of GA during test was 0.32 mg/m3 (below occupational exposure standards). Cellular findings can also just

							cationic protein (ECP), and mast-cell tryptase concentration	after GA in group with asthma and healthy volunteers (p<0.05).		indicate nasal rhinitis. Data suggest nasal washings can help diagnose work-related asthma in specific inhalational challenge testing procedures.
Vandenplas 1992 Diagnostic Study	N/A	20	Closed circuit SIC testing	History, SPT, spirometry, Challenge room method	20 subjects referred by WC Board or their physicians for evaluation of isocyanate-induced occupational asthma	None	Mean concentration of isocyanates above 20 ppb	Mean variances in isocyanate concentration: Closed circuit method = 6.3. Challenge room = 61.8 (p<0.001). Percentage of total exposure time above 20 ppb reduced from 11.3 to 3.5 % (p<0.001%).	"Specific inhalation challenges are essential to confirm or exclude isocyanate-induced occupational asthma…The closed-circuit method provides more reliable control of exposure levels during challenge test."	Small numbers. Duration of workplace exposure to isocyanates ranged from 0.5 to 36 years. Data suggest closed-circuit method and challenge room method give similar overall results, but there is less variance in isocyanate concentration with closed-circuit method.
Vally 2007 Double-blind, randomized study	N/A	13	Asthmatic response associated with high and low sulphite wine challenge	Spirometry variables, forced expiratory volume (FEV)	N = 7 (6 female, 1 male) aged 26-56 with history of bronchial hyper-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	Cut-off value determined to be a difference >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.	"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. owever, the lack of an obvious pattern in [BHR changes] suggests that positive responses	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.

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

Caron 2010 Diagnostic Study	N/A	44	Specific inhalational challenge by GenaSIC (closed circuit aerosol)	A previous SIC not done with "realistic method"	Subjects with occupational asthma	September 2007 through April 2009	Spirometry and FEV_1 values	No significant changes in spirometry in response to metha-choline. Causal agents are acrylates and isocyanates. Isocyanates: mean 13.98, SD 3.6.	"GenaSIC offers the possibility of reliable and safe exposures to dry particles, formaldehyde and isocyanates in the investigation of OA."	Study was of specific apparatus to deliver substance for specific inhalational challenges. Its main question was whether the machine would be useful. Study did not focus on diagnostic testing results.
Zeiler 2002 Diagnostic Study	N/A	9	Specific inhalational challenge with bovine dander. Using automatic, inhalation-synchron-ized dosimeter	Histamine challenge Skin prick test IgE	Dairy farmers with a clinical history "positive" for occupational asthma to cows	None	Spirometry results after and before histamine, IgE, skin prick test	There was a 275 fold difference in the amount of bovine protein needed for positive test. Histamine challenge was positive for 6/8 (75%).	"Our results support the use of purified major allergens for associating work-related asthma with the exposure to a specific allergen source."	Small numbers. Large variation in concentration of bovine protein needed for positive result. IgE and skin prick test seemed to help, but were less specific. Data suggest bovine protein may be used for specific inhalational challenge testing in dairy farmers.
Lin 1995 Diagnostic Study	N/A	9	Rotahaler device as the delivery method for specific inhalational challenge testing	Spirometry Methacholine challenge testing	9 patients referred for suspected red cedar asthma	None	Spirometry testing results after challenge	Of the 6/9 (66%) of the patients who reacted to plicatic acid, 3/6 (50%) reacted to challenge with red cedar dust delivered by the rotahaler.	"Our pilot study showed that a positive response to challenge with red cedar dust with the rotahaler was diagnostic for red cedar asthma but a negative test cannot rule out the diagnosis."	Small numbers, only 50% of test confirmed cases reacted with rotahaler. Data suggest rotahaler has low sensitivity and needs further testing in larger studies before it can be recommended.

Quirce 1992 Diagnostic Study	N/A	5	Specific inhalational challenge with alpha-amylase and cellulose by nebulizer	Skin prick test IgE REIA Histamine challenge test Methacholine	5 patients suspected of having occupational asthma to flour	None	Spirometry data Laboratory data	5/5 had positive skin prick test. 5/5 had positive IgE, positive methacholine test, and positive response to alpha-amylase. 3/5 (60%) positive response to cellulose on challenge testing.	"[A]lpha-amylase and cellulase behave as potential occupational allergens capable of sensitizing exposed bakers and giving rise to respiratory symptoms by an IgE-mediated mechanism."	Small numbers. No real comparison between diagnostic tests. This was more of a study to see if alpha-amylase and cellulose can cause respiratory symptoms.
Graneek 1987 Diagnostic Study	N/A	9	Specific inhalational challenge to various substances	Histamine provocative test	9 workers in various vocations with different exposures. All inpatient for diagnosis.	None	Spirometry after challenge testing	Histamine responsiveness significantly greater 3 hours after compared to 24 hours ($p<0.05$).	"[A]ttention should be focused not only on the period during and after late asthmatic reactions, but also particularly on the events which precede these reactions."	Small numbers. Study protocol varied between patients. Patients from various occupations. Limitations make it difficult to draw conclusions. Test appeared to cause decrease in FEV_1 in all patients.
Davison 1983 Case Series	N/A	8	Specific inhalational challenge test to castor beans after shaking trays of beans	IgE	5 people suspected of reacting to castor beans (3 Sudanese seamen, 2 lab workers, 3 controls)	None	Spirometry IgE levels	Of 3 patients, none had an immediate reaction, 2/3 (66%) of seamen had a decrease in FEV1. All 3 complained of skin irritations within an hour; 2/3 (66%) developed rhinitis and conjunctivitis.	"RAST inhibition, toxicological and haemagglutination tests suggest that the ricin and deracinated extracts contain distinct allergens."	Small numbers. Does not describe 3 controls. Case series suggests castor beans may cause allergic reactions and possibly occupational asthma.

Mapp 1986 Diagnostic Study	N/A	6	TDI inhalation challenge in an exposure chamber	Methacholine inhalation challenge	6 subjects with a history of sensitivity to TDI and positive results to bronchial challenge to TDI	Uncertain	FEV_1, PD_{20}	All subjects had normal airway responsiveness to methacholine (PD_{20} > 0.7 mg). 8 hours after TDI challenge, airway responsiveness increased significantly ($p<0.01$).	"[A]irway responsiveness is not necessary for the occurrence of toluene diisocyanate-induced asthma."	Small numbers. Baseline comparability different for age and FEV_1. With small numbers and baseline difference, conclusions are difficult to make from this study.

SPECIFIC IMMUNOLOGICAL TESTING

Author/Year	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Subiza 1991 MCC vs. SIC Case reports	N/A	11	Skin prick test, IgE testing, precipitin test, bronchial provo-cation test	Specific inhalational test	One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder and 10 control patients without asthma	Single testing period	Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls	Patient had slight bronchial hyper-responsiveness to methacholine challenge testing. In contrast, the patient had an immediate asthmatic response after challenge with the 1:1000 wt/vol dilution of Brazil ginseng extract (Pfaffia paniculata).	"The patient experienced asthma within a few months after starting to package Brazil ginseng-root dust at work with noticeable improvement while she was away from work during vacation…the results of this investigation demonstrate that Brazil ginseng dust is a health hazard as an Ag able to induce asthma."	One participant. Difficult to draw any significance. Patient had a reaction on bronchial provocation test to Brazil ginseng extract.
Riccardi 2003 Diagnostic Study	N/A	29	Specific/total IgE to iroko wood dust	Methacholine challenge after avoiding iroko dust exposure, skin prick test, intradermal test,	Group A (occ asthma subjects): n = 9 woodworkers with symptoms present after 6 months iroko	Not specified	Spirometry, IgE testing, PEF	PEF (in L/s) (mean±SD): Group A: while off work: 8.44±0.01; working w/iroko: 6.10±0.01; working w/ other wood: 8.31±0.02. Group B: off	"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	Small numbers. Patients were tested without blinding and co-intervention such as concurrent infections not well described. Data suggest occupational

				bronchial provocation test, peak expiratory flow w/iroko wood dust	exposure, Group B (no symptoms to any wood): n = 10 woodworkers, Group C (healthy control): n = 10			work: 8.4±0.01; w/iroko: 8.29±0.01; w/other wood: 8.29±0.01. Iroko SPT: all groups showed negative response. IgE (Iroko): all groups negative.	immunologic mechanisms other than IgE-mediated immediate hypersensitivity reactions."	asthma to iroko wood dust may be through a mechanism other than IgE.
Howe 1983 Diagnostic Study	N/A	22	RAST IgE to tetra-hydro-phthalic anhy-dride (TCPA)	Inhalation testing, TCPA-HSA, allergen discs, skin prick testing	7 women with respiratory symptoms, 8 volunteers from same factory, and 7 volunteers without TCPA exposure	10 months	IgE	In RAST inhibitions experiments, TCPA-HSA inhibited IgE binding to TCPA-HSA disc. In 7 women with respiratory problems, skin prick reactions occurred with 1.0% and 0.1% TCPA-HSA solutions.	"These results imply that occupational asthma caused by TCPA is an allergic reaction mediated by specific IgE antibody."	Small numbers. Baseline differences existed. Data suggest that TCPA can cause or aggravate asthma symptoms.
Topping 1986 Diagnostic Study	N/A	13	RAST IgE to trime-liitic (TMA), phtlaic (PA) and tetra-hydro-phathalic (TCPA) anhydrides	Other IgE immuno-assays	Workers exposed to acid anhydrides with respiratory symptoms	None	IgE binding	Antigen binding of the IgE antibody depended both on the acid anhydride and the hapten.	"Each anhydride stimulates the formation of a distinct population of antibodies in which the nature of the hapten profoundly influences antibody affinity."	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.
Aalto-Korte 2003 Diagnostic Study	N/A	7	IgE- per-sulfates	Skin prick test with ammonium and potassium persulfate salts	138 patients with allergic symptoms. 7 patients tested positive and were analyzed.	Uncertain	IgE	7 patients with positive skin prick were hairdressers; 2 had positive reactions to open application test of both ammonium and	"..The mechanism of immediate hypersensitivity to persulfate seems to be IgE-meditated at least in some patients."	Very small numbers; no baseline characteristics provided. Patients did not all have asthma. Data suggest hypersensitivity to

								potassium persulfate solutions.		persulfates may be IgE mediated.

SKIN PRICK TESTING

Author/Year	Score (0-11)	N	Test used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Walusiak 2000 Cohort Study	N/A	452	SPT to wheat flour	None	Apprentice bakers just starting their apprentices	None		3% of examined Polish apprentice bakers were found to have positive skin prick tests to occupational allergens before the onset of occupational exposure.	"In our opinion, the results of SPT should be very carefully examined, when diagnosing occupational allergy, as in some apprentice bakers positive results of SPT to flour allergens are found before vocational training."	Study is preliminary results of cohort study. Average age 16.2 years. "Baseline" SPT done during first month of apprentice work, indicating at least some work exposure before testing was done. WHEAT FLOUR
Subiza 1991 MCC vs. SIC Case reports	N/A	11	Skin prick test, IgE testing, precipitin test, bronchial provo-cation test	Specific inhalational test	One patient who developed symptoms of asthma after exposure to Pfaffia paniculata root powder and 10 control patients without asthma	Single testing period	Skin prick test, IgE testing, precipitin test, bronchial provocation test in 1 case vs. controls	Patient had slight bronchial hyper-responsiveness to methacholine challenge testing. In contrast, patient had an immediate asthmatic response after challenge with the 1:1000 wt/vol dilution of Brazil ginseng extract (Pfaffia paniculata).	"The patient experienced asthma within a few months after starting to package Brazil ginseng-root dust at work with noticeable improvement while she was away from work during vacation…the results of this investigation demonstrate that Brazil ginseng dust is a health hazard as an Ag able to induce asthma."	One participant. Difficult to draw any significance. Patient had reaction on bronchial provocation test to Brazil ginseng extract. BRAZILIAN GINSENG ROOT DUST
Alvarez 2001	N/A	3	Skin prick test, IgE testing,	Oilseed extract bronchial	3 nonsmoking farmers diagnosed	3 days	Oilseed rape extract bronchial	10 healthy subjects were also skin prick	"…[T]he identification of the agent causing OA	Small numbers. No blinding of evaluators to skin

Case reports			Metha-choline test	provocation test	with OA		provocation test compared to the results of the skin prick test and IgE levels	tested with OSR. Skin prick testing positive in al 3 cases, negative in all 10 controls. Methacholine sensitivity and eosinophils in sputum increased 24 hours after OSR-BRT.	should always be stressed and that allergy to OSR flour should be considered in the investigation of OA among farmers."	prick test. No true diagnostic comparison between tests. Data suggest OSR can cause BHR is sensitized patients diagnosed with OA to OSR. OILSEED RAPE EXTRACT
Park 2002 Diagnostic Study	N/A	4	Skin prick test – porcine extract	Bronchial provocation test	Nurses complaining of asthmatic symptoms when exposed to porcine extract (PPE) powder. Non-smokers.	None	Serum specific IgE antibodies to PPE, α-amylase, lipase.	Significant inhibitions were noted with additions of α-amylase and PPE in a dose-dependent manner, while minimal inhibitions were noted by lipase and D.pteronyssinus antigens.	"[C]ommonly used drug powders, such as PPE, can induce occupational asthma in exposed nurses working in a hospital. Evidence is presented to indicate that –α-amylase included in PPE is a major allergenic component that can induce IgE-mediated broncho constriction."	Small numbers. All nurses with asthma complaints when handling extract. Data suggest porcine extract can cause asthma symptoms. SPT with PPE positive: 4 patients with positive SIC to PPE, but negative in 20 controls. PORCINE EXTRACT (alpha amylase)

NITRIC OXIDE

Author/Year	Score (0-11)	N	Test Used	Comparison Test	Population	Length of Follow-up	Outcome Measures	Results	Conclusions	Comments
Smit 2009 Cross-sectional Study	3.5	425	Exhaled Nitric Oxide (FENO) and endo-toxin levels	None	425 agricultural farmers	None	Exhaled NO, specific immuno-globulin (IgE) antibodies	Exhaled NO levels associated with endotoxin exposure in non-smoking participants (p = 0.02). In non-smoking, non-	"[A] significant exposure-response relationship was found between exposure to endotoxins and exhaled NO in non-smoking, non-	Used flow rate of 50 ml/s for FENO testing. Baseline characteristics not included. Data suggest endotoxin exposed farmers who are non-

								atopic workers had endotoxins exposure levels and FENO (GMR 1.09; 95% CI 1.05- 1.17; p = 0.006).	atopic agricultural workers."	smokers and non-atopic can cause a dose-response increase in FENO.
Olin 2004 Diagnostic Study	3.5	246	Exhaled NO (eNO)	Nasal NO (nNo)	246 non-smoking, bleachery and paper-mill workers	None	Exhaled NO, nasal NO, FEV_1, FVC, FEV_1/FVC, and specific IgE	The eNO levels were higher in subjects with asthma compared to those without asthma (22.5 vs. 15.8 ppb; p = 0.0004).	"We found no difference in eNO levels between atopic and non-atopic subjects with no reported asthma or rhinitis. Atopic subjects with asthma or rhinitis had higher eNo levels than those without atopy."	Participants working with bleaching agents in paper mills. Flow rate ~50 ml/s. Data suggest atopy does affect FENO and patients with atopy but without current symptoms are similar to those without atopy.
Lund 2000 Diagnostic Study	3.0	226	Exhaled NO (FeNO)	Nasal NO (nNo)	186 aluminum workers from potroom at a smelter and 40 control subjects from same plant but different area	None	FeNO, FVC, FEV_1	Non-smoking potroom workers with asthma symptoms had higher levels had higher levels of FeNO 21.0 (19.3-41.4) ppb, than those without asthma symptoms 8.5 (5.9-12.8) ppb (p<0.001).	"[E]exhaled No concentrations in non-smoking potroom workers were 63% higher than in non-smoking control subjects recruited from the same plant."	All worked for single employer. Co-interventions not well controlled. No mention of FENO testing flow rate. Patients did not have asthma, but exposed to possible irritant at differing levels. Some had respiratory symptoms. Data suggest FENO is elevated in patients exposed to respiratory irritants even without a diagnosis of asthma or

										abnormal spirometry measures.
Reutman 2009 Diagnostic Study	1.5	43	Exhaled nitric oxide (ENO)	Pulmonary function tests (PFT)	43 nail technicians	None	ENO, cotinine metabolite, FEV_1, FVC	Years worked as a nail technician was significantly related to higher levels of NO ($p<0.05$).	"[J]ob latency and possibly hours of contact with methacrylates have measurable effects on PFT results and inflammation levels (ENO), as did smoking, in a select population of nail technicians....Thes e findings were inconclusive, but do warrant further investigation."	Pilot study. Small numbers. FENO was collected prior to spirometry. Did not include atopy at baseline. Data are difficult to interpret due to study shortcomings. Data suggest working as a nail technician may adversely affect lung function.

MANAGEMENT OF OA WITH INHALED CORTICOSTEROIDS

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
De Marzo 1988 Cross-over clinical trial No mention of industry sponsorship or COI.	NA	N = 9 sensitized to TDI with late asthmatic reactions	Beclomethasone 200ug BID Beclomethasone 1000ug BID Placebo All taken 7 days before TDI inhalational challenge. Washout period 1 week.	FEV_1 four hours after TDI exposure was: Placebo 2.6 +/- 0.17 L 200ug BID 3.3 +/- 0.12 L 1000ug BID 3.5 +/- 0.15 L	"These results suggest that the inhibitory effect of inhaled beclomethasone on TDI-induced late asthmatic reactions and increased responsiveness is dose-dependent."	Small numbers. Data suggest treatment with beclomethasone can be beneficial in employees with OA and TDI exposure.
Marabini 2003 Longitudinal study No mention of industry sponsorship or COI.	NA	N = 10 subjects sensitized to TDI, flour, wood, or cereal	Beclomethasone 1,000 ug Salmeterol 100 ug Salmeterol PRN	No statistically significant differences in any of the morbidity outcomes were found between the beginning of the study and each follow-up time point. No subjects recovered completely.	"…as workers often have to remain exposed to the environmental course of their mild-to-moderate persistent OA, regular treatment with inhaled corticosteroids and long-acting bronchodilators is recommended."	50% drop out rate. Minimal description of inclusion and exclusion criteria. The patients were from different professions, different exposures. No quantifiable data on exposure. Data

						suggest treatment is beneficial in OA, even with continued exposures.

MANAGEMENT OF OA WITH IMMUNOTHERAPY

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Patriarca 2002 Case-control study No mention of industry sponsorship or COI.	2.0	N = 24 (17 had asthma)	Active group had sublingual SIT with latex extract, treatment was 4 days for desensitization and then a continuous maintenance latex exposure.	Subligual, cutaneous and mucous challenges became negative in 12/12 active patients. They were able to wear latex gloves for 6 hours. No adverse events to treatment reported.	"We believe that our protocol of subligual rush desensitization provides a new important therapeutic approach to latex allergy, without clinically detectable side effects, in our study population."	Asthma status not well described. Minimal baseline information provided. Treatment of "control" group not well described. Data suggest subligual SIT to latex allergy can be beneficial to health care workers and others in allowing continued exposure.
Cistero 2004 Case series	NA	N = 26 with cutaneus latex allergy with some respiratory symptoms	All received SIT subligual therapy	Both glove-use test and rubbing test improved significantly after 10 weeks of treatment p<0.05. No change detected for SPTs.	"The long-term effect of the treatment deserves further investigation…Tolerance of sublingual SIT is better than tolerance for injective therapy."	No control or randomization. Asthma not well described.
De jong 1999 Case series	NA	N = 11 with anaphylaxis to bumblebee venom	All received venom immunotherapy (VIT). Maintenance dose reached in 5-8 weeks.	Follow up period was 1.5-5 years. All had decreased skin test reactivity after 1 year of immunotherapy.	"Immunotherapy with bumblebee venom is safe and effective, and is comparable with honeybee and yellow-jacket venom immunotherapy."	Small numbers. No asthma patients. No control group or alternative treatment group.
Leynadier 2000 RCT No mention of industry sponsorship or COI.	NA	N = 17 (9 had asthma) sensitized health care workers to latex	Active group received SIT vs. placebo.	Patients in active group had lower rhinitis score p<0.05, conjunctivitis score p<0.05, and cutaneous score p<0.03. Asthma symptoms not significantly different between groups up to 12 months of treatment.	"Latex-specific immunotherapy may allow sensitized personnel to remain at work, but further trials need to be conducted in a larger number of patients."	Small numbers of asthma patients. There was no benefit after 12 months of therapy in asthma symptoms.

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

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