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Diagnosis and Management of Work-Related Asthma

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Prepared by:
University of Alberta Evidence-based Practice Center
Edmonton, Alberta, Canada

Jeremy Beach, MBBS, MD, FRCP (Edin), FFOM, FRCP (C)
Brian H. Rowe, MD, MSc, CCFP (EM), FCCP
(Principal Investigators)

Sandra Blitz, MSc
Ellen Crumley, MLIS
Nicola Hooton, BSc
Kelly Russell, BSc
Carol Spooner, BScN, MSc

Terry Klassen, MD, MSc, FRCPC
(EPC Director)

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Kenneth S. Fink, M.D., M.G.A., M.P.H.
Director, EPC Program
Agency for Healthcare Research and Quality

Margaret Coopey, R.N., M.G.A., M.P.S.
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

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Structured Abstract

Context: Approximately 5 to 15 percent of adult onset asthma is thought to be occupational asthma (OA).

Objectives: To systematically review literature regarding the diagnosis and management of OA, and specifically, to compare specific inhalation challenge testing (SIC) with alternative tests, and to review management, including reduction or cessation of exposure.

Search Strategy: Electronic databases and trials registries were searched. Additional references were identified by bibliographic searches of included studies, hand searches of conference proceedings, and contact with authors.

Selection Criteria: ***Population:*** De-novo OA or a previous diagnosis of asthma that was exacerbated at work. ***Study design:*** Controlled clinical trials, prospective or retrospective cohort, cross-sectional, case-series. ***Diagnosis:*** *Intervention*: At least two diagnostic tests, including one or more from a pre-determined hierarchy of 'reference standard' tests. *Outcomes*: 2 x 2 or 2 x 1 table, sensitivity, specificity, likelihood ratios, time to diagnosis, cost of diagnosis, and adverse effects. ***Management:*** *Intervention*: Pharmacological treatment, removal, reduced, or continued exposure. *Outcomes*: Pulmonary function, medication use, quality of life, symptoms, economic consequences, and adverse events.

Data Extraction: Two researchers independently extracted data.

Data Analysis: ***Diagnosis:*** Pooled sensitivities and specificities for sensitizer-induced OA with 95% confidence intervals (CI) were derived using a random effects model. ***Management:*** Weighted pooling of means and standard deviations to combine results within studies. Quantitative analysis was not conducted due to heterogeneity.

Main Results: One-hundred and twenty-four unique diagnostic studies and 65 unique management studies were included. Much of the evidence relates to sensitizer induced OA. ***Diagnosis:*** Among the high molecular weight (HMW) asthmagens compared to SIC, non-specific bronchial provocation (NSBP) test, skin prick test (SPT), and serum specific IgE had sensitivities above 73 percent. The specificity was highest between serum specific IgE versus SIC (79.0 percent [95% CI: 50.5 to 93.3 percent]). The highest sensitivity among low molecular weight (LMW) asthmagens occurred between SPT and SIC (72.9 percent [95% CI: 59.7 to 83.0 percent]), but this applied only to LMW sensitizers for which SPT could be performed. When compared to SIC, serum specific IgE and SPT had similar specificities (88.9 percent [95% CI: 84.7 to 92.1 percent] and 86.2 percent [95% CI: 77.4 to 91.9 percent], respectively). For HMW asthmagens, a combined positive test result to NSBP test and SPT versus SIC yielded modest sensitivity (60.6 percent [95% CI: 21.0 to 89.9 percent]) yet high specificity (82.5 percent [95% CI: 54.0 to 95.0 percent]). ***Management:*** Removed workers showed improved lung function and decreased non-specific broncial responsiveness at follow-up; exposed workers were either no better or worse. Lack of data prevented conclusions about the effectiveness of reducing

exposure. Removed workers suffered from reduced income and/or unemployment. Fully or partially exposed workers also appeared to have reduced earnings over time.

Conclusions: ***Diagnosis:*** Single NSBP test, specific SPT, or serum specific IgE testing alone is insufficient to diagnose OA. While positive results would increase the likelihood of OA, a negative result would not exclude OA. The literature supports the concept of combined testing; however, additional research is required to determine which combination of tests would result in sufficient sensitivity and specificity that it could replace SIC. ***Management:*** OA appears to be slow to resolve, and may worsen irrespective of subsequent exposure status. Patients who are removed from the workplace rarely experience complete resolution, may require medications, and experience continued airflow limitation. Standard treatments for asthma appear to be effective in OA; however, there is limited research.

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The Appendixes and Evidence Tables cited in this report are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/asthmawork/asthwork.pdf

Evidence Report

Chapter 1. Introduction

The Problem of Work-Related Asthma

What is Occupational/Work-Related Asthma?

Occupational asthma (OA) is a heterogeneous clinical syndrome characterized by work-related symptoms, airway inflammation (partially or completely reversible), bronchoconstriction, and hyper-responsiveness induced by workplace exposures (asthmagens). In contrast to non-occupational asthma, the differentiating feature of occupational asthma is the causal asthmagen is a substance in the occupational environment.[1] The symptoms of OA are similar to non-occupational asthma and include wheezing, cough, dyspnea, and impaired quality of work and non-work life. More than 250 asthmagens have been implicated and identified as causative agents in the development of OA (e.g., di-isocyanates, western red cedar, enzymes, snow crab, latex, flour, and laboratory animals). However, there are likely a variety of workplace asthmagens that have yet to be identified. An attempt has been made to classify the majority of the known asthmagens into categories based on their molecular weight: high molecular weight (HMW; $\geq$ 5000 Daltons) versus low molecular weight (LMW; <5000 Daltons) compounds, as this is probably important in their mechanism of action.[2] Due to the nature and complexity of workplace exposures, this is not always possible. Examples of HMW asthmagens include flour and latex; common LMW asthmagens are di-isocyanates, metals, and dyes.[1]

OA can be broadly classified into two categories: OA with latency and OA without latency. Latency periods are observed in all instances of immunologically mediated asthma, even though the immunological mechanism may not yet have been clearly identified.[2] The latency period, which represents the time between the first exposure and onset of first symptoms, can range from weeks to years. When a worker has OA with latency, a specific inhalation test with the causal agent will usually be positive and often an immunological response for HMW and some LMW asthmagens is identified with specific skin prick tests (SPT) and/or serum specific IgE antibody testing. Generally, serum specific IgE antibodies, biomarkers for sensitization to the specific asthmagen, have been identified for HMW compounds; serum specific IgE antibodies associated with LMW OA have yet to be fully characterized, as the antibodies have yet to be discovered or occur in only a small portion of workers.[2] The need to produce appropriate hapten-protein conjugates is probably a common reason for the failure to detect antibodies to LMW agents. OA with latency for which serum specific IgE antibodies have been identified is referred to as IgE associated.

OA can also exist without a latency period and can occur after a single large exposure to irritant gases, fumes, or chemicals, such as nitrogen oxide, ammonia, and chlorine.[3] This type of exposure results in reactive airways dysfunction syndrome, or RADS. Occupational asthma has also been reported to occur in few instances from repeated exposures to lower doses of 'irritant' or non-sensitizing agents.[4] After exposure to an irritant, the asthmatic reaction occurs within a short time.[5] Since there is no sensitization, the battery of diagnostic tests for RADS does not include specific immunological tests, and specific inhalation challenge (SIC) is not

used. OA without latency is less common; it is believed to represent between 5 and 15 percent of all OA cases.[1,6,7]

For the purpose of this report, OA with and without latency and work-aggravated asthma were defined in concordance with the American College of Chest Physicians (ACCP) and are described in Table 1:

Table 1. Definitions of work-related asthma

Term	Defining Features
Occupational asthma with latency of allergic or presumed immunological mechanism	There is an immunologic/hypersensitivity component and the diagnostic tests include measures of specific sensitization (e.g.,SIC, skin prick test, serum specific IgE).
Occupational asthma without latency	There is no allergic component and the worker is not "sensitized" to an agent, but rather, the agent causes an inflammatory response through an irritant mechanism.
Work-aggravated asthma (no latency period)	The worker has a previous or concurrent history of asthma that was not induced by an exposure found in the workplace. The worker is not sensitized to an agent at work, but is irritated by a "non-massive" exposure (e.g., cold, exercise, non-sensitising dust, fumes, or sprays) that provokes an asthmatic reaction.

Abbreviations: **SIC** = specific inhalation challenge

Through the remaining report, the term OA refers to OA with and without a latency period. This approach is similar to that of the American Thoracic Society guidelines.[8] Where possible, we have noted where the results are derived from a RADS population. We recognize that some studies may also include individuals with work-aggravated asthma within their study population, although it is rarely possible to identify if this is so. When the individual studies provide adequate detail, we have included the proportion of workers with a previous history of asthma and this may indicate work-aggravated asthma rather than OA.

Epidemiology of Occupational/Work-Related Asthma

Amongst developed countries, OA has become one of the most prevalent occupational lung diseases.[2] The annual incidence of OA is estimated to be 50 per million United Kingdom (UK) workers and 140 per million Finnish workers.[9] In France, the mean annual incidence rate was 24 per million workers.[10] Among American workers belonging to a Health Maintenance Organization who were at risk for developing OA, the annual incidence of new-onset asthma was 1300 per million.[11] A review of 43 attributable risk estimates from 19 counties found the attributable risk of OA to be 9 percent (interquartile range [IQR] 5–19 percent).[12] Because of the high prevalence of OA, it has been recommended that OA be considered a diagnostic possibility in all adults undergoing initial asthma evaluation. Surveillance programs indicate that OA accounts for 26–52 percent of reported occupational lung conditions in the UK[13] and British Columbia, Canada[14]. Perhaps of even greater concern is the suggestion that OA is potentially more common than studies have previously reported.[15] This seems likely, as several factors make OA identification difficult: 1) most industries expose workers to a number of potential causative agents and exposure may vary widely within the same workplace setting, making exposure assessment complex; 2) OA symptoms are variable and non-specific, with late reactions often occurring after the working day has been completed; 3) specific diagnostic tests have limited availability making exact diagnosis difficult; and, 4) the symptom onset is unpredictable.[15]

Greater than 250 synthetic and naturally occurring agents in a variety of work settings have been identified as relevant workplace exposures[16]; one of the most common exposures being di-isocyanates used in the production of coatings, adhesives, and foams in a wide variety of settings. It is estimated that up to 11 percent of workers exposed to di-isocyanates will develop bronchial hyper-reactivity.[17] Other commonly reported agents include flour, wood dusts, and latex.[2] While a large number of the causative agents have been identified, many more sensitizers and irritants are not well characterized and/or known, thus making the diagnosis of OA even more elusive.

The contribution of work-aggravated asthma cannot be ignored. Work-aggravated asthma occurs in workers with a previous or concurrent history of asthma and is characterized by worsening symptoms at work in response to chemicals or physical stimuli encountered at work, such as dust or cold air.[2] Among employed asthmatics in a Finnish city, Saarinen et al. found the prevalence of work-aggravated asthma to be approximately 30 percent.[18] In a recent study, the annual incidence rate of work-aggravated asthma among employed workers with current asthma was 3.9 cases per 100,000 each year.[19] The highest incidence rate occurred among workers employed in the public administration industry (14.2 cases per 100,000 each year). The most commonly responsible agents were mineral and inorganic dusts.

Because workers often need to be away from work due to their illness, and the cornerstone of treatment is removal from the workplace, OA creates a significant economic burden for individuals, industry, health care providers, and society. Using the human capital method, Leigh et al. calculated the cost of OA in the United States to be $1.6 billion annually.[20] Sometimes, impaired lung function does not improve or reverse, even after extended periods away from the causative agent[21] and this can result in permanent unemployment. The United Kingdom's Surveillance of Work-related and Occupational Respiratory Disease program found that 30 percent of people reported to have OA between 1989 and 1992 were unemployed when contacted later.[22]

Diagnosis of Occupational/Work-Related Asthma

An ideal diagnostic test has both a high sensitivity and specificity. Sensitivity refers to the test successfully identifying the proportion of the people who truly have the disease, i.e., the test detects true positives. A test has high sensitivity when it identifies nearly all of the people who truly have the disease. A test has high specificity when it successfully identifies most of the people who truly are disease-free as not having the disease, i.e., the test detects true negatives. In general, the sensitivities and specificities of diagnostic test comparisons are more robust if the test results are reproducible. OA is a difficult diagnosis to make for a variety of reasons. The first step is to determine that the patient has asthma and not a similar syndrome, such as upper respiratory tract irritation or vocal cord dysfunction. Having diagnosed asthma, the next step is to show a causative link with exposure to an asthmagen at work and this process often commences with obtaining a history or completing a questionnaire.

While SIC is often cited as a 'gold standard', as yet there is no definitive diagnostic test for OA. The applicability of SIC is currently limited by its availability.[23] In addition, the possibilities of false negative and positive results have been recognized.[5] For example, a false negative can occur when a worker with OA is exposed to multiple asthmagens and is subsequently challenged with the non-offending asthmagen.[2] Further, SIC testing is usually not

considered useful in determining a diagnosis of irritant induced OA. As a result, throughout this report we will refer to SIC as a ***reference standard***.

There are several alternative techniques, used in isolation or in combination, which can be used to diagnose occupational and work-related asthma. We have summarized SIC and the alternative techniques in the categories below:

Specific inhalation challenge (SIC). There are several methodologies used to perform SIC; however, in general the approach is designed to expose the worker to a suspected asthmagen in a controlled, non-work, test environment. When a suspected asthmagen is a water-soluble compound, the test subject may inhale it in its nebulized form.[24] Initially, low concentrations are administered for safety reasons until a response is obtained or a maximum concentration has been tested. When the asthmagen cannot be nebulized because of low solubility, some have proposed tipping powders of the suspected asthmagen from one tray to another in an attempt to mimic the work environment and generate a dry aerosol.[25] More recently standardized techniques have been developed to deliver dry powder aerosols. Another method is to conduct a simulated occupational-type specific provocation test.[26] For example, when colophony (e.g., used as a solder flux by electronics workers) is suspected to cause OA, the worker is exposed to simulated work tasks in a controlled laboratory environment while lung function monitoring is conducted in an attempt to determine changes in flow volumes or hyper-responsiveness.

The first step of SIC is to perform a control challenge with a substance similar in physical characteristics to the suspected asthmagen, but not likely to cross-react immunologically. When the fluctuations in forced expiratory volume in one second (FEV_1) following the control challenge are less than 10 percent, it is generally considered safe for the worker to undergo formal SIC testing with the suspected agent.[27] The duration or intensity of exposure is increased progressively, usually commencing with a small dose. Lung function is measured for a period of time after each incremental challenge dose. When challenging with LMW agents, challenges of increasing time durations should occur on separate days, as LMW agents often produce isolated, late asthmatic reactions. When challenging with an HMW agent several doses may be given on the same day as they more typically produce an early asthmatic reaction.[27] Conducting SIC in a blinded fashion and ensuring that the results are reproducible can minimize false positive results. A typical definition of a positive response is a decrease from baseline FEV_1 (i.e., control exposure) of 15–20 percent.

The greatest advantage of SIC is that a positive test confirms a diagnosis of OA caused by the particular agent. When the appropriate agent is applied and the test is positive in workers with respiratory symptoms that are thought to be work-related asthma, SIC testing is considered confirmatory. However, there are several disadvantages to SIC. First, the suspected workplace agent may not have been identified, which precludes testing. Second, SIC can only be conducted in specialty facilities and these are rare. For example, a survey conducted in 2000 indicated that only 15 centers capable of performing SIC exist in the USA and Canada.[23] Moreover, there are many complexities associated with developing a SIC laboratory. These include the expense of purchasing and operating the laboratory and the ability to generate the appropriate concentrations of the putative asthmagens. Third, SIC can only be performed in relatively stable workers (FEV_1 >60–70 percent of predicted and/or >2L[28]) because SIC may induce a very severe asthma attack.[29] A fourth disadvantage is the potential for false positives that can occur when SIC is performed in a worker with unstable asthma or when the worker

suffers from marked non-specific bronchial hyper-reactiveness, as the non-specific irritant reaction can masquerade as an early reaction to SIC.[27] Finally, SIC testing can take several days. While SIC can be performed as an outpatient procedure, carefully monitoring is required for several hours after the challenge and oxygen, bronchodilators, steroids, and intubation equipment should be available.[15]

History and questionnaires. There are several questionnaires used to assess respiratory health.[30-33] Questionnaires and histories may focus on specific job duties and work processes and inquire about improvement during weekends and/or holidays and worsening when returning to work.[2] The 1995 ACCP guidelines recommend three components of history taking: 1) history detailing onset of illness, temporal relationship between exposure and exacerbation, description of airway disease, and severity of asthma; 2) medical history describing pre- and co-morbidities and associated symptoms; and, 3) occupational and environmental history.[15] In addition, material safety data sheets (MSDSs) can be collected for the chemicals used in the workplace. MSDSs describe the ingredients, concentration, and toxic properties of chemicals in the workplace.

Questionnaires and histories are easily administered. However, respiratory symptoms are a common complaint among all workers, thus questionnaires and histories tend to lack specificity. They may also lack sensitivity. The following circumstances can produce falsely negative results: exposure to the agent is indirect and/or sporadic; workers may be reluctant to disclose symptoms for fear of losing employment; or, the worker does not relate progression of OA to a workplace exposure.[5] While the utility of history and questionnaires has been established for surveillance purposes and case finding in the event of symptoms of rhinitis and/or asthma, little research exists that examines their usefulness as a diagnostic test.

History and questionnaires are used to identify patients with relevant symptoms and workplace exposures known to cause OA. These patients will have a higher pre-test probability of testing positive to other tests of OA, as the subsequent test is being conducted in a pre-screened population. This is of importance in the later considerations in this review.

Serial lung function testing. Comparing serial lung function at work and away from work has previously been used to diagnose OA, especially when SIC test is unavailable. Until the advent of modern compact flow based spirometers, there were practical problems with the portability of the required equipment. Modern compact spirometers will allow for the measurement of lung function parameters including FEV_1 and forced vital capacity (FVC). One solution to this was to measure serial peak expiratory flow rate (PEFR) as portable and inexpensive equipment to measure this has been available for many years. The current ACCP guidelines recommend that PEFR be measured at least four times each day: upon waking, at noon, at the end of the working day, and at bedtime.[15] During each measurement, three PEFR measures are performed and recorded once all three readings are within 20 L/min.[15] The optimal duration of PEFR recording appears to be at least 4 weeks with a minimum of eight readings each day and at least 4 consecutive days in each work period.[34] However, obtaining records of that quality for that period of time is cumbersome. It is noteworthy that the sensitivity and specificity of this procedure was similar to records that were collected for at least four readings per day and at least 3 consecutive days at work for approximately 18 days.[34]

Serial lung function testing is an inexpensive diagnostic test that may show a temporal association between lung function and occupational exposure.[35] Despite these advantages,

serial lung function testing is still associated with a number of difficulties. Unfortunately, this test is dependent upon the worker's effort, requires them to reliably perform a forced expiratory maneuver and record the results accurately, and assumes worker honesty in performing and recording the results of the test.[2] Spirometers and peak flow meters incorporating a data recording device have helped with this to some extent. Another disadvantage of serial lung function testing is that it may be difficult to measure lung function for long enough periods while the worker is not at work to exclude OA. It is important the worker understands that late asthmatic reactions may occur several hours after exposure ceases, and they may not be detected during the monitoring period if only cross-shift measurements are made. In addition, serial lung function testing may be of no value among patients who are no longer exposed to the causative agent, as an asthmatic response should not occur, and when a patient has advanced OA, their lung function may become relatively fixed and not substantially improve during fairly short periods away from work. Finally, there are no universally accepted, standardized methods, for interpreting the results.[15]

Non-specific bronchial provocation (NSBP) testing. There are several different protocols used to measure bronchial hyper-responsiveness (BHR).[15] In general, the first step of an NSBP test is to measure baseline lung function. Then, a worker inhales increasing doses of a bronchoconstrictor agent; the most commonly used agent in North America is methacholine.[15] Numerous other agents have been used for NSBP testing, including histamine, acetylcholine, hypertonic saline, bethanechol, and distilled water. In the most frequently described test method (used in North America) the inhalation of methacholine or histamine begins at a concentration of 0.03 mg/mL for 2 minutes and is typically increased in a doubling fashion up to 32 mg/mL.[15] Following each inhalation, the worker's FEV_1 is measured. The predicted concentration causing a 20 percent decrement (PC_{20}) in FEV_1 can then be estimated by linear interpolation.[36] There is no standardized definition of a positive response; however, a commonly used definition is a decrease from baseline FEV_1 of 20 percent or more at a methacholine concentration of 8 mg/mL or less.[37] For other techniques, a predicted dose causing a 20 percent decrement (PD_{20}) in FEV_1 can be similarly estimated.

When compared to SIC, the main advantages of NSBP testing approaches are that they are reasonably inexpensive, easier to perform, available in a larger number of facilities, and have proven safety records. In addition, the test can usually be completed in an hour, or considerably less if using an abbreviated protocol. However, a positive NSBP test only proves that the worker has hyper-reactive airways, which is typical of asthma due to any cause and it is not a definitive test for OA.[27] Serial NSBP testing can be performed at work and away from work. If the test demonstrates airways hyper-reactivity while an individual is at work and a significant reduction after the worker has been away from work for several weeks, then it is more likely the worker suffers from OA. From consensus recommendations, a threefold or greater increase in PC_{20} or PD_{20} when away from work as compared to at work is often considered a positive test result for OA[38], while a twofold change is suspicious, but not universally accepted as definitive of OA.[5]

Immunological testing. Classically, asthma is often thought of as a specific IgE mediated disease, most prevalent in atopic individuals. Common immunological tests include SPT and estimation of specific IgE/IgG, which is often measured by using the enzyme-linked immuno sorbent assay (ELISA) or radio allergo sorbent test (RAST) techniques. For SPT, a positive

response is often defined as a 3mm or greater wheal reaction to a skin prick.[39] SPT can be used to identify responses to common allergens, which would signify atopy, or responses to specific antigens. Similarly, a high total IgE would be used to signify atopy, while increased specific IgE or IgG can also be measured. OA caused by the majority of HMW agents is specific IgE mediated and a positive SPT or raised specific IgE will be present. In contrast, LMW-induced OA is generally not specific IgE mediated, and consequently SPT or a measurement of specific IgE in this situation is not usually helpful[40], nor is it useful for irritant induced asthma or work-aggravated asthma.

Further, while specific immunological testing confirms that a worker is sensitized to a particular workplace allergen, sensitization is not synonymous with asthma, since sensitization to a workplace exposure can exist in the absence of OA. A further disadvantage of immunological testing is that few allergens known to cause OA are available in a standardized commercial form to be used for allergy testing. Importantly, there is no immunological test available for the majority of LMW compounds.

Total IgE and atopic status are used as screening tools but are not specific for OA or a particular workplace exposure, but rather identify atopy. Atopy is a risk factor for developing some types of sensitizer-induced OA.[41]

Measures of airway inflammation. Nitrous oxide is produced by a number of cells located in the respiratory tract, such as inflammatory and epithelial cells, and is detectable in exhaled air.[42] It is hypothesized that asthmatic workers have higher levels of exhaled nitrous oxide (eNO) caused by airway inflammation than the normal population. Measuring eNO is a non-invasive procedure; however, it has yet to be fully validated as an effective diagnostic test for OA, as eNO seems to be increased in a number of inflammatory lung disorders.[43] Also, eNO testing is confounded by inhaled corticosteroid usage, as workers receiving inhaled steroid treatment tend not to have increased eNO.[42,44] Finally, it is a difficult test to perform for workers, is costly, and its availability in North American is limited. Perhaps, once techniques to measure and record eNO are widely available and fully validated, such a method may be more appealing.

A second measure of airway inflammation is sputum induction with identification of eosinophils and other cells or inflammatory markers in the expectorated material. The direct cellular and chemical evaluation of airway inflammation has traditionally been undertaken using bronchial biopsies and bronchial alveolar lavage. In both these latter techniques, individuals are usually sedated and bronchoscopes are used to sample the airways either through biopsy or saline lavages, respectively. Given the cost, inconvenience, and invasive nature of these tests, other methods of identifying and quantifying airway inflammation have been developed. One alternative is the use of sputum to examine the cellular and chemical agents responsible for inflammation. In many cases, asthmatic workers cannot produce sufficient sputum for examination, and so induction is performed using nebulized saline. Once a sample is expectorated, it is prepared and examined microscopically for cellular composition and chemically analyzed using a variety of techniques. The most important cells in the sputum include eosinophils and neutrophils. Standard normal concentrations of both have been reported[45] and these can be used to evaluate the samples.

This technique is safe and the repeatability of the technique has now been shown.[46] In the correct setting (qualified technologist, laboratory, and interpretation) this technique has been

shown to provide useful information about the underlying inflammatory activities in the airway and may be incorporated into the diagnostic testing options available for OA.[47,48]

In OA, induced sputum markers have been used to determine changes in cellular make-up between pre- and post-exposure samples.[49] This technique shows some promise for agents or circumstances in which SIC cannot be performed. A significant change in eosinophil and/or neutrophil concentration post-exposure signifies an airway response related to the asthmagen.

Management of Occupational/Work-Related Asthma

Once OA is identified, the general recommendation has been to remove workers from the workplace rather than introduce medications to control their symptoms.[15] There are, however, several different approaches used to manage OA. Firstly, workers can be treated pharmacologically in a manner that is similar to those with non-occupationally induced asthma. However, additional lung function deterioration may not be prevented in workers who receive pharmacological treatment and yet remain exposed to the causative agent.[50] Secondly, various mechanisms can alter the worker's environment to reduce exposures to an "acceptable" level by using personal protective equipment (PPE), making engineering changes to the workplace (e.g., improved ventilation, changing production materials or processes, etc.), or administrative changes to work tasks. Additionally, the worker can be relocated to a different job, or to a different area of the workplace, or it may be possible to substitute a non-hazardous agent for the causative agent in use. The final, and most drastic, management option is to remove the worker entirely from workplace. Removal from the workplace should ensure that exposure to the causative agent is ended completely which is considered by many to be the cornerstone of therapy; however, workers may not wish to be removed for financial and social reasons. In practice, it seems that many workers need to be removed from the workplace. Within 6 years, approximately one-third of workers are unemployed after their initial confirmed diagnosis of OA.[22,41] For those who are able to return to work, close medical follow-up is required to ensure that lung function does not continue to deteriorate at a rate quicker than would be anticipated as due to age alone.[2]

Reducing exposure. Reducing workplace exposures may benefit not only workers with OA, but also those that may go on to develop OA in the future[40]; however, not all workers with OA benefit similarly from this approach. Reducing exposure levels has been hypothesized to be of particular use in irritant-based OA where there is no allergic component and hence a more linear and predictable dose response relationship.[40] Workers with OA with latency (i.e., immunologically mediated) may often react to very low concentrations of the aetiological agent, and therefore effective management by reducing exposure levels is questionable.[2] The American Thoracic Society analyzed five studies that examined the effects of reducing workplace exposure on occupational and work-related asthma.[5] They found that OA improved or remained unchanged in approximately two-thirds of workers when exposure was reduced, while the other workers' asthma worsened.

One method to decrease exposure in the workplace is to reduce or eliminate the use of potential asthmagens from the workplace.[8] Compared to engineering changes, this method is advantageous because it does not require mechanical maintenance.[8] Examples of this method include using latex-free rubber gloves, latex gloves with lower protein content, or switching to

a spray paint that is di-isocyanate-free. However, it is not frequently applicable in practice as the substances used in a workplace rarely have an alternative that can easily be substituted.

Engineering or structural changes can decrease workplace exposure to an asthmagen. Such changes include building an enclosure for the process where the asthmagen is used, or the establishment of local ventilation that clears the asthmagen away from the worker's breathing space.[8] Administrative changes, such as job rotation, may also be useful in reducing exposure.

A third way to reduce exposure is to relocate the workers to a new job in an area of the building where the exposure is not present (or present in very low concentrations). The Americans with Disabilities Act recommends that large companies with adequate resources go to considerable effort to relocate workers with OA into an area or job with decreased exposure.[51]

Finally, exposure concentration can be reduced by the proper use of PPE. In order to be of value, PPE must be correctly worn, safely removed, properly maintained, and replaced as needed.[41] By creating a better atmospheric breathing environment for the worker, air-supplying respirators provide the highest level of protection.[52] The self-contained breathing respirator can protect against most exposures; however, it is cumbersome, expensive, and can not be comfortably worn for an entire work shift.[52] There is general consensus that PPE is more appropriate for managing irritant-induced OA with brief and infrequent exposure than sensitizer-induced OA for the reasons mentioned above.[8] PPE will reduce but not eliminate exposure and consequently is only recommended for short-term use.[8]

Removal from exposure. There have been numerous deaths reported among workers with OA who were not removed from exposure suggesting that complete asthmagen avoidance is important.[53] Previous authors have also suggested that for workers suffering from OA with latency (immunologically mediated OA), there is consistent evidence concluding that removal from the exposure results in an improved health outcome.[2,54] In addition, it appears that compared to late removal, earlier removal is associated with greater improvement in lung function and symptoms.[55,56] In contrast, workers with irritant-induced OA are more likely to be able to return to work and manage asthma pharmacologically.[5]

However, removal from the workplace has significant deleterious effects on the income and financial stability of the individual affected, as well imposing costs on the employer.[57,58] OA claims are also a financial burden to the government; the average accepted claim in Quebec, Canada in the early 1990's was approximately $50,000.[59]

Pharmacological treatments. Pharmacological treatment of OA does not differ from chronic non-occupational asthma treatment. Asthma is managed through a variety of methods including trigger avoidance (reduction of trigger or complete avoidance), education, and pharmacological measures. Asthma is managed pharmacologically using two large groups of agents: relievers (bronchodilators) and preventers (anti-inflammatory agents).

Relievers. Relievers generally act on the beta-receptors in the airway to dilate the airways and relieve symptoms. Examples of these agents include short-acting beta-agonists (SABA) such as salbutamol (Ventolin®) or terbutaline, long acting beta-agonists (LABA) such as salmeterol (Serevent®) and formoterol (Oxese®, Foradil®), and anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®). These agents may be taken for relief of symptoms or prior to work to avoid the drop in FEV_1 that normally occurs in workers

suffering from OA. There is some evidence that regular use of LABA agents, when administered with inhaled corticosteroids, can improve chronic asthma control.[60] Mono-treatment with LABA is not recommended. There is limited evidence that regular use of anticholinergic agents improve chronic asthma control.[61]

Preventers. Broadly, there are a number of preventers from which physicians and workers may choose to decide upon for therapy (corticosteroids, combination agents, leukotriene receptor antagonists or modifiers, and mast cell stabilizers):

- *Corticosteroids (CS).* Corticosteroids work by reducing inflammation, up-regulating beta-receptors, and decreasing airway edema by reducing capillary permeability. There are a variety of agents and delivery methods and doses of corticosteroids; however, the two main methods of delivery are systemic and inhaled. Systemic corticosteroids are effective in intravenous, intramuscular, and oral forms; oral is clearly the preferred method of delivery due to convenience, cost, and worker's adherence. However, long term systemic CS are associated with severe adverse effects, such as osteoporosis, skin changes, cataracts, impaired glucose regulation, and fluid retention (so called: moon-face and buffalo hump appearance). Prior to the introduction of inhaled corticosteroids (ICS), systemic CS agents were the mainstay for control of moderate-severe asthma. Since the introduction of ICS, these agents have largely replaced systemic CS as a treatment of choice.
- *Combination agents.* ICS and LABA agents may be taken separately as individual inhalational agents, or as new combination inhalers. The current recommendation states that LABAs should not be used without an ICS. Fluticasone combined with salmeterol (Serevent®) has been marketed as Advair® (Seritide® in Europe); budesonide in combination with formoterol (Oxese®) has been marketed as Symbicort®. These agents deliver both ICS + LABA in each inhalation and have the benefit of increased compliance and ease of use. In general, these agents are reserved for the treatment of moderate-severe work-related asthma unresponsive to increasing doses of ICS.
- *Leukotriene receptor antagonists (LKTRA) or modifiers.* Discovery of the cystenyl leukotriene pathway has been an important advancement in asthma care over the past decade. The pathway is particularly important in the inflammatory cascade involved in asthma, especially for children and in aspirin-sensitive workers. Agents that inhibit or block cystenyl leukotriene pathway, called LKTRA, have been marketed and are available for mild-moderate asthma in adults and children. In general, these agents are restricted to add-on treatment of moderate-severe work-related asthma unresponsive to increasing doses of ICS.
- *Mast cell stabilizers.* Infrequently, mast cell stabilizers are used to control asthma. These agents are often used in exercise-induced bronchoconstriction (EIB) and in children, due to their non-steroidal nature. Given the availability of more effective agents, these agents are infrequently used now and generally restricted to EIB and mild asthma in children.
- *Other agents.* A variety of other agents are available to treat asthma including methyl-xanthines, antibiotics (especially newer macrolides) and a non-traditional agents. Due to their general lack of effectiveness, these agents will not be described in detail in this report.

Objectives of this Review

OA is a common respiratory disease that is difficult to diagnose and treat. Several societies have created clinical practice guidelines for OA (Table 2). However, many do not address or there is not consensus on the key components identified for this review. In summary; the guidelines do not agree upon the role of SIC testing for diagnosing OA; when removal from work is mentioned, it appears to be the recommended treatment.

Table 2. Summary of occupational asthma guidelines

Guideline	Year	Location	Reccomendations: SIC	Reccomendations: Removal
The Asthma Management Handbook [62]	2002	Australia	SIC is rarely available in Australia. All workers with suspected OA should have spirometry.	The cornerstone of effective management is cessation of further exposure. Assessment of permanent respiratory impairment and disability should be deferred until two years after exposure cessation.
British Guideline on the Management of Asthma [63]	2003	United Kingdom	Carefully controlled exposures to workplace agents and suitable controls is the gold standard for diagnosis. SIC should only be conducted in specialized units.	Removal from exposure should occur within 12 months of the first work-related symptoms of asthma. Delay assessment of long-term impairment for at least 2 years following removal from exposure.
British Occupational Health Research Foundation [41]	2004	United Kingdom	A diagnosis of OA can generally be made without SIC testing. SIC is indicated when the worker's management is dependent upon knowing the exact cause of OA.	Symptoms and bronchial hyper-responsiveness may or may not improve when the worker is removed from exposure. Potential for a completely recovery is highest when the worker is removed early from exposure (relcoation or substitution of the hazard).
Canadian Asthma Consensus Report [64]	1999	Canada	Not mentioned	Once the diagnosis of OA has been confirmed, the worker should be removed from exposure to the causative substance.
Canadian Thoracic Society Guidelines for Occupational Asthma [54]	1998	Canada	Use of challenge tests are included as part of the diagnostic tests when needed.	Workers with confirmed OA due to a sensitizer should have no further respiratory exposure. The best medical prognosis occurs with early and complete removal from exposure.
The Diagnosis and Treatment of Adult Asthma [65]	2002	New Zealand	Not mentioned	Not mentioned
Global Initiative for Asthma [66]	1996	United States	Confirmation of OA should ideally be made with measurements such as PEF monitoring at home and at work or with supervised inhalation challenge.	Complete avoidance of exposure is mandatory to permit remission of OA.
Guidelines for Assessing and Managing Asthma Risk at Work, School and Recreation [8]	2004	United States	Assessing the impact of workplace exposures includes determining the pattern of symptoms, specific immunologic responses, and airway physiology. When a pattern of symptoms or airflow limitation in relation to work is not clearly identified, specialized tests including SIC may be essential for diagnosis.	Prompt and strict exposure control should be recommended when OA is induced by a workplace sensitizer, In some circumstances, such as LMW isocyanates, the individual should be removed from the workplace.
Long-term Management of Asthma [67]	2001	Finland	Not mentioned	Not mentioned
National Asthma Education and Prevention Program [68]	2003	United States	Not mentioned	Not mentioned

Table 2. Summary of occupational asthma guidelines (continued)

Guideline	Year	Location	Reccomendations: SIC	Reccomendations: Removal
The Primary Care Management of Asthma in Adults [69]	1999	United Kingdom	Not mentioned	Not mentioned

Abbreviations: **OA** = occupational asthma; **PEF** = peak expiratory flow; **SIC** = specific inhalation challenge; **LMW** = low molecular weight

The first aim was to review the diagnostic approaches for occupational asthma. Many studies have examined the utility of various diagnostic techniques that attempt to differentiate OA from non-occupational asthma. However, there is variability in study methodology and definitions of what constitutes a positive test, and a systematic review and meta-analysis of the existing literature is required to determine the most appropriate diagnostic technique and identify which workers should be undergoing SIC testing. The objective of this review was not to examine the utility of the different tests in screening for OA, such as might be performed in a working population potentially exposed to an asthmagen, but rather to reflect how the tests might be used in the clinical diagnosis of OA.

Similarly, the best methods for managing OA have yet to be established. As discussed above, there are various techniques for treating OA and many studies have followed cohorts of workers suffering from OA and measured markers of disease progression. Thus far, it is unclear which treatment option best improves lung function and symptoms. Also, it has yet to be established whether complete removal from exposure, with its attendant social and economic consequences, is imperative in all types of OA.

It was our objective to systematically gather the existing evidence to determine which diagnostic methods are effective at determining a case of OA and what the optimal treatment is for such workers.

Key Questions

The American College of Chest Physicians put forth the following four questions:

1. What is the best diagnostic approach for a patient with suspected occupational asthma? What are the advantages of SIC testing versus peak flow monitoring, serial methacholine challenges, immunological testing, or spirometry in making the diagnosis of occupational asthma?
2. In what situations would specific inhalation challenge testing provide additional useful diagnostic information?
3. Which treatment is most effective for asthma that is occupationally caused, such as removal from work environment versus reduced exposure through modification and treatment with optimal asthma anti-inflammatory medications (e.g., inhaled steroids)?
4. Must patients with asthma that is occupationally caused or aggravated be removed from the workplace environment to control symptoms and/or disease progression?

Chapter 2. Methods

Methods for the Systematic Reviews

Literature Search

Two medical librarians identified appropriate databases to search and developed search strategies based on the following terms: asthma, lung disease, respiratory disease, occupational disease, occupational exposure, worker, work-related, leave work, reduce exposure, personal protective equipment, pharmacological treatment, inhalation challenge, peak flow, forced expiratory flow rates, bronchial provocation test, medical history taking, diagnostic techniques, sensitivity, specificity, predictive value, and, likelihood function. A filter was applied to the search output to remove studies pertaining to children (defined as those under the age of 18 years).

These search terms were adapted appropriately to search the following electronic resources: MEDLINE®, EMBASE®, Dissertation Abstracts®, Expanded Academic®, National Agricultural and Safety Database®, CINHAL®, Biological Abstracts®, Agricola®, and trials registries (http://clinicaltrials.gov/; http://www.centerwatch.com/; http://www.cochrane.org/index0.htm; http://www.controlled-trials.com/; http://www.update-software.com/National/; http://www.trialscentral.org/). Web of Science® was searched by tracking the most sentinel articles forward. The Cochrane Airways Review Group has developed an "Asthma and Wheez* RCT" register through a comprehensive search of EMBASE®, MEDLINE®, and CINAHL®. In addition, hand searching of 20 common respiratory care journals has been completed and relevant randomized controlled trials (RCT) have been added to the register. This database was examined for articles pertaining to therapy for OA. The detailed search strategies appear in Appendix A.♦

Authors of included studies that had published at least two papers were contacted regarding any missing studies. The reference lists of all included articles and an internal report that was recently prepared for the Workplace Safety & Insurance Board of Ontario, Canada entitled "The Diagnosis of Occupational Asthma" were searched for any new studies we might have missed. Conference proceedings from ACCP, American Thoracic Society, and European Respiratory Society scientific meetings were hand searched for the years 2001–2003. In addition, clinical practice guidelines were examined for the following organizations: ACCP, American Thoracic Society, Canadian Asthma Consensus Guidelines, European Respiratory Society, Thoracic Society of Australia and New Zealand, British Thoracic Society, World Health Organization, International Labor Organization, International Commission on Occupational Health, and the Canadian Thoracic Society Guidelines on Occupational Asthma. The search was not limited by language or publication status and is considered current until February 2004. If potentially relevant studies were identified as part of the review process and met the inclusion criteria, they were included.

Selection and Inclusion

♦ **The Appendices and Evidence Tables cited in this report are provided electronically at** http://www.ahrq.gov/downloads/pub/evidence/pdf/asthmawork/asthwork.pdf

All duplicate references were removed from the initial electronic searches. Each title, and when available, abstract was independently screened by two reviewers. Using general inclusion criteria, that is, primary research describing the diagnosis and/or management of OA, each study was classified as "include", "exclude", or "unclear". An occupational medicine specialist with an interest in occupational asthma and an asthma researcher then screened the references identified as "include" and "unclear" and the full text of the potentially relevant articles were retrieved. Specific inclusion criteria pertaining to the diagnosis and management of OA were developed (Table 3, Appendix B). For example, articles involving workers with respiratory symptoms who were referred for assessment of OA at a pulmonary clinic were included. Similarly, if a group of workers were screened using a survey method, and only those with respiratory symptoms were reported (for diagnostic or treatment studies), the study was eligible. In the event a screening study of workers at a work site was identified and if those with respiratory symptoms could not be ascertained from the publication or author communication, the article was excluded. In this manner, this systematic review excluded studies designed to screen for workplace respiratory symptoms.

Using standard data forms, two reviewers independently applied the inclusion criteria. Disagreements were resolved through discussion and consultation with an occupational and asthma researcher. In situations where the studies were attempting to diagnose or manage workers with OA, respiratory symptoms, and/or rhinitis, studies were included if the results were stratified by specific disease and data for those with OA extractable, or if >90 percent of the included workers suffered from suspected OA, and data for just those subjects with OA could not be identified, all data were included. Case-reports and series involving less than two workers were excluded, as were studies that exclusively examine two different ways of measuring the same diagnostic test (e.g., Occupational Asthma System computer system versus visual assessment of PEFR records).

If needed, the investigators contacted the authors to clarify that individual publications reported on discrete workers. In cases where multiple publications involving the same or a portion of the same workers were identified, the most recent publication of the largest cohort was selected and any additional, unique information from previous publications was incorporated. If a study was published within the last 10 years and relevant health outcomes were not presented by ongoing exposure status, but the authors presented exposure status as an outcome (e.g., number remaining at same workplace), the authors were asked to provide outcome data by exposure status.

Table 3. Inclusion/exclusion criteria for review on diagnosing and managing occupational asthma

Criterion	Diagnosis Review	Management Review
Study Design	Include: RCT, CCT, prospective or retrospective cohort, cross-sectional, case-series (>2 subjects) Exclude: case studies	Include: RCT, CCT, prospective or retrospective cohort, cross-sectional, case-series (>2 subjects) Exclude: case studies
Participants	Include: de-novo asthma or a previous diagnosis of occupational asthma that is exacerbated at work	Include: de-novo asthma or a previous diagnosis of occupational asthma that is exacerbated at work

Table 3. Inclusion/exclusion criteria for review on diagnosing and managing occupational asthma (continued)

Intervention / Control	Reference Standard: SIC, supervised workplace challenge, serial lung function tests, serial measurement of non-specific airway reactivity, immunological testing, clinical expert diagnosis and exposure to an "asthmagen". Other Comparison: above tests and/or sputum, metabonomics, nitrous oxide.	Removal from the workplace, relocated to a position with decreased exposure to the "asthmagen" within the same workplace, PPE, engineering controls, or pharmacological treatment.
Outcome Measures	Absolute numbers to construct a 2 x 2 (comparing two diagnostic techniques) or 2 x 1 (assessing one diagnostic technique in workers with a previous diagnoses of occupational asthma) table, sensitivity, specificity, or likelihood ratios, cost, time to complete diagnosis, adverse effects.	Pulmonary function, use of medication, healthcare utilization, frequency of exacerbations, QOL, symptoms, economic consequences, adverse events.

Abbreviations: RCT = randomized controlled trial; **CCT** = clinical controlled trial; **SIC** = specific inhalation challenge; **PPE** = personal protective equipment; **QOL** = quality of life

Quality Assessment

Assessment of the methodological quality of included studies was completed independently by two reviewers, using a variety of methods of assessment based on the review topic as follows:

Diagnosis review. The methodological quality of each included diagnostic study was completed using a quality tool developed from Lijmer's empirical research examining biases in diagnostic studies (Appendix B). The quality tool was comprised of 12 questions and pilot tested by the research team prior to employment. Empirically validated questions included study design (case control versus cohort), levels of blinding of measurements, use of appropriate reference or gold standard, an adequate description of the reference standard and test(s), thorough description of the study population, and the occurrence of differential reference bias.[70] In addition, information regarding the occurrence of partial verification bias, timing of data collection, method of worker selection, reporting of inter-rater reliability, and the method of reporting results was also captured. Discrepancies were resolved through discussion. Whether or not the authors mentioned that medication was terminated (or attempted) before testing was considered an additional marker of methodological quality.

Management review. The quality of each included cohort therapy study was independently assessed using Downs and Black's partially validated "Checklist of the assessment of methodological quality of both randomized and non-randomized studies of health care interventions" (Appendix B).[71] This tool is composed of 28 questions that evaluate reporting (10 questions, total score 11), external validity (three questions, total score three), internal validity-bias (seven questions, total score seven), internal validity-confounding (six questions, total score six), and power (two questions, total score two). The maximum total score was 29 indicating high quality and the lowest possible score was 0 indicating low quality. The reviewers, asthma researchers, and occupational health specialist developed *a priori* guidelines regarding the application and implementation of the quality tool. In the event that a question was not applicable to the study design, the question was answered "no". Also, the funding

source was recorded for each study. Controlled clinical trials (CCT) were assessed with a second tool, the Jadad scale.[72] This validated five-point scale assesses randomization, double-blinding, and the reporting of withdrawals and dropouts. In addition, concealment of allocation was evaluated to be "adequate", "inadequate", or "unclear".[73] When there were multiple publications of the same workers, methodological quality was assessed on the most recent or largest study. Discrepancies were resolved through discussion.

Data Extraction

Two data extraction forms were developed, piloted, and used to extract data from the group of diagnostic or therapy studies (Appendix B). Data were extracted by one reviewer and checked for completeness and accuracy by a second reviewer. When data were presented graphically, the graphs were scanned into CorelDraw® (Version 9; Ottawa, Canada) to facilitate extracting the data points with greater accuracy. Discrepancies were resolved through discussion and input from the task leaders. Whenever possible, a task leader classified the exposures as high and low molecular weight based on published information.[74]

Diagnosis review. Data were extracted regarding the study population characteristics, diagnostic tests, and results (e.g., sensitivity, specificity, likelihood ratios [LR], etc.). The following patient characteristics were recorded: probable cause of OA, patient source, sex, race, duration of exposure and symptoms, history of atopy/allergy diagnosis, smoking status, history of asthma, medication usage, and baseline pulmonary function. For each diagnostic test, the methodology, timing, inclusion/exclusion criteria, medication use, and definition of a positive test result were extracted.

The reference standard was assigned an 'evidence grade' as per our Levels of Evidence (Appendix C) designed in consultation with the technical expert panel (TEP). Additional outcomes included cost of diagnosis, time to complete diagnosis, and presence of adverse events. Where possible, a 2 x 2 diagnostic table was constructed for the reference standard versus the comparison test(s). Where a comparison involved two 'reference' tests the highest ranked test for evidence grade (see Appendix C) was used as the reference test. The sensitivity and specificity were extracted or calculated from the 2 x 2 table.

Management review. Details concerning worker characteristics, interventions, tests used to measure outcomes, and outcomes were recorded. Workers were described by their sex, age, race, smoking status, history of asthma, history of atopy, probable cause of OA, diagnostic tests used to determine OA, duration or exposure and symptoms, current medication, and severity of asthma. Where applicable, appropriate workers characteristics, such as smoking status, at follow-up were documented. Interventions were described by change in exposure (decreased or removal from exposure), type of protective equipment employed, or the type, dosage, route, and timing of pharmaceutical treatment. The type of test, method followed, and when appropriate, definition of a positive test (e.g., follow-up NSBP test) was recorded for each of the tests used to measure outcomes. Outcomes extracted included lung function, symptoms and medication scores, and economic status. The length of follow-up was also recorded.

Data Analysis

All data analyses were performed using SAS® (Version 8.2, Cary, USA). Graphics were produced using S-Plus® (Version 6.0, Seattle, USA).

Diagnosis review. Whenever possible we re-created a standard 2 x 2 table (or 2 x 1 if only reference standard positive or reference standard negative subjects were included) for each comparison test or combination of tests. This was not possible when individual patient data (IPD) was presented without a documented cut-off value indicating the presence (i.e., a positive result) or absence of OA. When sensitivity and specificity could be calculated for more than one cut-off value or definition for the same diagnostic test, we included the table that produced the highest test efficiency defined as the proportion of correctly identified patients (reference standard positive and reference standard negative) by the comparison test.[75]

Sensitivity and specificity were calculated for each study using standard formulas. Results were pooled using the inverse variance method for random effects to calculate an overall estimate of sensitivity and specificity.[1] We pooled data from 2 x 1 tables separately (reference standard positive or reference standard negative only) from studies that presented data from which a 2 x 2 table could be generated (both reference standard positive and negative). Furthermore, results were only pooled for studies of similar molecular weight (HMW or LMW) asthmagens. When sensitivity and specificity could both be calculated, these values were plotted in receiver operator curve (ROC) space. When there were a sufficient number of studies (n>10), a summary ROC (SROC) curve was derived and added to the plot.

One drawback of pooling sensitivity and specificity is that it does not take between study heterogeneity into account. There are many sources of heterogeneity in any review, and a specific source for diagnostic reviews is that variation in sensitivity and specificity that results from heterogeneous definitions of a positive test result.[76,77] When the information was reported, we recorded the exact definition used to define a positive test and this information is presented in an evidence table (Appendix E). The inclusion of different asthmagens within each molecular weight category was an additional source of heterogeneity in this review. The study specific asthmagen is listed with the results on the test specific plots described later in this report.

Management review. Due to the extreme heterogeneity of the reporting of outcomes in the treatment articles, no meta-analytic techniques were employed and the summaries are descriptive in nature. Nonetheless, some re-organization of the data as reported was required to homogenize the information provided in the descriptive summary.

For continuous outcomes such as FEV_1 and some measures of BHR, a mean was used as the measure of central tendency when available. In cases where the mean was not reported or could not be obtained from an accompanying graph, the following substitutions (in order of preference) were used: median and midpoint of the range or IQR. When possible, a mean was calculated from IPD when it was available in a tabular format or plotted on a graph.

Similarly, standard deviation (SD) was used as the measure of variation. In cases where the SD was not reported or could not be determined from a graph, the following substitutions were used: (75^{th} percentile – 25^{th} percentile)/1.35 when IQR was reported; (maximum – minimum)/4

[1]**The following software was used for these calculations: Lau J. Meta-Test version 0.9. Tufts-New England Medical Center, Boston, 2003 and the Meta package for R (http://cran.r-project.org/).**

when range was reported and sqrt(n)*standard error of the mean (SEM) when SEM was reported. If individual data were available in tabular or graphic form, the SD was directly calculated.

Baseline characteristics and outcomes were grouped in various ways for the studies. When possible the data were grouped according to exposure status in follow-up as follows: continued exposure, reduced exposure, or ceased exposure. We used the following formulas to combine data when necessary:

Exposure Group mean=$(n_1*mean_1)+(n_2*mean_2)+\ldots(n_k*mean_k)/(n_1+n_2\ldots n_k)$

Exposure Group SD=$sqrt(((n_1-1)*(SD_1)^2+(n_2-1)*(SD_2)^2+\ldots(n_k-1)*(SD_k)^2)/(n_1+n_2\ldots+n_k-k))$

Because it was usually not reported, the mean difference between baseline (diagnosis) and follow-up was calculated as the difference between the mean at follow-up and the mean at baseline. Standard deviation of the difference was estimated assuming a between patient correlation of rho=0.5 between the baseline and follow-up values using the formula:

$Var(A-B)=sqrt(VarA+VarB-2*rho*sqrt(VarA*VarB))$ where $Var(X)=SD(X)^2$

For economic outcomes, currency measures were converted into US dollar (USD) equivalents based on exchange rates for the reported currency in the year of the studies' publication (http://www.oanda.com/convert/classic).

Peer Review

Twenty-six occupational asthma and/or methodological experts were approached to peer-review the draft of this report. Twelve experts agreed to do so and 11 provided comments within the allocated time period. We considered their comments and amended this report accordingly. Peer reviewers are listed in Appendix F and will be available on the AHRQ Web site.

Chapter 3. Results

Literature Search

Using database specific search strategies, the following electronic bibliographic databases were searched: MEDLINE®, EMBASE®, CINHAL®, Web of Science®, Biological Abstracts®, Agricultural Index®, Expanded Academia®, Dissertation Abstracts®, Clinical Trials Registry®, National Agricultural Safety Database®, and the Cochrane Airways Group Trials Registry. Contact with the authors (Drs. Alvarez, Burge, Lemiere, Malo, Palczynski, and Park) generated an additional 33 potential studies. Eleven potentially relevant studies were found hand searching pertinent conference proceedings (ACCP, American Thoracic Society, and the European Respiratory Society). Additional studies were found in the reference lists of included studies. In total, 671 unique studies were reviewed. Study retrieval and selection is outlined in the flow diagram.

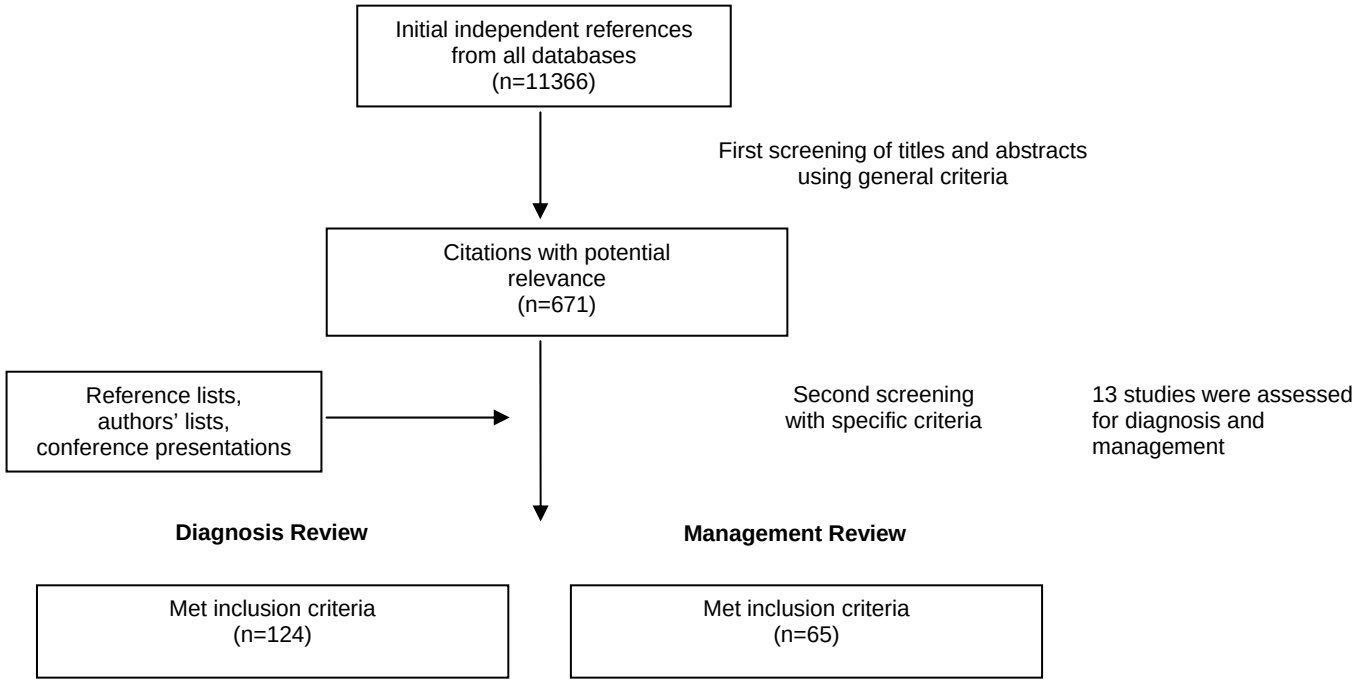
Studies were excluded for the following reasons: inappropriate study design (n=164); inappropriate topic (n=124); incorrect study population (n=63); inadequate data (n=58); or no tests or treatment (n=13). Upon further examination, seven studies within the diagnosis review did not provide sufficient detail to calculate a sensitivity and/or specificity, and subsequently were excluded.[78-84]

The majority of the included studies were of subjects with OA with latency (i.e., immunologically mediated). There are few studies examining the diagnosis or management of OA without latency (i.e., caused by irritants). Therefore, the bulk of the results pertain to diagnosis and management of sensitizer induced OA.

Within the diagnosis and management review, there were several cases where there appeared to be multiple publications involving the same, or a portion of the same, cohort of workers. In such situations, the most complete study was included, and where unique information was presented, additional outcomes were extracted from the other papers. A description of these cohorts and the main outcomes reported in each publication are detailed in Appendix D.♦

♦ **The Appendices and Evidence Tables cited in this report are provided electronically at** http://www.ahrq.gov/downloads/pub/evidence/pdf/asthmawork/asthwork.pdf

Flow Diagram. Study retrieval and selection for diagnosis and management of occupational asthma



* 38 studies were unobtainable or not translated

Diagnosis Review

Description of Included Studies

One hundred twenty-four unique cohorts were included in the diagnosis review (Appendix E: Evidence Table E-1; Table 6). The median year of publication was 1991 and all but 20 studies were published in English. Twenty-two studies were conducted in the UK, followed by 19 studies in each of Canada and Italy. The baseline characteristics of the patients are outlined in Evidence Table E-2. Excluding studies that only included patients with a confirmed diagnosis of OA, the prevalence of OA among studies including suspected OA cases ranged from 5 to 88 percent; the median prevalence of OA was 54 percent.

Evidence Table E-3 describes the reference and comparison tests. SIC was the most commonly identified reference standard; it was performed in 105 of the studies. The next most commonly used reference standard was clinical diagnosis. Over half of the studies (67) included workers exposed to LMW agents; HMW agents were investigated in 33 studies and the probable cause could not be classified in one study. Various chemicals were most often believed to be the agent responsible for OA, of which di-isocyanates were the most represented chemical. The second most commonly identified agent was wood dust. Not all studies had workers with a uniform exposure and/or type of OA: 23 studies included workers from several different occupations with various probable causes of OA. Eighty-five studies reported single NSBP test as one of their outcome measures. Other frequently reported outcomes were: atopy and/or specific SPT, serum specific IgE, eosinophil counts obtained either from serum or sputum, and serial PEFR. Only one study examined workers with RADS.

Methodological Quality of Included Studies

The methodological quality is described in Appendix E: Evidence Table E-4; Table 7. Workers were infrequently selected consecutively or randomly; 37 studies failed to report the selection method and the remaining studies used alternative methods, such as choosing some workers in a factory or some clinic patients. The majority of the included studies collected data prospectively. Data were collected retrospectively in 14 studies and whether the study was prospective or retrospective could not be established in six other studies. Blinded assessment of either the reference standard or comparison test occurred in 21 trials; however, only three studies reported that both the reference standard and comparison test results were assessed blindly. Partial blinding was inadequate in four trials. The remaining studies did not mention blinding status. The methodology used for the reference standard test, most commonly SIC, was adequately described in approximately 73 percent of the studies; the description was inadequate in the remaining studies.

Differential bias is likely to have occurred in 26 of the studies and could not be assessed in 18 studies; the other studies did not have this bias. Partial verification bias was present in 31 studies and it was unclear if it had occurred in a further 18 studies. Partial verification bias did not occur in the remaining 75 studies. Forty-one of the studies reported that workers stopped, or attempted to stop, asthma medication prior to diagnostic testing. Funding was not reported in 78 of the 124 studies. Among studies with one source of funding, funding was most commonly provided by a government agency; 10 studies had multiple sources of funding.

Quantitative Results

One hundred thirty-one publications reporting data on 124 cohorts met the inclusion criteria for the diagnostic component of this review. After selecting the most efficient comparison within a study for each comparison test, and ensuring that a comparison test was only reported once for a cohort, the most frequently reported comparison tests included single NSBP test (n=61), specific SPT (n=47), serum specific IgE antibodies (n=41), clinical diagnoses (n=9), serial pulmonary function tests (generally PEFR) (n=9), eosinophil count (n=6), and serial NSBP test (n=6).

In addition, some studies reported sufficient information to investigate the utility of combining comparison tests. These combinations primarily consisted of single NSBP test with SPT and/or serum specific IgE. For the most frequently reported comparisons, results based on the molecular weight of the suspected agent are summarized below and individual study results have been plotted in figures. In addition, pooled results from less frequently reported comparisons and combinations of comparison tests are reported. However, due to the between-study heterogeneity, which can be seen in the figures, pooled results should be interpreted with caution. Finally, because the majority of the workers included in the individual studies were screened-in, the results presented below are probably best interpreted as the patients also being "positive" for history, questionnaire, and/or referral to a specialist. For example, the comparison should be interpreted as screening and single NSBP test versus screening and SIC.

A summary of sensitivity and specificity of comparison tests that used SIC as the reference test is provided in Appendix H.

Single NSBP test versus SIC. Sixty-one studies reported sensitivity and/or specificity for single readings of NSBP testing compared to SIC. Individual study results for LMW, HMW and mixed agents are shown in Figures 1, 2, and 3 respectively. The sensitivity/specificity pairs are plotted in Figure 4. When we considered the methodological parameters of the studies, no clear patterns emerged (Appendix G).

Among the 37 studies that investigated patients exposed to LMW agents, 24 reported both sensitivity and specificity. The pooled estimate of sensitivity was 66.7 percent (95% confidence interval [CI]: 58.4 to 74.0 percent) and of specificity was 63.9 percent (95% CI: 56.1 to 71.0 percent). Pooled estimates for studies that reported only sensitivity were higher (n=13; 76.6 percent; 95% CI: 59.0 to 88.2 percent).

Of the 13 studies that reported results from investigations of HMW agents, 10 reported sensitivity and specificity. The pooled estimate for sensitivity was 79.3 percent (95% CI: 67.7 to 87.6 percent) and for specificity was 51.3 percent (95% CI: 35.2 to 67.2 percent). The estimated sensitivity in the five studies reporting only this data was similar (75.5 percent; 95% CI: 56.4 to 88.1 percent).

Nine studies reported results for various suspected agents of differing molecular weights and five studies reporting both sensitivity and specificity. For these mixed populations, the pooled estimate of sensitivity was 83.7 percent (95% CI: 66.8 to 92.9 percent) and specificity was 48.4 percent (95% CI: 25.9 to 71.6 percent). Sensitivity was lower in the three studies reporting only this value (43.7 percent; 95% CI: 10.9 to 83.0 percent).

Specific skin prick test versus SIC. Forty-seven studies reported comparisons of specific SPT to SIC.

Sixteen studies reported results of SPT using the following LMW agents: bleaching powder, reactive dyes, wood dust (exotic and western red cedar), chemicals, and di-isocyanates (see Figure 5). Among the five studies reporting both sensitivity and specificity, the pooled estimate of sensitivity was 72.9 percent (95% CI: 59.7 to 83.0 percent) and of specificity was 86.2 percent (95% CI: 77.4 to 91.9 percent). Sensitivity was lower in the 11 studies reporting only this result (51.8 percent; 95% CI: 28.5 to 74.4 percent).

Of the 16 studies that reported both sensitivity and specificity for patients exposed to HMW agents, the pooled estimate of sensitivity was 80.6 percent (95% CI: 69.8 to 88.1- percent) and of specificity was 59.6 percent (95% CI: 41.7 to 75.3 percent). Sensitivity was similar (80.9 percent; 95% CI: 60.5 to 92.1 percent) in the 10 studies reporting only that result. Results are shown in Figure 6.

Among the five studies that included patients exposed to various agents, the pooled estimates for sensitivity and specificity were lower than either high or low molecular weight agents. The pooled estimate of sensitivity was 63.0 percent (95% CI: 41.5 to 80.3 percent) and specificity was 59.2 percent (95% CI: 45.4 to 71.7 percent). Results are shown in Figure 7.

The sensitivity/specificity pairs for each molecular weight group are plotted in Figure 8.

Serum specific IgE antibodies versus SIC. Forty studies reported sensitivity and 19 reported specificity for serum specific IgE compared to SIC. Of those, 21 studies included patients exposed to LMW substances such as bleaching powder, reactive dyes, wood dust (exotic and western red cedar), chemicals, and, di-isocyanates (see Figure 9); 16 included patients exposed to HMW agents (see Figure 10); and three included patients exposed to substances with variable molecular weights (see Figure 11). The sensitivity/specificity pairs are plotted in Figure 12.

Eleven out of the 21 studies considering LMW agents reported both sensitivity and specificity; the pooled estimate of sensitivity was 31.2 percent (95% CI: 22.9 to 40.8 percent) and of specificity was 88.9 percent (95% CI: 84.7 to 92.1 percent). Of the 10 studies that only reported sensitivity, the pooled estimate was 35.9 percent (95% CI: 23.2 to 50.9 percent).

Sensitivity was higher in the studies where HMW agents were examined; the pooled estimate of sensitivity was 73.7 percent (95% CI: 63.9 to 81.0 percent) for the nine studies reporting sensitivity and specificity and 81.7 percent (95% CI: 57.8 to 93.5 percent) for the nine studies reporting sensitivity alone. The pooled estimate of specificity was 79.0 percent (95% CI: 50.5 to 93.3 percent).

The two studies using a variety of molecular weight agents reported both sensitivity and specificity. The pooled estimate for sensitivity was 85.1 percent (95% CI: 40.3to 98.0 percent) and of specificity was 61.2 percent (95% CI: 7.0 to 97.1 percent).

Combined results with single NSBP test, serum specific IgE, and specific SPT compared to SIC. When possible, results were combined for the most frequently reported comparison tests. In the first assessment, all tests in combination had to be positive for the combined result to be considered positive. If any result was negative, the combination testing was considered negative. We report results from studies reporting sensitivity and specificity for LMW and HMW agents.

When a single NSBP test and specific SPT were considered in combination, four studies investigated patients exposed to HMW agents.[85-88] The pooled estimate of sensitivity was 60.6 percent (95% CI: 21.0 to 89.9 percent) and of specificity was 82.5 percent (95% CI: 54.0 to 95.0 percent) respectively. Sensitivity was 100 percent (95% CI: 74.1 to 100 percent) and specificity was 80 percent (95% CI: 49.0 to 94.3 percent) in the one study that investigated green tea (a LMW agent).[89]

Single NSBP test and serum specific IgE results could be combined for only three studies reporting both sensitivity and specificity. For two studies of HMW agents, the pooled sensitivity was 35.6 percent (95% CI: 1.2 to 96.1 percent) and 84.6 percent specificity (95% CI: 48.2 to 97.0 percent). [86,87] The third study examined OA caused by isocyanates and resulted in 0 percent sensitivity (95% CI: 0 to 49.0 percent) and 100 percent specificity (95% CI: 61.0 to 100 percent).[90]

In a second analysis, the combination of a positive single NSBP test and either a positive specific SPT or positive serum specific IgE was considered positive. Three studies of HMW agents yielded results which could be combined in this manner [86-87] The pooled estimate of sensitivity was 60.4 percent (95% CI: 11.8 to 94.5 percent) and specificity 81.5 percent (95% CI: 47.8 to 95.5 percent).

Other comparisons. Nine studies reported serial pulmonary function tests versus SIC; all but one study[91] recorded PEFR. Of these, five studies investigated mixed agents and reported both sensitivity and specificity.[35,92-95] The pooled estimate of sensitivity was 63.6 percent (95% CI: 43.4 to 79.9 percent) and of specificity was 77.2 percent (95% CI: 66.5 to 85.2 percent). One study of a LMW agent reported 86.7 percent (95% CI: 59.5 to 96.6 percent) sensitivity and 90 percent (95% CI: 53.3 to 98.6 percent) specificity.[96] Two other studies only reported sensitivity resulting in a pooled estimate of 56.2 percent (95% CI: 17.2 to 88.8 percent).[91,97] Finally, one study of a HMW agent reported 100 percent (95% CI: 56.6 to 100 percent) sensitivity and no results for specificity.[98]

All nine studies that compared clinical diagnosis to SIC reported both sensitivity and specificity. Clinical diagnosis ranged from physician assessment to a combination of tests, which may have included pulmonary function tests, NSBP test, symptom questionnaires, etc. Five studies investigated LMW agents and the pooled estimate of sensitivity was 93.6 percent (95% CI: 85.0 to 97.5 percent) and of specificity was 68.9 percent (95% CI: 54.7 to 80.3 percent).[99-103] The pooled estimates of sensitivity and specificity were 93.7 percent (95% CI: 69.3 to 99.0 percent) and 32.3 percent (95% CI: 7.5 to 73.8 percent) respectively in the two studies reporting results for HMW agents.[104,105] Combined results of the two studies considering agents of various molecular weight yielded a sensitivity of 95.1 percent (95% CI: 86.8 to 98.3 percent) and specificity of 47.7 percent (95% CI: 26.7 to 69.7 percent).[106,107]

Six studies reported serial NSBP tests compared to SIC and all reported sensitivity and specificity. Pooled results from the three studies investigating mixed agents yielded 50 percent sensitivity (95% CI: 35.5 to 64.5 percent) and 66.8 percent specificity (95% CI: 53.3 to 78.0 percent).[92,95,108] Two studies involved only patients exposed to LMW agents; pooled sensitivity was 67.5 percent (95% CI: 42.6 to 85.3 percent) and specificity was 65.6 percent (95% CI: 41.1 to 84.0 percent).[109,110] A study of OA caused by oil seed rape flour (a HMW agent) yielded 100 percent sensitivity and specificity.[87]

Six studies reported eosinophil counts from sputum, blood, or broncho-alveolar lavage versus SIC of which four considered various agents causing OA. Of these, three[94,111,112]

reported sensitivity and specificity. The pooled estimate of sensitivity was 54.9 percent (95% CI: 23.7 to 82.7 percent) and of specificity was 72.3 percent (95% CI: 54.1 to 85.3 percent); one study reported 100 percent sensitivity only.[113] Two studies of LMW agents reported sensitivity only.[26,114] The pooled estimate of sensitivity was 53.1 percent (95% CI: 10.3 to 91.8 percent).

RADS. Only one study examined workers with RADS.[115] Fifty-six hospital workers were exposed to 100 percent acetic acid; within 24 hours eight workers met the RADS criteria. Eight months later, a questionnaire was administered to determine the degree to which workers experienced respiratory symptoms after the chemical spill. Fifty-one workers completed the survey. Approximately 9 months after the spill, a NSBP test was performed among 24 of the exposed workers, including seven of the eight workers who met the criteria for RADS (persistent respiratory symptoms). Four of the seven workers had a positive methacholine challenge, defined as provocative dose causing a 20 percent drop in FEV_1 [(PD_{20}) FEV_1] >20 percent (no dose cut-off was reported).

None of the included studies reported cost of diagnosis, time to complete diagnosis, or the presence of adverse events.

Management Review

Description of Included Studies

Cohort. There were 67 publications referring to 52 cohorts included in the review (Appendix E: Evidence Table E-5; Table 8). The median year of publication was 1996. Eleven studies were conducted in the UK, followed in decreasing order by Italy, Canada, and the United States. Two studies examined workers with RADS; the workers were exposed to sulfur dioxide in a pyrite mine explosion in one study[116] and pipefitters were exposed to chlorine at a paper mill over a 3 month period.[4] The baseline characteristics of the included workers are described in Evidence Table E-6.

The most commonly identified asthmagens in these studies were chemicals, of which 14 of the studies examined di-isocyanates. Thirteen studies included workers with OA caused by various agents. Workers were most often recruited from an OA clinic or the workplace. The median sample size of the included studies was 26 workers (range: 3–1011). Length of follow-up was variable within and between studies.

The interventions and outcomes are outlined in Evidence Table E-7. Twenty-nine cohorts reported results on one group of workers who all received the same intervention. Seventeen cohorts reported results from two intervention groups; three cohort studies reported on three intervention groups; and three cohorts reported on four intervention groups. The most common intervention was removal from the workplace (n=42 [81%]). Fourteen studies reported results for subjects who continued exposure and, reduced exposure was assessed in 18 studies. Eight studies examined the effectiveness of PPE, while two studies compared the use of medication. The most commonly reported outcomes were NSBP tests and pulmonary function tests. Other tests reportedly completed at follow-up visits included: questionnaires, SPT, SIC, and serum specific IgE.

Trials. Thirteen trials were included in this review (Appendix E: Evidence Table E-8). The median year of publication was 1990 and all but two trials[117,118] were conducted in Europe. Patients were not randomized to the treatment groups in four of the trials[119-122] and eight employed a crossover design.[117,119,120,123-127] The most common asthmagen studied was di-isocyanates[120,122,124-128], followed by flour[121,129]. Evidence Table E-9 describes the baseline characteristics of workers.

Evidence Table E-10 depicts the interventions and outcomes examined in the trials. Two trials assessed methods to reduce the level of asthmagen exposure[119,123], including using a respirator and using hypo-allergenic latex gloves. The remaining studies examined the efficacy of various drugs, including anti-inflammatory agents, bronchochodilators, and immunotherapy. Specifically, the types of drugs tested included: beclomethasone (four trials[117,125,126,128]), theophylline (two trials[124,126]), salbutamol (one trial[118]), indomethacin (one trial[122]), atropine (one trial[120]), nifedipine (one trial[127]), verapamil (one trial[126]), cromolyn (one trial[126]), fenoterol (one trial[129]), prednisone (one trial[122]), and immunotherapy (one trial[121]). All but one of the pharmacological trials was placebo controlled.[122] The length of study intervention and follow-up varied; three studies followed patients for at least 6 months[117,121,128] and the remaining studies were shorter. Response to SIC was a commonly assessed outcome and was measured in ten (77 percent) trials.[118,119,122-127,129,130]

Methodological Quality of Included Studies

Cohort. The mean Downs and Black score of the 52 included studies was 16.4 (SD 4.0) (Appendix E: Evidence Table E-11; Table 9) of a total possible score of 29. Table 4 depicts the mean scores within each component of the quality assessment tool.

Table 4. Summary of components of Downs and Black score

	Reporting	External Validity	Bias	Confounding	Power	Overall
Maximum Score	11	3	7	6	2	29
Actual Score Mean (SD)	8.2 (1.8)	1.6 (1.0)	3.9 (1.1)	2.3 (1.1)	0.5 (0.5)	16.4 (4.0)

Abbreviations: SD = standard deviation

Apart from one study, data were collected prospectively. Approximately half (27/52) of the studies provided some IPD. When reported, the most common funding source was provided by a government agency; 31 of the studies did not disclose their funding source and few were industry sponsored.

Trials. Of the thirteen clinical trials, the median Jadad score was 2 (IQR: 2, 3) (Appendix E: Evidence Table E-12). Concealment of allocation was adequately reported in two of the trials[117,129], and inadequately in four trials[119-122]. The method of concealing allocation was unclear in the remaining seven trials.[118,123-128] Six trials did not report their source of funding[118,119,121,123,127,129] and two trials were supported solely by government grants.[126,128] The remaining trials received grants from at least two different types of sources, including private

industry, government bodies, foundations, or other sources. Eight of the studies reported that workers stopped medication prior to the beginning of the trial.[118-120,122,124-126,128]

Qualitative Results

Cohort Studies

Lung function. Twenty-seven studies reported FEV_1 at diagnosis (see Appendix E: Evidence Table E-7) and we attempted to synthesize the change in lung function over time. In order to assess this outcome, we examined the difference between the mean percent predicted FEV_1 at follow-up and baseline in relation to average length of follow-up. Baseline mean percent predicted FEV_1 of the included studies is shown in Figure 13.[55,58,130-147]

Severity at diagnosis. Of the 17 studies (n=666 patients) where patients were completely removed from exposure to the offending asthmagen, 16 reported a mean baseline percent predicted FEV_1 >80 percent, indicating primarily mild impairment to normal pulmonary function. Among the studies examining patients who remained fully exposed, six of seven studies reported mean baseline percent predicted FEV_1 >80 percent. Four of the five studies describing subjects with reduced exposure reported mean baseline percent predicted FEV_1 >80 percent. Based on these findings, it does not appear that lung function at diagnosis was associated with exposure status during follow-up. No specific pattern emerged when we considered the molecular weight of the asthmagen studied.

Follow-up. Less than half of the studies where patients were removed from exposure[58,132,138-140,144,146] or had reduced their exposure[131,138,139], had improved FEV_1 over time (change >0) (Figure 14). Only one study where patients remained exposed to the work environment had a positive change in mean percent predicted FEV_1.[144] No specific pattern emerged when we considered the molecular weight of the asthmagen studied.

NSBP test. A variety of test characteristics were used to describe non-specific BHR. Generally, hyper-responsiveness was defined as the provocative concentration or dose of histamine or methacholine required to elicit a pre-determined change in FEV_1, usually a 15 or 20 percent decline ($PC_{15/20}$ and $PD_{15/20}$, respectively). In most cases, PC_{20} values <16 mg/mL were considered to reflect significant BHR; however, cutoff levels of <8 mg/mL and <32 mg/mL were also reported. These results were eventually reported as either the number of patients who were hyper-responsive at a specified concentration cut-off value (e.g., <8 mg/mL, <16 mg/mL, <32 mg/mL) or as the mean or geometric mean of the concentrations that produced the required FEV_1 drop. Of the 13 studies that reported the presence of hyper-responsiveness at diagnosis, between 36 percent and 100 percent of patients with OA were classified as hyper-responsive.[56,130,132,134,135,141,144,148-152]

Follow-up. The change in hyper-responsiveness over time (i.e., from baseline) was investigated by calculating the ratio of average hyper-responsive concentration at follow-up to the average baseline concentration. This measure was chosen because it is independent of the measurement unit and because the baseline measures of NSBP test varied. Therefore, all studies that reported or provided sufficient information to calculate a mean or geometric mean

of a hyper-responsiveness measure at baseline and at follow-up were included. A ratio greater than 1.0 indicates improved hyper-responsiveness (follow-up/baseline) because the average concentration to achieve the specified bronchial response was greater at follow-up than at diagnosis. Conversely, a ratio less than 1.0 indicates worsening hyper-responsiveness because the average concentration to elicit a bronchial response was lower at the follow-up visit, signifying that the airways of patients were more hyper-responsive.

Figure 15 demonstrates that 14 of 15 studies of individuals who were removed from exposure had decreased hyper-responsiveness at follow-up.[130-133,135-137,143,148,153-157] Conversely, patients who remained exposed were overall more hyper-responsive at follow-up testing, although two of the five studies showed improved hyper-responsiveness at follow-up.[133,150] There were insufficient data (three studies) to draw conclusions about change in hyper-responsiveness among patients with reduced exposure. No specific pattern emerged when we considered the molecular weight of the asthmagen studied.

Medications. Medication needs were used as a proxy measure for disease severity and continued asthma symptoms. Twenty-two studies reported some medication data at baseline or diagnosis. The number of patients taking specific types of medications (bronchodilators, corticosteroids, etc.) was most frequently reported in insufficient detail to form an analytic approach.[58,134,136,146,158-162] Eight studies reported the percent of patients using asthma medications at baseline; however, did not specify type.[49,123,131,132,141-143,163] Two studies categorized patients by frequency of medication use[130,138] and three studies reported a mean score based on the frequency of medication use.[56,100,137] Follow-up data were reported in a similar manner.

There was no clinically meaningful way to combine the continuous measure outcomes with the frequency data. In addition, not all studies reported medication use at baseline and follow-up, thus we explored the percent of patients taking medications at follow-up. When the usage level was specified, only those that reported daily or frequent use of medications were counted.[138,141,142,147,158,164]

Follow-up. Of the patients removed from exposure, the percentage of patients using medication at follow-up ranged from 17 to 100 percent (Figure 16).[56,98,116,130-132,134-136,138,141,147,154,158,162,165-168] Within this group of 17 studies, there was no indication that fewer patients were using medication as time from removal increased. Only nine studies reported medication use among patients who remained exposed[131,139,141,157,162] or had reduced exposure to the asthmagen[131,138,139,142,165]; no clear pattern of changes in medication use emerged.

Symptoms/improvement. Thirty publications reported a variety of symptom outcomes by intervention status of continued exposure, reduced exposure, and cessation of exposure. Outcome measures included mean symptom scores[137,138,145], categorical symptom scores[164,166], and the number of subjects who were asymptomatic or recovered, remained symptomatic, or had specific symptoms.[50,56,58,131-133,139,142,144,148,157-159,169-176] Four studies included statements regarding non-quantified "improvement".[136,149,154,163] Due to the disparity of outcomes, only a qualitative assessment was possible.

Among the studies that examined workers removed from exposure the majority reported some improvement in workers' symptoms following removal.[50,56,58,131-133,136-138,144,148,154,157-159,163,164,166,169-174] This was measured by either a symptom score or reporting that the majority

of patients had improved symptoms or were considered "asymptomatic". The same pattern emerged in the nine studies describing symptoms for subjects whose exposure had been reduced by a workplace intervention.[131,138,139,142,149,163,170,175,176] Very few studies reported a complete resolution of symptoms among the majority of workers.[148,159,174]

Three groups examined the effectiveness of respiratory protective equipment in reducing symptoms caused by workplace exposures. In general, these papers reported that while respiratory protective equipment did reduce the severity of acute symptoms, they did not eliminate symptoms altogether.[152,169,177,178]

Finally, most of the studies of workers who remained exposed to the asthmagen at work showed that symptoms either remained stable or deteriorated with continued exposure.[50,58,133,137,139,144,145,157,163] Only two studies reported improved symptoms among those who remained exposed to the asthmagen.[166,176]

Socioeconomic consequences. Seven studies examined socioeconomic outcomes among workers with OA (Table 5). In all but three studies[138,164,179], the subjects were comprised of a group primarily removed from workplace exposure and a continued exposure group. Vandenplas et al.[138] compared two groups of workers: reduced or removed from exposure. In two instances, all of the workers were removed from the offending workplace.[164,179] Five of the studies included mixed causes of OA, while one study examined latex-induced OA[138], and the other included patients with red cedar asthma.[50] Time since OA diagnosis ranged from 1 year to 5.5 years.

Of the four studies that measured financial situation after OA diagnosis, all found that workers who were removed from the workplace causing their OA suffered a loss in income. In one study conducted, 85 workers who were removed from exposure were compared to 117 workers who continued to work for the same employer (46 used PPE, 20 had the same job, 38 workers were relocated, and 13 were on chronic sick leave).[57] The response rate to economic questions was high (89 percent). When compared to workers who were completely removed from the causative workplace, exposed workers were less likely to have suffered diminished earnings; the mean loss of annual income was significantly less among the exposed workers. Another study examined 25 workers with SIC-confirmed OA; 13 workers were removed from exposure and 12 workers continued their exposure.[166] After one year, a significantly greater number of removed workers reported deterioration in their economic situation. Compared to 1 year earlier, both monthly and annual income significantly decreased among the removed workers. Earnings also decreased in the workers with continued exposure; however, this difference was not significant. Interestingly, this study also reported that pharmaceutical expenses significantly decreased for those removed from exposure, while they increased among workers with continued exposure. A third study compared 78 workers with OA removed from the workplace to 34 workers with OA who continued to be exposed.[58] While 140 participants were identified, 112 completed the follow-up questionnaire. Fewer workers who were still exposed felt they had lost money than workers who were removed. The perceived median annual loss of income and the perceived percentage loss of annual income were higher among the workers who ceased workplace exposure. The authors did not perform any tests of statistical significance. The final study examined red cedar asthma workers who were exposed workers (48), non-exposed workers (27), and unemployed workers (53).[50] Monthly income among the unemployed cohort was significantly less than the working exposed and working non-exposed groups.

Vandenplas et al. compared 20 workers who had reduced levels of latex exposure to 16 workers who were removed from latex.[138] Among the reduced exposure group, 7/20 workers reported work disability, defined as changed or left work, while 11/16 of workers removed from latex exposure reported work disability and the remaining five workers were not working because of their latex-induced OA. More workers who were removed from latex reported a decrease in income compared with workers with reduced latex exposure. The actual reduction in earning was 20 percent among the non-exposed workers, while there was no reduction in earnings for the workers with reduced exposure.

Two studies assessed the rate of worker's compensation claims and associated acceptance.[50,138] In Vandenplas' et al. study, only 12 of the 36 workers stated they had attempted to seek compensation. The Belgian Workers' Compensation Board (WCB) more frequently approved claims among workers who were removed from the workplace than those who reduced their exposure. In contrast, the Canadian WCB approved more claims than its Belgian equivalent. Among those who filed for compensation, the acceptance rate was similar between workers with continued exposure, workers who ceased exposure, and the unemployed.[50]

Two studies followed a cohort of workers who were removed from exposure. Gassert et al. conducted a study of 55 patients with "definite/probable" OA of mixed origins.[164] Seventy-two patients were identified and 55 were interviewed. At follow-up, approximately one-third of the subjects were employed and their exposure was reduced (17/55). The remaining subjects were unemployed. Prior to a diagnosis of OA, 54 workers had health insurance; at follow-up, 49/55 patients were not insured and had to pay for their asthma medication and care. The final study reported findings on 211 Quebec workers with OA caused by mixed exposures were awarded workers' compensation between 1986 and 1988. One hundred and thirty-four of the 211 eligible workers were followed up 2 years after removal from exposure. The average cost of disability/impairment for each worker was $35,529 USD. A significant portion of the workers were either unemployed (11/134) or took an early retirement (22/134).

Table 5. Economic consequences of occupational asthma

Citation	Removed/Unemployed	Exposed or Reduced
Employment		
Gassert et al. [164]	38*/55	17+/55
Dewitte et al.[59]	33*/134	
Income		
Ameille et al.[57]	-50 percent (69/82^)	-19 percent (20/104^)
Moscato et al.[166]	-$4,203.72 USD/year	-$268.71 USD/year
Gannon et al.[58]	-$5,863.88 USD/year	-$3,820.27 USD/year
Gannon et al.[58]	-54 percent (56/78^)	-35 percent (14/34^)
Marabini et al.[50]	-$368.14 USD/month	-$256.38 USD/month
Marabini et al [50]	-$609.96 USD/month*	
	-20 percent (10/16^)	0 percent (6/20^+)
Insured		
Gassert et al. [164]	49/55	
WCB Claim Acceptance		
Vandenplas et al.[138]	3/7	1/5
Marabini et al.[50]	17/20 / 42/45	31/33
Pharmaceutical Costs/Month		
Moscato et al.[166]	-$12.46 USD	+$13.17 USD

Abbreviations: **USD** = United States dollars; **WCB** = Workers' Compensation Board
Note: * = unemployed; **+** = reduced exposure; **^** = perception of reduced income

Quality of life (QOL). Two studies measured quality of life. Vandenplas et al. examined 36 subjects with SIC confirmed latex induced OA.[138] At a median follow-up time of 56 months, 16 subjects were no longer exposed to latex and 20 subjects had reduced their exposure. Two methods to reduce latex exposure were employed: using less than 20 pairs of latex gloves in the room or department each week; and using low allergen sterile and latex-free examination gloves. QOL was measured using a French version of the Asthma Quality of Life Questionnaire (AQOL). AQOL did not significantly differ among those removed from exposure versus those who reduced their exposure.

In the second study, 211 workers with OA, 134 participated in a follow-up survey assessing QOL.[93] SIC or serial PEFR was used to diagnose Quebec workers with OA; all the workers were removed from the exposure and received compensation from the WCB. Ninety-one workers with OA were matched to 91 similar patients with non-occupational asthma. This study also utilized the AQOL that considers five components of asthma: self-determined activities that were limited by OA, other activities, symptoms, emotional function, and exposure to environmental stimuli. When compared to the control group, both the total and component scores of the QOL survey were significantly lower among workers with OA than those with non-occupational asthma.

RADS. Piirila et al. followed six men who were exposed to sulfur dioxide during an explosion at a pyrite mine.[116] At follow-up, three patients continued to work in the same workplace, two had retrained and no longer worked underground, and one had retired because of respiratory disability sustained after the explosion; 13 years later, chest radiographs, spirometry, and NSBP testing were assessed. All of the workers, except one of the men who was retrained, continued to suffer from non-specific BHR. NSBP testing was not performed in one worker who continued in the same workplace because of dyspnea, wheezing, and moderate obstructive ventilatory impairment. There were no changes in chest radiographs.

A second study reported findings among a group of 29 men who were repeatedly exposed to chlorine over three months and subsequently diagnosed with RADS.[4] The men were no longer exposed to chlorine and 20 men were assessed one-year post diagnosis. While percent predicted FEV_1 was not significantly different between diagnosis and follow-up, some of the workers showed improvement in non-specific BHR. Six workers had a significant improvement in PC_{20} (3.2 fold difference from baseline to follow-up); non-specific BHR significantly deteriorated in one worker. Compared to diagnosis, significantly fewer workers required medication to control their OA symptoms.

Trials

Pharmacological outcomes. Ten trials examined the effectiveness of various pharmaceutical interventions for preventing exacerbations of OA.

Prednisone, but not indomethacin, was found to be effective in preventing late asthmatic responses among workers with toluene di-isocyanates (TDI)-induced OA.[122] Five workers completed four SIC and NSBP tests in the following order: 1) before treatment to establish baseline airway responsiveness; 2) after prednisone treatment (50 mg/d for 3 days); 3) after indomethacin (50 mg four times a day for 3 days); and 4) no treatment to assess reproducibility of baseline lung function values. After prednisone treatment, there was no significant decrease in FEV_1 measured 4 and 8 hours post-SIC. There was also no significant change in PD_{20} FEV_1.

Conversely, treatment with indomethacin resulted in FEV_1 and PD_{20} FEV_1 significantly decreasing 4 and 8 hours after SIC and NSBP test.

Two trials studied the effect of inhaled beclomethasone versus placebo among workers who had been removed from exposure.[117,128] The first study, conducted by Malo et al., compared beclomethasone (dose: 500 µg twice daily) to placebo; workers were randomized to the first treatment for 1 year and then crossed over to the other for 6 months[117]. Forty-four workers exposed to HMW and LMW agents were randomized; however, 12 refused to continue treatment for reasons not related to OA and thus, 32 completed the study. When taking beclomethasone, there was a significant reduction in nocturnal symptoms and cough. FEV_1 and FVC also significantly decreased during both the beclomethasone and placebo periods. However, when compared to placebo, PEF and global QOL significantly improved when taking beclomethasone; no such difference was observed when taking placebo. Greater improvement was noted among those who were first randomized to beclomethasone. The second trial compared beclomethasone (1000 µg daily for 5 months) to placebo among 15 workers who were SIC positive to TDI; seven workers received the active treatment.[128] Outcomes were measured at diagnosis, 2, 4, and 6 months. At 6 months, both groups still exhibited a significant late fall in FEV_1 during SIC; workers randomized to beclomethasone no longer had an early fall in FEV_1. Among workers receiving beclomethasone, PD_{20} measured using FEV_1 significantly improved at 2 months and continued to improve at 6 months. PD_{20} measured using FEV_1 did not change among those receiving placebo.

De Marzo et al. conducted a three-way randomized crossover trial of TDI-sensitive workers who had had not been exposed for 2 weeks prior to the trial beginning.[125] The treatment arms consisted of high dose (2000 µg) beclomethasone, low dose (400 µg) beclomethasone, and placebo; the washout period was at least 1 week. SIC and NSBP tests were performed on the seventh day. When receiving placebo and low dose beclomethasone, FEV_1 was significantly lower after SIC; FEV_1 did not change among the workers when they were taking high dose beclomethasone. Neither high-dose nor low-dose beclomethasone improved BHR and the hyper-responsiveness decreased over time among all three groups.

Mapp et al. examined the effectiveness of four drugs for the treatment of TDI-induced OA.[126] Twenty-four workers received one of the following drugs for 7 days: aerosolized beclomethasone (1 mg/kg twice a day), oral theophylline (6.5 mg/kg twice a day), verapamil (120 mg twice a day), or aerosolized cromolyn (20 mg/kg four times a day). Each worker was also crossed-over to placebo; placebo and active treatment ordering were assigned randomly. NSBP test was performed on the sixth day and 8 hours post-SIC, which was conducted on the seventh day. Workers randomized to beclomethasone experienced less airway responsiveness and did not suffer an asthma exacerbation after SIC. Theophylline reduced the severity of asthma exacerbations after SIC; however, airway responsiveness did not decrease. FEV_1 decreased and airway responsiveness increased among workers receiving verapamil, cromolyn, or placebo.

Crescioli et al. compared theophylline to placebo in a randomized crossover trial of six male workers with TDI-induced OA.[124] In random order, workers received theophylline (5 +/- 1 mg/kg twice daily) or placebo for 7 days; the washout period was 1 week. SIC was performed on the seventh day and airway hyper-responsiveness was measured on day 6 and 8 hours after SIC. Theophylline had no effect on airway hyper-responsiveness; however, it did significantly reduce the severity of late asthmatic reactions. After placebo, three of the six

workers required salbutamol after SIC; when treated with theophylline, none of the workers needed salbutamol after SIC.

To determine if atropine was effective in reducing asthmatic reactions, Paggiaro et al. performed SIC before and after administering atropine to 10 workers with TDI-induced OA.[120] Workers with hyper-responsive airways (PD_{15} FEV_1<0.200 mg) received 0.012 mg/kg of subcutaneous atropine; the remaining workers received 0.008 mg/kg. Atropine was delivered 30 minutes prior to SIC and in 90-minute intervals for 6.5 hours. While atropine did inhibit an immediate asthma reaction in one worker, the severity of late asthma reactions was unchanged in the other nine workers. All workers suffered side effects commonly associated with atropine, such as dry mouth, cycloplegia, and increased heart rate.

Eighteen male workers suffering from flour-induced OA were randomized to two 0.4 mg aerosol doses of Fenoterol®.[129] Body plethysmography was used to measure airway resistance and end expiratory thoracic gas volume. Woitowitz et al. found that workers randomized to Fenoterol® experienced a significantly normalized airway resistance within 5 minutes. End expiratory thoracic gas volume also improved with the use of Fenoterol®, however this difference was not significant. The drug remained effective for 4 hours and the maximum effect was achieved within 30–120 minutes. There was no significant change in pulse rate or blood pressure.

Moscato et al. compared the effects of nifedipine and placebo on bronchial responsiveness to TDI among five workers with TDI-induced OA.[127] In a crossover trial, five patients received two capsules of nifedipine (20 mg sublingually) or placebo 45 minutes before SIC. The test was repeated with alternate treatment 1 week later. Placebo did not prevent asthmatic exacerbations. Immediate asthmatic reactions and reactions within 1 hour were prevented by nifedipine. Two patients required a second dose of 10 mg of nifedipine at 2 hours to prevent a late response.

Malo et al. examined 25 workers who had SIC confirmed OA and displayed late asthmatic reactions; three workers refused to continue and were excluded from the analysis.[118] Post SIC, workers were given either salbutamol (200 μg) or placebo and spirometry was measured to determine recovery in FEV_1. When compared to placebo, workers receiving salbutamol consistently showed greater improvement in FEV_1, measured by percent FEV_1 improvement, improvement of ≥20 percent FEV_1, and return of FEV_1 as percent of baseline.

Immunotherapy. Armentia et al. conducted a double-blind trial examining the effectiveness of wheat flour extract immunotherapy.[121] Thirty workers with bakers' asthma were included, however four withdrew because they left their job and their symptoms improved. Ten workers received injections of placebo, eight received immunotherapy for 10 months, and the remaining eight workers received immunotherapy for 20 months; immunotherapy was administered weekly. Compared to workers in the placebo group, immunotherapy resulted in significantly less skin prick sensitivity and non-specific bronchial reactivity; significant subjective clinical improvement was also noted among the treatment groups. Workers receiving immunotherapy for 20 months experienced a significant decrease in serum specific IgE levels. Overall, the immunotherapy appeared to be safe; a single worker had urticaria after a dose of immunotherapy.

Reducing workplace exposure. Two trials examined the effect of reducing exposure on asthma outcomes in workers with OA. The first study was a crossover trial examining the

efficacy of respiratory devices among 26 farmers with SIC-verified OA.[119] The farmers wore various respiratory devices with P2 filters (21 Dustmasters®, 4 Airstream®, 1 Airlite®), and SIC was repeated approximately 21 weeks later. Both airway resistance and specific airway resistance were significantly improved when SIC was performed while wearing the respiratory device. During the SIC without respiratory devices, all of the farmers required bronchodilator treatment; only six farmers needed bronchodilator treatment when SIC was performed while wearing a respiratory device. While the respiratory devices did reduce bronchial obstruction, they failed to provide complete protection.

The second study compared healthcare workers' asthmatic reactions to various latex gloves.[27] Eight healthcare workers with latex-induced OA were included; all of the workers were SIC positive to the latex powdered gloves (Triflex®) used in their workplace. Each worker had SIC performed in random order while handling at least two of the three types of hypoallergenic latex gloves: low-powdered Triflex®, non-powdered Nutex®, and/or powdered SensiTouch®. Two of the seven workers tested were SIC positive to low-powdered Triflex® gloves. The other two hypoallergenic gloves did not elicit an SIC response. Non-specific BHR to hypoallergenic gloves occurred in two of the eight workers. Among the eight healthcare workers, the use of hypoallergenic gloves reduced the risk of latex asthma exacerbations.

Figure 1. Sensitivity and specificity extracted from studies comparing single NSBP test to SIC among LMW asthmagens

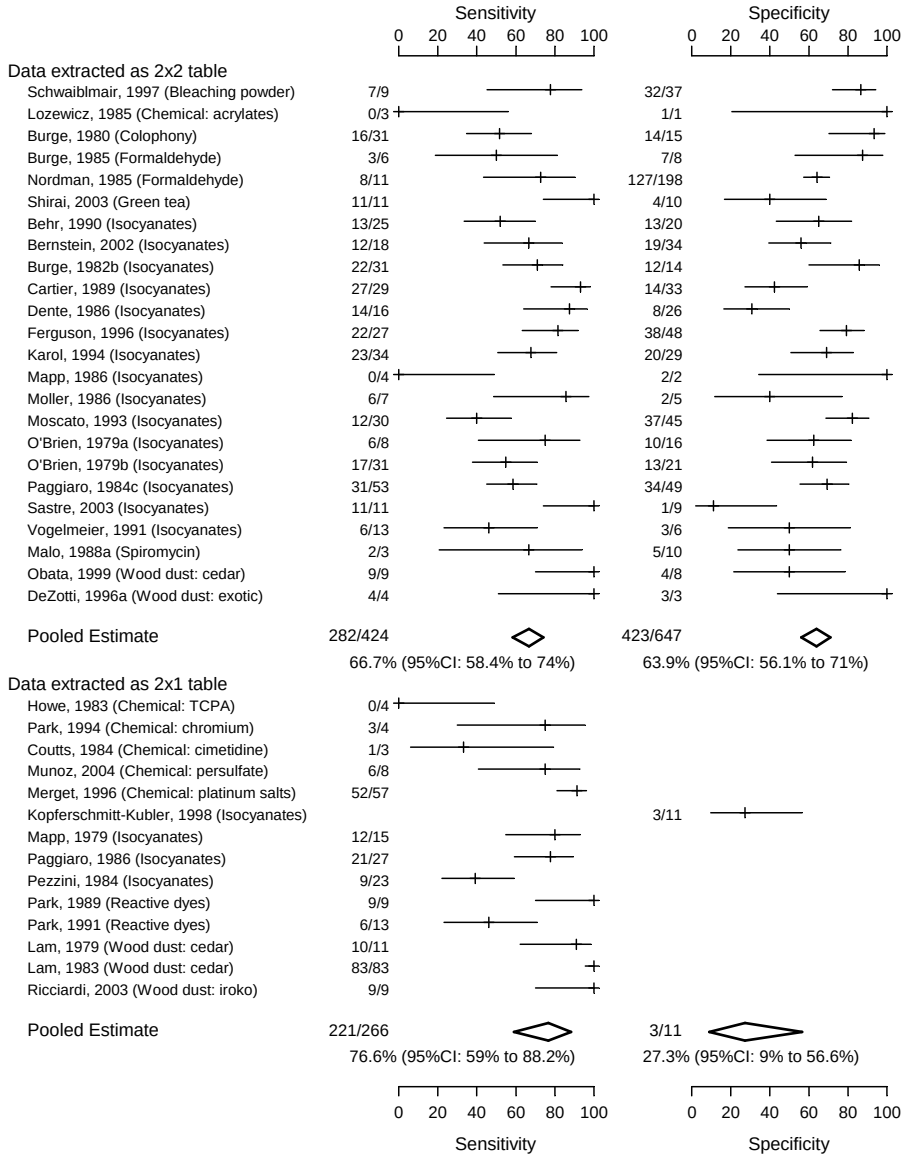


Figure 2. Sensitivity and specificity extracted from studies comparing single NSBP test to SIC among HMW asthmagens

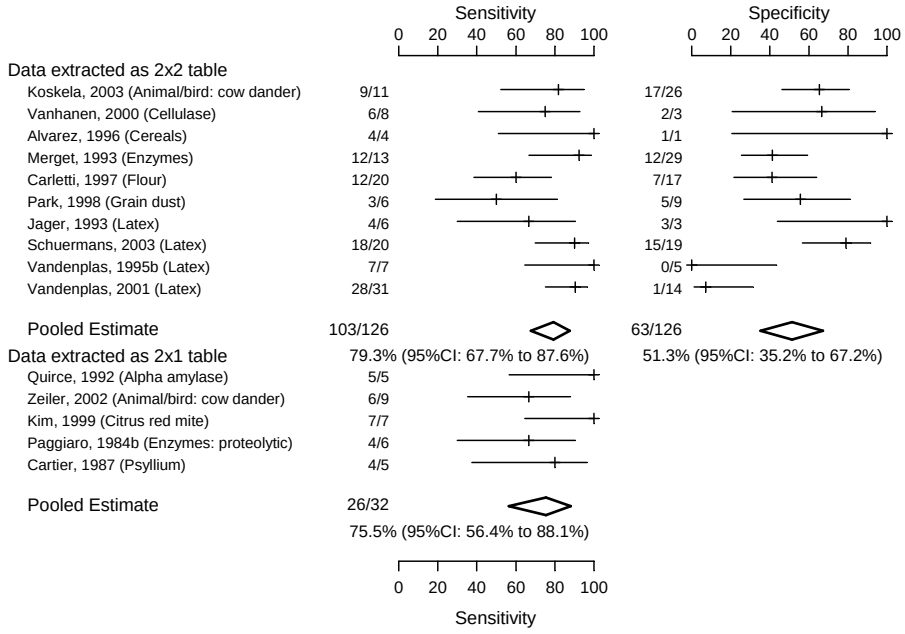


Figure 3. Sensitivity and specificity extracted from studies comparing single NSBP test to SIC among mixed asthmagens

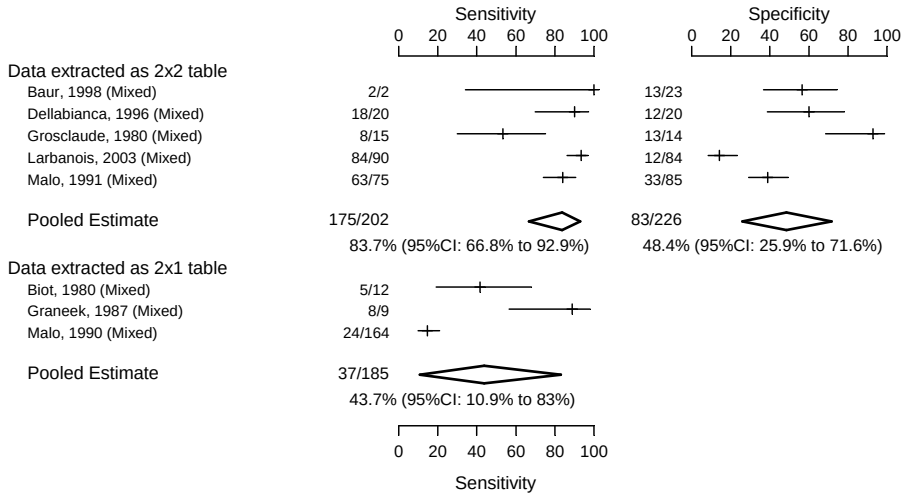


Figure 4. Sensitivity and specificity pairs from studies comparing NSBP test with SIC
The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).

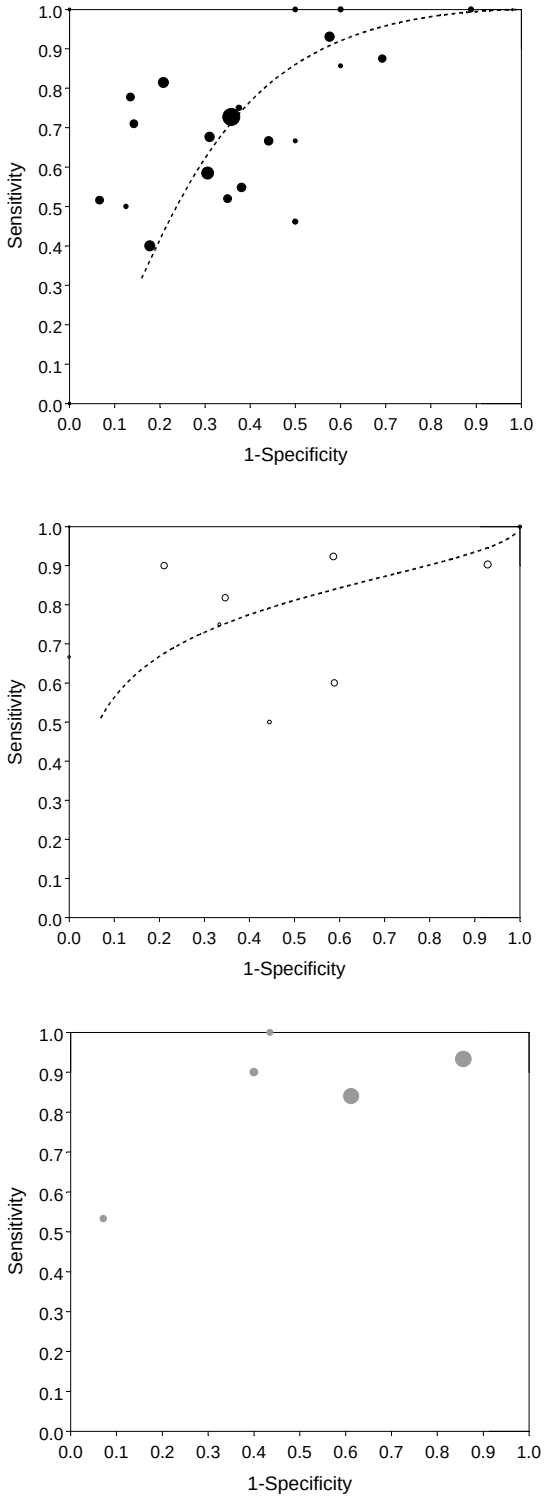


Figure 5. Sensitivity and specificity extracted from studies comparing specific SPT test to SIC among LMW asthmagens

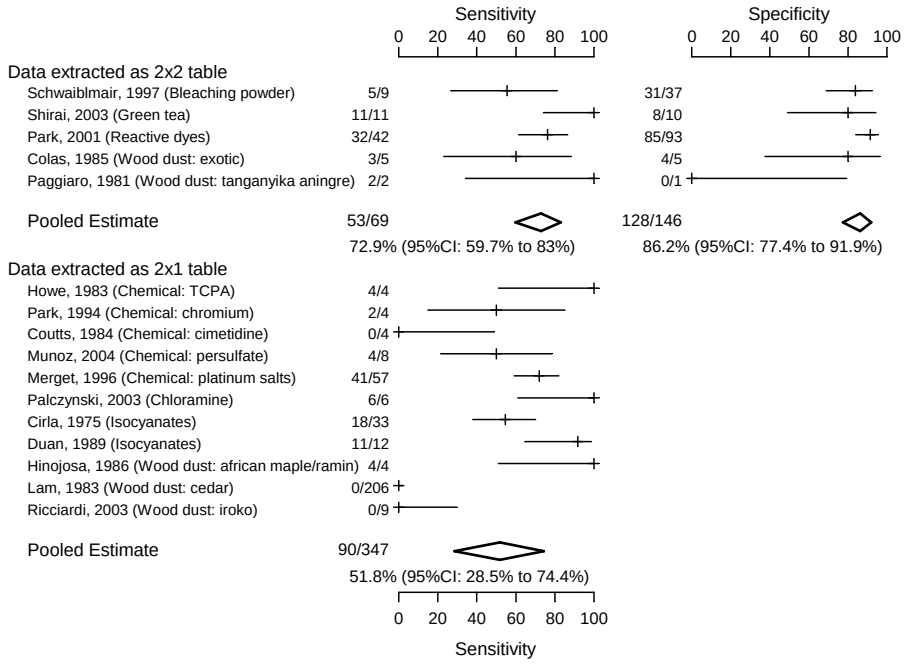


Figure 6. Sensitivity and specificity extracted from studies comparing specific SPT test to SIC among HMW asthmagens

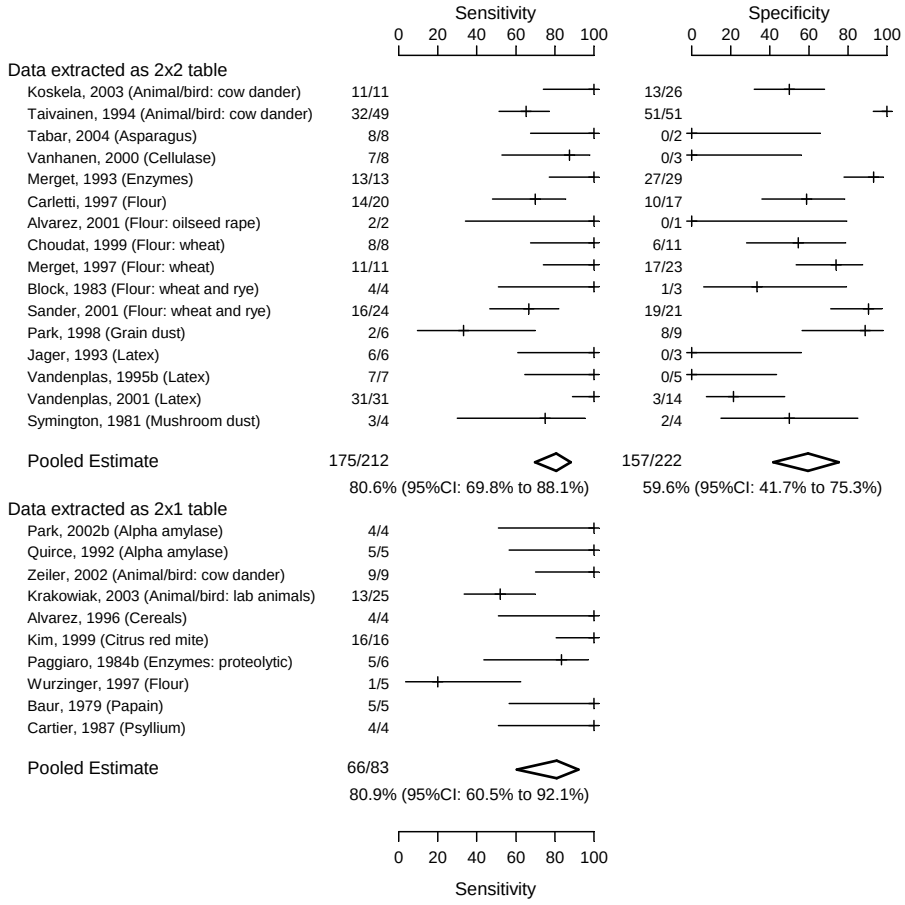


Figure 7. Sensitivity and specificity extracted from studies comparing specific SPT test to SIC among mixed asthmagens

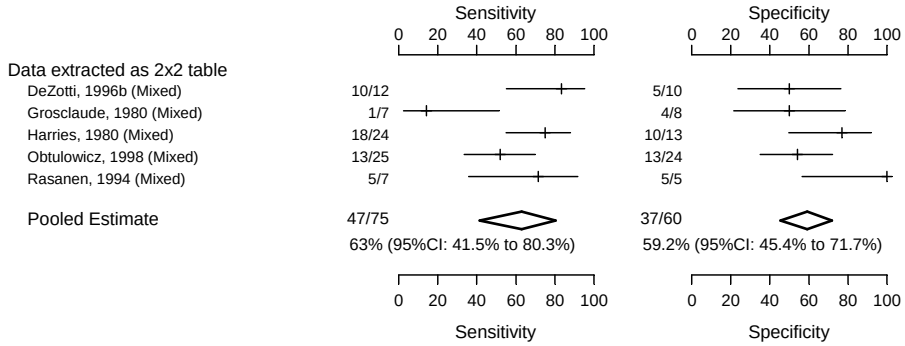
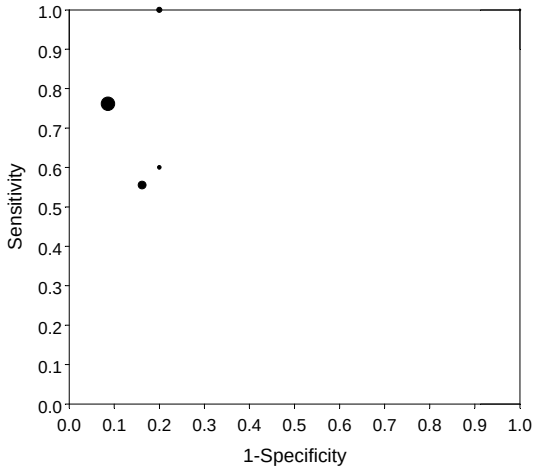
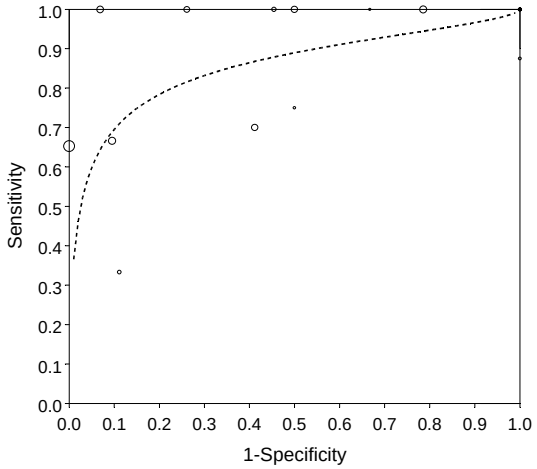


Figure 8. Sensitivity and specificity pairs from studies comparing SPT to SIC
The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).





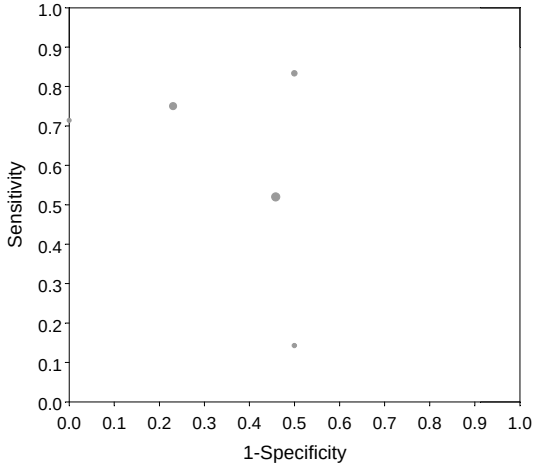


Figure 9. Sensitivity and specificity extracted from studies comparing serum specific IgE test to SIC among LMW asthmagens

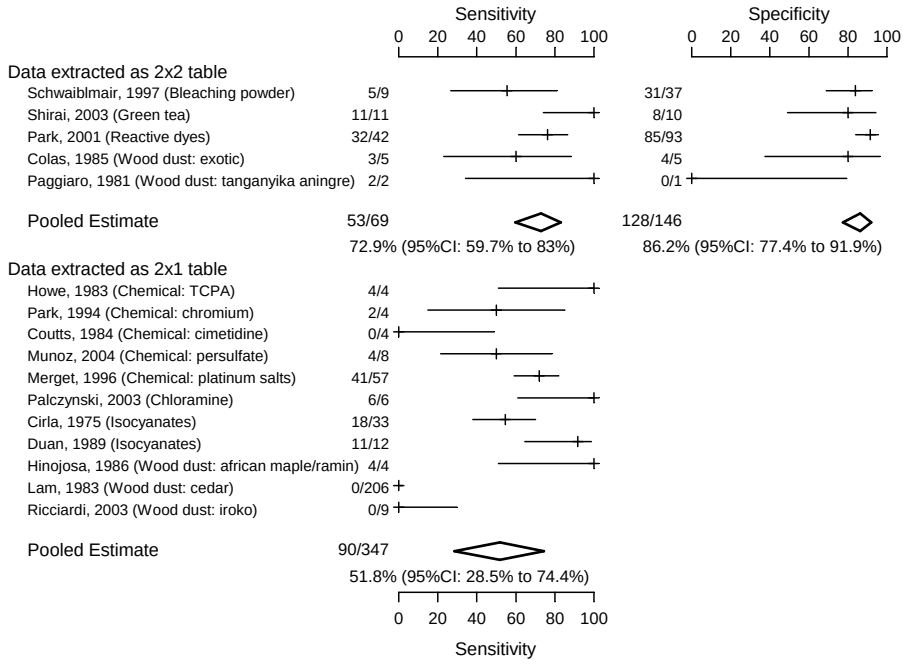


Figure 10. Sensitivity and specificity extracted from studies comparing serum specific IgE test to SIC among HMW asthmagens

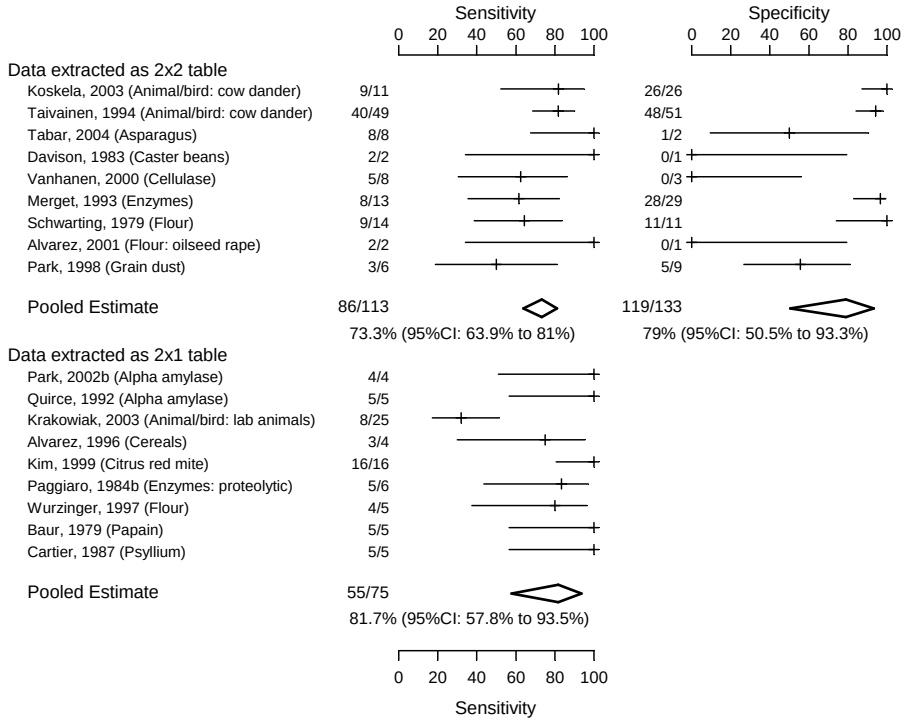


Figure 11. Sensitivity and specificity extracted from studies comparing serum specific IgE test to SIC among mixed asthmagens

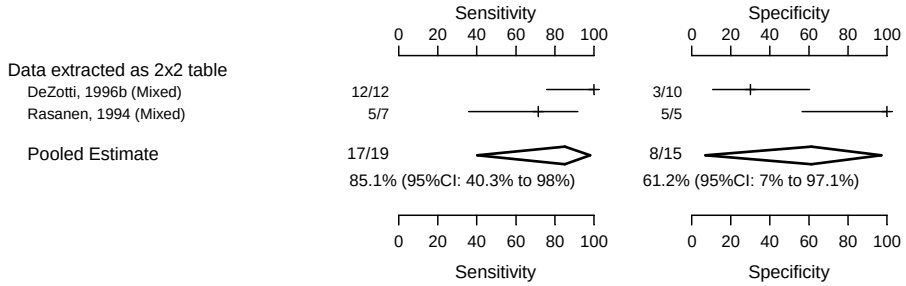
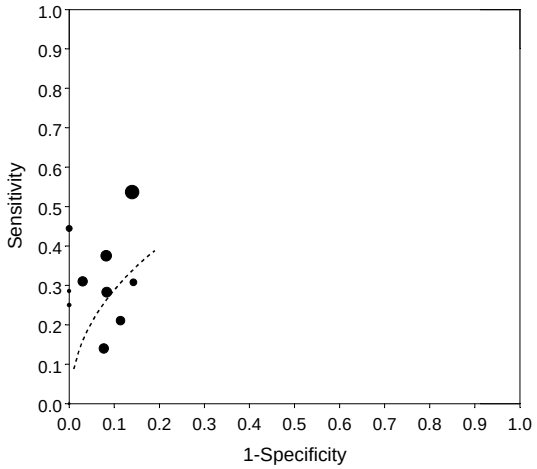
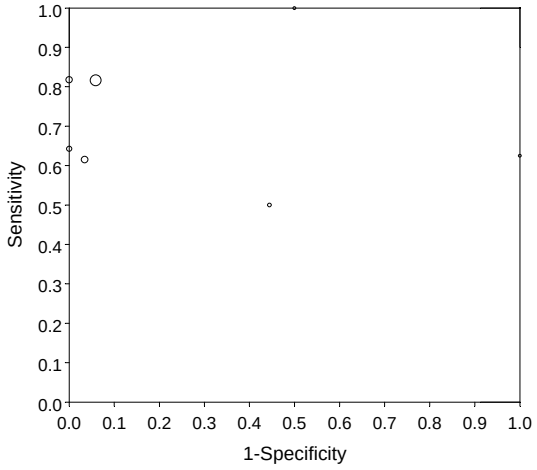


Figure 12. Sensitivity and specificity pairs from studies comparing specific IgE with SIC
The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).





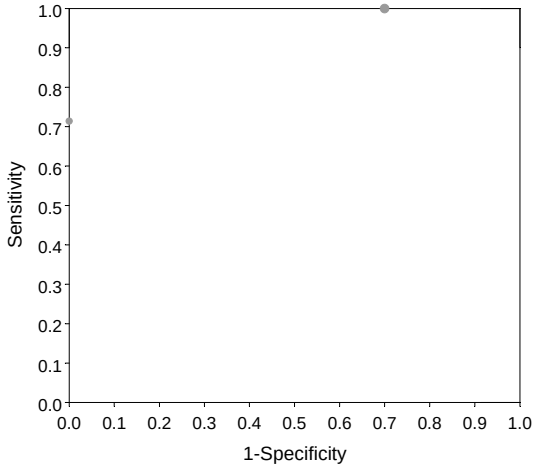


Figure 13. Average percent predicted FEV_1 at baseline for groups of patients who remained exposed, were removed from contact, or reduced exposure to the suspected asthmagen
The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).

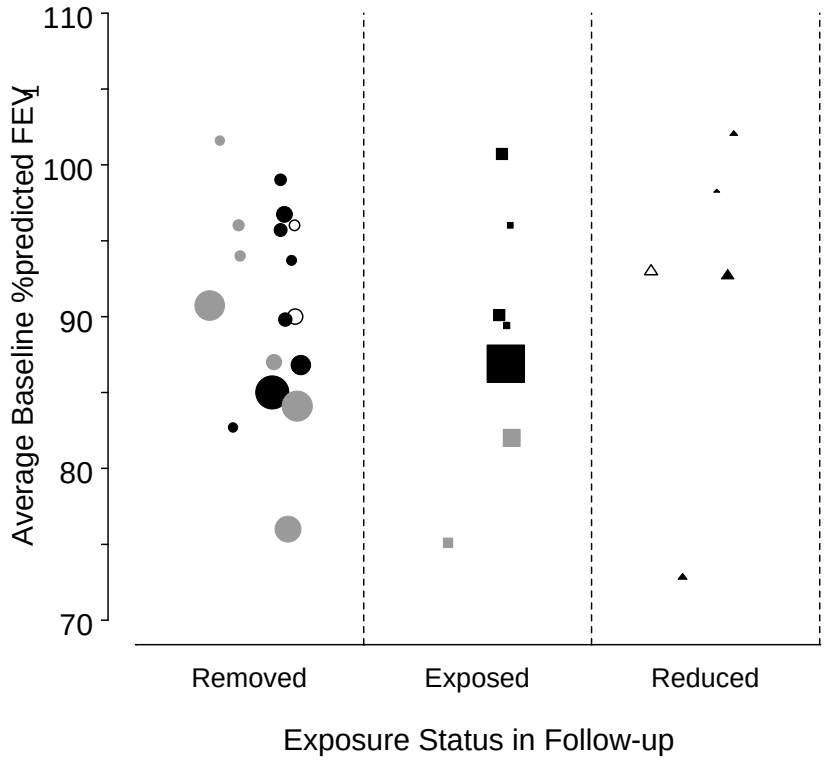


Figure 14. Difference between average percent predicted FEV_1 in follow-up and average percent predicted FEV_1 at baseline plotted against average length of follow-up by exposure status in follow-up
Improved percent predicted FEV_1 over time is indicated by values greater than zero (0). No change in percent predicted FEV_1 in indicated by a dashed line at percent predicted FEV_1=0. Observations from cohorts with multiple follow-up visits are joined by a dotted line. The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).

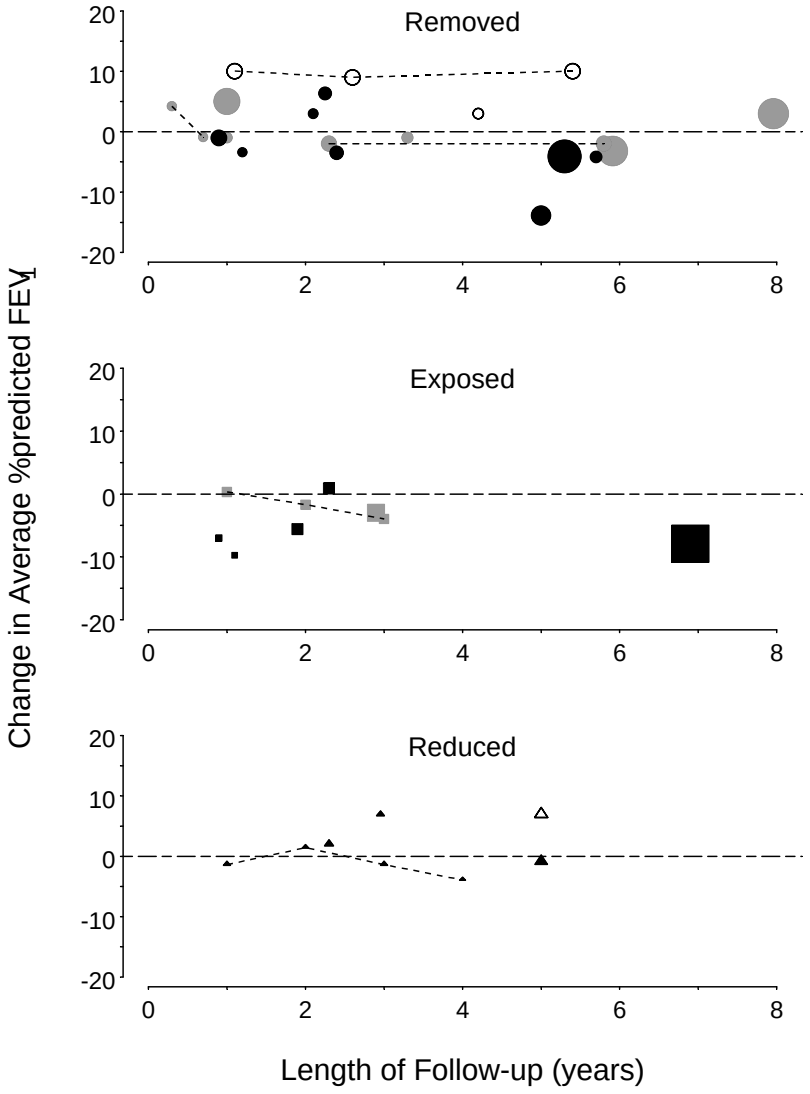


Figure 15. Ratio of mean NSBP test at follow-up visit to mean NSBP test at baseline plotted against average length of follow-up by exposure status in follow-up

Improved hyper-responsiveness is indicated by values greater than 1. No change in responsiveness is indicated by a dashed line where the ratio=1. Observations from cohorts with multiple follow-up visits are joined by a dotted line. The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).

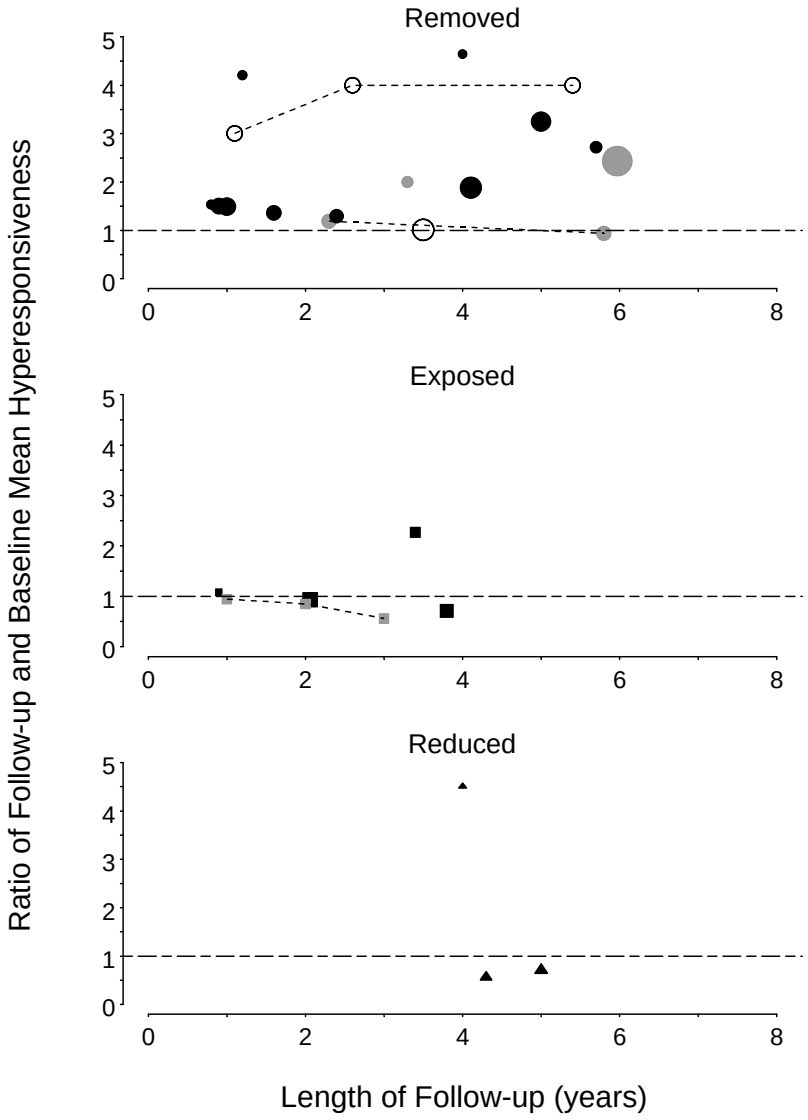


Figure 16. Percentage of patients taking asthma medications in follow-up plotted against average length of follow-up by exposure status in follow-up

Using medication need as a surrogate for disease severity, decreasing percentages of subjects on medication over time may indicate decreasing disease severity. Observations from cohorts with multiple follow-up visits are joined by a dotted line. The size of the plotting character is proportional to the number of patients in the group and the color indicates the molecular weight of the suspected asthmagen (white=HMW, black=LMW, grey=mixed).

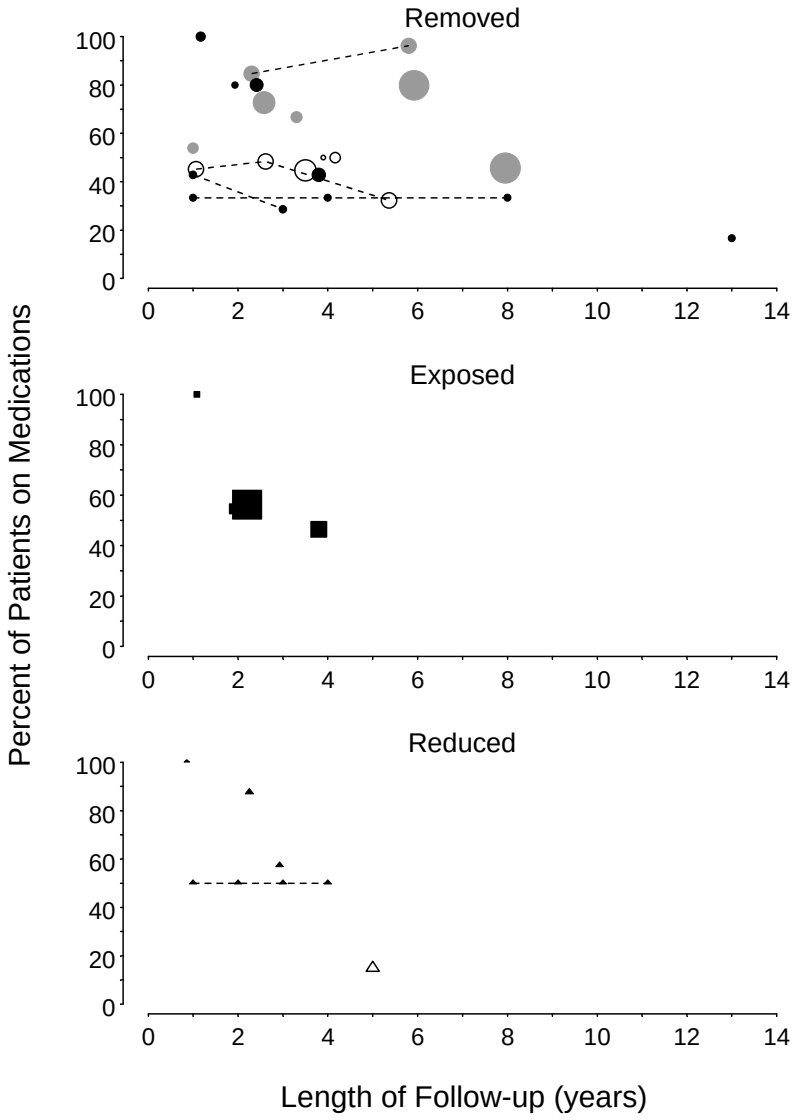


Table 6. Description of studies for the diagnosis of OA

	References
Published in language other than English	
Italian	180, 181, 182, 107, 183, 184, 185, 186
German	103, 85, 187, 188, 189
French	190, 191, 192, 193
Chinese	194
Finnish	104
Country of study origin	
United Kingdom	34, 195, 101, 99, 196, 197, 198, 102, 199, 91, 200, 201, 202, 203, 98, 204, 205, 206, 207, 208, 209
Canada	210, 211, 212, 213, 214, 96, 215, 94, 216, 111, 35, 110, 146, 217, 93, 43, 218, 95, 219
Italy	180, 181, 182, 220, 221, 222, 113, 107, 183, 223, 184, 224, 225, 185, 186, 226, 227, 228
Germany	106, 103, 85, 229, 230, 187, 231, 188, 232
Korea	233, 234, 235, 236, 151, 86, 237, 236, 238
Spain	88, 87, 239, 97, 240, 241, 90, 242
United States	243, 244, 245, 115, 246, 247, 114, 248
Finland	249, 250, 251, 104, 252, 160, 253
France	190, 191, 254, 192, 193, 255
Reference standard other than SIC	
Clinical diagnosis	34, 243, 182, 91, 200, 98, 233, 184, 256, 257, 241, 209, 160, 248, 102, 115, 246, 207
Serial PEFR	258
Suspected asthmagen	
Low molecular weight	
Di-isocyanates	243, 103, 210, 99, 196, 244, 214, 181, 222, 194, 215, 245, 249, 233, 255, 183, 223, 247, 224, 205, 206, 186, 226, 237, 227, 114, 90, 209, 232
Chemical	198, 102, 91, 203, 115, 204, 230, 246, 97, 256, 151, 259, 207, 248
Wood dust	192, 96, 260, 239, 216, 43, 225, 218, 241, 228, 219
High molecular weight	
Flour	87, 211, 180, 254, 229, 257, 187, 188, 189
Animal/Bird	261, 262, 104, 160, 253
Latex	85, 263, 264, 105
Mixed	34, 190, 106, 191, 265, 220, 221, 113, 200, 94, 201, 193, 202, 107, 266, 111, 35, 146, 217, 93, 184, 112, 95, 251
Comparison tests	
Single NSBPT	88, 87, 190, 106, 103, 210, 191, 211, 265, 196, 197, 180, 213, 214, 254, 181, 192, 198, 220, 260, 221, 222, 113, 91, 215, 201, 193, 85, 245, 115, 234, 258, 255, 261, 262, 216, 266, 111, 35, 204, 110, 146, 217, 183, 223, 267, 229, 230, 184, 247, 224, 97, 256, 250, 205, 206, 43, 225, 185, 186, 226, 218, 268, 235, 236, 151, 86, 237, 238, 227, 257, 240, 114, 228, 90, 263, 231, 89, 259, 264, 105, 252, 232, 189, 253
Specific skin prick test	88, 87, 195, 211, 26, 180, 212, 213, 214, 181, 192, 182, 198, 199, 220, 260, 91, 194, 94, 193, 202, 239, 203, 85, 249, 234, 261, 262, 107, 216, 111, 35, 204, 110, 146, 217, 183, 223, 267, 229, 230, 224, 97, 256, 206, 43, 112, 225, 185, 226, 218, 268, 235, 236, 151, 86, 237, 236, 238, 227, 257, 240, 241, 251, 228, 187, 231, 188, 89, 259, 207, 208, 242, 104, 209, 264, 105, 252, 232, 189, 253, 248
Serum specific IgE	88, 87, 190, 195, 210, 211, 244, 212, 213, 214, 254, 102, 199, 220, 194, 215, 239, 203, 85, 245, 249, 233, 234, 261, 262, 267, 229, 246, 256, 225, 185, 218, 268, 235, 236, 86, 237, 236, 238, 227, 240, 241, 251, 228, 90, 188, 259, 242, 104, 209, 219, 252, 160, 232, 189, 253, 248
Eosinophil counts	87, 26, 192, 220, 260, 113, 94, 202, 258, 262, 111, 110, 246, 250, 43, 112, 268, 86, 114, 228, 259
Serial PFT	34, 101, 99, 96, 200, 98, 35, 110, 217, 93, 97, 250, 151, 95, 228, 207, 255, 246

Table 7. Methodological quality of studies for the diagnosis of OA

	References
Subject selection	
Random or consecutive	34, 96, 221, 98, 249, 261, 266, 110, 146, 230, 250, 43, 104, 105, 160, 253
Not reported	190, 195, 103, 191, 197, 244, 180, 213, 192, 182, 220, 222, 194, 193, 239, 107, 183, 223, 184, 256, 206, 185, 186, 226, 235, 151, 95, 227, 251, 114, 187, 90, 263, 219, 252, 232, 189
Data collection	
Retrospective	34, 99, 244, 213, 249, 35, 217, 93, 224, 250, 225, 240, 242, 209
Could not be determined	201, 85, 107, 266, 188, 189
Blinded assessment of outcome	
Reference standard and comparison test	111, 35, 110
Reference standard or comparison test	87, 210, 99, 265, 212, 182, 96, 113, 94, 201, 98, 258, 262, 204, 217, 256, 43, 268, 236, 209, 105
Inadequate	194, 226, 252, 248
Adequately described reference standard	88, 87, 34, 106, 103, 210, 211, 26, 101, 99, 265, 180, 212, 213, 214, 254, 181, 192, 96, 199, 220, 260, 221, 91, 194, 215, 94, 201, 193, 202, 239, 203, 85, 245, 115, 249, 234, 255, 261, 262, 216, 266, 111, 35, 110, 146, 93, 183, 223, 267, 229, 230, 184, 246, 224, 97, 256, 250, 205, 206, 43, 225, 185, 186, 226, 218, 235, 236, 151, 86, 237, 236, 238, 227, 240, 251, 228, 90, 231, 89, 242, 104, 209, 264, 105, 252, 160, 232, 189, 253, 248
Differential bias	88, 195, 211, 212, 113, 200, 201, 203, 234, 261, 107, 35, 146, 93, 246, 205, 236, 86, 236, 228, 90, 208, 242, 219, 264, 160
Could not be determined	190, 103, 26, 180, 214, 181, 199, 91, 194, 98, 216, 250, 186, 218, 227, 241, 187, 263
Partial verification bias	88, 190, 195, 211, 214, 182, 199, 113, 91, 200, 98, 85, 233, 234, 204, 110, 146, 183, 184, 225, 185, 236, 86, 251, 228, 231, 188, 104, 219, 264, 189
Could not be determined	243, 103, 26, 180, 181, 198, 220, 194, 258, 107, 216, 250, 206, 186, 227, 241, 187, 263
Asthma medication stopped prior to testing	88, 87, 265, 254, 96, 220, 221, 113, 91, 215, 94, 202, 245, 115, 255, 261, 216, 35, 146, 223, 267, 229, 230, 247, 224, 97, 250, 43, 226, 218, 268, 237, 227, 240, 251, 90, 231, 89, 242, 104, 253
Source of funding	
Government	243, 211, 96, 113, 94, 115, 234, 266, 223, 268, 227, 219
Foundation	195, 216, 111, 256, 43, 240, 160
Internal	261, 235, 86, 236, 114
Private	205, 206, 238, 105
Other (including multiple sources)	34, 210, 244, 212, 214, 200, 245, 247, 253, 248, 88, 254, 203, 229, 237, 257, 264, 232

Table 8. Description of studies for the management of OA

	References
Published in language other than English	
German	172
Italian	140
Spanish	169
Country of study origin	
United Kingdom	158, 131, 58, 163, 141, 22, 159, 177, 176, 269, 173
Canada	134, 136, 143, 55, 147, 132, 179, 4, 270, 135
Italy	133, 145, 166, 144, 130, 153, 137, 56, 148, 140
United States	142, 167, 164, 174, 175, 178
Finland	116, 152
France	57, 139
Germany	170, 172
Korea	151, 171
Spain	165, 169
Other	271, 149, 154, 150
Suspected asthmagen	
Low molecular weight	
Di-isocyanates	142, 163, 143, 141, 133, 169, 144, 130, 153, 171, 137, 139, 148, 269
Chemical	158, 174, 175, 4, 170, 165, 151, 116, 56, 173
Other	131, 150, 172, 149, 55
High molecular weight	
Latex	167, 178, 138
Animal/Bird	177, 152
Flour	154, 176
Other	271, 132, 159
Mixed	134, 57, 58, 164, 136, 147, 179, 270, 145, 166, 135, 22, 140
Subject source	
Clinic	134, 57, 158, 131, 58, 164, 154, 178, 136, 143, 55, 141, 147, 179, 4, 145, 166, 165, 169, 151, 171, 135, 137, 56, 139, 150, 140, 152, 138
Workplace	142, 175, 163, 170, 172, 149, 153, 116, 159, 177, 269, 173
Not reported	167, 174, 271, 132, 270, 133, 144, 130, 22, 148, 176
Exposure Status	
Removed	134, 57, 158, 167, 131, 58, 164, 154, 174, 175, 163, 136, 143, 55, 141, 147, 132, 179, 4, 270, 133, 170, 172, 166, 165, 169, 144, 130, 153, 151, 171, 135, 116, 137, 56, 139, 22, 148, 159, 150, 138, 173
Reduced	57, 142, 167, 131, 218, 175, 163, 141, 170, 166, 153, 272, 116, 137, 139, 176, 138, 269
Continued exposure	57, 167, 58, 55, 133, 145, 170, 166, 149, 144, 56, 139, 150, 176
Used PPEs	57, 167, 178, 165, 169, 139, 177, 152
Medications (+/- removal)	271, 140
Outcomes	
NSBP tests	134, 142, 158, 131, 43, 59, 154, 141, 147, 132, 4, 270, 133, 145, 170, 172, 166, 165, 149, 144, 130, 153, 151, 155, 135, 116, 137, 56, 139, 148, 150, 140, 138, 173
Pulmonary function tests	134, 142, 158, 131, 59, 154, 174, 175, 163, 55, 141, 147, 132, 4, 133, 145, 170, 166, 165, 144, 135, 116, 137, 56, 139, 150, 177, 140, 152, 138, 269, 173
Questionnaires	134, 57, 142, 158, 131, 43, 59, 58, 164, 154, 174, 175, 136, 143, 141, 147, 132, 170, 166, 135, 56, 139, 22, 138, 269, 173
Specific skin prick test	158, 167, 168, 154, 136, 143, 141, 170, 165, 144, 135, 137, 56, 177, 173
SIC	178, 136, 143, 141
	133, 156, 165, 144, 153, 56, 148, 150, 138
Serum specific IgE	158, 154, 174, 175, 271, 136, 143, 132, 171, 272, 159, 173

Table 9. Methodological quality of studies for the management of OA

	References
Report IPD	142, 158, 174, 163, 271, 178, 136, 143, 132, 4, 133, 165, 144, 130, 153, 151, 171, 135, 116, 56, 139, 148, 159, 150, 177, 152, 173
Data collection	
Prospective	134, 57, 142, 158, 167, 131, 55, 58, 164, 154, 174, 175, 163, 271, 178, 136, 143, 141, 147, 132, 179, 4, 270, 133, 145, 170, 172, 166, 165, 149, 169, 144, 130, 153, 151, 171, 135, 116, 137, 56, 139, 148, 159, 150, 177, 176, 140, 152, 138, 269, 173
Retrospective	22
Source of funding	
Government	142, 158, 167, 164, 271, 166, 130, 153, 22, 148
Other	174, 175, 178, 136, 143, 4, 133, 145, 171, 135, 138
Not reported	134, 57, 131, 55, 58, 154, 163, 141, 147, 132, 179, 270, 170, 172, 165, 149, 169, 144, 151, 116, 137, 56, 139, 159, 150, 177, 176, 140, 152, 269, 173

Chapter 4. Discussion

Diagnosis Systematic Review

This report summarizes all of the identified available scientific evidence relating to tests used for the diagnosis of OA. Before considering the usefulness of diagnostic tests in OA, it is important to recognize that perhaps the only unique characteristic of OA is that it is caused by workplace exposure. The symptoms, signs, results of many investigations, and the range of patho-physiologies encountered are similar to those of non-occupational asthma. Consequently, the tests that attempt to specifically diagnose OA must try to identify the causative asthmagen. Given that asthma does, by its very nature, demonstrate variability in symptoms, signs, and airflow limitation, this is unlikely to ever be a straightforward proposition.

Prior to determining the accuracy of diagnostic tests, a referenced standard must be available for comparison. The reference test in OA is SIC, described in detail in a previous section of this report. There are a number of issues that make this test problematic. First, SIC is not readily available in many countries[23], thus, this reference standard diagnostic test is not often employed in diagnostic research. Second, testing with some agents may involve considerable technical challenges, particularly outside of major centers. In addition, workers are often exposed to multiple asthmagens and it may be difficult to determine precisely which asthmagen is causing OA. If the worker is challenged with the incorrect asthmagen, a false negative test result can occur.

Further, the criteria used to signify a positive SIC test varies. A 15–20 percent drop in the measured airflow (FEV_1) generally signifies a "positive" response; however, other outcomes have also been used.[273-275] It is unclear how this corresponds with some important components in the definition of asthma, including inflammatory changes in the airways. Using outcome measures such as induced sputum may be one way of circumventing this problem but this is not, as yet, widely available.[276] Moreover, the reliability of the SIC is hard to determine. It seems likely that operator experience and volume-quality relationships are important in determining the validity of SIC testing but this has not to our knowledge been formally evaluated. Despite these limitations, SIC remains the best test available to use as a reference standard and we have elected to use this as our highest ranked "gold standard".

Using a comprehensive search strategy and methodologically rigorous approaches to identifying diagnostic studies, there were only sufficient data available for us to meaningfully analyze the following comparisons:

- SIC versus NSBP test;
- SIC versus skin prick testing;
- SIC versus serum specific IgE.

There were other comparisons identified in the search, such as serial PEFR, sputum eosinophilia, and clinical diagnosis. However, the insufficient volume of evidence comparing these diagnostic tests to SIC prevented drawing firm conclusions. From within the available evidence, there are some valuable observations that can be made. First, a single measurement of NSBP demonstrates moderate sensitivity and a somewhat lower specificity in predicting the

outcome of SIC. For HMW substances, the pooled estimate of sensitivity was 79.3 percent, while pooled specificity was 51.3 percent (positive likelihood ratio [LR+]=1.6; negative likelihood ratio [LR -]=0.4). It has been suggested that the sensitivity of a single NSBP test can be improved by measuring BHR within hours of exposure to the asthmagen.[90,105] It is important to recognize that these results are primarily derived from highly selected populations (usually either referred to a specialty clinic or seen as part of a workplace survey) and these results effectively represent a population with a high pre-test probability of disease. Presumably, the selection process of referral or participation in a workplace survey identified a relevant workplace exposure while NSBP confirmed asthma. Based on these data, we would suggest that a positive test would assist the clinician to rule-in OA without being completely confirmatory; however, a negative NSBP test would not rule-out OA unlikely, especially in lower-risk groups.

Second, immunological testing may be of importance, depending on the compounds tested. Clearly such testing will be more useful for those sensitizers that are known to work via an immunological response and may be of little use where immunological sensitizers are either unknown or not present. Overall, it appears that when compared to serum specific IgE, SPT shows higher sensitivity in comparison with SIC. It appears the converse is perhaps true for specificity. However, from these data is appears that SPT and serum specific IgE levels alone have limited sensitivity or specificity in at least some settings, and therefore cannot rule-in or rule-out OA with sufficient reliability to reassure the patient, the physician, or the employee of the presence or absence of OA.

Third, combining tests may enhance the specificity of testing and may be a suitable alternative to SIC in the diagnosis of OA in some people. The highest specificity seems to arise from a combination of a single measurement of NSBP test along with SPT or specific IgE in pre-screened patients. In a single study of a LMW asthmagen, combined tests provided a sensitivity of 100 percent and a specificity of 80.0 percent (LR+ = 4.2; LR- = 0.05). For NSBP test and SPT, the pooled sensitivity in HMW asthmagens is 60.6 percent and the specificity is 82.5 percent (LR+ = 3.5; LR- = 0.5). If it is assumed that clinical referral or participation in a workplace survey for suspected OA due to HMW asthmagen produces a high pre-test probability of disease (~50%), a positive combined test would support a diagnosis of OA (78% probability); negative combined testing would provide the clinician with limited certainty that OA was absent (33% probability). Further, in the setting of a lower pre-test probability (such as an un-screened sample of workers), the combined test is less confirmatory and more likely to rule-out OA.

Unfortunately, the body of research identified is insufficient to support other combinations as accurate substitutes for SIC. For example, the combination of a clinic referral, positive NSBP test, positive SPT, and positive serial peak flow monitoring has not been compared to SIC in sufficient detail to draw any conclusions. Moreover, serial testing has not been examined in sufficient detail to draw firm conclusions. While clinical diagnosis versus SIC resulted in high sensitivities among LMW, HMW, and mixed asthmagens, the specificity was lower. Moreover, due to the small number of studies for other relevant comparisons, we would be cautious in interpreting pooled estimates of sensitivity and specificity for some relevant comparisons such as serial peak flow recordings versus SIC.

A large number of different tests have been reported and used in an effort to reliably diagnose OA. In addition to SIC, these include single and serial NSBP test, serial peak flow recording, lung function testing, immunological testing, and inflammatory markers.

Unfortunately, there are few comparisons that are repeated with sufficient frequency to allow a meaningful analysis. There has been considerable interest in the use of serial PEFR in the diagnosis of OA. Surprisingly, a low sensitivity (63.6 percent; 95% CI: 43.4 to 79.9 percent) and specificity (77.2 percent; 95% CI: 66.5 to 85.2 percent) was reported for serial PEFR versus SIC among a number of mixed asthmagens. The sensitivity and specificity were higher among the one study that evaluated serial PEFR versus SIC in LMW asthmagens. This may have been related to technical issues in making the recordings, such as the timing of serial measurements and the proximity of these measurements to the on/off work cycle. Further, some combinations of these tests have been suggested as useful methods for diagnosing OA. For example, combining serial PEFR and symptom diaries is recommended as a method to diagnose OA[8]; however, few studies have specifically evaluated this method.

Although we had anticipated that there might be comparisons involving reference standards other than SIC, we were not able to identify sufficient comparisons utilizing these to undertake analyses that we would consider statistically meaningful. In some instances the paucity of comparative data were further compounded by the use of non-standardized methodology and the use of various end points. In addition, these studies related to different putative asthmagens and it is likely that these are associated with different mechanisms in causing OA; the performance of each of the tests may vary depending upon the agents involved in causing the asthma originally.

Further, within diagnostic test comparisons that included many studies, the sensitivity and specificity was inconsistent at predicting the outcome of SIC. Thus, although we have estimated a pooled sensitivity and specificity for some combinations of these tests we recommend caution in their interpretation. The pooled estimates of sensitivity and specificity tend to have wide confidence intervals and often the sensitivities and or specificities from individual tests ranged from 0 to 100 percent. The variation may reflect the wide range of agents that were causing OA, and hence the true reason for the tests' performance may be that the underlying mechanisms of OA are different.

Although the sensitivity and specificity of some of these tests appear to provide some value in assisting in the diagnosis of OA, it must be recognized that these results are generally produced from a very select population, as the majority of the included workers had been screened by either a questionnaire, referral to a specialist, or a medical/occupational history compatible with OA. Essentially, all the subjects who were involved in comparisons of SIC against other diagnostic techniques were pre-screened and therefore, had a high pre-test probability for testing positive to SIC. These data cannot and should not be generalized to an unselected, or unscreened population of workers. However, in a clinical setting where patients are being investigated for OA, most patients have undergone screening that is similar to that of subjects included in the studies. Alternatively, patients seen in specialty clinics by OA experts would require similar screening and that would produce similar high pretest probabilities of disease. Consequently, it may seem reasonable to apply the pooled estimates of sensitivity and specificity derived from these analyses to those groups.

The second question the diagnostic review tried to address was "in what situations would specific inhalation challenge testing provide additional useful diagnostic information?". Unfortunately we were unable to identify sufficient relevant studies that addressed the comparative usefulness of SIC as a diagnostic tool with different agents and in different settings. Consequently any advice about the situations where SIC should be applied must remain based on expert opinion and consensus until further evidence is available.

Management Systematic Review

This systematic review examined the best available evidence upon which to base management decisions for OA. From nearly 15,000 references, we identified 52 cohort studies and 13 CCT examining the treatment of OA. In general, the populations studied (etiological agents), study designs and quality, and outcomes reported varied considerably. Moreover, the majority of the interventions were non-randomized, so the rationale for the intervention decision was largely unknown. Overall, the primary questions proved too disparate and the results too heterogeneous to pool. Not withstanding the above concerns, some valuable general information does arise from this review.

Cohort

First, most OA reports indicate patients have mild-moderate airflow limitation, with most studies reporting >80 percent predicted FEV_1 at the time of initial assessment. We attempted to compare the different treatment groups using baseline percent predicted FEV_1 data as it related to exposure status (e.g., removed from exposure, reduced exposure, and remaining exposed) to ensure that selection for the various treatments was not unduly influenced by severity of disease at baseline (time of diagnosis). We had anticipated that patient groups removed from exposure at work might demonstrate the lowest group FEV_1 and those who continued exposure at work would demonstrate the highest group FEV_1. It does not appear, however, that a selection bias occurred with respect to subsequent work exposure based on baseline FEV_1 status. While formal statistical testing cannot be completed on these data, we argue that the display in Figure 10 demonstrates similar FEV_1 irrespective of subsequent exposure risk. Conclusions based on reduced exposure groups are complicated by the paucity of studies included in this comparison.

Second, given the available data on follow-up, the review team constructed a picture of the outcomes of workers with OA, based on their exposure status and duration of follow-up. Once again, due to the vagaries of reporting we have not been able to produce statistical analyses; however, the graphic display in Figure 11 suggests several important general summary comments. Most importantly, those who remain exposed (either partially or fully) experience continued deterioration in FEV_1 status compared to baseline and over time. In addition, most of those groups who are removed from their workplace appear to generally report improvement compared to baseline lung function at diagnosis. Despite removal, improvement does not appear to be dramatic nor progressive with time. Moreover, while most studies reported group improvement, some indicated deterioration, suggesting that the impact of OA is long-lived and difficult to "cure". Finally, in contradistinction to the diagnosis review, no clear trends were identified based on the LMW versus HMW sensitizer agent division with respect to clinical outcomes.

Third, similar results are demonstrated for the small group of studies where NSBP were recorded at baseline and at follow-up. Once again, those groups who remained exposed experienced continued deterioration in NSBP test results compared to baseline and over time. Almost all of those groups who report being removed from their workplace appeared to have improved compared to NSBP test results at the time of diagnosis. Improvement in non-specific BHR appears to be more impressive and progressive with time than FEV_1 results. Few groups

appeared to deteriorate, suggesting that continued exposure may be required for non-specific BHR to continue to decline. Conclusions based on reduced exposure groups are complicated by the paucity of studies included in this comparison. No clear trend was identified based on the LMW versus HMW asthmagen division.

Fourth, while many studies reported symptoms and/or improvement, the definitions and measurements were too variable to analyze quantitatively. Symptoms appeared to persist and potentially worsen among workers who continued exposure. The picture is less certain among workers who were removed; there was evidence that while some workers' symptoms improve after removal from exposure, other workers failed to improve. Among workers who reduced their exposure, symptoms abated in some workers but the overall effect seemed to be persistence of symptoms. Because symptoms were often measured subjectively and using different methods, this outcome is problematic in determining the effect of removal, reduction, and continuation of exposure.

Medication use was a confounder and outcome that was incompletely reported in the majority of studies; however, using available data, we attempted to examine the three exposure status groups based on their medication use at follow-up. The conclusions from these studies are harder to draw, due to small study numbers. Overall, workers with OA, irrespective of subsequent exposure, often require medication treatment long after diagnosis. No clear trend was identified based on the LMW versus HMW asthmagen division.

Finally, the economic consequences of developing OA are impressive. From the published literature, those who leave the workplace clearly suffer economic repercussions of reduced income and/or unemployment. Workers who reduce their exposure or stay employed at the same workplace still appear to lose income over time, and their costs of medication increase. Furthermore, medical insurance coverage among workers, an important consideration in the United States, is reduced after the diagnosis of OA.

Trials

There were a limited number of clinical trials performed in the OA field. Overall, the 13 included clinical trials were of only moderate methodological quality. For example, while eight (62 percent) were randomized, none reported their method of randomization; seven (54 percent) were double-blinded, yet none described their methods of ensuring double-blinding; and only two (15 percent) demonstrated adequate concealment of allocation. All studies reported losses to follow-up and withdrawals.

From the 13 clinical trials examining OA interventions, the total number of study patients is 210, with the largest trial enrolling only 32 patients. One study involved immunotherapy, two involved reducing exposure via protective measures and the remaining were medication studies. Overall, the immunotherapy results, based on a small overall sample (n=30 patients) examining wheat flour antigen, suggest spirometric, immunological, and symptomatic improvement when workers experiencing OA are treated with immunotherapy. A comprehensive Cochrane Review supports benefit from this therapeutic approach. From 75 trials involving 3,188 patients with asthma, Abramson et al. demonstrated that immunotherapy reduced asthma symptoms and the use of asthma medications and improved bronchial hyper-reactivity.[277] While this therapy may be as effective as ICS, it is complicated by its long duration (10–20 months), limited availability, and that many OA patients have a disease for which the relevant antigen for immunotherapy has yet to be identified. Finally, the possibility

of adverse effects, such as allergic reactions and anaphylaxis, is a concern for some patients. It is likely most patients either would not qualify or elect to use other forms of therapy.

Trial evidence examining reduction in exposure is limited to only two clinical trials. Evidence does suggest that protective devices can reduce bronchial obstruction; however, they failed to provide complete protection and workers were required to be compliant with their use. In the situation of latex allergy-induced OA, the use of non-latex or low protein, powder-free latex gloves in the work environment appears to be a successful method of improving OA symptoms and outcome measures.[123]

Finally, medication research in OA is limited and conclusions are difficult to draw. These medication trials suffer from small sample sizes, limited duration of treatment, and various dissimilar comparisons. Consequently, statistical pooling was not possible. In general, there is evidence that corticosteroid agents (both systemic and inhaled) are effective in the treatment of OA, although this was primarily evaluated in patients with di-isocyanate induced OA. Well recognized and parallel evidence is available regarding the effectiveness of corticosteroid treatments for chronic asthma from a variety of resources including guidelines and the Cochrane Library. Theophylline, a weak bronchodilator, reduced the severity of asthma exacerbations after SIC; however, airway responsiveness did not decrease. Other agents such as non-steroidal anti-inflammatories, calcium channel blockers, cromolyn, or placebo demonstrated limited or no benefit in the acute treatment of OA. Once again, these general effectiveness trends appear to be similar for OA and chronic asthma.

Potential Limitations

There is a possibility of publication bias in this systematic review. For example, by missing unpublished and/or poor performing diagnostic test studies, we may be over-estimating the psychometric properties of diagnostic tests. Also, by missing unpublished negative studies we may be over-estimating the effect of OA treatment. However, a comprehensive search of the published literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. This was followed by attempts to contact corresponding and first authors. Grey (i.e., unpublished or difficult to find) literature was repeatedly searched; some unpublished studies were identified and several negative studies were uncovered. Despite these efforts, we do recognize that more of these types of studies may exist.

There is also a possibility of study selection bias; however, we employed at least two independent reviewers, and feel confident that the studies excluded were done so for consistent and appropriate reasons. Our search was comprehensive, so it is unlikely that there are many studies in press or publication that were missed.

Overall, OA literature is not indexed well and authors are not consistently using the term "occupational asthma" in article titles or abstracts. Using the subject heading “occupational diseases” will pick up many relevant articles; however, this is a very sensitive heading and includes almost 75,000 references. A second issue is that some of the relevant articles do not mention the word “asthma” or any of the terms used to describe OA in lines 1–18 of the search strategy (see Appendix A♦). There are also a huge variety of allergens, such as chemicals, animals, and trees, which can potentially cause OA. It is impossible to account for every variation and term within the search strategy. Knowing this, the strategy was designed to be

♦ **The Appendices and Evidence Tables cited in this report are provided electronically at** http://www.ahrq.gov/downloads/pub/evidence/pdf/asthmawork/asthwork.pdf

highly sensitive in order to avoid missing any potentially relevant articles. In addition, 10 databases were searched in order to retrieve as many pertinent studies as possible.

The classification of agents into HMW and LMW is of relevance because of their likely differing mechanisms and the implications this has for diagnostic tests. While for many agents the relevant allergens are well characterized, this classification was not without problems. For example, while grain dust contains a number of HMW agents, it likely also contains other constituents that may be LMW, or that work by other mechanisms. There was one study included in the diagnosis section of this review that examined grain dust; there is some controversy regarding the classification of grain dust as a HMW or mixed asthmagen. It is noteworthy that when this study is included with other HMW asthmagens for comparisons to SIC with NSBP test and SPT, estimates yielded a pooled sensitivity of 60.6 and specificity of 82.5. When this study is excluded from the comparison, the sensitivity and specificity improve to 83 and 100, respectively. Further combination testing research is needed to resolve this debate.

For other agents, such as platinum, their mechanism of action may be a more important characteristic than their molecular weight, but characterization by molecular weight seemed the best categorization available. Analyses of results by other methods of categorization were not undertaken. The results are presented to allow for the calculation of an individual asthmagen's sensitivity and specificity.

Diagnosis Review

The evidence concerning the harms (false positive and false negative) of diagnosis of OA is even less developed than the evidence for the benefits. Essentially, these patients have not been followed for the anxiety of an incorrect diagnosis, nor have the consequences been followed in any comprehensive manner. Costs of asthma care are largely borne by the patients, families, and the employers, and the costs of OA care are largely borne by the same groups. Falsely diagnosing respiratory symptoms as OA may force patients to inappropriately change work or become unemployed. Not diagnosing respiratory symptoms as OA when such is the case may lead patients to further asthmagen exposure, worsening health, impaired QOL, and later unemployment without compensation.

While SIC is considered the reference standard test in the diagnosis of OA, some studies did not have this result available for all patients, if at all. Some studies used a clinical "consensus" diagnosis to determine the presence of OA, which may or may not have included SIC in the diagnostic process, and it was usually not clear which patients had undergone SIC and why. In other studies, only data from patients who had a positive SIC result were reported. Two forms of bias may be present as a result of these characteristics: different reference standard bias and partial verification bias.[70] For HMW agents, we noted that the sensitivity generated from SIC positive subjects was similar to that generated from workers with suspected OA in two of the three comparison tests we considered in depth (single NSBP testing and specific SPT). Among LMW asthmagens, the sensitivity of SPT was substantially lower in studies when only SIC positive subjects were included in the study.

The studies included in the diagnosis review display considerable heterogeneity. This heterogeneity likely arises because many different asthmagens can cause OA and the diagnostic tests do not behave identically among the various asthmagens. Unfortunately, there were not enough studies to pool sensitivities and specificities by the specific asthmagen; however, in an

effort to reduce heterogeneity, the results are presented by HMW and LMW and subgrouped by the specific asthmagen. Because of the heterogeneity between studies, pooled results for sensitivity and specificity are presented separately for each of the comparison tests. A drawback to this approach is that because the calculations are done independently, the pooled results of sensitivity and specificity are not explicitly paired as they are for each of the contributing studies. The plots of sensitivity/specificity pairs in ROC space demonstrate this artifact but do not allow for a link to the detail on specific asthmagen which we believe is valuable to the reader. Controversy exists with respect to pooling of heterogeneous data. Some would argue that the pooling in this setting is unhelpful and potentially misleading, while others believe this approach provides the best estimate of the test property. We have utilized random effects modeling, as appropriate for pooling heterogenous studies. However, we advise the reader to use caution in interpreting the results presented in this report, but believe that the utility of these values should be judged by the reader. We have provided sufficient data to recalculate the sensitivity and specificity for a number of specific asthmagens. This will allow clinicians to calculate the most appropriate pooled result for use in their practice.

Among the included studies, there were various definitions of a positive test result and different protocols were used to conduct the same test. For example, a positive test result for a single NSBP test was frequently reported as PC_{20} or PD_{20} $FEV_1 \leq 8$ or 16 mg. Similarly for SPT, studies reported a positive SPT as ≥ 3 mm or compared the size of the reaction among workers with suspected OA to the size among a control population. For the purpose of this review, we treated one SIC methodology to be equivalent to another; this report does not attempt to evaluate the various methodologies used to conduct SIC.

A further limitation was that not all studies we identified were designed to be diagnostic studies and the data presented were not in a useful form to evaluate the diagnostic accuracy of a comparison test. That is, it had to be possible to generate a 2 x 2 or 2 x 1 table of the reference standard test result with a comparison test result based on one or more cut-offs of the comparison test. It is not possible to use results presented as a difference between mean values of the comparison test when grouped by the reference test result. In other cases, IPD data were available; however, the absence of an established cut-off value to define a "positive" test excluded these results. Resources and/or the long length of time between the publication of the results to the writing of this report precluded contact with most authors to obtain the necessary data in a usable form. This would have increased the number of studies that could be pooled in some of the comparisons.

Management Review

The main limitation of the management review is that the design of the included studies was weak. For example we found very few RCTs and the methodological quality of these was, at best, moderate. Most importantly, the interventions were generally divided into removal, reduced exposure, or continued exposure; however, the definition of these approaches differed and allocation was non-randomized.

Another limitation of the management studies is that the populations differed considerably. For example, while all groups attempted to confirm the diagnosis of OA, the methods used varied and the types of asthmagens that workers were exposed to differed. We attempted to retain the HMW versus LMW division employed in the diagnostic section of the review to

investigate the heterogeneity of the results; however, this was not helpful. Treatment co-interventions were also incompletely reported in these studies.

Finally, the outcome assessments were often not comparable and tended to focus on short-term spirometric results (e.g., pulmonary function tests, NSBP test, SIC, etc.) rather than QOL. There was variability in length of follow-up within and between studies, making pooling difficult. Only four studies had repeated outcome measurements at different follow-up times for the same cohort.

Conclusions

OA is an important health care problem, particularly in certain work settings: paint use and production (di-isocyanates), the lumber industry (red cedar), bakers (flour), health care workers (latex), and other occupations. Workers with this disease generally present with respiratory symptoms such as cough, wheeze, shortness of breath, and exercise intolerance. Diagnosis and management of OA is designed to reduce morbidity and improve QOL; fortunately, mortality is rare, unless severe sensitivities exist.

Diagnosing OA is a contentious and hotly debated issue, largely because of the social and economic implications of the diagnosis to the employer and the employee. Furthermore, controversy exists because of the relative paucity of high-quality research in this field. Until such time as there is considerable more high quality information on which to base decisions, the findings from this systematic review may be unsatisfying to some.

Following a comprehensive search and selection of the electronic and grey literature using English and foreign language literature, we identified a large number of studies examining diagnostic tests in OA. Based on the evidence, the following conclusions can be made:

- The general weaknesses associated with the quality and quantity of the research evidence suggests that caution should be used in interpreting these results;
- In the diagnosis review, the sensitivities and specificities varied widely for some of the comparison tests. We elected to pool heterogeneous data from individual studies, but would encourage clinicians to interpret these results cautiously and conservatively. Moreover, we have provided sufficient data to allow clinicians to calculate values that would be most useful in their practice.
- Overall, SIC appears to be the main reference standard for the diagnosis of OA; however, its availability is limited where studied;
- If SIC is not available and the population has a high pre-test probability (e.g., screened by history, questionnaire, and/or referral to a specialist), a single NSBP testing is a common test that assists in supporting the diagnosis and is of some use in excluding OA. Its sensitivity and specificity alone are insufficiently discriminative to definitively diagnose OA;
- In isolation, none of the diagnostic tests (NSBP test, SPT, serum specific IgE, serial PEFR, serial NSBP test, etc.) yielded a sufficiently high combination of sensitivity and specificity which would be required for a test to be a used routinely as a substitute for the reference standard used in this report (SIC);
- The specificity of NSBP testing can be enhanced by the addition of other testing, especially SPT or serum specific IgE;

- Many other combination tests (e.g., repeat of the NSBP testing which demonstrates decreases associated with removal from the workplace, serum specific IgE, serial peak flow, etc.) have not be evaluated in sufficient detail to provide recommendations;
- While current clinical recommendations suggest a diagnosis be made by examining the results of a number of sequential tests, we did not find sufficient data to evaluate this option.

Following a similar comprehensive search, we identified a moderate number of studies examining the treatment of OA. Based on the evidence, the following conclusions can be drawn:

- The general, weaknesses associated with the methodological quality of the research evidence suggests that caution should be used in interpreting these results;
- Overall, the baseline FEV_1 does not appear to predict which worker groups will leave the workplace or remain exposed (either partially or fully);
- Workers with OA who remain exposed to the workplace asthmagens tend to experience decreased FEV_1 over time, increased non-specific BHR, and will continue to require medications to control their symptoms;
- Most workers with OA who cease being exposed to the workplace sensitizer appear to experience improved FEV_1 over time and less non-specific BHR; despite these improvements, many workers will continue to require medications to control their symptoms;
- Some workers with OA can be expected to continue to experience a decrease in their FEV_1 over time despite ceasing sensitizer exposure;
- The evidence of outcome for workers who reduce their exposure is insufficient to draw firm conclusions but from the limited evidence, it seems likely they continue to have ongoing disease;
- In general, the anti-inflammatory agents (i.e., preventers) appear to be effective short-term therapy for OA; however, limited OA-specific research has been performed.

Future Research Opportunities

Overall, this area is fraught with heterogeneity and methodological problems. It would be helpful if the methodology used in this field could be further standardized. Further, given the small number of patients reported in each study, perhaps a larger (national) agenda for the diagnosis and treatment of OA is needed. Collaborative efforts to resolve the many remaining issues will require sufficient funding, multi-centered collaboration, and innovative thinking.

The following future research priorities are recommended:

- Future OA studies should use common and internationally accepted definitions for asthma severity, other relevant population characteristics, and outcome measures;
- There in an urgent need for clear comparisons between reference standards (preferably SIC) and alternative test approaches, performed independently, and reported using standardized diagnostic test methods (sensitivity, specificity, and likelihood ratios). Combinations of comparison tests should also be assessed;

- Studies comparing diagnostic tests should ideally collect information regarding the cost of diagnosis, time to complete diagnosis, and presence of adverse events;
- SIC is not widely available and the presence of OA is often determined by non-reference standard testing. A prospective cost-benefit analysis of the non-reference standard procedures should be conducted to determine the costs and benefits associated with using tests other than SIC to determine the presence or absence of OA;
- There is an urgent need for prospective long-term outcome studies to further understand the outcomes of OA using standardized reporting;
- Longer-term medication studies are under-represented in the present literature. It is imperative to develop an evidence base that supports clinical decision making on the intensity of treatment, optimization of medication regimens, and utility of disease management interventions for various OA populations;
- There is limited evidence specifically examining work-aggravated asthma and OA without latency. Greater research is needed to determine optimal diagnostic and management techniques of these types of OA;
- Priority should be given to ensuring the highest methodological quality of the research and reporting of research conducted to investigate the diagnosis and treatment of OA;
- Because many workers with OA do not appear to improve, research should also focus on the primary prevention of OA.

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Excluded Studies

Four hundred and sixty-one studies were excluded from the review. Reasons for exclusion include: study design (n=164), inappropriate topic (n=124), population (n=63), inadequate data (n=58), and no treatment or tests (n=13). The reports of 38 studies were unobtainable at the time of this writing and one was realized upon completion of the final report.

Study Design

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Inappropriate Topic

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Addendum

After the review was completed, the authors were made aware of the following study:

1. Sastre J, Fernandez-Nieto M, Rico P et al. Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. J Allergy Clin Immunol 2003;111:985-94.

Abbreviations

ACCP: American College of Chest Physicians
AC: Azodicarbonamide
BHR: Bronchial hyper-responsiveness
C: Current
CAP: Developed by Pharmacia Diagnostics for measuring specific IgE
cbu: Cumulative breath unit
CCT: Controlled clinical trial
CI: Confidence intervals
CO-HSA: Conjugated human serum albumin
cpm: Counts per minute
CS: Corticosteroids
DCP: Diagnostics products corp.
EAST: Enzyme allergosorbent test
ECG: Electrocardiogram
ECP: Eosinophilic cationic protein
ECSC: European coal and steel community
ED: Emergency department
ELISA: Enzyme-linked immuno sorbent assay
EIB: Exercise-induced bronchoconstriction
eNO: Exhaled nitric oxide
Ex: Ex
FEF: Forced expiratory flow
FEV_1: Forced expiratory volume in one second
FU: Follow-up
FVC: Forced vital capacity
H: High
HDI: Hexamethylene di-isocyanate
HHPA: Hexahydrophthalic anhydride
HMW: High molecular weight
ICS: Inhaled corticosteroids
IL-8: Interleukin-8
IQR: Interquatrile range
kPa: Kilopascal
L: Low
LABA: Long acting beta-agonists
LKTRA: Leukotriene receptor antagonists
LMW: Low molecular weight
LR: Likelihood ratios
M: Mixed
MCP-1: Monocyte chemoattractant protein-1
MDI: Diphenylmethane di-isocyanate
MEF: Maximal expiratory flow
MEF_{25}: Maximal expiratory flow at 25% of vital capacity

MEF_{50}: Maximal expiratory flow at 50% of vital capacity
MPO: Myeloperoxidase
MSDS: Material safety data sheet
N: Never
NDI: Naphthalene di-isocyanate
NRL: Natural rubber latex
NSBP test: Non-specific bronchial provocation test
NSBR: Non-specific bronchial reactivity
OA: Occupational asthma
OASYS-2: Occupational asthma systems
OD: Optical density
PaO_2: Arterial oxygen partial pressure
PC_{20}: Provocative concentration causing a 20% drop in FEV_1
PD_{15}: Provocative dose causing a 15% drop in FEV_1
PD_{20}: Provocative dose causing a 20% drop in FEV_1
PD_{50}: Provocative dose causing a 50% drop in FEV_1
PEF: Peak expiratory flow
PEFR: Peak expiratory flow rate
PFT: Pulmonary function test
PPE: Personal protective equipment
PRIST: Paper radioimmunosorbent test
PTRIA: Polystyrene-tube radioimmunoassay
PRU: Phadebas RAST units
QOL: Quality of life
RADS: Reactive airways dysfunction syndrome
RAST: Radio allegro sorbent test
RCT: Randomized controlled trial
REIA: Reverse enzyme immunoassay
RIA: Radioimmunoassay
RIACT: Radioimmunoassay kit for measuring IgE
RV: Residual volume
USD: United States dollar
SABA: Short acting beta-agonists
SD: Standard deviation
SDS: Sodium dodecyl sulphate
SEM: Standard error of the mean
sGaw: Specific airways conductance
SIC: Specific inhalation challenge
SOB: Shortness of breath
SPBRIA: Solid-phase bead radioimmunoassay;
SPT: Skin prick test
sRAW: Specific airway resistance
SWORD: Surveillance of work-related occupational respiratory disease
TCPA: Tetrachlorophthalic anhydride
TCPA-HSA: Tetrachlorophthalic anhydride human serum albumin
TDI: Toluene di-isocyanates

TDI-HSA: Toluene di-isocyanates human serum albumin
TEP: Technical expert panel
TLco: Single breath carbon monoxide
TMA: Trimellitic anhydride
WCB: Workers' Compensation Board
IU: International unit
UniCAP: Fluoroenzymeimmunoassay kit developed by Pharmacia Diagnostics
Vmax: Maximum flow

Appendix A: Exact Search Strings

Diagnosis of Occupational Asthma Searches

Table A-1: Agricola and Biological Abstracts
Table A-2: Cinahl
Table A-3: Embase
Table A-4: Medline
Table A-5: Web of Science

Management of Occupational Asthma Searches

Table A-6: Agricola and Biological Abstracts
Table A-7: Cinahl
Table A-8: Cochrane Airways Group
Table A-9: Embase
Table A-10: Medline
Table A-11: Web of Science

Occupational Asthma Searches

Table A-12: Dissertation Abstracts
Table A-13: Expanded Academia
Table A-14: NASD

Table A-1. Agricola and Biological Abstracts: Diagnosis of occupational asthma (1970 to September 2003)

Set # and Keyword Search
1. (asthma or wheez* or respiratory sound* or airway obstruction* or airway*
2. (respiratory or pneumonitis or alveol* or bronchial or airway* or lung*) silo filler* disease or bird fancier* lung or pneumoconiosis or baker* or skin prick* or respiratory function test* or bronchial provocation test* or work caus* or work aggravat* or concurrent or job or employ* or occupation*
3. 1 or 2
4. (occupational disease* or agricultural worker* disease* or farmer* lung or
5. (animal* or fowl or farmer* or pheasant* or bird* or pigeon* or hen or
6. occupation* asthma*
7. 4 or 5
8. 3 and 7
9. 6 or 8 and (hypersensitiv* or hyperreactiv* or hyper reactiv* or allerg* or breath test* or spirometry or spirometr* or bronchospirometry or physical bronchial responsive* or nsbr or nsbh or bronchospas* or bronchoconstric* or chloride or immunologic test* or immunosorbent technique* or skin test* or dysfunction* or airway obstruct* or reactive airway* or lung disease* or epoxy resin* or latex or red cedar* or occupation* air pollutant* or exam* or medical history taking or questionnaire*) expiratory flow rate* or pef or pefr or forced expiratory volume or fev1 or expiratory flow-volume curve* or maximal midexpiratory flow rate* or peak forced expiratory flow rate* or maximal expiratory flow rate* or maximal grain* or industry or worker* or worksite* or work site* or work relat* or handler*) (hens) and (fancier* or worker* or breeder* or keeper* or raiser* or hyperreactiv* or bronchial spasm* or bronch* spas* or bronchial disease* or hyperresponsiv* or non specific bronchial responsive* or non-specific inhalation expos* or occupational expos* or di-isocynate* or isocynate* or insufficien*) methacholine or pulmonary or inhal* or antigen* or allergen* or hypertonic monitor* or measur* or provocation) non specific bronchial hyperresponsiv* or nonspecific bronchial obstructive lung disease* or respiratory tract disease or bronchial occupational airway*) or environment* or workplace or employment or environmental expos* or isocapnic or hyperosmolar) and (challenge* or test or tests or testing or rhonchi or twitchy airway*)
10. (induced sputum* or inhalation challeng* or peak flow* or methacholine
11. (bronchial or carbachol or serial or cold air or histamine* or
12. 10 or 11
13. 9 and 12

Table A-2. Cinahl: Diagnosis of occupational asthma (1982 to February Week 1 2004)

Set # and Keyword Search
1. asthma/ or asthma$.tw.
2. wheez$.tw.
3. respiratory sounds/
4. airway obstruction/
5. (airway$ adj3 (dysfunction$ or obstruct$)).tw.
6. reactive airway$.tw.
7. lung diseases/
8. lung diseases, obstructive/
9. respiratory tract diseases/
10. bronchial hyperreactivity/
11. bronchial spasm/ or (bronch$ adj5 spas$).tw.
12. bronchial diseases/
13. (non specific bronchial hyperresponsiv$ or nonspecific bronchial hyperresponsiv$).tw.
14. (non specific bronchial responsiv$ or nonspecific bronchial responsiv$).tw.
15. (nsbr or nsbh).tw.
16. (bronchospas$ or bronchoconstric$ or rhonchi).tw.
17. twitchy airway$.tw.
18. (respiratory or pneumonitis or alveol$ or bronchial or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or hyper reactiv$ or allerg$ or insufficien$)).mp.
19. or/1-18
20. occupational diseases/
21. pneumoconiosis/
22. ((animal$ or fowl or farmer$ or pheasant$ or bird$ or pigeon$ or hen or hens) adj3 (fancier$ or worker$ or breeder$ or keeper$ or raiser$ or handler$)).mp.
23. (baker$ or grain$).tw.
24. exp industry/
25. (worker$ or worksite$ or work site$ or work relat$ or work caus$ or work aggravat$ or concurrent or job or employ$ or occupation$ or environment$).tw.
26. (workplace or employment).mp.
27. environmental exposure/
28. occupational exposure/
29. (environmental exposur$ or inhalation exposur$ or occupational exposur$).mp.
30. (di-isocynate$ or isocynate$).tw.
31. (epoxy resin$ or latex or red cedar$).mp.
32. air pollutants, occupational/
33. occupational airway$.mp.
34. (occupation$ adj5 asthma$).mp.
35. or/20-33
37. 19 and 35
38. 37 or 34
39. induced sputum$.tw.
40. inhalation challeng$.tw.
41. ((bronchial or carbachol or serial or cold air or histamine$ or methacholine or pulmonary or inhal$ or antigen$ or allergen$ or hypertonic or isocapnic or hyperosmolar) adj3 (challenge$ or test or tests or testing or monitor$ or measur$ or provocation)).tw.
42. peak flow$.tw.
43. methacholine chloride/du
44. immunologic tests/ or exp immunosorbent techniques/
45. exp skin tests/ or skin prick$.mp.
46. respiratory function tests/
47. bronchial provocation tests/
48. forced expiratory flow rates/
49. maximal expiratory flow rate/
50. maximal expiratory flow-volume curves/
51. peak expiratory flow rate/
52. (pef or pefr).tw.
53. forced expiratory volume.mp. or fev1.tw.
54. breath tests/
55. spirometry/ or spirometr$.tw.
56. physical examination/

Table A-2. Cinahl: Diagnosis of occupational asthma (1982 to February Week 1 2004) (continued)

Set # and Keyword Search
57. medical history taking/
58. questionnaires/
59. diagnostic techniques, respiratory system/
60. or/39-59
61. diagnostic accuracy.tw.
62. exp diagnosis/
63. diagnos$.tw.
64. "sensitivity and specificity"/
65. (sensitivity or specificity).tw.
66. (predictive adj4 value$).tw.
67. diagnostic errors/
68. false negative reactions/
69. false positive reactions/
70. (false negativ$ or false positiv$).tw.
71. observer variation$.mp.
72. ((roc or receiver operating) adj curve$).tw.
73. roc curve/
74. (likelihood adj4 ratio$).tw.
75. likelihood function/
76. (di or du or et or ae or ci).fs.
77. or/61-76
78. and/38,60,77
79. limit 78 to (newborn infant <birth to 1 month>or infant <1 to 23 months>or preschool child <2 to 5 years>or child <6 to 12 years>or adolescence <13 to 18 years>)
80. 78 not 79
81. limit 80 to (case study or review)
82. 80 not 81

Table A-3. Embase: Diagnosis of occupational asthma (1988 to January Week 0 2004)

Set # and Keyword Search
1. asthma/
2. asthma$.tw.
3. Wheezing/
4. wheez$.tw.
5. abnormal respiratory sound/
6. breathing disorder/
7. Airway Obstruction/
8. respiratory tract disease/ or bronchus disease/ or lung disease/ or respiratory distress/ or respiratory function disorder/ or respiratory tract inflammation/
9. reactive airway$.tw.
10. ((airway$ or lung$) adj3 (dysfunction$ or obstruct$)).tw.
11. Bronchus Hyperreactivity/
12. Bronchospasm/
13. (bronch$ adj3 (disease$ or spas$)).tw.
14. (non-specific bronchial hyperresponsiv$ or nonspecific bronchial hyperresponsiv$).tw.
15. (non-specific bronchial responsiv$ or nonspecific bronchial responsiv$).tw.
16. (nsbr or nsbh).tw.
17. (bronchospas$ or bronchoconstrict$ or rhonchi).tw.
18. twitchy airway$.tw.
19. ((respiratory or pneumonitis or alveol$ or bronchial or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or hyper reactiv$ or allerg$ or insufficien$)).mp.
20. Lung Insufficiency/
21. or/1-20
22. occupational disease/ or occupational allergy/ or occupational lung disease/
23. bird breeder lung/
24. allergic pneumonitis/
25. Pneumoconiosis/
26. ((animal$ or fowl or farmer$ or pheasant$ or bird$ or pigeon$ or hen or hens) adj3 (fancier$ or worker$ or breeder$ or keeper$ or raiser$ or handler$)).mp.
27. farmer$ lung.tw.
28. ((agricultur$ or silo filler$) adj3 disease$).tw.
29. (baker$ or grain$).tw.
30. (worker$ or worksite$ or work site$ or work relate$ or work cause$ or work aggravat$ or concurrent or job or employ$ or occupation$ or environment$).mp.
31. work/ or work environment/
32. exp worker/
33. environmental exposure/
34. exposure/
35. occupational exposure/
36. (environment$ exposur$ or inhalation exposur$ or occupation$ exposur$).tw.
37. Isocyanate/
38. (di-isocynate$ or isocyanate$).mp.
39. (Epoxy Resin or latex or "red cedar").mp.
40. air pollutant/
41. occupational airway$.tw.
42. (occupation$ adj5 asthma$).mp.
43. exp Occupational Asthma/
44. 42 or 43
45. or/22-41
46. 21 and 45
47. 46 or 44
48. sputum analysis/
49. induced sputum$.tw.
50. provocation test/

Table A-3. Embase: Diagnosis of occupational asthma (1988 to January Week 0 2004) (continued)

Set # and Keyword Search
51. inhalation challenge$.tw.
52. ((bronchial or carbachol or serial or cold air or histamine$ or methacholine or pulmonary or inhal$ or antigen$ or allergen$ or hypertonic or isocapnic or hyperosmolar) adj3 (challenge$ or test or tests or testing or monitor$ or measur$ or provocation)).tw.
53. METHACHOLINE CHLORIDE/
54. enzyme linked immunosorbent assay/
55. ((bronchial or carbachol or serial or cold air or histamine$ or methacholine or pulmonary or inhal$ or antigen$ or allergen$ or hypertonic or isocapnic or hyperosmolar or immunologic$) adj3 (challenge$ or test or tests or testing or monitor$ or measur$ or provocation)).tw.
56. skin test/
57. prick test/
58. exp lung function test/
59. inhalation test/
60. forced expiratory flow/
61. forced expiratory volume/
62. maximal expiratory flow$.tw.
63. (maximal expiratory flow$ or maximal midexpiratory flow$).tw.
64. peak expiratory flow/
65. (pef or pefr).tw.
66. peak flow.tw.
67. (forced expiratory volume or fev1).tw.
68. breath analysis/
69. breath test$.tw.
70. spirometr$.tw.
71. bronchospirography/
72. bronchospirometry.tw.
73. physical examination/
74. anamnesis/
75. questionnaire/
76. exp respiratory tract examination/
77. or/48-76
78. diagnostic accuracy/
79. exp diagnosis/
80. diagnos$.tw.
81. "sensitivity and specificity"/
82. (sensitivity or specificity).tw.
83. (predictive adj4 value$).tw.
84. diagnostic error/
85. (false negativ$ or false positiv$).tw.
86. observer variation$.mp.
87. roc curve/
88. receiver operating characteristic/
89. (likelihood adj4 ratio$).tw.
90. statistical model/
91. (di or du or et or ae or ci).fs.
92. or/78-91
93. and/47,77,92
94. limit 93 to (embryo <first trimester>or infant <to one year>or child <unspecified age>or preschool child <1 to 6 years>or school child <7 to 12 years> or adolescent <13 to 17 years>)
95. 93 not 94
96. limit 95 to (report or review)
97. 95 not 96
98. exp case report/
99. 97 not 98

Table A-4. Medline: Diagnosis of occupational asthma (1966 to January Week 3 2004)

Set # and Keyword Search
1. asthma/ or asthma$.tw.
2. wheez$.tw.
3. respiratory sounds/
4. airway obstruction/
5. (airway$ adj3 (dysfunction$ or obstruct$)).tw.
6. reactive airway$.tw.
7. lung diseases/
8. lung diseases, obstructive/
9. respiratory tract diseases/
10. bronchial hyperreactivity/
11. bronchial spasm/ or (bronch$ adj5 spas$).tw.
12. bronchial diseases/
13. (non specific bronchial hyperresponsiv$ or nonspecific bronchial hyperresponsiv$).tw.
14. (non specific bronchial responsiv$ or nonspecific bronchial responsiv$).tw.
15. (nsbr or nsbh).tw.
16. (bronchospas$ or bronchoconstric$ or rhonchi).tw.
17. twitchy airway$.tw.
18. ((respiratory or pneumonitis or alveol$ or bronchial or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or hyper reactiv$ or allerg$ or insufficien$)).mp.
19. or/1-18
20. occupational diseases/
21. agricultural workers' diseases/
22. farmer's lung/
23. silo filler's disease/
24. bird fancier's lung/
25. pneumoconiosis/
26. ((animal$ or fowl or farmer$ or pheasant$ or bird$ or pigeon$ or hen or hens) adj3 (fancier$ or worker$ or breeder$ or keeper$ or raiser$ or handler$)).mp.
27. (baker$ or grain$).tw.
28. exp industry/
29. (worker$ or worksite$ or work site$ or work relat$ or work caus$ or work aggravat$ or concurrent or job or employ$ or occupation$ or environment$).tw.
30. (workplace or employment).mp.
31. environmental exposure/
32. inhalation exposure/
33. occupational exposure/
34. (environmental exposur$ or inhalation exposur$ or occupational exposur$).mp.
35. (di-isocynate$ or isocynate$).tw.
36. (epoxy resin$ or latex or red cedar$).mp.
37. air pollutants, occupational/
38. occupational airway$.mp.
39. (occupation$ adj5 asthma$).mp.
40. or/20-39
41. 19 and 40
42. 39 or 41
43. induced sputum$.tw.
44. inhalation challeng$.tw.
45. ((bronchial or carbachol or serial or cold air or histamine$ or methacholine or pulmonary or inhal$ or antigen$ or allergen$ or hypertonic or isocapnic or hyperosmolar) adj3 (challenge$ or test or tests or testing or monitor$ or measur$ or provocation)).tw.
46. peak flow$.tw.
47. methacholine chloride/du
48. immunologic tests/ or exp immunosorbent techniques/
49. exp skin tests/ or skin prick$.mp.
50. respiratory function tests/

Table A-4. Medline: Diagnosis of occupational asthma (1966 to January Week 3 2004) (continued)

Set # and Keyword Search
51. bronchial provocation tests/
52. forced expiratory flow rates/
53. maximal expiratory flow rate/
54. maximal expiratory flow-volume curves/
55. maximal midexpiratory flow rate/
56. peak expiratory flow rate/
57. (pef or pefr).tw.
58. forced expiratory volume.mp. or fev1.tw.
59. breath tests/
60. spirometry/ or spirometr$.tw.
61. bronchospirometry/
62. physical examination/
63. medical history taking/
64. questionnaires/
65. diagnostic techniques, respiratory system/
66. or/43-65
67. diagnostic accuracy.tw.
68. exp diagnosis/
69. diagnos$.tw.
70. "sensitivity and specificity"/
71. (sensitivity or specificity).tw.
72. (predictive adj4 value$).tw.
73. diagnostic errors/
74. false negative reactions/
75. false positive reactions/
76. (false negativ$ or false positiv$).tw.
77. observer variation$.mp.
78. ((roc or receiver operating) adj curve$).tw.
79. roc curve/
80. (likelihood adj4 ratio$).tw.
81. likelihood function/
82. (di or du or et or ae or ci).fs.
83. or/67-82
84. and/42,66,83
85. limit 84 to (all infant <birth to 23 months> or all child <0 to 18 years> or newborn infant <birth to 1 month> or infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescent <13 to 18 years>)
86. 84 not 85
87. limit 86 to (case reports or review or review, academic or review literature or review, tutorial)
88. 86 not 87

Table A-5. Web of Science: Diagnosis of occupational asthma (1966 to January Week 3 2004)

Set # and Keyword Search
1. Burge PS, O'Brien IM, Harries MG. Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. Thorax 1979;34:317-323.
2. Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of pc20 and peak expiratory flow rate in cedar asthma. J Allergy Clin Immunol 1990;85:592-598.
3. Perrin B, Lagier F, L'Archeveque J, Cartier A, Boulet LP, Cote J, Malo JL. Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge. Eur Respir J. 1992;5:40-8.

Table A-6. Agricola and Biological Abstracts: Management of occupational asthma (1970 to September 2003)

Set # and Keyword Search
1. (asthma or wheez* or respiratory sound* or airway obstruction* or airway* dysfunction* or airway obstruct* or reactive airway* or lung disease* or obstructive lung disease* or respiratory tract disease or bronchial hyperreactiv* or bronchial spasm* or bronch* spas* or bronchial disease* or non specific bronchial hyperresponsiv* or nonspecific bronchial hyperresponsiv* or non specific bronchial responsive* or non-specific bronchial responsive* or nsbr or nsbh or bronchospas* or bronchoconstric* or rhonchi or twitchy airway*)
2. (respiratory or pneumonitis or alveol* or bronchial or airway* or lung*) and (hypersensitiv* or hyperreactiv* or hyper reactiv* or allerg* or insufficien*)
3. 1 or 2
4. (occupational disease* or agricultural worker* disease* or farmer* lung or silo filler* disease or bird fancier* lung or pneumoconiosis or baker* or grain* or industry or worker* or worksite* or work site* or work relat* or work caus* or work aggravat* or concurrent or job or employ* or occupation* or environment* or workplace or employment or environmental expos* or inhalation expos* or occupational expos* or di-isocynate* or isocynate* or epoxy resin* or latex or red cedar* or occupation* air pollutant* or occupational airway*)
5. (animal* or fowl or farmer* or pheasant* or bird* or pigeon* or hen or hens) and (fancier* or worker* or breeder* or keeper* or raiser* or handler*)
6. occupation* asthma*
7. 4 or 5
8. 3 and 7
9. 6 or 8
10. (work or job or occupation* or profession* or employe*) and (remov* or modif* or adjust* or transfer* or alter* or leave or terminat* or cease or cessation or return*)
11. change and (employe* or work* or occupation* or work* or process* or procedur*)
12. (prevent* or reduc* or eliminat* or minimiz* or minimis* or minimal* or control*) and (expos* or agent* or irritant* or sensitizer*) 13 (change or retrain* or alter*) and (employe* or work* or occupation* or work* or process* or procedur*)
14. 10 or 11 or 12 or 13
15. 9 and 14

Table A-7. Cinahl: Management of occupational asthma (1982 to February Week 1 2004)

Set # and Keyword Search
1. asthma/ or asthma$.tw.
2. wheez$.tw.
3. respiratory sounds/
4. airway obstruction/
5. (airway$ adj3 (dysfunction$ or obstruct$)).tw.
6. reactive airway$.tw.
7. lung diseases/
8. lung diseases, obstructive/
9. respiratory tract diseases/
10. bronchial hyperreactivity/
11. bronchial spasm/ or (bronch$ adj5 spas$).tw.
12. bronchial diseases/
13. (non specific bronchial hyperresponsiv$ or nonspecific bronchial hyperresponsiv$).tw.
14. (non specific bronchial responsiv$ or nonspecific bronchial responsiv$).tw.
15. (nsbr or nsbh).tw.
16. (bronchospas$ or bronchoconstric$ or rhonchi).tw.
17. twitchy airway$.tw.
18. ((respiratory or pneumonitis or alveol$ or bronchial or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or hyper reactiv$ or allerg$ or insufficien$)).mp.
19. or/1-18
20. occupational diseases/
21. pneumoconiosis/
22. ((animal$ or fowl or farmer$ or pheasant$ or bird$ or pigeon$ or hen or hens) adj3 (fancier$ or worker$ or breeder$ or keeper$ or raiser$ or handler$)).mp.
23. (baker$ or grain$).tw.
24. exp industry/
25. (worker$ or worksite$ or work site$ or work relat$ or work caus$ or work aggravat$ or concurrent or job or employ$ or occupation$ or environment$).tw.
26. (workplace or employment).mp.
27. environmental exposure/
28. occupational exposure/
29. (environmental exposur$ or inhalation exposur$ or occupational exposur$).mp.
30. (di-isocynate$ or isocynate$).tw.
31. (epoxy resin$ or latex or red cedar$).mp.
32. air pollutants, occupational/
33. occupational airway$.mp.
34. (occupation$ adj5 asthma$).mp.
35. or/20-33
37. 19 and 35
38. 37 or 34
39. ((work or job or occupation$ or profession$ or employe$) adj5 (remov$ or modif$ or adjust$ or transfer$ or alter$ or leave or terminat$ or cease or cessation or return$)).tw.
40. (change adj5 (employe$ or work$ or occupation$ or work$ or process$ or procedur$)).tw.
41. ((prevent$ or reduc$ or eliminat$ or minimiz$ or minimis$ or minimal$ or control$) adj5 (expos$ or agent$ or irritant$ or sensitizer$)).tw.
42. ((change or retrain$ or alter$) adj5 (employe$ or work$ or occupation$ or work$ or process$ or procedur$)).tw.
43. or/39-42
44. 38 and 43

Table A-8. Cochrane Airways Group: Management of occupational asthma (March 2004)

Set # and Keyword Search
1. Searched using the following free text terms: occupation* or work* or baker* or mining or miner* or asbestos* or silicosis or wheat or flour* or farmer* or latex*

Table A-9. Embase: Management of occupational asthma (1988 to February Week 6 2004)

Set # and Keyword Search
1. asthma/
2. asthma$.tw.
3. Wheezing/
4. wheez$.tw.
5. abnormal respiratory sound/
6. breathing disorder/
7. Airway Obstruction/
8. respiratory tract disease/ or bronchus disease/ or lung disease/ or respiratory distress/ or respiratory function disorder/ or respiratory tract inflammation/
9. reactive airway$.tw.
10. ((airway$ or lung$) adj3 (dysfunction$ or obstruct$)).tw.
11. Bronchus Hyperreactivity/
12. Bronchospasm/
13. (bronch$ adj3 (disease$ or spas$)).tw.
14. (non-specific bronchial hyperresponsiv$ or nonspecific bronchial hyperresponsiv$).tw.
15. (non-specific bronchial responsiv$ or nonspecific bronchial responsiv$).tw.
16. (nsbr or nsbh).tw.
17. (bronchospas$ or bronchoconstrict$ or rhonchi).tw.
18. twitchy airway$.tw.
19. ((respiratory or pneumonitis or alveol$ or bronchial or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or hyper reactiv$ or allerg$ or insufficien$)).mp.
20. Lung Insufficiency/
21. or/1-20
22. occupational disease/ or occupational allergy/ or occupational lung disease/
23. bird breeder lung/
24. allergic pneumonitis/
25. Pneumoconiosis/
26. ((animal$ or fowl or farmer$ or pheasant$ or bird$ or pigeon$ or hen or hens) adj3 (fancier$ or worker$ or breeder$ or keeper$ or raiser$ or handler$)).mp.
27. farmer$ lung.tw.
28. ((agricultur$ or silo filler$) adj3 disease$).tw.
29. (baker$ or grain$).tw.
30. (worker$ or worksite$ or work site$ or work relate$ or work cause$ or work aggravat$ or concurrent or job or employ$ or occupation$ or environment$).mp.
31. work/ or work environment/
32. exp worker/
33. environmental exposure/
34. exposure/
35. occupational exposure/
36. (environment$ exposur$ or inhalation exposur$ or occupation$ exposur$).tw.
37. Isocyanate/
38. (di-isocynate$ or isocyanate$).mp.
39. (Epoxy Resin or latex or "red cedar").mp.
40. air pollutant/
41. occupational airway$.tw.
42. (occupation$ adj5 asthma$).mp.
43. exp Occupational Asthma/
44. 42 or 43
45. or/22-41
46. 21 and 45
47. 46 or 44
48. ((work or job or occupation$ or profession$ or employ$) adj5 (remov$ or modif$ or adjust$ or transfer$ or alter$ or leave or terminat$ or cease or cessation or return$)).tw.
49. (change adj5 (employ$ or work$ or occupation$ or work$ or process$ or procedur$)).tw.
50. ((prevent$ or reduc$ or eliminat$ or minimiz$ or minimis$ or minimal$ or control$) adj5 (expos$ or agent$ or irritant$ or sensitizer$)).tw.

Table A-9. Embase: Management of occupational asthma (1988 to February Week 6 2004) (continued)

Set # and Keyword Search
51. ((change or retrain$ or alter$) adj5 (employ$ or work$ or occupation$ or process$ or procedur$)).tw. 52. or/48-51 53. 47 and 52

Table A-10. Medline: Management of occupational asthma (1966 to January Week 4 2004)

Set # and Keyword Search
1. ASTHMA/
2. asthma$.tw.
3. wheez$.tw.
4. respiratory sounds/
5. airway obstruction/
6. (airway$ adj3 (dysfunction$ or obstruct$)).tw.
7. reactive airway$.tw.
8. Lung Diseases/
9. Lung Diseases, obstructive/
10. Respiratory Tract Diseases/
11. bronchial hyperreactivity/
12. bronchial spasm/ or (bronch$ adj5 spas$).tw.
13. bronchial diseases/
14. (non-specific bronchial hyperresponsiv$ or nonspecific bronchial hyperresponsiv$).tw.
15. (non-specific bronchial responsiv$ or nonspecific bronchial responsiv$).tw.
16. (nsbr or nsbh).tw.
17. bronchospas$ or bronchoconstrict$ or rhonchi).tw.
18. twitchy airway$.tw.
19. ((respiratory or pneumonitis or alveol$ or bronchial or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or hyper reactiv$ or allerg$ or insufficien$)).mp.
20. or/1-19
21. occupational diseases/
22. agricultural workers' diseases/
23. farmer's lung/
24. silo filler's disease/
25. bird fancier's lung/
26. pneumoconiosis/
27. ((animal$ or fowl or farmer$ or pheasant$ or bird$ or pigeon$ or hen or hens) adj3 (fancier$ or worker$ or breeder$ or keeper$ or raiser$ or handler$)).mp.
28. (baker$ or grain$).tw.
29. (worker$ or worksite$ or work site$ or work relate$ or work cause$ or work aggravat$ or concurrent or job or employ$ or occupation$ or environment$).tw.
30. (workplace or employment).mp.
31. environmental exposure/
32. inhalation exposure/
33. Occupational Exposure/
34. (environmental exposur$ or inhalation exposur$ or occupational exposur$).mp.
35. (di-isocynate$ or isocynate$).tw.
36. (epoxy resin$ or latex or "red cedar").mp.
37. air pollutants, occupational/
38. occupational airway$.mp.
39. (occupation$ adj5 asthma$).mp.
40. or/21-38
41. 20 and 40
42. 39 or 41
43. ((work or job or occupation$ or profession$ or employe$) adj5 (remov$ or modif$ or adjust$ or transfer$ or alter$ or leave or terminat$ or cease or cessation or return$)).tw.
44. (change adj5 (employe$ or work$ or occupation$ or work$ or process$ or procedur$)).tw.
45. ((prevent$ or reduc$ or eliminat$ or minimiz$ or minimis$ or minimal$ or control$) adj5 (expos$ or agent$ or irritant$ or sensitizer$)).tw.
46. ((change or retrain$ or alter$) adj5 (employe$ or work$ or occupation$ or work$ or process$ or procedur$)).tw.
47. or/43-46
48. 42 and 47

Table A-11. Web of Science: Management of occupational asthma (1966 to January Week 4 2004)

Set # and Keyword Search
1. Pisati G, Baruffini A, Zedda S. Toluene diisocyante induced asthma: outcome according to persistence or cessation of exposure. Br J Ind Med 1993;50:60-64.
2. Cote J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. Am Rev Respir Dis 1990;141:373-6.

Table A-12. Dissertation Abstracts: Occupational asthma (searched February 2004)

Set # and Keyword Search
1. Searched using keyword: "occupational asthma"

Table A-13. Expanded Academic: Occupational asthma (1980 to February 2004)

Set # and Keyword Search
1. Searched using keyword: "occupational asthma"

Table A-14. NASD: Occupational asthma (searched January 2004)

Set # and Keyword Search
1. Searched using keywords: "occupational asthma", work related asthma, work caused asthma, occupation* disease, respiratory disease, specific inhalation challenge, peak flow, methacholine, forced expiratory volume, spirometry

Appendix B: Sample Data Forms

Inclusion/Exclusion Criteria

Form B-1: Inclusion form: Diagnosis of occupational asthma
Form B-2: Inclusion form: Management of occupational asthma

Quality Assessment

Form B-3: Assessment of methodology for diagnostic studies: Diagnosis of occupational asthma
Form B-4: Assessment of methodology for non-randomized controlled trials: Management of occupational asthma
Form B-5: Assessment of methodology for randomized controlled trials: Management of occupational asthma

Data Extraction

Form B-6: Data extraction form: Diagnosis of occupational asthma
Form B-7: Data extraction form: Management of occupational asthma

Form B-1. Inclusion form: Diagnosis of occupational asthma

Reviewer: _____ Date: _____ Reference Number: _____

TOPIC, include if either:
[ ] Examining the diagnostic utility of one test in workers with a previous diagnosis of work-related or occupational asthma [previous diagnosis of asthma counts as one of the reference standards]
[ ] Comparing the diagnostic utility of two or more tests in workers with suspected occupational asthma
[ ] Examining the role of specific inhalation challenge testing in the diagnosis of occupational asthma

DESIGN, include if any of the following:
[ ] Randomized clinical trial
[ ] Controlled clinical trial
[ ] Prospective cohort
[ ] Retrospective cohort/case-series
[ ] Cross-sectional

PARTICPIANTS, include if:
Workers with either:
[ ] De novo occupationally induced asthma
[ ] A previous diagnosis of asthma that is exacerbated at work (i.e. work related asthma). 'Exacerbated at work' refers to underlying asthma that is made worse by a workplace exposure. This includes an episode of bronchoconstriction triggered by cold air or exercise.

REFERENCE STANDARD, include if there is at least one of the following:
[ ] Specific inhalation challenge testing
[ ] Supervised workplace challenge
[ ] Serial peak flow or serial spirometry monitoring (some type of serial lung function)
[ ] Serial measurement of non-specific airway reactivity, such as methacholine, histamine, or other challenges
[ ] Immunological testing
[ ] Clinical diagnosis of occupational asthma by an expert (occupational or pulmonary medicine specialist) and exposure to an "asthmagen"

OTHER COMPARISON TEST, include if there is at least one of the following:
[ ] Specific inhalation challenge testing
[ ] Supervised workplace challenge
[ ] Serial peak flow or serial spirometry monitoring (some type of serial lung function)
[ ] Serial measurement of non-specific airway reactivity, such as methacholine, histamine, or other challenges
[ ] Immunological testing

[ ] Clinical diagnosis of occupational asthma by an expert (occupational or pulmonary medicine specialist) and exposure to an "asthmagen"
[ ] Sputum, metabonomics, etc
[ ] Nitrous oxide
[ ] Other: _____

OUTCOMES, include if there is at least one of the following:
[ ] Absolute numbers are presented to construct a 2 x 2 (comparing two diagnostic techniques) or 2 x 1 (assessing one diagnostic technique in patients with a previous diagnoses of occupational asthma) table
[ ] Sensitivity, specificity, or likelihood ratios
[ ] Cost of diagnosis
[ ] Time to complete diagnosis
[ ] Adverse effects

FINAL DECISION:
[ ] INCLUDE (meets all of the above inclusion criteria)
[ ] EXCLUDE
[ ] CAN'T TELL
    [ ] Further information is required
    [ ] Not English (state language): _____

If disagreement between reviewers, final outcome:

[ ] INCLUDED [ ] EXCLUDED

Check box if study provides useful background information □

Form B-2. Inclusion form: Management of occupational asthma

Reviewer: _____ Date: _____ Reference Number: _____

TOPIC, include if either:
[ ] Examining the treatment or management in workers with a previous diagnosis of occupational asthma

DESIGN, include if any of the following:
[ ] Randomized clinical trial
[ ] Controlled clinical trial
[ ] Prospective cohort
[ ] Retrospective cohort/case-series
[ ] Cross-sectional

PARTICPIANTS, include if:
Currently employed workers or previously employed workers with either:
[ ] De novo occupationally induced asthma
[ ] A previous diagnosis of asthma that is exacerbated at work. This includes an episode of bronchoconstriction triggered by cold air or exercise.
[ ] Can't tell, but participants have occupational asthma

INTERVENTION, include if there is at least one of the following:
[ ] Removal from the offending workplace
[ ] Relocated to a position with decreased exposure to the "asthmagen" within the same workplace
[ ] Provided personal protective equipment (e.g. masks, respirators)
[ ] Engineering controls
[ ] Pharmacological treatment (e.g. bronchodilators, inhaled corticosteroids)
[ ] Other: _____

OUTCOMES, include if there is at least one of the following:
[ ] Pulmonary function
[ ] Use of medication
[ ] Healthcare utilization (e.g. admissions, ED visits, visits to primary care providers, referral to specialist)
[ ] Frequency of exacerbations
[ ] Quality of life
[ ] Symptoms
[ ] Economic consequences (to worker, employer, society)
[ ] Adverse events

FINAL DECISION:

[ ] INCLUDE (meets all of the above inclusion criteria)
[ ] EXCLUDE
[ ] CAN'T TELL
    [ ] Further information is required
    [ ] Not English (state language): _____

If disagreement between reviewers, final outcome:

[ ] INCLUDED [ ] EXCLUDED

Check box if study provides useful background information □

Form B-3. Assessment of methodology for diagnostic studies: Diagnosis of occupational asthma

Reviewer: _____ Date: _____ Reference Number: _____

(Empirically validated items marked with an asterisk- Adapted from Lijmer et al.)

1. Design *
    a. Case control
    b. Cohort
    c. Other – specify_____

2. Blinding of measurements (test vs. reference standard) *
    a. Both measurements blinded
    b. One measurement blinded- specify (test vs. reference)_____
    c. Other – specify_____
    d. Neither measurements blinded
    e. Unclear

3. Appropriate reference standard *
    a. Level of evidence reference standard:_____
    b. Other – specify_____

4. Description of reference standard *
    a. Adequate (e.g. referral to standard SIC methodology, timing of lung function tests, referral to standard challenge dosages and methodology, how an OA specialist made the diagnosis; there is enough information to reproduce the test)
    b. Inadequate

5. Description of test *
    Test I: _____
        a. Adequate (i.e. referral to standard methodology; there is enough information to reproduce the test)
        b. Inadequate
    Test II: _____
        a. Adequate (i.e. referral to standard methodology; there is enough information to reproduce the test)
        b. Inadequate
    Test III: _____
        a. Adequate (i.e. referral to standard methodology; there is enough information to reproduce the test)
        b. Inadequate
    Test IV: _____
        a. Adequate (i.e. referral to standard methodology; there is enough information to reproduce the test)
        b. Inadequate

Test V: _____

a. Adequate (i.e. referral to standard methodology; there is enough information to reproduce the test)
b. Inadequate

6. Description of population *
    a. Adequate (i.e. patients described in terms of age, sex and presenting signs and symptoms)
    b. Inadequate

7. Differential reference bias * (i.e. those who test negatively or strongly positive are given a less or more thorough reference test for verification of the negative test; those who test negative or strongly positive are given a less thorough reference standard)
    a. Yes
    b. No
    c. Unclear

8. Partial verification bias (i.e. decision to perform the reference test is based upon the results of the test under examination; result of the test predicts patient moving on to the reference standard or vice versa)
    a. No – specify number _____ (must be ≥90% for the risk of partial verification bias to be minimal)
    b. Yes
    c. Unclear

9. Data collection
    a. Retrospective
    b. Prospective (may be selected retrospectively but data is collected prospectively)
    c. Unclear

10. Patient selection
    a. Consecutive or random selection
    b. Other – specify _____
    c. Not reported

11. Inter-rater reliability
    a. Reported
    b. Not reported

12. Reporting of results
    a. Allows for re-creation of contingency tables
    b. Does not allow for recreation of contingency tables

Form B-4. Assessment of methodology for non-randomized controlled trials: Management of occupational asthma

Reporting

1. **Is the hypothesis/aim/objective of the study clearly described?** This question refers to a clear statement of the objective, i.e. to measure the effectiveness of x in population y with respect to z, even if x, y and z are not clearly described (see questions 2, 3 and 4)

Yes	1	
No	0	

2. **Are the main outcomes to be measured clearly described in the Introduction or Methods section?** If the main outcomes are first mentioned in the Results section, the question should be answered no. In case-control studies the case definition should be considered the outcome.

Yes	1	
No	0	

3. **Are the characteristics of the patients included in the study clearly described in the Introduction or Methods section?** In cohort studies and trials, inclusion and or exclusion criteria should be given. In case-control studies, a case definition and the source for controls should be given.

Yes	1	
No	0	

4. **Are the interventions of interest clearly described in the Introduction or Methods section?** Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1	
No	0	

5. **Are the distributions of principal confounders in each group of subjects to be compared clearly described?** A list of principal confounders is provided.

Yes	2	
Partially	1	
No	0	

6. **Are the main findings of the study clearly described?** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. This question does not cover statistical tests, which are considered below.

Yes	1	
No	0	

7. **Does the study provide estimates of the random variability in the data for the main outcomes?** In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1	
No	0	

8. **Have all important adverse events that may be a consequence of the intervention been reported?** This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

Yes	1	
No	0	

9. **Have the characteristics of patients lost to follow-up been described?** This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does no report the number of patients lost to follow-up.

Yes	1	
No	0	

10. **Have 95% CIs and/or actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?** (both CI and p value, either CI or p value, neither)

Yes	1	
No	0	

External validity

11. **Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	1	
No	0	
Unable to determine	0	

12. **Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	1	
No	0	
Unable to determine	0	

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the study to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	1	
No	0	
Unable to determine	0	

Internal validity – bias

14. Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes	1	
No	0	
Unable to determine	0	

16. If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	1	
No	0	
Unable to determine	0	

17. **In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?** Where follow-up was the same for all study patients that answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	1	
No	0	
Unable to determine	0	

18. **Were the statistical tests used to assess the main outcomes appropriate?** The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

19. **Was compliance with the interventions reliable?** Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

20. **Were the main outcome measures used accurate (valid and reliable)?** For studies where the outcome measured are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

Yes	1	
No	0	
Unable to determine	0	

Internal validity – confounding (selection bias)

21. **Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?** For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

Yes	1	
No	0	
Unable to determine	0	

22. **Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?** For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	1	
No	0	
Unable to determine	0	

23. **Were the subjects randomized to intervention groups?** Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes	1	
No	0	
Unable to determine	0	

24. **Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?** All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes	1	
No	0	
Unable to determine	0	

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders different between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	1	
No	0	
Unable to determine	0	

26. Were losses to patients to follow-up take into account? (yes, no, unable to determine) If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

Yes	1	
No	0	
Unable to determine	0	

Power

27. Was a power calculation reported for the primary outcome?

Yes	1	
No	0	
Unable to determine	0	

28. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance in less than 5%?

Yes	1	
No	0	
Unable to determine	0	

Form B-5. Assessment of methodology for randomized controlled trials: Management of occupational asthma

JADAD SCORE: circle the appropriate response and total for the final Jadad score

Randomization:

1.	Was the study described as being randomized?	1 = Yes 0 = No
2.	Was the method of randomization appropriate?	1 = Yes 0 = No
3.	Was the method of randomization inadequate?	-1 = Yes 0 = No

Double Blindedness:

4.	Was the study described as double-blind?	1 = Yes 0 = No
5.	Was the method of double-blinding appropriate?	1 = Yes 0 = No
6.	Was the method of double-blinding inadequate?	-1 = Yes 0 = No

Withdrawals:

7.	Was there an adequate description of withdrawals?	1 = Yes 0 = No

Total Score:

CONCEALMENT OF ALLOCATION: was the method used to conceal the randomization list

[ ] adequate
[ ] inadequate
[ ] unclear

Form B-6. Data extraction form: Diagnosis of occupational asthma

ID_____ Reviewer_____ Checker_____ Date_____

Study Characteristics

First author:		
Title: (short)		
Journal citation:		
Year published:	Language:	Country where conducted:
Funding: ❑ Private industry □ Government □ Internal □ Foundation □ Other □ NR		
Probable Cause(s) of OA □ Isocyanates □ Flour □ Cedar/wood dust □ Latex □ Fish/shellfish □ Chemical □ Disinfectant □ Pharmaceutical □ Animal/bird □ LMWS □ HMWS □ Metal dust □ Potroom □ Other_____ □ Mixed causes □ Unidentified agent □ NR		
Subject Source □ Clinic(s) □ Workplace □ Mixed □ Other _____	**Recruitment** □ Random □ Consecutive □ All eligible □ Other_____ □ NR Time frame _____ □ NR	
Description of Subjects (e.g. referred for _ ___)	Occupation(s) (list if 4 or less) □ > 4 identified	
Reference Standard □ SIC with _____ □ Other _____ □ NR		
Comparison Test(s): □ Supervised work challenge □ Serial PEF or FEV_1 □ NSBPT (histamine or methacholine) □ Pulmonary Function Test (single e.g. Reversibility) □ Immunological testing □ Total IgE □ Specific IgE □ SPT (specific and/or for atopy) □ Eosinophils □ Other _____	□ Sputum, metabonics, etc. □ NO □ Clinical Dx by expert	

Patient Flow

1. Initial number selected/screened/eligible: n=_____

2. Total agreed to participate: n= _____

3. Exclusions: □ Yes n=_____ □ No □ Unclear □ NR
   Reasons:

4. Withdrawals / dropouts / refusals: □ Yes n=_____ □ No □ Unclear □ NR
   Reasons:

5. Number who completed the study: n=_____

6. Was there a comparison group or control subgroup within cohort □ Yes n=____ □ No

Methods

Anti-asthma medications stopped pre-testing: □ Yes (attempted) □ No □ NR

Baseline Characteristics

Please indicate the statistic, (%, SD, SEM, range, AND the units) (insert a ' - ' if no data available)

	Group A: _____ **N** ___	**Group B:** _____ **N** ___	**ALL** _____ **N** ___
Males/females (%)			
Age: Mean; SD			
Race: (White %)			
Mean duration work related symptoms (yr)			
Mean duration workplace exposure (yr)			
Latency (yr)			
Atopic (%)			
Smokers: (%) Current smokers			
Ex-smokers			
Never smoked			
Hx asthma (%)			
Pulmonary function (single measure - specify)			
Other -Specify			
Other -Specify			

Current medications documented □ Yes □ No

Other outcomes reported □ Yes □ No

	Group A: _____ N ___	**Group B: _____ N ___**	**ALL _____ N ___**
Costs mean; sd			
Time to complete Dx mean; sd			
Adverse events			
Other - specify			
Other - specify			

Test Characteristics

1. SIC Method followed _____ □ referenced □ described in text

a. Inclusion criteria

_____

□ **NR**

b. Exclusion criteria

_____

□ **NR**

c. +ve test or significant change:

_____

□ **NR**

2. NSBPT Method followed _____ □ referenced □ described in text

□ Methacholine □ Histamine □ Both

□ Single □ Serial (i.e. >1 challenge)

a. Inclusion criteria

_____

□ **NR**

b. Exclusion criteria

_____

□ **NR**

c. +ve test or significant change:

_____

Serial measure:

_____

□ **NR**

3. Single Pulmonary Function Measure

(specify)_____

□ Reversibility reported □ Yes □No

a. Inclusion criteria

_____

□ **NR**

b. Exclusion criteria

_____

□ **NR**

c. +ve test or significant change:

_____

□ **NR**

4. Serial Pulmonary Function

Duration: _____@ work_____@ away from work;
recorded_____ times/day
Measure taken: □ FEV_1 □ PEF

a. Inclusion criteria

_____

□ **NR**

b. Exclusion criteria

_____

□ **NR**

c. +ve test or significant change:

_____

□ **NR**

5. Other: _____

Method _____ □ Referenced □ Described in text

a. Inclusion criteria

_____

b. Exclusion criteria

_____

c. +ve test or significant change:

_____

□ **NR**

6. Clinical Diagnosis of OA (as defined in article)

_____

□ **NR**

7. Immunological Testing

a. Skin prick test: Method followed _____□ Referenced □ Described in text

Reason □ Atopy (common allergens) □ Specific □ Both

+ve test: _____□ NR

b. **Total IgE** □ Yes □ No +ve test or significant change:_____ □ NR

Method: □ RAST □ ELISA □ Other, Specify_____

c. Specific IgE □ yes □ no +ve test or significant change: _____ □ NR

Method: □ RAST □ ELISA □ Other, Specify_____

d. Other:_____+ve test or significant change:_____ □ NR

Method: □ RAST □ ELISA □ Other, Specify_____

e. Other:_____+ve test or significant change:_____ □ NR

Method: □ RAST □ ELISA □ Other, Specify_____

Results Reported

Test results (put highest level of evidence test at the top, comparison test on the left side)

1. _____ compared to _____

_____ 2 x 2 table □ Reported □ Calculated

		OA	not OA	
_____	+ve			_____
	-ve			_____
		_____	_____	_____

Sensitivity:_____ Specificity:_____

2. _____ compared to _____

_____ 2 x 2 table □ Reported □ Calculated

		OA	not OA	
_____	+ve			_____
	-ve			_____
		_____	_____	_____

Sensitivity:_____ Specificity:_____

3. _____ compared to _____

_____ 2 x 2 table □ Reported □ Calculated

		OA	not OA	
_____	+ve			_____
	-ve			_____
		_____	_____	_____

Sensitivity:_____ Specificity:_____

4._____ compared to _____

_____ 2 x 2 table □ Reported □ Calculated

		OA	not OA	
_____	+ve			_____
	-ve			_____
		_____	_____	_____

Sensitivity:_____ Specificity:_____

5. _____ compared to _____

_____ 2 x 2 table □ Reported □ Calculated

		OA	not OA	
_____	+ve			_____
	-ve			_____
		_____	_____	_____

Sensitivity:_____ Specificity:_____

6. _____ compared to _____

_____ 2 x 2 table □ Reported □ Calculated

		OA	not OA	
_____	+ve			_____
	-ve			_____
		_____	_____	_____

Sensitivity:_____ Specificity:_____

Form B-7. Data extraction form: Management of occupational asthma

ID_____ Reviewer_____ Checker_____ Date_____

Study Characteristics

First author:		
Title: (short)		
Journal citation:		
Year of publication:	Language:	Country where conducted:

Funding:
❑ Private industry □ Government □ Internal □ Foundation □ Other □ NR

Probable Cause(s) of OA
□ Isocyanates □ Flour □ Cedar/wood dust □ Latex □ Fish/shellfish □ Chemical
□ Disinfectant □ Pharmaceutical □ Animal/bird □ LMWS □ HMWS □ Metal dust
□ Potroom □ Other_____ □ Mixed causes □ Unidentified agent □ NR

Subject Source □ Clinic(s) □ Workplace □ Mixed □ Other _____ □ NR	**Recruitment** □ Random □ Consecutive □ All eligible □ WCB □ NR □ Other _____ Time frame _____ □ NR
Description of Subjects (e.g. referred for _ ___)	Occupation(s) (list if 4 or less) □ > 4 identified
OA Diagnosis Confirmed by: □ SIC □ Supervised work challenge □ SPF □ SPT (specific) □ NSBPT □ CD by expert □ Questionnaire □ Immunological testing □ Wk-Hx □ NR	**Time Since Dx** FU 1: _____ Min _____ Max _____ FU 2: _____ Min _____ Max _____ FU 2: _____ Min _____ Max _____

Follow-up Test(s):

□ SIC □ Sputum cell counts □ Sputum cytokines □ Spirometry (PF)
□ Serial PEF □ SPT (atopy / specific) □ Nitrous oxide
□ NSBPT □ CD by expert □ Immunological testing (total IgE, specific IgE, IgG,)
□ Bronchodilator response □ Serum Eosinophils □ Neutrophils □ Disease related costs
□ Questionnaire □ Interview
□ Other
_____

Patient Flow

1. Initial number eligible (i.e. confirmed Dx of OA): n=_____ □ Not known

2. Total agreed to participate: n= _____

3. Exclusions: □ Yes n=_____ □ No □ Unclear □ NR
   Reasons:

4. Withdrawals / dropouts / refusals: □ Yes n=_____ □ No □ Unclear □ NR
   Reasons:

5. Number who completed the study / follow-up: n=_____

6. Was there a comparison group or control subgroup within cohort □ Yes n=____ □ No
   Describe:

Intervention: □ Removal from offending workplace n=_____
□ Advised to avoid exposure n=_____
□ Remained at same workplace:
□ Moved to reduced exposure n=_____
□ Moved to no exposure n= _____
□ Used protective equipment n=_____
type: _____
□ Used medications n=_____
type: _____
□ Remained fully exposed n=_____

Methods

Data Collection: □ Questionnaire □ Interview □ Clinical review □ Retrospective chart review

Medications (anti-asthma) stopped pre-testing: □ Yes (attempted) □ No □ NR

Baseline Characteristics at Diagnosis:

Please indicate the statistic, e.g. %, mean, SD, range AND the units (which gets filled in will depend on how reported)

	Group A _____ **n=**	**Group B** _____ **n=**	**Group C** _____ **n=**	**Group D** _____ **n=**	**Group E** _____ **n=**
Males %					
Age: Mean; SD					
Race: White %					
Hx asthma: %					
Atopic: %					
Smokers: % CS					
ExS					
NS					
Duration of exposure (y)					
Duration of symptoms (y)					
Latency (y)					
Medications (yes %)					
ICS %					
OCS %					
BD %					
BD + steroids %					
Others %					
Asthma/symptom severity					

Notes:

Other Baseline Data at Diagnosis: (specify measure plus metric)

	Group A n=	Group B n=	Group C n=	Group D n=	Group E n=

Follow-Up Results:

		Group A n=	Group B n=	Group C n=	Group D n=	Group D n=
Smokers: n (%)	CS					
	ExS					
	NS					

Test Characteristics and Results

Test _____
Method followed _____

□ Referenced □ Described in text

+ve test or significant change:
_____ □ NR

FU time_____	**Group A** _____ **n=**	**Group B** _____ **n=**	**Group C** _____ **n=**	**Group D** _____ **n=**	**Group D** _____ **n=**

Notes:

Test _____
Method followed _____

□ Referenced □ Described in text

+ve test or significant change:
_____ □ NR

FU time_____	**Group A** _____ **n=**	**Group B** _____ **n=**	**Group C** _____ **n=**	**Group D** _____ **n=**	**Group D** _____ **n=**

Test _____
Method followed _____

□ Referenced □ Described in text

+ve test or significant change:
_____ □ NR

FU time_____	**Group A** _____ **n=**	**Group B** _____ **n=**	**Group C** _____ **n=**	**Group D** _____ **n=**	**Group D** _____ **n=**

Test _____
Method followed _____

□ Referenced □ Described in text

+ve test or significant change:
_____ □ NR

FU time_____	**Group A** _____ **n=**	**Group B** _____ **n=**	**Group C** _____ **n=**	**Group D** _____ **n=**	**Group D** _____ **n=**

Appendix C: Levels of Evidence

Levels of Evidence: Diagnosis of Occupational Asthma

Table C-1: Levels of evidence: Occupational asthma with latency of allergic or presumed immunological mechanism
Table C-2: Levels of evidence: Occupational asthma without latency
Table C-3: Levels of evidence: Work-aggravated asthma

Table C-1. Levels of evidence: Occupational asthma with latency of allergic or presumed immunological mechanism

Test	Level
Specific inhalation challenge test OR supervised workplace inhalation challenge	Level Ia
Lung function test* and methacholine challenge test^, and immunological testing**	Level Ib
Combination of lung function tests* and methacholine challenge test^	Level II
Combination of methacholine challenge^ testing and immunological testing**	Level IIIa
Combination of lung function tests* and immunological testing**	Level IIIb
Combination of lung function testing* or serial methacholine challenge testing and cessation of symptoms following removal from the workplace	Level IV
^^Clinical diagnosis of occupational or work-related asthma by a physician specializing in Occupational Medicine or Pulmonary Medicine and exposure to an "asthmagen"	Level V

*****Lung function tests include FEV_1 and PEF and must be done serially at work and away from work;
^Methacholine testing must be done at and away from work;
******Immunological testing refers to skin prick tests or specific IgE;
^^We propose that, regardless of the final hierarchy, that 'physician diagnosis' be the lowest acceptable reference standard for the purposes of comparisons made in this review. The physician's diagnosis may have been reached using a variety of historical information, examination and tests, and this will differ from study to study. It is recognized that a physician diagnosis in the absence of any objective testing would not usually be considered sufficient acceptable evidence in an individual clinical case of suspected occupational asthma.

Table C-2. Levels of Evidence: Occupational asthma without latency

Test	Level
Combination of: No preceding symptoms *Symptoms after single specific exposure incident *Exposure to irritant gas/smoke/fume/vapour in high concentrations *Symptom onset <24hours after exposure *Symptoms persist >3months after onset Symptoms similar to asthma with cough wheeze and dyspnoea predominant *PFTs show airflow obstruction with significant bronchial response (180mL/12%) *Non-specific airway responsiveness present Other pulmonary disease excluded	Level I
One of above * criteria not documented or not present	Level II
Two of above * criteria not documented or not present	Level III
Three of above * criteria not documented or not present	Level IV
^Clinical diagnosis of occupational or work-related asthma by a physician specializing in Occupational Medicine or Pulmonary Medicine	Level V

^ We propose that, regardless of the final hierarchy, that 'physician diagnosis' be the lowest acceptable reference standard for the purposes of comparisons made in this review. The physician's diagnosis may have been reached using a variety of historical information, examination and tests, and this will differ from study to study. It is recognized that a physician diagnosis in the absence of any objective testing would not usually be considered sufficient acceptable evidence in an individual clinical case of suspected occupational asthma.

Table C-3. Levels of Evidence: Work-aggravated asthma

Test	Level
Previous history of asthma. Documented work related changes in lung function* with documented exposure to a relevant precipitating or 'triggering' agent, but not a recognised asthmagen, at work	Level Ia
Previous history of asthma. Documented work related changes in lung function* with documented exposure to a relevant precipitating or 'triggering' agent at work. Exposure also to an asthmagen(s) at work, but negative specific inhalation challenge to asthmagen(s)	Level Ib
Previous history of asthma. History of worsening symptoms related to periods at work with improvements when away from work, and exposure to a relevant precipitating or 'triggering' agent, but not a recognised asthmagen, at work	Level II
No previous or concurrent history of asthma. History of worsening symptoms related to periods at work with improvements when away from work, and exposure to a relevant precipitating or 'triggering' agent, but not a recognised asthmagen, at work	Level III
Clinical diagnosis of work aggravated asthma by a physician specializing in Occupational Medicine or Pulmonary Medicine**	Level IV

***** Lung function tests include FEV_1 and PEF

****** We propose that, regardless of the final hierarchy, that 'physician diagnosis' be the lowest acceptable reference standard for the purposes of comparisons made in this review. The physician's diagnosis may have been reached using a variety of historical information, examination and tests, and this will differ from study to study. It is recognized that a physician diagnosis in the absence of any objective testing would not usually be considered sufficient acceptable evidence in an individual clinical case of suspected occupational asthma.

Appendix D: Multiple Publications

Occupational Asthma Cohorts

Table D-1: Diagnosis cohorts
Table D-2: Management cohorts
Table D-3: Trial cohort

During the study screening and data extraction processes, several articles were identified where different outcomes were reported for what appeared to be the same clinical cohort. We did not want to exclude any relevant results, but also did not want to over-represent results when the same outcome had been reported for a cohort in different publications. A main (usually most recent) publication for these cohorts was identified based on a careful review of the paper for references to prior publications, contact with the authors when possible, and cross-referencing descriptions of patient demographics. These references are described below for the diagnosis and management systematic reviews respectively.

Table D-1. Diagnosis cohorts

Linked References (* indicates the primary publication)	Rational
Cartier, 1986*[1]; Cartier, 1984[2]	Cartier et al. (1986) describe results from IgE testing of snow crab processors diagnosed with OA. The authors refer to Cartier et al. (1984) in the description of subjects included in the present analysis.
Cote, 1993*[3]; Cote, 1990[4]	Cote et al. (1992) investigated the utility of serial PEFR in 25 subjects investigated for OA caused by red cedar. In 1990, the same authors report results on 23 subjects; study design, subject, and methods sections are very similar to the later publication. We assumed the 1992 paper extends the results of the 1990 publication.
Howe, 1983*[5]; Venables, 1990[6]	Howe et al. (1983) report results from seven patients investigated for OA caused by TCPA. Venables et al. (2003) refer to Howe et al. (1983) stating that it "presented only the tests with highest TCPA concentrations"; this paper presented results using "data from all the tests".
Liss, 1991*[7]; Tarlo, 1991[8]	Liss and Tarlo (1991) report on an investigation of serial PEFR measurements in a cohort of 50 subjects referred to a clinic in Toronto, Canada. The authors refer to Tarlo and Broder (1991) in their methods section with respect to how patients were identified and diagnosed.
Malo, 1991*[9]; Perrin, 1992[10]	Malo et al. (1991) describe diagnostic findings from a cohort of 162 patients with OA caused by various agents. Perrin et al. (1992) appear to report on a subset of 61 patients with serial PEFR measurements.
Moscato, 1993*[11]; Moscato, 1991[12]	Moscato et al. (1993) report results from an assessment of two NSBPT substances for diagnosing OA caused by TDI. The authors refer to Moscato et al. (1991) in their description of the methacholine NSBPT. Moscato et al. (1993) appears to report on a subset of patients, originally identified in the 1991 paper, who underwent both tests.
Paggiaro, 1987*[13]; Lam, 1983[14]	Paggiaro and Chan-Yeung (1987) report on a cohort of 332 subjects investigated for OA caused by exposure to red cedar noting that it includes "206 previously reported subjects". Lam et al. (1983) is the publication for those 206 subjects.

Abbreviations: **NSBPT** = non-specific bronchial provocation test; **OA** = occupational asthma; **PEFR** = peak expiratory flow rate; **TCPA** = tetrachlorophthalic anhydride; **TDI** = toluene di-isocyanates

Table D-2. Management cohorts

Linked References (* indicates the primary publication)	Rational
Grammer, 2000*[15]; Grammer, 1993[16]	Grammer et al. (2000) describe a cohort of 29 OA patients; 22 who had been transferred to low exposure and seven who had been completely removed. The authors state that the purpose of the study was to "extend our previous observations", referring to their 1993 paper.
Lin, 1996*[17]; Chan-Yeung, 1987[18]; Chan-Yeung, 1982[19]; Chan-Yeung, 1977[20]; Lam, 1987[21]; Chan-Yeung, 1988[22]; Cote, 1990b[23]; Marabini, 1993[24]; Chan-Yeung, 1999[25]	Lin et al. (1996) describes the largest cohort of subjects followed at a clinic in Vancouver, Canada after diagnosis with OA caused by exposure to western red cedar. Outcomes are assessed based on each patient's symptoms and exposure status at follow-up. Chan-Yeung et al. (1987), Chan-Yeung et al. (1982) and Chan-Yeung et al. (1977) are previous reports of smaller cohorts of similarly described subjects. Lam et al. (1987) describes a subset of patients who underwent bronchial lavage before and at various intervals after SIC. Chan-Yeung et al. (1988) considered similar outcomes in a group of subjects who had been removed from exposure for at least 1 year. Cote at al. (1990) report clinical outcomes of a subset of patients who continued exposure and categorized them as stable or deteriorated. Socioeconomic and clinical outcomes were reported by Marabini et al. in 1993. Chan-Yeung et al. (1999) describes airway inflammation and exhaled nitric oxide in a subset of patients followed for at least one year; patients were classified according to exposure and medication status.
Malo, 1988*[26]; Hudson, 1985[27]	Malo et al. (1988) describe a cohort of 31 subjects with OA from working in a snow crab processing facility and report results from three follow-up visits at approximately 1, 2.5, and 5 years. Hudson et al. (1985) report on two cohorts, one of which is a group of 31 workers with OA caused by snow crab with 12 months of follow-up. Results from this paper were similar to the first follow-up visit in Malo et al. (1988).
Malo 1993*[28] Dewitte 1994[29]	Malo et al. (1993) included 134 Quebec workers diagnosed with OA who are removed from exposure and receiving compensation. Outcomes included quality of life and pulmonary function, bronchial responsiveness, and asthma severity. Dewitte et al. (1994) describes 134 workers with OA that were diagnosed at the same clinic during the same time period; economic consequences of OA are evaluated. Also, the baseline characteristics of the patients in the two studies are similar.
Merget, 1999*[30]; Merget, 1994[31]	Merget et al. (1999) reports results from a cohort of 74 patients with OA due to platinum salts who are grouped by exposure status at follow-up. This publication refers to Merget et al. (1994) and states "the present study was designed to describe a larger cohort of workers".
Park, 2002a*[32]; Park, 1997[33]	Park et al. (2002) report follow-up results from 41 patients with OA caused by TDI who had been removed from exposure who were categorized as not improved, improved, and in remission. In Park et al. (1997), 35 patients were categorized using the same definitions. Park et al. (2002) refers to Park et al. (1997), but does not state that the results are an extension of previous work.
Perfetti, 1998a*[34]; Perfetti, 1998b[35]	Perfetti et al. (1998a) reports results of 99 patients with OA who had been removed from exposure and followed for various lengths of times; outcomes are assessed comparing those followed for less than 5 years and those followed for more than 5 years. Perfetti et al. (1998b) from the same clinical group, describes the same study design; however, outcomes are compared based on molecular weight of the suspected asthmagen.
Saetta, 1995*[36]; Saetta, 1992[37]	Saetta et al. (1995) describe a cohort of 10 subjects with OA caused by isocyanates. The authors state that this publication is an extension of their previous work (Saetta 1992).

Abbreviations: **OA** = occupational asthma; **TDI** = toluene di-isocyanates

Table D-3. Trial cohort

Linked References (* indicates the primary publication)	Rational
Armentia, 1990*[38]; Armentia, 1992[39]	Armentia et al. have two publications describing an immunothearpy trial of 30 asthmatic bakers. Armentia et al. (1990) describes skin prick tests, NSBPT, and serum specific IgE results before and after treatment. Armentia et al. (1992) evaluates immune complexes in these patients.

Abbreviations: **NSBPT** = non-specific bronchial provocation test

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Appendix E: Evidence Tables

Diagnosis of Occupational Asthma

Table E-1: Description of included studies (Diagnosis review)
Table E-2: Demographic characteristics of included patients (Diagnosis review)
Table E-3: Description of diagnostic tests (Diagnosis review)
Table E-4: Methodological quality of included studies (Diagnosis review)

Management of Occupational Asthma: Cohorts

Table E-5: Description of included studies (Management cohorts review)
Table E-6: Demographic characteristics of included patients (Management cohorts review)
Table E-7: Description of interventions and outcomes (Management cohorts review)

Management of Occupational Asthma: Trials

Table E-8: Description of included studies (Management trials review)
Table E-9: Demographic characteristics of included patients (Management trials review)
Table E-10: Description of interventions and outcomes (Management trials review)

Management of Occupational Asthma: Methodological Quality

Table E-11: Methodological quality of included studies (Management cohorts review)
Table E-12: Methodological quality of included studies (Management trials review)

References

Reference listing: Diagnosis
Reference listing: Cohort
Reference listing: Trials

Table E-1. Description of included studies (Diagnosis review)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Alvarez, 2001	Spain	English	Yes	Eosinophils, single NSBPT, skin prick, serum specific IgE	Flour: oilseed rape (H)	Farmers with respiratory symptoms related to fodder manipulation	Clinic
Alvarez, 1996	Spain	English	Yes	Single NSBPT, skin prick, serum specific IgE	Cereals (H)	Bakers, millers, and farmers diagnosed with OA over a five yr period	Clinic
Anees, 2004	United Kingdom	English	No	Serial PFT (PEFR)	Mixed (M)	Consecutive workers of mixed occupation with definite OA	Clinic
Avery, 1969	United States	English	No	Lymphocyte blast cell transformation, TDI-HSA	Isocyanates (L)	Workers exposed toTDI; some with severe symptoms at low exposure, others with less symptoms at higher exposures	NR
Balland, 1989	France	French	Yes	Single NSBPT, serum specific IgE, serum total IgE	Mixed (M)	Workers presenting with symptoms of suspected work-related asthma and rhinitis	Workplace
Baur, 1998	Germany	English	Yes	Clinical diagnosis, single NSBPT	Mixed (M)	Healthcare workers, bakers, isocyanate workers, and hairdressers who consulted clinic because of suspected OA	Clinic
Baur, 1979	United Kingdom	English	Yes	Skin prick, serum specific IgE	Papain (H)	Meat or pharmaceutical plant workers exposed to airborne papain	Other
Behr, 1990	Germany	German	Yes	Clinical diagnosis, single NSBPT	Isocyanates (L)	Workers exposed to isocyanates with workplace related respiratory symptoms	Clinic and workplace
Bernstein, 2002	Canada	English	Yes	Di-isocyanate antigen stimulation of MCP-1, single NSBPT, serum specific IgE	Isocyanates (L)	Di-isocyanate exposed workers with history of OA, referred for SIC testing	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Biot, 1980	France	French	Yes	Basophils granules liberation, single NSBPT, serum total IgE	Mixed (M)	Workers complaining of allergic manifestations in practicing their profession	Workplace
Block, 1983	Canada	English	Yes	Single NSBPT, skin prick, serum specific IgE	Flour: wheat and rye (H)	Bakers with respiratory symptoms identified from workplace survey or referred to study	Clinic
Burge, 1985	United Kingdom	English	Yes	Single NSBPT	Formaldehyde (L)	Workers of mixed occupation referred for investigation of symptoms suggestive of OA	Clinic
Burge, 1982b	United Kingdom	English	Yes	Single NSBPT	Isocyanates (L)	Workers with respiratory symptoms when exposed to TDI, MDI, or colophony	NR
Burge, 1980	United Kingdom	English	Yes	Single NSBPT	Colophony (L)	Electronics workers referred for investigation of respiratory symptoms	Clinic
Burge, 1979a	United Kingdom	English	Yes	Clinical diagnosis, serial PFT (PEFR)	Colophony (L)	Electronics factory workers who had had a bronchial provocation test by exposure to solder-flux fumes in the hospital and had kept a record of their PEFR at home and at work for at least two wks	Clinic
Burge, 1979b	United Kingdom	English	Yes	Clinical diagnosis, serial PFT (PEFR)	Isocyanates (L)	Workers from factories printing and laminating flexible packaging who had been admitted for SIC and had kept at least two wks of PEFR records	Clinic
Burge, 1978	United Kingdom	English	Yes	Eosinophils, single PFT, skin prick	Colophony (L)	Electronics industry workers exposed to colophony who developed asthma or evidence of a peripheral airway reaction	NR
Butcher, 1980	United States	English	Yes	Serum specific IgE, serum total IgE	Isocyanates (L)	Workers previously shown to give adverse bronchial reactions to SIC with TDI	Other

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Carletti, 1997	Italy	Italian	Yes	Clinical diagnosis, single NSBPT, single PFT, skin prick	Flour (H)	Millers and bakers with suspected OA	Workplace
Cartier, 1989	Canada	English	Yes	Serial NSBPT, single NSBPT, skin prick, serum specific IgE, serum specific IgG	Isocyanates (L)	Subjects of various occupations who were being investigated for possible OA caused by isocyanates who underwent SIC	Clinic
Cartier, 1987	Canada	English	Yes	Single NSBPT, skin prick, serum specific IgE	Psyllium (H)	Nurses with history of asthmatic symptoms after exposure to psyllium	Clinic
Cartier, 1986	Canada	English	Yes	Skin prick, serum specific IgE	Snow crab (H)	Snow crab workers previously diagnosed with OA	Clinic
Choudat, 1999	France	English	Yes	Single NSBPT, serum specific IgE	Flour: wheat (H)	Bakers and pastry makers referred for assessment of OA caused by flour	Clinic
Cirla, 1975	Italy	Italian	Yes	Single NSBPT, skin prick	Isocyanates (L)	Furniture manufacturing workers with symptoms of asthma at work	Clinic
Colas, 1985	France	French	Yes	Carbon dioxide diffusion, eosinophils, single NSBPT, single PFT, skin prick, serum total IgE	Wood dust: exotic (L)	Workers who had been hospitalized for OA due to exotic woods	Clinic
Cortona, 1980	Italy	Italian	No	Skin prick	Enzymes: bromolin (H)	Workers from a pharmacuetical industry handling bromelin	Workplace
Cote, 1993	Canada	English	Yes	Serial PFT (PEFR)	Wood dust: cedar (L)	Consecutive sawmill workers referred by family physician for work related increases in dyspnea and cough	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Coutts, 1984	United Kingdom	English	Yes	Single NSBPT, skin prick	Chemical: cimetidine (L)	Syptomatic workers manucturing cimetidine tablets	Workplace
Curran, 1996	United Kingdom	English	No	Serum specific IgE, serum total IgE	Chemical: glutaraldehyde (L)	Health professionals exposed to glutaraldehyde, some had been diagnosed with OA by respiratory physician, some had respiratory symptoms without diagnosis	Clinic
Davison, 1983	United Kingdom	English	Yes	Skin prick, serum specific IgE	Castor beans (H)	Merchant seamen and laboratory workers who developed allergic symptoms following exposure to castor beans	Workplace
DeZotti, 1996a	Italy	English	Yes	Eosinophils, single NSBPT, single PFT, skin prick	Wood dust: exotic (L)	Furniture manufacturers and wood processors complaining of respiratory symptoms at work	Clinic
DeZotti, 1996b	Italy	Italian	Yes	Eosinophils, single NSBPT, single PFT, skin prick, serum specific IgE	Mixed (M)	Workers with OA due to isocyanate or wheat exposure	Clinic
Dellabianca, 1996	Italy	English	Yes	Single NSBPT, single NSBPT	Mixed (M)	Consecutive subjects of mixed occupation referred to clinic for probable OA due to low molecular weight chemicals- both SIC reactors and non-reactors	Clinic
Dente, 1986	Italy	English	Yes	Single NSBPT	Isocyanates (L)	Workers with occupational exposure to TDI	NR
DiFranco, 1998	Italy	English	Yes	Eosinophils, single NSBPT	Mixed (M)	Workers with OA induced by low or high molecular weight compounds seen in a clinic over a two yr period	Clinic
DiStefano, 1999	United Kingdom	English	No	Single NSBPT, skin prick	Chemical: glutaraldehyde (L)	Health care workers with symptoms suggestive of OA due to exposure to glutaraldehyde	Other

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Duan, 1989	China	Chinese	Yes	Clinical diagnosis, serial NSBPT, serial PFT, single PFT, skin prick, serum specific IgE	Isocyanates (L)	Symptomatic TDI factory workers compared to non-symptomatic workers and ordinary asthma workers	Mixed
Ferguson, 1996	Canada	English	Yes	Single NSBPT, single PFT, serum specific IgE	Isocyanates (L)	Auto manufacturers and spray painters with chest symptoms compatible with asthma and prior exposure to isocyanates	Other
Gannon, 1996	United Kingdom	English	No	Serial PFT (PEFR)	Mixed (M)	Records from workers from different industries attending an occupational lung disease clinic with suspected OA, and from a cross sectional survey of respiratory symptoms in post office sorting workers	Mixed
Girard, 2004	Canada	English	Yes	Eosinophils, serial NSBPT, serial PFT, skin prick	Mixed (M)	Subjects referred to OA reference centres for possible OA	Clinic
Graneek, 1987	United Kingdom	English	Yes	Single NSBPT	Mixed (M)	Workers from various industries who were admitted to hospital for investigation of OA	Other
Grosclaude, 1980	France	French	Yes	Single NSBPT, skin prick, serum total IgE	Mixed (M)	Workers of mixed occupation with OA due to various causes	Workplace
Harries, 1980	United Kingdom	English	Yes	Eosinophils, skin prick	Mixed (M)	Workers of various occupation with a history of respiratory illness worsening at work	Clinic
Hinojosa, 1986	Spain	English	Yes	Skin prick, serum specific IgE, serum total IgE	Wood dust: African maple and ramin (L)	Workers exposed to African maple dust who were admitted for study after being away from work for at least two wks	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Howe, 1983	United Kingdom	English	Yes	Skin prick, serum specific IgE	Chemical: TCPA (L)	Factory workers with respiratory symptoms referred by factory management	Workplace
Huggins, 2003	United Kingdom	English	No	Serial PFT (PEFR)	Enzymes: detergent (H)	Factory workers with work-related respiratory symptoms and positive serum specific IgE or skin prick tests to one of the enzymes used in biological detergents	Clinic and workplace
Jager, 1993	Germany	German	Yes	Single NSBPT, skin prick, serum specific IgE, supervised work challenge, serum total IgE	Latex (H)	Health care workers with an immediate allergic-type reaction to latex gloves	Clinic
Karol, 1994	United States	English	Yes	Clinical diagnosis, single NSBPT, serum specific IgE, serum specific IgG, serum total IgE	Isocyanates (L)	Workers with a history of sensitization to isocyanates, referred for evaluation of respiratory symptoms	Clinic
Kern, 1991	United States	English	No	Single NSBPT	Chemical: glacial acetic acid (L)	Hospital laboratory and radiology workers exposed to a one time spill of 100% acetic acid for two and a half hrs	Workplace
Keskinen, 1988	Finland	English	Yes	Skin prick, serum specific IgE	Isocyanates (L)	Workers of mixed occupation with verified asthma due to di-isocyanates based on symptoms and SIC	Clinic
Kim, 1999	Korea	English	Yes	Single NSBPT, single PFT, skin prick, serum specific IgE, serum total IgE	Citrus red mite (H)	Citrus fruit farmers with respiratory symptoms	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Kim, 1997	Korea	English	No	Single PFT, serum specific IgE, serum specific IgG	Isocyanates (L)	Workers who had been exposed to TDI in workshops manufacturing furniture or musical instruments or repairing motor vehicles	Workplace
Kongerud, 1992	Norway	English	No	Clinical diagnosis, eosinophils, serial NSBPT, single NSBPT, symptom score, serum total IgE	Potroom (L)	Potroom workers with a history suggestive of OA after standardized interview and methacholine challenge PC_{20} <32 g/L	Clinic
Kopferschmitt-Kubler, 1998	France	English	Yes	Serial PFT (FEV_1), single NSBPT	Isocyanates (L)	Workers with clinical history of isocyanate-induced asthma with reversibility and no positive reaction to low doses of TDI	Clinic
Koskela, 2003	Australia and Finland	English	Yes	Exhaled nitric oxide, single NSBPT, skin prick, serum specific IgE, serum total IgE	Animal/bird: cow dander (H)	Dairy farmers who were referred to the laboratory because of a suspicion of OA due to bovine allergens	Clinic
Krakowiak, 2003	Poland	English	Yes	Clinical diagnosis, eosinophils, single NSBPT, skin prick, serum specific IgE	Animal/bird: lab animals (H)	Laboratory animal workers referred to an occupational disease clinic for asthma and allergic rhinitis	Clinic
Lam, 1979	Canada	English	Yes	Single NSBPT, skin prick	Wood dust: cedar (L)	Subjects with OA that were tested while symptomatic or after removed from exposure	Clinic
LaPaglia, 1986	Italy	Italian	Yes	Clinical diagnosis, skin prick	Mixed (M)	Subjects with a work-associated respiratory disease	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Larbanois, 2003	Belgium	English	Yes	Serial PFT (sGaw), single NSBPT	Mixed (M)	Consecutive subjects of various occupations who were investigated for OA and underwent SIC	Clinic
Lemiere, 2001	Canada	English	Yes	Eosinophils, single NSBPT, skin prick	Mixed (M)	Workers of various occupations referred to clinic for possible OA and subjects who had a diagnosis of asthma (concentration of methacholine inducing a 20% fall in FEV_1 of less than 8mg/mL and who could produce sputum)	Clinic
Liss, 1991	Canada	English	Yes	Serial PFT (PEFR), single NSBPT, single PFT, skin prick	Mixed (M)	Consecutive workers with mixed occupations referred for assessment of possible OA	Clinic
Lozewicz, 1985	United Kingdom	English	Yes	Single NSBPT, skin prick	Chemical: acrylates (L)	Subjects with asthma associated with exposure to cyanoacrylates	NR
Malo, 1993a	Canada	English	Yes	Serial PFT (PEFR)	Mixed (M)	Workers of mixed occupation referred for investigation of possible OA	Clinic
Malo, 1991	Canada	English	Yes	Questionnaire, serial NSBPT, serial PFT (PEFR), single NSBPT, skin prick	Mixed (M)	Workers of mixed occupation referred because of possible OA	Clinic
Malo, 1990	Canada	English	Yes	Single NSBPT, skin prick	Mixed (M)	Records of subjects with late asthmatic reactions and isolated immediate reactions to SIC	Clinic
Malo, 1988a	Canada	English	Yes	Eosinophils, questionnaire, serial PFT (PEFR), single NSBPT, skin prick	Spiromycin (L)	All workers in a pharmaceutical company, intermittently exposed to spiromycin, investigated to determine frequency of OA	Workplace
Mapp, 1986	Italy	English	Yes	Single NSBPT, skin prick	Isocyanates (L)	Subjects with sensitivity to TDI	NR

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Mapp, 1979	Italy	Italian	Yes	Single NSBPT, skin prick	Isocyanates (L)	Employees who worked in paint, varnish and plastics manufacturing with chronic respiratory symptoms at work	Workplace
Merget, 1997	Germany	English	Yes	Single NSBPT, skin prick, serum specific IgE, serum total IgE	Flour: wheat (H)	Highly selected bakers referred to clinic for assessment of OA	Clinic
Merget, 1996	Germany	English	Yes	Single NSBPT, skin prick, serum total IgE	Chemical: platinum salts (L)	Platinum refinery and catalyst production workers who were considered to have OA due to platinum salts	Clinic
Merget, 1993	Germany	English	Yes	Single NSBPT, skin prick, serum specific IgE, serum total IgE	Enzymes (H)	Enzyme manufacturing plant workers referred to the pulmonary department with work related symptoms	Workplace
Mole, 1977	Italy	Italian	No	Single NSBPT, skin patch test	Mixed (M)	Workers of many occupations with suspected OA	Clinic
Moller, 1986	United States	English	Yes	Clinical diagnosis, single NSBPT, single PFT	Isocyanates (L)	Workers of various occupations referred for possible TDI asthma based on consistent clinical and occupational history	Clinic
Moller, 1985	United States	English	No	Eosinophils, questionnaire, serial PFT (FEV_1), serum specific IgE	Chemical: hexahydrophthalic anhydride (L)	Workers in a plant manufacturing bushings for electrical transformers who reported symptoms of asthma	Workplace
Moscato, 1993	Italy	English	Yes	Single NSBPTs, single PFT, skin prick	Isocyanates (L)	Workers in furniture and plastics industries, auto body repair workers, and carpenters referred for probable OA due to TDI	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Munoz, 2004	Spain	English	Yes	Serial PFT (PEFR), single NSBPT, skin prick, serum total IgE	Chemical: persulfate (L)	Hairdressers and cosmetic industry workers exposed to hair bleaches diagnosed with OA	Clinic
Nielsen, 1988	Sweden	English	No	Single NSBPT, skin prick, serum specific IgE, serum specific IgG, serum total IgE	Chemical: phthalic anhydride (L)	Workers from factories producing polyester resins reporting asthma symptoms during exposure	Workplace
Nordman, 1985	Finland	English	Yes	Eosinophils, serial PFT (PEFR), single NSBPT, single PFT, serum total IgE	Formaldehyde (L)	Workers with various occupations investigated because of suspected formaldehyde-induced asthma	Clinic
O'Brien, 1979a	United Kingdom	English	Yes	Single NSBPT	Isocyanates (L)	Subjects referred for investigation of possible work related respiratory symptoms	Clinic
O'Brien, 1979b	United Kingdom	English	Yes	Exercise test, single NSBPT, skin prick	Isocyanates (L)	Workers occupationally exposed to TDI referred for investigation of possible work related asthma symptoms	Clinic
Obata, 1999	Canada	English	Yes	Eosinophils, exhaled nitric oxide, single NSBPT, skin prick	Wood dust: cedar (L)	Sawmill workers or carpenters referred to respiratory clinic with symptoms of cough, wheeze and chest tightness after working with red cedar for at least six mos	Clinic
Obtulowicz, 1998	Poland	English	Yes	Eosinophils, skin prick, serum total IgE	Mixed (M)	Steel and tobacco factory workers with bronchial asthma suspected to be of occupational origin	Other
Paggiaro, 1987b	Canada	English	Yes	Single NSBPT, skin prick, serum specific IgE	Wood dust: cedar (L)	Workers with OA due to western red cedar	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Paggiaro, 1986	Italy	English	Yes	Single NSBPT, skin prick	Isocyanates (L)	Furniture industry workers with OA induced by TDI	Clinic
Paggiaro, 1984b	Italy	Italian	Yes	Single NSBPT, skin prick, serum specific IgE, serum total IgE	Enzymes: proteolytic (H)	Workers in a factory producing detergents with symptoms of OA	Workplace
Paggiaro, 1984c	Italy	Italian	Yes	Clinical diagnosis, single NSBPT	Isocyanates (L)	Workers from a furniture industry exposed to isocyanates	Workplace
Paggiaro, 1981	Italy	English	Yes	Single NSBPT, skin prick, serum specific IgE	Wood dust: tanganyika aningre (L)	Woodworkers exposed to tanganyika aningre with symptoms of dyspnea, cough, and wheezing	Other
Palczynski, 2003	Poland	English	Yes	Eosinophils, single NSBPT, skin prick, serum specific IgE, serum total IgE	Chloramine (L)	Healthcare workers with a history of respiratory symptoms related to chloramine T	Other
Park, 2002b	Korea	English	Yes	Immunoblotting, single NSBPT, skin prick, serum specific IgE	Alpha amylase (H)	Nurses with asthma symptoms when exposed to porcine pancreatic extracts at work	Clinic
Park, 2001	Korea	English	Yes	Skin prick, serum specific IgE	Reactive dyes (L)	Workers with OA from reactive dyes (SIC positive) who visited clinic in last ten yrs, asymptomatic workers in a reactive dye factory, and unexposed subjects with negative SIC to reactive dyes	Mixed
Park, 1999	Korea	English	Yes	Single NSBPT, single PFT, skin prick, serum specific IgE	Isocyanates (L)	Workers with TDI induced asthma, as well as SIC negative workers and control subjects with allergic asthma	Other

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Park, 1998	Korea	English	Yes	Eosinophils, immunoblotting, single NSBPT, skin prick, serum specific IgE	Grain dust (H)	Animal feed industry workers exposed to grain dust	Workplace
Park, 1994	Korea	English	Yes	Serial PFT (PEFR), single NSBPT, skin patch test, skin prick	Chemical: chromium (L)	Metal plating factory, cement manufacturers and construction workers complaining of work related symptoms	Clinic
Park, 1991	Korea	English	Yes	Single NSBPT, skin prick, serum specific IgE, serum total IgE	Reactive dyes (L)	Symptomatic textile dye industry workers with bronchial hyperreactivity	Workplace
Park, 1989	Korea	English	Yes	Single NSBPT, single PFT, skin prick, serum specific IgE	Reactive dyes (L)	Dye process workers who complained of asthmatic symptoms following various lengths of exposure to reactive dyes	Workplace
Perrin, 1990	Canada	English	Yes	Serial NSBPT, serial PFT (PEFR)	Mixed (M)	Subjects referred for OA to various agents	Clinic
Pezzini, 1984	Italy	English	Yes	Single NSBPT, skin prick, serum specific IgE	Isocyanates (L)	Polyurethane foam shoe factory and furniture plant workers with diagnosis of isocyanate-induced OA based on symptoms and SIC	NR
Prichard, 1984	Australia	English	No	Single NSBPT, skin prick	Flour: wheat (H)	Bakers and bakery workers of fulfilled the definition of work related asthma	Workplace
Quirce, 2000	Spain	English	No	Skin prick, serum specific IgE	Wood dust: obeche (L)	Woodworkers with symptoms of asthma after exposure to obeche wood dust	NR

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Quirce, 1992	Spain	English	Yes	Single NSBPT, skin prick, serum specific IgE	Alpha amylase (H)	Bakers evaluated in clinic because of respiratory symptoms due to exposure to flours and enzymes at work	Clinic
Rasanen, 1994	Finland	English	Yes	Basophil histamine release, skin prick, serum specific IgE, serum total IgE	Mixed (M)	Workers of mixed occupation with challenge-proven occupational rhinitis or asthma and workers with seasonal rhinitis or other respiratory symptoms	NR
Redlich, 1996	United States	English	Yes	Bronchial alveolar lavage, eosinophils, single NSBPT	Isocyanates (L)	Currently exposed workers with isocyanate asthma	NR
Ricciardi, 2003	Italy	English	Yes	Eosinophils, serial PFT (PEFR), single NSBPT, skin prick, serum specific IgE, serum total IgE	Wood dust: iroko (L)	Wood workers who reported asthma symptoms	Clinic
Sander, 2001	Germany	German	Yes	Skin prick	Flour: wheat and rye (H)	Bakers with asthma symptoms	NR
Sastre, 2003	Spain	English	Yes	Single NSBPT, serum specific IgE	Isocyanates (L)	Workers with a suspected clinical history of di-isocyanate-induced asthma	Other
Schuermans, 2003	Belgium	English	Yes	Single NSBPT	Latex (H)	Workers of unreported occupation referred to centre for suspected latex OA	Clinic
Schwaiblmair, 1997	Germany	English	Yes	Single NSBPT, single PFT, skin prick	Bleaching powder (L)	Hairdressers who had regular contact with various hair products and a clinical history of job related rhinitic/asthma symptoms	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Schwarting, 1979	Germany	German	Yes	Clinical diagnosis, skin prick, serum specific IgE	Flour (H)	Bakers who were exposed to flour dust for at least eight hrs per day	Workplace
Shirai, 2003	Japan	English	Yes	Clinical diagnosis, single NSBPT, skin prick	Green tea (L)	Green tea factory workers with clinical history suggestive of asthma referred to Internal Medicine and associated hospitals	Clinic
Shirakawa, 1988	Japan	English	Yes	Antibodies (CO-HSA), eosinophils, single NSBPT, skin prick, serum specific IgE	Chemical: cobalt (L)	Hard metal plant workers who met clinical criteria for OA	Clinic
Slovak, 1981	United Kingdom	English	No	Serial PFT (PEFR), skin prick	Chemical: AZO dicarbonamide (L)	Personnel with positive history of wheezing or chest tightness (+/- cough) related to exposure to azodicarbonamide dust on screening at a manufacturing plant	Workplace
Symington, 1981	United Kingdom	English	Yes	Skin prick	Mushroom dust (H)	Food manufacturing workers presenting with work related symptoms to dried mushroom dust	Workplace
Tabar, 2004	Spain	English	Yes	Immunoblotting, skin patch test, skin prick, serum specific IgE, serum total IgE	Asparagus (H)	Workers with various occupations diagnosed with asparagus allergy in the past five yrs	Clinic
Taivainen, 1994	Finland	Finnish	Yes	Clinical diagnosis, skin prick, serum specific IgE	Animal/bird: cow dander (H)	Farmers refered to a clinic for investigation of OA	Clinic

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Tee, 1998	United Kingdom	English	No	Skin prick, serum specific IgE	Isocyanates (L)	All workers exposed to isocyanates who were referred for investigation of OA from whom blood was available for measurement of serum specific IgE and in whom a firm diagnosis was reached	Clinic
Tse, 1982	Canada	English	Yes	Serum specific IgE	Wood dust: cedar (L)	Workers suspected to have red cedar asthma who were referred to the clinic to undergo antigenic bronchoprovocation test to have the diagnosis confirmed	Clinic
Vandenplas, 2001	Belgium	English	Yes	Clinical diagnosis, serial NSBPT, single NSBPT, skin prick	Latex (H)	Consecutive workers who were referred for the investigation of possible OA and who were exposed at work to airborne allergens from natural rubber latex gloves	Clinic
Vandenplas, 1995b	Belgium	English	Yes	Single NSBPT, skin prick	Latex (H)	Hospital employees (nurses, lab technologists, cleaning staff) exposed to latex	Workplace
Vanhanen, 2000	Finland	English	Yes	Single NSBPT, skin prick, serum specific IgE	Cellulase (H)	Workers with suspected OA or rhinitis due to cellulase who were referred to a clinic	Clinic
Virtanen, 1996	Finland	English	No	Serum specific IgE, serum specific IgG	Animal/bird: cow dander (H)	Randomly selected dairy farmers diagnosed with cow asthma who were workers of the pulmonary clinic	Clinic
Vogelmeier, 1991	Germany	English	Yes	Single NSBPT, skin prick, serum specific IgE	Isocyanates (L)	Workers who had occupational contact with TDI and/or MDI and a strong clinical history or workplace-related asthma and normal volunteers; subjects with asthma and no isocyanate exposure	NR

Table E-1. Description of included studies (Diagnosis review) (continued)

Author, Year	Location	Language of Publication	SIC used as Reference Standard	Comparison Tests	Suspected Agent (molecular weight)	Description of Included Workers	Patient Source
Wurzinger, 1997	Austria	German	Yes	Single NSBPT, skin prick, serum specific IgE, serum total IgE	Flour (H)	Cooks, bakers, farmers, and confectioners with suspected OA	Clinic
Zeiler, 2002	Finland	English	Yes	Single NSBPT, skin prick, serum specific IgE, serum specific IgG	Animal/bird: cow dander (H)	Consecutive dairy farmers referred to pulmonary clinic for confirmation of the bovine origin of their OA	Clinic
Zeiss, 1977	United States	English	No	Skin prick, serum specific IgE, serum specific IgG	Chemical: trimellitic anhydride (L)	Chemical plant workers with asthma and/or rhinitis symptoms due to TMA exposure	Clinic

Abbreviations: **AC** = azodicarbonamide; **CO-HSA** = conjugated human serum; **FEV_1** = forced expiratory volume in one second; **H** = high; **L** = low; **M** = mixed; **MCP-1** = monocyte chemoattractant protein-1; **MDI** = diphenylmethane di-isocyanate; **mos** = months; **NR** = not reported; **NSBPT** = non-specific bronchial provocation; **OA** = occupational asthma; **PC_{20}** = provocative concentration causing a 20% drop in FEV_1; **PEFR** = peak expiratory flow rate; **PFT** = pulmonary function test; **sGaw** = specific airways conductance; **SIC** = specific inhalational challenge; **TCPA** = tetrachlorophthalic anhydride; **TDI-HSA** = toluene di-isocyanates human serum albumin; **TMA** = trimellitic anhydride; **wks** = weeks; **yr** = year; **yrs** = years

Table E-2. Demographic characteristics of included patients (Diagnosis review)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Alvarez, 2001	3	66.7	40.3 (13.6)	0	C: 0 Ex: 0 N: 100	-	94.7 (1.5)	-	1.7 (0.6)	No
Alvarez, 1996	21	95.2	38.3 (15.7)	42.9	C: 14.3	-	-	-	5.5 (7.7)	No
Anees, 2004	141	73.8	46 (10.2)	45.4	C: 17.7 Ex: 33.3 N: 48.9	-	-	-	-	Yes
Avery, 1969	18	-	-	-	-	-	-	-	-	No
Balland, 1989	75	61.3	-	24	-	52	-	-	-	-
Baur, 1998	229	66.4	35.1 (11.4)	-	-	-	-	8.6 (8.4)	-	No
Baur, 1979	7	-	-	-	-	-	-	4.8 (2.8)	-	-
Behr, 1990	70	-	-	-	-	-	-	-	-	No
Bernstein, 2002	54	96.3	39.9	-	-	-	-	11.2 (11.1)	-	No
Biot, 1980	12	-	41.6 (11.4)	-	-	-	-	-	-	-
Block, 1983	7	100	50 (13.6)	85.7	C: 42.9 Ex: 42.9 N: 14.3	-	101.7 (28.8)	28.4 (16)	-	Yes
Burge, 1985	15	93.3	45.7 (11.1)	46.7	C: 26.7 Ex: 40 N: 33.3	0	-	-	-	No
Burge, 1982b	136	-	-	-	-	-	-	-	-	No
Burge, 1980	49	-	-	-	-	-	-	-	-	No
Burge, 1979a	29	-	-	-	-	-	-	-	-	-

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Burge, 1979b	23	-	-	-	-	-	-	-	-	No
Burge, 1978	21	14.3	45.2 (12.5)	42.9	C: 23.8 Ex: 14.3 N: 66.7	23.8	88.3 (16.5)	-	-	No
Butcher, 1980	26	-	-	-	-	-	-	-	-	No
Carletti, 1997	37	100	41 (12)	37.8	C: 48.6	-	-	-	-	No
Cartier, 1989	62	93.5	-	40.3	C: 27.4 Ex: 37.1 N: 35.5	-	94 (22)	8.8 (8.5)	-	-
Cartier, 1987	5	20	38.8 (9.9)	100	-	20	90 (16.3)	12.6 (4.3)	0.7 (0.3)	Yes
Cartier, 1986	54	-	-	-	-	-	-	-	-	No
Choudat, 1999	21	95.2	29.6 (5.7)	-	-	-	97 (12.3)	11.6 (6.4)	-	No
Cirla, 1975	33	-	-	-	-	-	77 (7.8)	-	-	No
Colas, 1985	10	100	47	30	-	10	-	21.6	3.4	No
Cortona, 1980	76	-	35	-	-	-	-	-	-	No
Cote, 1993	25	100	-	-	-	-	-	-	-	No
Coutts, 1984	4	100	38 (13)	-	-	-	-	-	-	No
Curran, 1996	20	10	46.7 (11.4)	-	-	-	-	-	-	-
Davison, 1983	3	100	29 (2.7)	100	C: 66.7 Ex: 0 N: 33.3	0	PEF: 193.3 (135.8)	-	-	No

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
DeZotti, 1996a	4	75	47.3 (12.3)	50	N: 100	-	-	-	-	-
DeZotti, 1996b	54	61.1	30.6 (9.6)	25.9	C: 24.1	44.4	-	8.7 (9.6)	-	No
Dellabianca, 1996	40	47.5	35.6 (11.1)	20	C: 20 Ex: 40 N: 42.5	-	-	-	2.35 (10.6)	-
Dente, 1986	42	-	-	-	-	-	-	-	-	-
DiFranco, 1998	24	75	45.3 (9.6)	25	C: 0 Ex: 54.2 N: 45.8	-	-	-	7.33 (4.5)	Yes
DiStefano, 1999	24	12.5	38.6 (8.8)	37.5	C: 29.2 Ex: 16.7 N: 54.2	12.5	75.8 (14.6)	-	-	-
Duan, 1989	18	33.3	-	-	-	100	-	9.5 (4.8)	-	No
Ferguson, 1996	90	63.3	34.3 (10.2)	-	C: 46.7 Ex: 35.6 N: 16.7	-	-	5.7 (5.9)	1.92 (3.3)	Yes
Gannon, 1996	127	-	-	-	-	-	-	-	-	No
Girard, 2004	52	57.7	40.4 (11.5)	69.2	C: 23.1 Ex: 44.2 N: 26.9	-	-	7.2 (8.1)	10.65 (11.4)	-
Graneek, 1987	9	-	-	-	-	-	-	-	-	-
Grosclaude, 1980	30	73.3	38.7	10	-	-	-	10	1.9	No
Harries, 1980	37	45.9	37.5 (9.8)	59.5	-	-	-	-	-	No

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Hinojosa, 1986	4	100	40 (6.2)	25	C: 25 Ex: 25 N: 50	-	-	8.8 (3.3)	4.8 (2.6)	-
Howe, 1983	7	0	41.1 (5)	14.3	C: 100 Ex: 0 N: 0	0	-	-	-	No
Huggins, 2003	52	-	-	-	-	-	-	-	-	No
Jager, 1993	14	14.3	34.7 (8.1)	42.9	-	71.4	-	-	-	No
Karol, 1994	63	73	30.6	-	-	-	-	10.1 (9)	3.08 (3.9)	-
Kern, 1991	51	19.6	37.9 (10.3)	23.5	C: 41.2 Ex: 13.7 N: 45.1	5.9	-	-	-	No
Keskinen, 1988	35	80	37 (10.5)	31.4	C: 34.3 Ex: 0 N: 65.7	-	-	-	-	No
Kim, 1999	16	56.3	48.6 (10.4)	37.5	C: 6.3	-	-	20 (5)	-	No
Kim, 1997	81	50.6	41.8 (8.1)	-	-	-	-	-	-	No
Kongerud, 1992	14	92.9	38.1 (9.7)	28.6	C: 50 Ex: 14.3 N: 35.7	-	94.9 (9.9)	-	-	No
Kopferschmitt -Kubler, 1998	11	90.9	36.1 (7.3)	54.5	C: 18.2 Ex: 54.5 N: 27.3	9.1	FEV_1: 3.4 (0.5)	-	-	-
Koskela, 2003	37	35.1	42.8 (8.3)	-	C: 13.5	-	-	-	-	Yes
Krakowiak, 2003	25	-	41.9 (11.6)	72	C: 20 Ex: 12 N: 68	16	FEV_1: 3.9 (0.4)	13 (7)	-	No

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Lam, 1979	86	-	41.4 (10.5)	23.3	C: 7 Ex: 18.6 N: 74.4	-	-	-	-	No
LaPaglia, 1986	309	-	55.6 (10.1)	-	-	5.2	-	32.8 (10.5)	-	No
Larbanois, 2003	174	62.6	38.4 (10)	58	N: 59.8	-	-	-	3.41 (4.5)	Yes
Lemiere, 2001	31	90.3	42.1 (13)	71	C: 58.1 Ex: 0 N: 41.9	-	-	-	3.35 (4.9)	No
Liss, 1991	50	72	44	56	-	-	-	12	3.5	No
Lozewicz, 1985	7	42.9	43 (11)	42.9	C: 14.3	-	-	-	-	No
Malo, 1993a	74	91.9	-	-	C: 13.5 Ex: 41.9 N: 44.6	-	91 (18)	9.4 (8.1)	-	Yes
Malo, 1991	162	77.2	39.6 (11.8)	54.3	C: 30.2 Ex: 40.7 N: 27.2	-	92.7 (16.4)	6.5 (8.8)	1.9 (2.7)	Yes
Malo, 1990	164	76.2	38.8 (12.2)	57.3	C: 27.4 Ex: 34.8 N: 37.8	-	-	8.8 (8.4)	3.15 (3.4)	No
Malo, 1988a	51	49	37 (10)	39.2	N: 49	7.8	-	10 (8)	-	No
Mapp, 1986	6	66.7	31.7 (13)	33.3	C: 16.7 Ex: 33.3 N: 50	-	104 (20.6)	11.6 (10)	2.11 (2.3)	No
Mapp, 1979	15	86.7	36.8 (12.2)	-	C: 6.7 Ex: 13.3 N: 80	-	FEV_1: 3.6 (0.7)	7	-	No
Merget, 1997	34	76.5	26 (10.5)	-	-	-	-	7.7 (8.4)	-	-

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Merget, 1996	57	94.7	37 (10)	49.1	C: 54.4 Ex: 17.5 N: 10.5	0	98 (14)	-	5.25 (5.3)	Yes
Merget, 1993	42	-	-	38.1	C: 35.7 Ex: 42.9 N: 21.4	-	-	9.5 (8.5)	-	No
Mole, 1977	40	100	34.6 (6)	-	C: 37.5	-	-	-	-	No
Moller, 1986	12	83.3	41.1 (14.6)	16.7	C: 25 Ex: 25 N: 50	16.7	-	2.1 (3)	-	Yes
Moller, 1985	7	-	-	28.6	-	28.6	-	-	-	No
Moscato, 1993	75	85.3	40.1 (10.5)	41.3	C: 29.3 Ex: 26.7 N: 42.7	-	-	19.5 (31.8)	4.2 (5.4)	No
Munoz, 2004	8	0	37 (7.3)	37.5	C: 37.5	-	FEV_1: 2.9 (0.7)	11 (5.5)	-	No
Nielsen, 1988	5	-	-	-	-	-	-	13.8 (9.7)	-	No
Nordman, 1985	12	25	-	16.7	-	-	FEV_1: 2.8 (0.7)	-	-	No
O'Brien, 1979a	24	100	-	-	-	-	-	-	-	No
O'Brien, 1979b	63	-	43 (8.8)	36.5	C: 22.2 Ex: 23.8 N: 36.5	-	-	-	-	-
Obata, 1999	17	100	35.3 (10.6)	70.6	C: 0 Ex: 5.9 N: 94.1	-	-	6.2 (9.2)	2.1 (2.7)	Yes
Obtulowicz, 1998	49	59.2	48.5 (8.3)	36.7	C: 46.9	-	-	-	-	Yes

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Paggiaro, 1987b	332	-	25.5 (12)	36.1	N: 67.8	-	-	-	-	No
Paggiaro, 1986	114	75.4	46.2 (11.8)	20.2	C: 19.3 Ex: 22.8 N: 57	-	-	-	3.69 (3.5)	No
Paggiaro, 1984b	6	33.3	37.2 (11.7)	50	C: 50 Ex: 0 N: 50	-	95.5 (20.2)	11.8 (4.4)	5.7 (1.3)	No
Paggiaro, 1984c	-	-	-	-	-	-	-	-	-	No
Paggiaro, 1981	3	100	49.3 (13.4)	33.3	C: 100 Ex: 0 N: 0	-	93.3 (14)	3.3 (3.9)	3.1 (4.1)	Yes
Palczynski, 2003	6	16.7	43.7 (7.9)	16.7	C: 0	-	-	-	-	No
Park, 2002b	4	-	24.8 (1.3)	75	C: 0 Ex: 0 N: 100	-	-	-	-	No
Park, 2001	136	89	40.8 (8.7)	38.2	-	-	-	9.2 (5.2)	-	No
Park, 1999	63	73	38.5 (10.6)	52.4	-	-	-	5.7 (5.6)	-	No
Park, 1998	15	100	-	93.3	-	-	-	-	-	No
Park, 1994	4	100	42 (13)	75	C: 0 Ex: 100 N: 0	-	-	-	-	No
Park, 1991	13	-	-	-	-	-	-	-	-	No
Park, 1989	9	100	35.6 (6)	33.3	C: 44.4 Ex: 55.6 N: 0	-	FEV_1: 3.5 (0.6)	1.5 (0.5)	-	No

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Perrin, 1990	23	-	-	-	-	-	-	-	-	-
Pezzini, 1984	28	64.3	-	25	-	-	-	12.2 (8.5)	-	No
Prichard, 1984	20	100	32	-	C: 45 Ex: 15 N: 40	-	FEV_1: 4	-	-	No
Quirce, 2000	5	80	49.2 (9.5)	60	C: 0 Ex: 20 N: 80	-	-	23.8 (12.8)	11.7 (5.9)	No
Quirce, 1992	5	80	40.8 (17.2)	80	C: 60 Ex: 0 N: 40	-	90 (8.2)	22.2 (15.8)	7.4 (5.6)	No
Rasanen, 1994	28	39.3	37.6 (9)	-	-	-	-	-	-	Yes
Redlich, 1996	3	-	-	-	-	-	-	-	-	No
Ricciardi, 2003	9	77.8	47.3 (10.6)	11.1	C: 11.1 Ex: 0 N: 88.9	-	FEV_1: 4.4 (0)	-	-	No
Sander, 2001	7	-	-	-	-	-	-	-	-	No
Sastre, 2003	22	81.8	38.6 (10.6)	36.4	C: 4.5 Ex: 9.1 N: 81.8	-	-	13.7 (9.1)	3.7 (3.1)	No
Schuermans, 2003	39	-	-	-	-	-	-	-	-	No
Schwaiblmair, 1997	55	0	30.8 (14.1)	14.5	C: 34.5	-	FEV_1: 3 (0.7)	15.1 (14.8)	4.8 (5.2)	No
Schwarting, 1979	-	-	-	-	-	-	-	-	-	No

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Shirai, 2003	21	42.9	44 (14.5)	52.4	C: 14.3 Ex: 33.3 N: 52.4	-	-	-	3.17 (4.3)	No
Shirakawa, 1988	12	-	48.3 (5.4)	66.7	C: 41.7	-	-	-	-	Yes
Slovak, 1981	28	100	41 (8.5)	46.4	C: 42.9 Ex: 32.1 N: 25	0	-	-	-	No
Symington, 1981	8	37.5	-	25	-	-	-	8.1 (4)	-	No
Tabar, 2004	10	20	38.3 (10.2)	60	-	-	-	-	-	No
Taivainen, 1994	100	47	44 (10.8)	-	C: 4 Ex: 28 N: 68	97	-	-	-	No
Tee, 1998	101	93.1	-	-	-	-	-	-	-	-
Tse, 1982	28	-	-	-	-	-	-	-	-	-
Vandenplas, 2001	45	4.4	33.6 (6.1)	68.9	N: 73.3	20	-	-	3.01 (2.8)	No
Vandenplas, 1995b	13	0	33 (4)	53.8	C: 15.4 Ex: 23.1 N: 61.5	-	97.4 (9.7)	-	4 (3)	Yes
Vanhanen, 2000	11	36.4	36.5 (7.2)	63.6	C: 27.3	-	93.5 (8.2)	-	-	-
Virtanen, 1996	11	63.6	46 (7.3)	-	-	-	-	-	-	No
Vogelmeier, 1991	19	94.7	49.4 (2.5)	-	-	-	-	6 (5.8)	-	No

Table E-2. Demographic characteristics of included patients (Diagnosis review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	%predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)	
Wurzinger, 1997	5	40	39.6 (19.3)	-	-	-	-	-	-	No
Zeiler, 2002	9	66.7	40 (10)	66.7	C: 0 Ex: 44.4 N: 55.6	-	-	-	-	No
Zeiss, 1977	4	-	40.3 (13.4)	25	-	-	-	2 (2.7)	-	No

Abbreviations: **C** = current; **Ex** = ex; **FEV_1** = forced expiratory volume in one second; **N** = never; **PEF** = peak expiratory flow; **SD** = standard deviation

Table E-3. Description of diagnostic tests (Diagnosis review)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Alvarez, 2001	SIC: oilseed rape flour	≧20% decline in FEV_1	Referenced (Chatham et al., 1982)	Eosinophils: sputum Single NSBPT: methacholine Skin prick: atopy and specific Serum specific IgE	Not reported Not reported Wheal diameter ≧3 mm >0.35 KU/L	Described in text Referenced (Chatham et al., 1982) Referenced (Dreborg, 1989) CAP
Alvarez, 1996	SIC: cereals (wheat, alpha amylase, soyabean, l.destructor)	≧20% decline in FEV_1	Described in text	Single NSBPT: methacholine Skin prick: atopy Serum specific IgE	PD_{20} FEV_1 ≦250 cbu Wheal diameter ≧3 mm with no reaction to negative control CAP score ≧class 1	Referenced (Chatham et al., 1982) Referenced (Chatham et al., 1982) CAP
Anees, 2004	Other: clinical diagnosis	SIC and/or serum specific IgE and/or serial NSBPT	Not reported	Serial PFT (PEFR): monitored at least 3 times/day for at least 5 work (4-6 days) and rest (2-3 days) periods	OASYS-2 score >2.5	Referenced (Burge et al., 1999)
Avery, 1969	Other: clinical diagnosis	Not reported	Not reported	Other: TDI-HSA	Not reported	Described in text
Balland, 1989	SIC: suspected agent	≧100% increase in specific airway resistance	Not reported	Single NSBPT: methacholine Serum specific IgE Serum total IgE	≧2 fold increase in airway resistance between 0-1500 gamma of methacholine Not reported Not reported	Not reported RAST Not reported
Baur, 1998	SIC: suspected agent	≧40% decline in sGaw	Referenced (Jaeger et al., 1992; Marek et al., 1994; Schwaiblmair et al.1991)	Clinical diagnosis Single NSBPT: methacholine	Case history: reversible airway narrowing in the sense of SOB and wheezing causally related to exposure in the working environment PD_{40} sGaw <0.3 mg	Described in text Described in text

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Baur, 1979	SIC: papain	Not reported	Not reported	Skin prick: atopy and specific Serum specific IgE	Not reported Not reported	Referenced (Aas and Belin, 1972) RAST
Behr, 1990	SIC: isocyanates	≧100% increase in sRaw from baseline and absolute values ≧2.0 kPa/s	Described in text	Clinical diagnosis Single NSBPT: methacholine	Not reported ≧100% increase in sRaw from baseline and absolute values ≧2.0 kPa/s	Not reported Described in text
Bernstein, 2002	SIC: isocyanates	≧20% decline in FEV_1	Referenced (Ryan et al., 1981; Stark et al., 1993)	Other: di-isocyanate antigen stimulation of MCP-1 Single NSBPT: methacholine Serum specific IgE	Maximal antigen stimulation of MCP-1 ≧mean + 2SD of control subjects PC_{20} FEV_1 ≦8 mg/ml OD at 405 ≧0.1	Described in text Referenced (Cockcroft et al., 1977) ELISA
Biot, 1980	SIC: suspected agent	Not reported	Described in text	Other: basophils granules liberation Single NSBPT: acetylcholine Serum total IgE	Not reported Not reported Not reported	Referenced (Benveniste et al., 1976) Not reported Not reported
Block, 1983	SIC: wheat and/or rye flour	≧20% decline in FEV_1	Referenced (Lam et al., 1979)	Single NSBPT: methacholine Skin prick: atopy and specific Serum specific IgE	PC_{20} FEV_1: no cutoff reported Wheal diameter ≧2 mm Not reported	Referenced (Lam et al., 1979) Referenced (Cockcroft et al., 1979) RAST
Burge, 1985	SIC: formaldehyde	Not reported	Described in text	Single NSBPT: histamine	PC_{20} FEV_1 ≦32 mg/ml	Referenced (deVries et al., 1964)
Burge, 1982b	SIC: suspected agent	Not reported	Described in text	Single NSBPT: histamine	PD_{20} FEV_1 <32 mg/mL	Referenced (O'Brien et al., 1979)
Burge, 1980	SIC: colophony, abietic acid, methyl ester, glycerol ester, amine hydrocholride	≧15% decline in FEV_1	Described in text	Single NSBPT: histamine	PC_{20} FEV_1 ≦16 mg/ml	Referenced (deVries et al., 1964)

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Burge, 1979a	SIC: solder-flux fumes	≧15% decline in FEV_1	Referenced (Burge et al., 1978)	Clinical diagnosis	History and effects of subsequent exposure at work	Described in text
				Serial PFT (PEFR): monitored every hour while away for at least 2 wks at work and at least 2 wks away	Comparison of recordings taken at work compared to those taken away from work	Described in text
Burge, 1979b	SIC: isocyanates	≧15% decline in FEV_1	Referenced (O'Brien et al., 1979)	Clinical diagnosis	Final assessment based on subsequent course of asthma on re-exposure at work	Described in text
				Serial PFT (PEFR): monitored every hour or 2 hrs for at least 2 wks at work and 2 wks away	≧25% of cases demonstrated specific daily pattern with a weekly pattern	Referenced (Burge et al., 1979)
Burge, 1978	SIC: colophony	>15% decline in FEV_1	Not reported	Eosinophils: blood	Not reported	>400/mm^3
				Single PFT: FEV_1, FVC	Not reported	Described in text
				Skin prick: atopy	Mean wheal diameter >2 mm with negative control	Not reported
Butcher, 1980	SIC: TDI	Not reported	Not reported	Serum specific IgE	2 definitions: ratio >2; test cpm >control mean + 3SD	RAST
				Serum total IgE	Not reported	PRIST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Carletti, 1997	SIC: wheat flour	>20% decline in FEV_1	Described in text	Clinical diagnosis	Symptoms of cough, expectoration,wheezing, dyspnea, difficulties breathing associated with exposure to wheat powder/flour	Described in text
				Single NSBPT: methacholine	PD_{20} FEV_1 <1 mg	Referenced (Piaggaro et al., 1990)
				Single PFT: FVC, FEV(25-75)	Not reported	Described in text
				Skin prick: atopy and specific	Mean wheal diameter ≧5 mm for atopy and ≧3 mm for specific	Described in text
Cartier, 1989	SIC: isocyanates	≧3 consecutive values with ≧20% decline in FEV_1 and fluctuations not exceeding 10% on the control	Referenced (Pepys and Hutchcroft, 1975)	Serial NSBPT: histamine or methacholine	≧3.2 fold change in PC_{20} FEV_1 before and after SIC	Not reported
				Single NSBPT: histamine or methacholine	PC_{20} FEV_1 ≦16 mg/ml	Not reported
				Skin prick: atopy and specific	Wheal diameter ≧3 mm without dermographism and with wheal diameter ≧3 mm to histamine control	Described in text
				Serum specific IgE	OD reading ≧two times the OD of the mean of the negative controls	ELISA
				Serum specific IgG	OD reading ≧two times the OD of the mean of the negative controls	ELISA
Cartier, 1987	SIC: psyllium	≧20% decline in FEV_1	Referenced (Pepys and Hutchcroft, 1975)	Single NSBPT: histamine	PC_{20} FEV_1 <8 mg/ml	Referenced (Cockcroft et al., 1977)
				Skin prick: atopy and specific	Not reported	Described in text
				Serum specific IgE	Not reported	RAST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Cartier, 1986	SIC: snowcrab extract	Not reported	Not reported	Skin prick: specific[1]	Wheal diameter >2 mm larger than control	Referenced (Pepys, 1975)
				Serum specific IgE[1]	2 cutoff values: >2; >4.5	RAST
				Eosinophils: blood[2]	>500 cells/cc	Not reported
				Serial NSBPT: histamine[2]	≧3.2 fold change in PC_{20} FEV_1 upon return to work	Referenced (Cockcroft et al., 1977)
				Single NSBPT: histamine[2]	PC_{20} FEV_1 ≦16 mg/ml	Referenced (Cockcroft et al., 1977)
Choudat, 1999	SIC: wheat flour	≧20% decline in FEV_1	Referenced (Cloutier et al., 1989)	Single NSBPT: methacholine	PD_{20} FEV_1: no cutoff	Referenced (Sterk et al., 1993)
				Serum specific IgE	Not reported	CAP
Cirla, 1975	SIC: TDI	Not reported	Described in text	Single NSBPT: acetylcholine	Not reported	Described in text
				Skin prick: atopy and specific	Not reported	Described in text
Colas, 1985	SIC: wood dust (exotic)	≧100% increase in specific airway resistance	Described in text	Eosinophils: blood	Not reported	Not reported
				Other: carbon dioxide diffusion	Not reported	Not reported
				Single NSBPT: carbachol	≧100% increase in airways resistance (threshold dose)	Not reported
				Single PFT: FEV_1, FVC	Presence of "trouble ventilatoire obstructif" (airway obstruction)	Not reported
				Skin prick: atopy and specific	Not reported	Not reported
				Serum total IgE	Not reported	Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Cortona, 1980	Other: clinical diagnosis	Included results from ECSC questionnaire and lung function testing	Described in text	Skin prick: atopy and Specific	Not reported	Referenced (Pepys, 1969)
Cote, 1993	SIC: plicatic acid	≧15% decline in FEV_1	Referenced (Chan-Yeung et al., 1973)	Serial PFT (PEFR): monitored 6 times/day for 3 wks at work and 2 wks away[3] Other: questionnaire[3] Serial NSBPT: methacholine[4]	2 of 3 physicians agreed that PEF graphs showed work related change in 2 of 3 work wks Not reported >2 fold decrease in PC_{20} FEV_1 after 3 work wks compared to after 2 holiday wks	Referenced (Burge et al., 1979) Not reported Referenced (Lam et al., 1979)
Coutts, 1984	SIC: cimetidine powder	Not reported	Not reported	Single NSBPT: histamine Skin prick: atopy and specific	Not reported Not reported	Not reported Not reported
Curran, 1996	Other: clinical diagnosis	Not reported	Not reported	Serum specific IgE Serum total IgE	>0.88 net RAST % binding with serum total IgE equal to or less than 150 kU/L <150 kU/L	RAST RIACT
Davison, 1983	SIC: castor beans	Not reported	Referenced (Davies et al., 1974)	Skin prick: atopy Serum specific IgE	Not reported % binding >2 times the control	Not reported RAST
DeZotti, 1996a	SIC: wood dust (exotic)	≧15% decline in FEV_1	Described in text	Eosinophils: blood Single NSBPT: methacholine Single PFT: FEV_1, FVC Skin prick: atopy	Not reported PD_{20} FEV_1: no cutoff Not reported Wheal diameter >3 mm	Not reported Not reported Described in text Described in text

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
DeZotti, 1996b	SIC: suspected agent	≧15% decline in FEV_1	Described in text	Eosinophils: blood Single NSBPT: methacholine Single PFT: FEV_1 Skin prick: atopy Serum specific IgE	Not reported PD_{20} FEV_1: no cutoff Not reported Wheal diameter ≧3 mm Not reported	Described in text Described in text Described in text Not reported RAST
Dellabianca, 1996	SIC: suspected agent	≧15% decline in FEV_1	Not reported	Single NSBPT: methacholine	PD_{20} FEV_1 ≦1560 µg	Described in text
Dente, 1986	SIC: TDI	Not reported	Described in text	Single NSBPT: methacholine	PD_{15} FEV_1 <1.0 mg	Not reported
DiFranco, 1998	SIC: suspected agent	Not reported	Not reported	Eosinophils: sputum Single NSBPT: methacholine	>1% PD_{20} FEV_1 <1 mg	Described in text Described in text
DiStefano, 1999	Other: clinical diagnosis	Included SIC and/or serial PFT	Described in text	Single NSBPT: histamine Skin prick: atopy	Not reported Wheal diameter >3 mm	No reference (Yan method) Not reported
Duan, 1989	SIC: TDI	≧15% decline in FEV_1 (lasted 15 minutes)	Described in text	Clinical diagnosis Serial NSBPT: methacholine Serial PFT: PEFR Single PFT: FEV_1 (including reversibility) Skin prick: specific Serum specific IgE	Asthma symptoms at work, better or no symptoms away from work 2 times (Chinese translation) Not reported FEV_1 decrease 15-20% Not reported Not reported	Described in text Referenced (Cockcroft et al., 1977) Described in text Described in text Described in text ELISA
Ferguson, 1996	SIC: isocyanates	≧15% decline in FEV_1 (persistent)	Described in text	Single NSBPT: histamine Single PFT: FEV_1, FVC (including reversibility) Serum specific IgE	Not reported Reversibility: ≧15% increase in FEV_1 Not reported	Referenced (Cockcroft et al., 1977) Referenced (American Thoracic Society, 1987) RAST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Gannon, 1996	Other: clinical diagnosis	Included SIC and/or bronchial hyperreactivity and/or serum specific IgE (RAST) and/or asymptomatic	Not reported	Serial PFT (PEFR): monitored every 2 hrs for 2 wks at work and 2 wks away	OASYS-2 score ≧2.51	Referenced (Burge et al., 1979)
Girard, 2004	SIC: suspected agent	Not reported	Referenced (Cartier, 1997)	Eosinophils: sputum Serial NSBPT: methacholine Serial PFT: PEFR Skin prick: atopy	3 cutoffs used: >1%, 2%, or 6.4% ≧3.2 fold change in PC_{20} FEV_1 between at work and away 2 definitions: OASYS-2 score ≧2.51; clinical opinion Not reported	Referenced (Pizzichini et al., 1996) Referenced (Juniper et al., 1994) Referenced (Burge et al., 1979) Not reported
Graneek, 1987	SIC: suspected agent	>15% decline in FEV_1	Referenced (Pepys and Hutchcroft, 1975)	Single NSBPT: histamine	PC_{20} FEV_1 ≦16 mg/ml	Referenced (Cockcroft et al., 1977)
Grosclaude, 1980	SIC: suspected agent	≧50% increase in airway resistance	Described in text	Single NSBPT: acetylcholine Skin prick: atopy and specific Serum total IgE	Dose provoking augmentation of 50% of airway resistance ≦1000 µg Not reported Not reported	Not reported Not reported Not reported
Harries, 1980	SIC: suspected agent	≧15% decline in FEV_1	Described in text	Eosinophils: blood Skin prick: atopy	Not reported Wheal diameter >3 mm to at least 1 allergen with negative reaction to control	Not reported Described in text
Hinojosa, 1986	SIC: wood dust (African maple and ramin)	≧20% decline in FEV_1	Described in text	Skin prick: atopy and specific Serum specific IgE Serum total IgE	Not reported Not reported Not reported	Described in text REIA Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Howe, 1993	SIC: lactose powder, TCPA powder, epoxy resin powder, blue pigment powder	≧15% decline in FEV_1	Described in text	Skin prick: atopy and specific[5] Serum specific IgE[5] Single NSBPT: histamine[6]	Wheal diameter >2 mm larger than control Not reported Not reported	Described in text RAST Not reported
Huggins, 2003	Other: clinical diagnosis	Included symptoms and/or serum specific IgE and/or SPT	Not reported	Serial PFT (PEFR): monitored every 2 hrs for 4 wks	Various definitions: expert interpretation; OASYS-2 score ≧2.75; rest-work PEF ≧16 L/min; daily variation at work >daily variation away	Referenced (OASYS)
Jager, 1993	SIC: latex	100% increase in sRaw to at least 5 cm H2O/L/s	Described in text	Other: supervised work challenge Single NSBPT: methacholine Skin prick: atopy and specific Serum specific IgE Serum total IgE	Not reported Not reported Not reported Not reported Not reported	Described in text Not reported Described in text Not reported Not reported
Karol, 1994	SIC: TDI	≧20% decline in FEV_1	Referenced (Mapp et al., 1988)	Clinical diagnosis Single NSBPT: methacholine Serum specific IgE Serum specific IgG Serum total IgE	Clinical and workplace history PD_{20} FEV_1 <1.4 mg >mean + 2SD of control subjects Not reported >114 IU/ml	Described in text Referenced (Chai et al., 1975) RAST ELISA IgE RIA
Kern, 1991	Other: clinical diagnosis	Based on criteria for diagnosis of RADS	Referenced (Harkonen et al., 1983)	Single NSBPT: methacholine	PD_{20} FEV_1: no cutoff	Referenced (O'conner et al., 1987)

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Keskinen, 1988	SIC: isocyanates	≧20% decline in PEF or 15-19% if other supporting findings	Referenced (Newman-Taylor and Davies, 1981)	Skin prick: atopy	Reaction >1/2 reaction to histamine to at least 1 allergen with negative reaction to dilutant	Referenced (Belin and Wass, 1981)
				Serum specific IgE	Ratio values ≧2 with absorbance reading ≧1/2 of the D-reference point	RAST
Kim, 1999	SIC: citrus red mite	Not reported	Described in text	Single NSBPT: methacholine	PC_{20} FEV_1 <16 mg/ml	Referenced (Chai et al., 1975)
				Single PFT: FEV_1	Reversibility: ≧15% increase in FEV_1	Not reported
				Skin prick: atopy and specific	Allergen:histamine wheal diameter ratio >1	Described in text
				Serum specific IgE	Absorbance value >0.24	ELISA
				Serum total IgE	≧160 IU/ml	DPC kit
Kim, 1997	Other: clinical diagnosis	Included symptoms and serial PFT	Described in text	Single PFT: FEV_1, FVC	Not reported	Described in text
				Serum specific IgE	Counts per minute of reference disk was >2 times control disk	RAST
				Serum specific IgG	OD ratio >mean +/- 3SD for negative control	ELISA
Kongerud, 1992	Other: serial PFT	>15% variation in diurnal PEF	Referenced (Burge, 1982)	Clinical diagnosis	Criteria proposed by Burge (1982)	Described in text
				Eosinophils: blood	Not reported	Not reported
				Other: symptom score	Not reported	Described in text
				Serial NSBPT: methacholine	>2 fold change in PC_{20} FEV_1 between work and away periods	Referenced (Cockcroft et al., 1977)
				Single NSBPT: methacholine	PC_{20} FEV_1 <8 mg/ml	Referenced (Cockcroft et al., 1977)
				Serum total IgE	Not reported	Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Kopferschmitt-Kubler, 1998	SIC: TDI	≧20% decline in FEV_1	Described in text	Serial PFT (FEV_1): monitored at least 3 times/day on a 1 month diary card	Not reported	Described in text
				Single NSBPT: methacholine	PD_{20} FEV_1 <3200 µg	Not reported
Koskela, 2003	SIC: bovine dander	>15% decline in FEV_1	Not reported	Exhaled nitric oxide	>46 ppm	Not reported
				Single NSBPT: histamine or mannitol	Histamine: PC_{20} FEV_1 <8mg/mL / mannitol: >15% decrease in FEV_1	Referenced (histamine: Cockcroft et al., 1974; mannitol: Anderson et al., 1997)
				Skin prick: specific	Wheal diameter ≧3 mm	Referenced (Pepys, 1975)
				Serum specific IgE	>5 IU/L	CAP
				Serum total IgE	Not reported	Immulite 2000
Krakowiak, 2003	SIC: rodent flour/dust	>20% decline in FEV_1	Described in text	Clinical diagnosis	Included medical history, physical examination and spirometry	Not reported
				Eosinophils: nasal lavage	Not reported	Described in text
				Single NSBPT: histamine	PC_{20} FEV_1: no cutoff	Referenced (Cockcroft et al., 1977)
				Skin prick: atopy and specific	Wheal 4mm >control; flare 5mm >control	Described in text
				Serum specific IgE	Not reported	RAST
Lam, 1979	SIC: red cedar, aerosol inhalation or exposure to work environment	Not reported	Referenced (Chan-Yeung et al., 1973)	Single NSBPT: methacholine	PC_{20} FEV_1 ≦16 mg/ml	Referenced (Cockcroft et al., 1977)
				Skin prick: atopy	≧2 positive reactions	Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
LaPaglia, 1986	SIC: wheat, straw, hay, wood, animal allergens	≧15% decline in FEV_1	Described in text	Clinical diagnosis	Significant reduction in FEV_1, shortness of breath, wheezing episodes	Described in text
				Skin prick: atopy and specific	Not reported	Described in text
Larbanois, 2003	SIC: suspected agent	≧20% decline in FEV_1	Referenced (Vandenplas and Malo, 1997)	Serial PFT (sGaw): before and after SIC	2 cutoff values: >35 decrease; >50% decrease	Described in text
				Single NSBPT: histamine	PC_{20} FEV_1 <16 mg/ml	Referenced (Cockcroft et al., 1977)
Lemiere, 2001	SIC: suspected agent	≧20% decline in FEV_1	Referenced (Cartier, 1994)	Eosinophils: sputum	≧$0.26x10^6$ cells/ml	Referenced (Pin et al., 1992)
				Single NSBPT: methacholine	PC_{20} FEV_1 <8 mg/ml	Referenced (Cockcroft et al., 1977)
				Skin prick: atopy and specific	Wheal diameter ≧3 mm to at least 1 allergen with positive reaction to histamine and negative reaction to diluent	Not reported
Liss, 1991	SIC: suspected agent	Not reported	Referenced (Pepys and Hutchcroft, 1975)	Serial PFT (PEFR): monitored 4 times/day for at least 2 wks at work and 2 wks away[7]	≧20% diurnal variation on at least 2 days with lowest value on a work day	Described in text
				Single NSBPT: methacholine[7]	PC_{20} FEV_1 ≦8 mg/ml	Referenced (Juniper et al., 1978)
				Single PFT: FEV_1 (including reversibility)[7]	Reversibility: ≧15% increase in FEV_1	Described in text
				Skin prick: atopy and specific[7]	Wheal diameter >2 mm larger than control	Not reported
				Serial NSBPT: methacholine[8]	≧4 fold shift in PC_{20} FEV_1 between after a day at work and after 10 to 14 days off work	Referenced (Cockcroft et al., 1977)

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Lozewicz, 1985	SIC: cyanoacrylate based susbstances	Not reported	Not reported	Single NSBPT: histamine Skin prick: atopy	PC_{10} FEV_1 ≦32 mg Not reported	Referenced (DeVries, 1960 and Cockcroft et al., 1977) Not reported
Malo, 1993a	SIC: suspected agent	Not reported	Not reported	Serial PFT (PEFR): monitored every 2 hrs for 2 wks at work and 2 wks away	Not reported	Referenced (Burge et al., 1979)
Malo, 1991	SIC: red cedar, flour, psyllium, guar gum	>20% decline in FEV_1	Referenced (Pepys and Hutchcroft, 1975)	Other: Questionnaire Serial NSBPT: histamine or methacholine Serial PFT (PEFR): monitored every 2 hrs or at least 4 times/day Single NSBPT: histamine or methacholine Skin prick: atopy	Not reported ≧3.2 fold change in PC_{20} FEV_1 between work and away Interpreted by experienced physicians PC_{20} FEV_1 ≦16 mg/ml Wheal diameter ≧3 mm to at least 1 allergen with positive reaction to histamine and negative reaction to diluent	Not reported Referenced (Cockcroft et al., 1977) Referenced (Burge et al., 1979) Referenced (Cockcroft et al., 1977) Not reported
Malo, 1990	SIC: suspected agent	Immediate: ≧15% decline in FEV_1; late: ≧12% decline in FEV_1	Referenced (Pepys and Hutchcroft, 1975)	Single NSBPT: histamine or methacholine Skin prick: atopy	PC_{20} FEV_1 <16 mg/ml Immediate reaction within 10-15 minutes	Referenced (Cockcroft et al., 1977) Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Malo, 1988a	SIC: spiromycin	≧20% decline in FEV_1	Referenced (Pepys and Hutchcroft, 1975)	Eosinophils: blood	Not reported	Not reported
				Other: questionnaire	Not reported	Not reported
				Serial PFT (PEFR): monitored 4 times/day and when they had chest symptoms for 2 wks including weekends	>20% variation	Described in text
				Single NSBPT: methacholine	PD_{20} FEV_1 ≦16 mg/ml	Referenced (Cockcroft et al., 1977)
				Skin prick: atopy	Not reported	Described in text
Mapp, 1986	SIC: TDI	Not reported	Described in text	Single NSBPT: methacholine	PD_{20} FEV_1 ≦0.7 mg	Referenced (Chai et al., 1975)
				Skin prick: atopy	Not reported	Not reported
Mapp, 1979	SIC: isocyanates	>15% decline in FEV_1, change in Vmax >20% and change in sGaw >25%	Referenced (Fantuzzi et al., 1973)	Single NSBPT: carbachol	>15% decline if FEV_1: no cutoff, change in Vmax >20% and change in sGaw >25%/ND	Referenced (Orehek et al., 1977)
				Skin prick: atopy	Not reported	Described in text
Merget, 1997	SIC: wheat flour	≧50% decline in sGaw after inhalation of 100 mg/ml flour extract, seven cumulative capsules or less	Not reported	Single NSBPT: methacholine	PD_{50} sGaw ≦1 mg	Referenced (Merget et al., 1994)
				Skin prick: atopy and specific	Wheal diameter ≧3 mm larger than saline control	Referenced (Pepys, 1975)
				Serum specific IgE	RAST ≧0.35 Phadebus RAST units/ml	RAST
				Serum total IgE	Not reported	Enzymun-Test

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Merget, 1996	SIC: platinum salts	≧50% decline in sGaw with platinum salt concentration ≦0.01 mol/L	Referenced (Merget et al., 1991)	Single NSBPT: methacholine	PD_{50} sGaw ≦8 mg/ml	Referenced (Merget et al., 1991)
				Skin prick: atopy and specific	Atopy: wheal diameter ≧4 mm / Specific: wheal diameter ≧2 mm	Referenced (Pepys, 1975)
				Serum total IgE	Not reported	PRIST
Merget, 1993	SIC: enzymes	≧50% decline in sGaw with enzyme concentration ≦10mg/ml	Described in text	Single NSBPT: methacholine	PD_{50} sGaw with dose <mg	Described in text
				Skin prick: atopy and specific	Wheal diameter ≧histamine control	Described in text
				Serum specific IgE	≧0.35 PRU	EAST
				Serum total IgE	Not reported	PRIST
Mole, 1977	Other: clinical diagnosis	Included pulmonary function tests, ECG, chest x-ray, and skin prick tests	Described in text	Other: skin patch test	Not reported	Not reported
				Single NSBPT: acetylcholine	>10% decrease in FEV_1	Referenced (Sadoul and Aubertin, 1956)
Moller, 1986	SIC: TDI	≧20% decline in FEV_1	Described in text	Clinical diagnosis	Clinical and occupational history	Described in text
				Single NSBPT: methacholine	PD_{20} FEV_1: no cutoff	Described in text
				Single PFT: FEV_1, FVC, PEFR	Not reported	Criteria established by the American Thoracic Society
Moller, 1985	Other: physician diagnosis	Based on shortness of breath, wheezing or coughing exacerbated at work and/or at night, improvement	Described in text	Eosinophils: not reported	Not reported	Not reported
				Other: questionnaire	Not reported	Not reported
				Serial PFT (FEV_1): pre- and post- shift	>20% decline in FEV_1 post-shift compared to pre-shift	Described in text
				Serum specific IgE	≧1 ng/ml	SPBRIA

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Moscato, 1993	SIC: TDI	≧15% decline in FEV_1	Described in text	Single NSBPT: methacholine Single PFT: FEV_1, FVC Skin prick: atopy	PD_{15} FEV_1 <0.85 mg Not reported Wheal diameter >5 mm	Referenced (Moscato et al., 1991) Described in text Not reported
Munoz, 2004	SIC: potassium persulfate	>20% decline in FEV_1 more than placebo challenge	Referenced (Pepys and Hutchcroft, 1975)	Serial PFT (PEFR): monitored every 4 hrs for 2 wks at work and 2 wks away Single NSBPT: methacholine Skin prick: atopy and specific Serum total IgE	Qualitative assessment revealed evident changes between periods PC_{20} FEV_1 <8 mg/ml Average of largest and smallest wheal diameter >3mm and more than reaction to histamine control >150 IU	Described in text Referenced (Chai et al., 1975) Referenced (Pepys, 1975) UniCAP
Nielsen, 1988	Other: clinical diagnosis	Included symptoms during employment and unequivocal and plausible relation to irritant exposure	Described in text	Single NSBPT: methacholine Skin prick: atopy and specific Serum specific IgE Serum specific IgG Serum total IgE	Not reported Wheal area >1/2 of histamine reaction Ratio >2.2 Not reported Not reported	Not reported Not reported RAST ELISA Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Nordman, 1985	SIC: formaldehyde	Immediate: ≧15% decline in PEF; late: ≧20% decline in PEF	Referenced (Pepys et al., 1972; Newman-Taylor and Davies, 1981)	Eosinophils: not reported	Not reported	Not reported
				Serial PFT (PEFR): monitored every 3 hrs for at least 24 hrs before SIC	Not reported	Not reported
				Single NSBPT: histamine or methacholine	Histamine: ≧15% drop in PEF / methacholine: Not reported	Referenced (histamine: Laitinen, 1974; methacholine: Hargreave et al., 1981)
				Single PFT: FEV_1, FVC (including reversibility)	Reversibility: ≧15% increase and 150 ml in FEV_1	Described in text
				Serum total IgE	Not reported	Not reported
O'Brien, 1979a	SIC: isocyanates	≧15% decline in FEV_1	Described in text	Single NSBPT: histamine	≧20% decline in FEV_1 ≦32 mg/ml	Described in text
O'Brien, 1979b	SIC: TDI	≧15% decline in FEV_1	Described in text	Other: exercise test	>9% fall in FEV_1 or PEFR	Described in text
				Single NSBPT: histamine	PC_{20} FEV_1 ≦32 mg/ml	Described in text
				Skin prick: atopy	Not reported	Not reported
Obata, 1999	SIC: plicatic acid	>20% decline in FEV_1 or PEF	Referenced (Chan-Yueng et al., 1982)	Eosinophils: sputum	Not reported	Described in text
				Exhaled nitric oxide	Not reported	Described in text
				Single NSBPT: methacholine	PC_{20} FEV_1 ≦8 mg/ml	Referenced (Lam et al., 1979)
				Skin prick: atopy	Wheal diameter ≧3 mm larger than negative control	Described in text
Obtulowicz, 1998	SIC: suspected agent	>20% decline in FEV_1 and MEF 25-75%	Described in text	Eosinophils: blood	Not reported	Not reported
				Skin prick: atopy and specific	Not reported	Described in text
				Serum total IgE	Not reported	ELISA

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Paggiaro, 1987b	SIC: plicatic acid	>20% decline in FEV_1	Referenced (Lam et al., 1983)	Single NSBPT: methacholine	PC_{20} FEV_1: no cutoff reported	Referenced (Lam et al., 1979)
				Skin prick: atopy and specific	Wheal diameter ≧3 mm	Described in text
				Serum specific IgE	Ratio >2.0	RAST
Paggiaro, 1986	SIC: TDI	≧15% decline in FEV_1	Described in text	Single NSBPT: methacholine	PD_{20} FEV_1 ≦2 mg	Described in text
				Skin prick: atopy	Wheal diameter >5 mm	Not reported
Paggiaro, 1984b	SIC: enzymes	>15% decline in FEV_1	Described in text	Single NSBPT: bethanechol	>15% decline in FEV_1: no cutoff reported	Referenced (Parlanti et al., 1983)
				Skin prick: atopy and specific	Wheal diameter ≧5 mm	Described in text
				Serum specific IgE	Not reported	RAST
				Serum total IgE	Not reported	PRIST
Paggiaro, 1984c	SIC: isocyanates	≧15% decline in FEV_1	Referenced (Zedda et al., 1976)	Clinical diagnosis	Presence of dyspnea, wheezing from exposure to TDI or MDI and a positive response to SIC	Described in text
				Single NSBPT: bethanechol	PD_{15} FEV_1 ≦8	Described in text
Paggiaro, 1981	SIC: wood dust (tanganyika aningre)	Not reported	Referenced (Pickering et al., 1972)	Single NSBPT: acetylcholine or bethanechol	Not reported	Not reported
				Skin prick: atopy and specific	Not reported	Not reported
				Serum specific IgE	Not reported	RAST
Palczynski, 2003	SIC: chloramine	Not reported	Not reported	Eosinophils: nasal lavage	Not reported	Referenced (Greiff et al., 1990)
				Single NSBPT: histamine	Not reported	Referenced (Cockcroft et al., 1977)
				Skin prick: atopy and specific	Wheal diameter >3 mm larger than negative control	Not reported
				Serum specific IgE	>35 KU/L	RAST
				Serum total IgE	>35 KU/L	RAST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Park, 2002b	SIC: porcine pancreatic extract	≧20% decline in FEV_1	Referenced (Park and Nahm, 1997)	Other: immunoblotting Single NSBPT: methacholine Skin prick: specific Serum specific IgE	Not reported Not reported Not reported >mean + 2SD of unexposed controls	Described in text Referenced (Chai et al., 1977) Not reported ELISA
Park, 2001	SIC: reactive dyes	≧20% decline in FEV_1	Not reported	Skin prick: atopy and specific Serum specific IgE	Wheal diameter >2 mm larger than negative control and erythema reaction >21 mm OD at 410 >0.013	Described in text ELISA
Park, 1999	SIC: TDI	Not reported	Referenced (Park et al., 1999)	Single NSBPT: methacholine Single PFT: not reported Skin prick: atopy Serum specific IgE	PC_{20} FEV_1: no cutoff reported Not reported Not reported >mean + 2SD of control subjects	Referenced (Park et al., 1999) Not reported Not reported ELISA
Park, 1998	SIC: grain dust	≧20% decline in FEV_1	Referenced (Park and Nahm, 1997)	Eosinophils: blood Other: Immunoblotting Single NSBPT: methacholine Skin prick: atopy and specific Serum specific IgE	Not reported Not reported PD_{20} FEV_1 ≦25 mg/ml Allergen:histamine area ratio between 0.1 and 1 and erythema >21 mm ≧0.064	SDS-Page Not reported Referenced (Chai et al., 1975) Described in text ELISA

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Park, 1994	SIC: chromium salts	≧20% decline in FEV_1	Described in text	Other: skin patch test	Not reported	Described in text
				Serial PFT (PEFR): monitored every 2 hrs for 2 days at work	Not reported	Not reported
				Single NSBPT: methacholine	PC_{20} FEV_1 ≦25 mg/ml	Referenced (Chai et al., 1975)
				Skin prick: atopy and specific	Not reported	Described in text
Park, 1991	SIC: reactive dyes	≧20% decline in FEV_1	Referenced (Park et al., 1989)	Single NSBPT: methacholine	PC_{20} FEV_1 ≦5 mg/ml	Referenced (Chai et al., 1975)
				Skin prick: atopy and specific	Allergen: histamine area ratio between 0.1 and 1 and erythema >21 mm	Not reported
				Serum specific IgE	binding ≧2%	RAST
				Serum total IgE	>160 IU/ml	PRIST
Park, 1989	SIC: reactive dyes	≧20% decline in FEV_1	Referenced (Chai et al., 1975)	Single NSBPT: methacholine	PC_{20} FEV_1: no cutoff reported	Referenced (Chai et al., 1975)
				Single PFT: FEV_1	Not reported	Not reported
				Skin prick: atopy and specific	Not reported	Described in text
				Serum specific IgE	RAST binding >2%	RAST
Perrin, 1990	SIC: suspected agent	Not reported	Not reported	Serial NSBPT: histamine or methacholine	≧2 fold increase in PC_{20} FEV_1 between at work and away	Not reported
				Serial PFT (PEFR): monitored every 2 hrs for 2 wks or less at work and 2 wks away	Various definitions: number of days with ≧20% variation in PEFR ≧20%; lower maximum PEFR values at work; lower minimum PEFR values at work; lower mean PEFR values at work	Referenced (Burge et al., 1979)

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Pezzini, 1984	SIC: isocyanates	≧20% fall in FEV_1 or 35% drop in FEF(25-75)	Referenced (Zedda et al., 1976)	Single NSBPT: bethanechol Skin prick: atopy Serum specific IgE	PD_{20} FEV_1: no cutoff ≧2 positive reactions NBR level >0.9	Described in text Referenced (Vanselow, 1964) RAST
Prichard, 1984	Other: clinical diagnosis	Included symptoms and physician diagnosed asthma since began working in industry	Described in text	Single NSBPT: methacholine Skin prick: atopy and specific	PD_{20} FEV_1 <30 µg Wheal ≧3 mm more than negative control	Described in text Described in text
Quirce, 2000	Other: clinical diagnosis	Included SIC or serial PFT	SIC: Referenced (Hinojosa et al., 1984)	Skin prick: specific Serum specific IgE	Not reported ≧4 times more serum specific IgE than mean titer of control sera	Described in text ELISA
Quirce, 1992	SIC: alpha-amylase from aspergillus oryzae and cellulase from a. niger	≧20% decline in FEV_1	Described in text	Single NSBPT: methacholine Skin prick: atopy and specific Serum specific IgE	Not reported Wheal diameter ≧3 mm Not reported	Referenced (Cockcroft et al., 1977) Described in text REIA (alpha-amylase and cellulase) or RAST (wheat and rye)
Rasanen, 1994	SIC: suspected agent	≧15% decline in FEV_1 and PEFR	Not reported	Other: basophil histamine release Skin prick: atopy and specific Serum specific IgE Serum total IgE	≧8% Wheal diameter ≧1/2 the size of the reaction to histamine standard ≧0.7 kU/L Not reported	Referenced (Rasanen et al., 1992) Described in text RAST IgE RIA
Redlich, 1996	SIC: isocyanates	Not reported	Not reported	Eosinophils: blood Other: bronchial alveolar lavage Single NSBPT: methacholine	Not reported Not reported Not reported	Described in text Described in text Not reported

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Ricciardi, 2003	SIC: wood dust (iroko)	≧25% decline in FEV_1	Referenced (Frolund, 1996)	Eosinophils: blood	Not reported	Described in text
				Serial PFT (PEFR): monitored every two hrs for 1 wk at work and 1 wk away	Not reported	Not reported
				Single NSBPT: methacholine	≧20% decline in FEV_1: no cutoff	Not reported
				Skin prick: atopy and specific	Wheal diameter >7 mm	Described in text
				Serum specific IgE	Not reported	RAST
				Serum total IgE	Not reported	RAST
Sander, 2001	SIC: wheat and rye	Not reported	Not reported	Skin prick: specific	≧1/2 of histamine wheal	Described in text
Sastre, 2003	SIC: isocyanates	≧20% decline in FEV_1	Not reported	Single NSBPT: methacholine	PC_{20} FEV_1 <16 mg/ml	Referenced (Cockcroft et al., 1977)
Schuermans, 2003	SIC: latex	Not reported	Not reported	Single NSBPT: histamine	PC_{20} FEV_1 <0.5 mg/ml	Not reported
Schwaiblmair, 1997	SIC: bleaching powder	≧100% increase in specific airway resistance and reached at least 2.0 kPa/s	Described in text	Single NSBPT: methacholine	≧100% increase in specific airway resistance and reached 2.0 kPa	Referenced (Hargreave et al., 1981)
				Single PFT: FVC, MEF_{50}, FEV_1, RV, TLco, Raw $Pa0_2$	Not reported	Described in text
				Skin prick: atopy and specific	Wheal diameter >3 mm larger than negative control	Referenced (Pepys, 1975)
Schwarting, 1979	SIC: flour	Not reported	Not reported	Clinical diagnosis	Included medical history, skin prick test, bronchial provocation test, nasal provocation, conjuctivities, and serum specific IgE	Described in text
				Skin prick: specific	Not reported	Not reported
				Serum specific IgE	Not reported	RAST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Shirai, 2003	SIC: epigallocatechin gallate (EGCg)	≧20% decline in FEV_1	Referenced (Shirai et al., 1997)	Clinical diagnosis Single NSBPT: methacholine Skin prick: specific	Clinical history, postive SIC, positive SPT PC_{20} FEV_1 <10 mg/ml Wheal diameter >7 mm	Described in text Referenced (Makino et al., 1984 Described in text
Shirakawa, 1988	SIC: cobalt chloride	Not reported	Referenced (Chai et al., 1975)	Eosinophils: blood Other: antibodies (CO-HSA) Single NSBPT: methacholine Skin prick: specific Serum specific IgE	>200/mm^3 Not reported Not reported Wheal diameter >9 mm at <0.1% >673 cpm (upper normal limit)	Not reported Referenced (Ouchterlony, 1968) Referenced (Hargreave et al., 1981) Not reported RAST
Slovak, 1981	Other: clinical diagnosis	Based history of repeated episodes of wheezing or chest tightness (with or without cough) related to	Described in text	Serial PFT (PEFR): monitored every 2 hrs while awake for 3 mos Skin prick: atopy and specific	Not reported Wheal diameter >3 mm	Not reported Described in text
Symington, 1981	SIC: mushroom dust	Not reported	Described in text	Skin prick: atopy and specific	Wheal diameter ≧3 mm	Described in text
Tabar, 2004	SIC: asparagus	≧20% decline in FEV_1	Described in text	Other: immunoblotting Skin prick: atopy and specific Serum specific IgE Serum total IgE	Not reported Wheal area ≧7 mm^2 Not reported Not reported	Not reported Referenced (Dreborg, 1993) Not reported Not reported
Taivainen, 1994	SIC: cow dander	Immediate: ≧15% change in PEFR; late: ≧20% change in PEFR	Described in text	Clinical diagnosis Skin prick: specific Serum specific IgE	Described in text Two cutoff values: wheal diameter ≧3 mm or >than positive control Two cutoff values: ≧0.35 kU/L or ≧0.70 kU/L	Described in text Described in text RAST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Tee, 1998	Other: clinical diagnosis	Included SIC and/or clinical history and/or serial PFT and/or NSBPT	SIC: Referenced (Newman-Taylor and Davies, 1981)	Skin prick: atopy Serum specific IgE	Wheal diameter >3 mm Two cutoff values: ratio ≧2; ratio ≧3	Not reported RAST
Tse, 1982	SIC: plicatic acid	Not reported	Referenced (Chan-Yeung et al., 1973)	Serum specific IgE	>mean + 2SD of control subjects	RAST
Vandenplas, 2001	SIC: latex	≧20% decline in FEV_1	Referenced (Vandenplas et al., 1995)	Clinical diagnosis Serial NSBPT: histamine Single NSBPT: histamine Skin prick: atopy and specific	Questionnaire and clinical history with OA considered likely or highly likely on the basis of consensus assessment by 4 observers >3 fold change in PC_{20} FEV_1 before and after SIC PC_{20} FEV_1 <16 mg/ml ≧1 positive reaction	Described in text Referenced (Cockcroft et al., 1977) Referenced (Cockcroft et al., 1977) Referenced (Vandenplas et al., 1995)
Vandenplas, 1995b	SIC: latex	≧20% decline in FEV_1	Described in text	Single NSBPT: histamine Skin prick: atopy and specific	PC_{20} FEV_1 <16 mg/ml Wheal ≧3mm greater than control	Described in text Described in text
Vanhanen, 2000	SIC: cellulase (econase ECP)	≧15% decline in FEV_1	Not reported	Single NSBPT: histamine Skin prick: atopy and specific Serum specific IgE	PD_{15} FEV_1 ≦1.6 mg Not reported >35 KU/L	Referenced (Sovijarvi et al., 1993) Referenced (Vanhanen et al., 1996) RAST

Table E-3. Description of diagnostic tests (Diagnosis review) (continued)

Author, Year	Highest Reference Standard			Comparison Tests		
	Test	**Positive Response**	**Methodology**	**Test**	**Positive Response**	**Methodology**
Virtanen, 1996	Other: clinical diagnosis	Included SIC and/or SPT and/or serum specific IgE	Serum specific IgE: described in text	Serum specific IgE Serum specific IgG	Not reported Not reported	ELISA ELISA
Vogelmeier, 1991	SIC: TDI	≧50% decline in sGaw from the zero value	Referenced (Dharmarajan and Rando, 1979; O'Brien et al. 1979)	Single NSBPT: methacholine Skin prick: specific Serum specific IgE	≧50% decline in specific airway conductance Not reported Not reported	Described in text Not reported RAST
Wurzinger, 1997	SIC: flour	Not reported	Described in text	Single NSBPT: histamine Skin prick: atopy and specific Serum specific IgE Serum total IgE	Not reported Not reported Not reported Not reported	Described in text Described in text RAST ELISA
Zeiler, 2002	SIC: Bos d2 and standard bovine dander allergen	≧15% decline in FEV_1 or PEF	Described in text	Single NSBPT: histamine Skin prick: specific Serum specific IgE Serum specific IgG	PD_{15} FEV_1 <1.6 mg Wheal diameter ≧3 mm Not reported Not reported	Referenced (Sovijarvi et al., 1993) Described in text RAST and ELISA ELISA
Zeiss, 1977	Other: clinical diagnosis	Included history, physical, and skin tests when indicated	Described in text	Skin prick: atopy and specific Serum specific IgE Serum specific IgG	Not reported Not reported Not reported	Not reported PTRIA PTRIA

Abbreviations: **CAP** = developed by Pharmacia Diagnostics for measuring specific IgE; **cbu** = cumulative breath unit; **CO-HSA** = conjugated human serum albumin; **cpm** = counts per minute; **DPC** = diagnostics products corp.; **EAST** = enzyme allergosorbent test; **ECG** = electrocardiogram; **ECP** = eosinophilic cationic protein; **ECSC** = European coal and steel community; **ELISA** = enzyme-linked immuno sorbent assay; **FEF** = forced expiratory flow; **FEV_1** = forced expiratory volume in one second; **FVC** = forced vital capacity; **kPa** = kilopascal; **MCP-1**= monocyte chemoattractant protein-1; **MEF** = maximal expiratory flow; **mos** = months; **NSBPT** = non-specific bronchial provocation; **OASYS-2** = occupational asthma system; **OD** = optical density; **PC_{20}** = provocative concentration causing a 20% drop in FEV_1; **PaO_2 =** arterial oxygen partial pressure; **PD_{15}** = provocative dose causing a 15% drop in FEV_1; **PD_{50}** = provocative dose causing a 50% drop in FEV_1; **PD_{20}** = provocative dose causing a 20% drop in FEV_1; **PEF** = peak expiratory flow; **PEFR** = peak expiratory flow rate; **PFT** = pulmonary function test; **PRIST** = paper radioimmunosorbent test; **PRU** = phadebas RAST units; **PTRIA** = polystyrene-tube radioimmunoassay; **RADS** = reactive airways dysfunction syndrome; **RAST** = radio allegro sorbent test; **REIA** = reverse enzyme immunoassay; **RIA** = radioimmunoassay; **RIACT** = radioimmunoassay kit for measuring IgE; **RV** = residual volume; **SD** = standard deviation; **SDS** = sodium dodecyl sulphate; **sGaw** = specific airway conductance; **SIC** = specific inhalational challenge; **SOB** = shortness of breath; **SPBRIA** = solid-phase bead radioimmunoassay; **sRaw** = specific airway resistance; **TCPA** = tetrachlorophthalic anhydride; **TDI** = toluene di-isocyanates; **TDI-HSA** = toluene di-isocyanates human serum albumin; **TLco** = single breath carbon monoxide; **IU** = international units; **UniCAP** = fluoroenzymeimmunoassay kit developed by Pharmacia Diagnostics; **Vmax** = maximum flow; **wk** = week; **wks** = weeks

Table E-4. Methodological quality of included studies (Diagnosis review)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Alvarez, 2001	Prospective	Other	Partial	Yes	No	No	Not reported
Alvarez, 1996	Prospective	Other	Unclear	Yes	Yes	Yes	Other
Anees, 2004	Retrospective	Consecutive or random selection	Unclear	Yes	No	No	Foundation, other
Avery, 1969	Prospective	Other	Unclear	No	No	Unclear	Government
Balland, 1989	Prospective	Not reported	Unclear	No	Unclear	Yes	Not reported
Baur, 1998	Prospective	Other	Unclear	Yes	No	No	Not reported
Baur, 1979	Prospective	Not reported	Unclear	No	Yes	Yes	Foundation
Behr, 1990	Prospective	Not reported	Unclear	Yes	Unclear	Unclear	Not reported
Bernstein, 2002	Prospective	Other	Partial	Yes	No	No	Government, private
Biot, 1980	Prospective	Not reported	Unclear	No	No	No	Not reported
Block, 1983	Prospective	Other	Unclear	Yes	Yes	Yes	Government
Burge, 1985	Prospective	Not reported	Unclear	No	No	No	Not reported
Burge, 1982	Prospective	Other	Unclear	No	No	No	Not reported
Burge, 1980	Prospective	Other	Unclear	Yes	No	No	Not reported
Burge, 1979a	Prospective	Other	Partial	Yes	No	No	Not reported
Burge, 1979b	Retrospective	Other	Partial	Yes	No	No	Not reported
Burge, 1978	Prospective	Other	Unclear	Yes	Unclear	Unclear	Not reported

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Butcher, 1980	Retrospective	Not reported	Unclear	No	No	No	Government, private, foundation
Carletti, 1997	Prospective	Not reported	Unclear	Yes	Unclear	Unclear	Not reported
Cartier, 1989	Prospective	Other	Partial	Yes	Yes	No	Foundation, internal, government
Cartier, 1987	Retrospective	Not reported	Unclear	Yes	No	No	Not reported
Cartier, 1984	Prospective	Other	Unclear	Yes	Unclear	Yes	Government, other
Choudat, 1999	Prospective	Other	Unclear	Yes	No	No	Other
Cirla, 1975	Prospective	Other	Unclear	Yes	Unclear	Unclear	Not reported
Colas, 1985	Prospective	Not reported	Unclear	Yes	No	No	Not reported
Cortona, 1980	Prospective	Not reported	Partial	No	No	Yes	Not reported
Cote, 1990	Prospective	Consecutive or random selection	Partial	Yes	No	No	Government
Coutts, 1984	Prospective	Other	Unclear	No	No	Unclear	Not reported
Curran, 1996	Prospective	Other	Unclear	No	No	No	Not reported
Davison, 1983	Prospective	Other	Unclear	Yes	Unclear	Yes	Not reported
Dellabianca, 1996	Prospective	Consecutive or random selection	Unclear	Yes	No	No	Not reported
Dente, 1986	Prospective	Not reported	Unclear	No	No	No	Not reported
De Zotti, 1996a	Prospective	Other	Unclear	Yes	No	No	Not reported
De Zotti, 1996b	Prospective	Not reported	Unclear	Yes	No	Unclear	Not reported

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
DiFranco, 1998	Prospective	Other	Partial	No	Yes	Yes	Government
Duan, 1989	Prospective	Not reported	Inadequate	Yes	Unclear	Unclear	Not reported
Ferguson, 1996	Prospective	Other	Unclear	Yes	No	No	Not reported
Gannon, 1996	Prospective	Other	Unclear	No	Yes	Yes	Government, foundation
Girard, 2004	Prospective	Other	Partial	Yes	No	No	Government
Graneek, 1988	Unclear	Other	Partial	Yes	Yes	No	Not reported
Grosclaude, 1980	Prospective	Not reported	Unclear	Yes	No	No	Not reported
Harries, 1980	Prospective	Other	Unclear	Yes	No	No	Not reported
Hinojosa, 1986	Prospective	Not reported	Unclear	Yes	No	No	Not reported
Howe, 1983	Prospective	Other	Unclear	Yes	Yes	No	Other
Huggins, 2003	Prospective	Consecutive or random selection	Partial	No	Unclear	Yes	Not reported
Jager, 1993	Unclear	Other	Unclear	Yes	No	Yes	Not reported
Karol, 1994	Prospective	Other	Unclear	Yes	No	No	Government, private
Kern, 1991	Prospective	Other	Unclear	Yes	No	No	Government
Keskinen, 1988	Retrospective	Consecutive or random selection	Unclear	Yes	No	No	Not reported
Kim, 1999	Prospective	Other	Unclear	No	No	Yes	Not reported
Kim, 1997	Prospective	Other	Unclear	Yes	Yes	Yes	Government

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Kopferschmitt-Kubler, 1998	Prospective	Other	Unclear	Yes	No	No	Not reported
Kongerud, 1992	Prospective	Other	Partial	No	No	Unclear	Not reported
Koskela, 2003	Prospective	Consecutive or random selection	Unclear	Yes	Yes	No	Internal
Krakowiak, 2003	Prospective	Other	Partial	Yes	No	No	Not reported
Lam, 1979	Prospective	Other	Unclear	Yes	Unclear	Unclear	Foundation
La Paglia, 1986	Unclear	Not reported	Unclear	No	Yes	Unclear	Not reported
Larbanois, 2003	Unclear	Consecutive or random selection	Unclear	Yes	No	No	Government
Lemiere, 1999	Prospective	Other	Full	Yes	No	No	Foundation
Liss, 1991	Retrospective	Other	Full	Yes	Yes	No	Not reported
Lozewicz, 1985	Prospective	Other	Partial	No	No	Yes	Not reported
Malo, 1993	Retrospective	Other	Partial	No	No	No	Not reported
Malo, 1991	Prospective	Consecutive or random selection	Full	Yes	No	Yes	Not reported
Malo, 1990	Retrospective	Other	Unclear	Yes	Yes	No	Not reported
Malo, 1988	Prospective	Consecutive or random selection	Unclear	Yes	Yes	Yes	Not reported
Mapp, 1986	Prospective	Not reported	Unclear	Yes	No	No	Government
Mapp, 1979	Prospective	Not reported	Unclear	Yes	No	Yes	Not reported
Merget, 1997	Prospective	Other	Unclear	Yes	No	No	Not reported

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Merget, 1996	Prospective	Other	Unclear	Yes	No	No	Other
Merget, 1993	Prospective	Consecutive or random selection	Unclear	Yes	No	No	Not reported
Mole, 1977	Prospective	Not reported	Unclear	Yes	No	Yes	Not reported
Moller, 1986	Prospective	Other	Unclear	Yes	Yes	No	Not reported
Moller, 1985	Prospective	Other	Unclear	No	No	No	Government, foundation
Moscato, 1991	Retrospective	Other	Unclear	Yes	No	No	Not reported
Munoz, 2004	Prospective	Other	Unclear	Yes	No	No	Not reported
Nielsen, 1988	Prospective	Not reported	Partial	Yes	No	No	Foundation
Nordman, 1985	Retrospective	Consecutive or random selection	Unclear	Yes	Unclear	Unclear	Not reported
Obata, 1999	Prospective	Consecutive or random selection	Partial	Yes	No	No	Foundation
O'Brien, 1979b	Prospective	Not reported	Unclear	Yes	No	Unclear	Private
O'Brien, 1979a	Prospective	Other	Unclear	Yes	Yes	No	Private
Obutulowicz, 1998	Prospective	Other	Unclear	No	No	No	Not reported
Paggiaro, 1987	Retrospective	Other	Unclear	Yes	No	Yes	Not reported
Paggiaro, 1986	Prospective	Other	Unclear	Yes	Unclear	No	Not reported
Paggiaro, 1984c	Prospective	Not reported	Unclear	Yes	Unclear	Unclear	Not reported
Paggiaro, 1984b	Prospective	Not reported	Unclear	Yes	No	Yes	Not reported

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Paggiaro, 1981	Prospective	Not reported	Inadequate	Yes	No	No	Not reported
Palczynski, 2003	Prospective	Other	Partial	No	No	No	Government
Park, 2002	Prospective	Other	Unclear	Yes	No	No	Private
Park, 2001	Prospective	Other	Partial	Yes	Yes	No	Internal
Park, 1999	Prospective	Other	Unclear	Yes	No	No	Other
Park, 1998	Prospective	Other	Unclear	Yes	Yes	Yes	Internal
Park, 1994	Prospective	Not reported	Unclear	Yes	No	No	Not reported
Park, 1991	Prospective	Other	Unclear	Yes	Yes	Yes	Not reported
Park, 1989	Prospective	Not reported	Unclear	Yes	No	No	Internal
Perrin, 1990	Prospective	Not reported	Unclear	No	No	No	Not reported
Pezzini, 1984	Prospective	Not reported	Unclear	Yes	Unclear	Unclear	Government
Prichard, 1984	Prospective	Other	Unclear	No	No	No	Other
Quirce, 2000	Prospective	Other	Unclear	No	Unclear	Unclear	Not reported
Quirce, 1992	Retrospective	Other	Unclear	Yes	No	No	Foundation
Rasanen, 1994	Prospective	Not reported	Unclear	Yes	No	Yes	Not reported
Redlich, 1996	Prospective	Not reported	Unclear	No	No	No	Internal
Ricciardi, 2003	Prospective	Other	Unclear	Yes	Yes	Yes	Not reported

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Sander, 2001	Prospective	Not reported	Unclear	Inadequate	Unclear	Unclear	Not reported
Sastre, 2003	Prospective	Not reported	Unclear	Yes	Yes	No	Not reported
Schuermans, 2003	Prospective	Not reported	Unclear	No	Unclear	Unclear	Not reported
Schwaiblmair, 1997	Prospective	Other	Unclear	Yes	No	Yes	Not reported
Schwarting, 1979	Unclear	Other	Unclear	No	No	Yes	Not reported
Shirai, 2003	Prospective	Other	Unclear	Yes	No	No	Not reported
Shirakawa, 1988	Prospective	Other	Unclear	No	No	No	Not reported
Slovak, 1981	Prospective	Other	Unclear	No	No	No	Not reported
Stefano, 1999	Prospective	Other	Unclear	Yes	Unclear	Yes	Not reported
Symington, 1981	Prospective	Other	Unclear	No	Yes	No	Not reported
Tabar, 2004	Retrospective	Other	Unclear	Yes	Yes	No	Not reported
Taivainen, 1994	Prospective	Consecutive or random selection	Unclear	Yes	No	Yes	Not reported
Tee, 1998	Retrospective	Other	Partial	Yes	No	No	Not reported
Tse, 1982	Prospective	Not reported	Unclear	No	Yes	Yes	Government
Vandenplas, 2001	Prospective	Consecutive or random selection	Partial	Yes	No	No	Private
Vandenplas, 1995	Prospective	Other	Unclear	Yes	Yes	Yes	Other
Vanhanen, 2000	Prospective	Not reported	Inadequate	Yes	No	No	Not reported

Table E-4. Methodological quality of included studies (Diagnosis review) (continued)

Author, Year	Data Collection	Patient Recruitment	Blinding	Adequate Description of Reference Standard	Avoidance of Differential Bias	Avoidance of Partial Verification Bias	Funding
Virtanen, 1996	Prospective	Consecutive or random selection	Unclear	Yes	Yes	No	Foundation
Vogelmeier, 1991	Prospective	Not reported	Unclear	Yes	No	No	Other
Wurzinger, 1997	Unclear	Not reported	Unclear	Yes	No	Yes	Not reported
Zeiler, 2002	Prospective	Consecutive or random selection	Unclear	Yes	No	No	Internal, foundation
Zeiss, 1977	Prospective	Other	Inadequate	Yes	No	No	Government, internal, private

Table E-5. Description of included studies (Management cohorts review)

Author, Year	Location	Language of Publication	Intervention Categories	Suspected Agent (molecular weight)	Subject Source	Description of Included Subjects
Allard, 1989	Canada	English	Removed	Mixed (M)	Clinic	Workers with OA due to mixed causes, no longer exposed >5 yrs
Ameille, 1997	France	English	Exposed, protection, reduced, removed	Mixed (M)	Clinic	Workers diagnosed with OA due to mixed causes between 1989-93, follow-up approximately 3 yrs later
Banks, 1990	United States	English	Reduced	Isocyanates (L)	Workplace	Polyurethane foam workers with OA due to TDI, follow-up 1982-86
Barker, 1998	United Kingdom	English	Removed	Chemical: TCPA (L)	Clinic	Female electronic factory workers diagnosed with OA due to TCPA, follow-up at 12 yrs
Bernstein, 2003	United States	English	Exposed, protection, reduced, removed	Latex (H)	Other	Volunteer health care workers with NRL allergy
Burge, 1982a	United Kingdom	English	Reduced, removed	Colophony (L)	Clinic	Electronics workers with OA due to colophony fumes
Gannon, 1993	United Kingdom	English	Exposed, removed	Mixed (M)	Clinic	Workers with OA due to various causes diagnosed at least 1 yr ago
Gassert, 1998	United States	English	Removed	Mixed (M)	Clinic	Workers with OA
Gorski, 1999	Poland	English	Removed	Flour (H)	Clinic	Workers with bakers asthma, no longer exposed, follow-up approximately 2 yrs
Grammer, 2000	United States	English	Reduced, removed	Chemical: trimellitic anhydride (L)	Workplace	Workers at TMA manufacturing plant with OA, moved to low exposure jobs >1 yr
Grammer, 1996	United States	English	Removed	Chemical: anhydride (L)	Other	Workers that prepare epoxy resin with HHPA-induced respiratory disease, non-exposed for approximately 1 yr
Harries, 1979	United Kingdom	English	Reduced, removed	Isocyanates (L)	Workplace	Workers in rubber manufacturing plant with isocyanate-induced asthma, follow-up approximately 3 yrs
Jyo, 1989	Japan	English	Medications	Sea squid (H)	-	Oyster shuckers with asthma and sea squirt allergy
Laoprasert, 1998	United States	English	Protection	Latex (H)	Clinic	Female health care workers with OA due to latex
Lemiere, 2000	Canada	English	Removed	Isocyanates (L)	Clinic	Workers diagnosed with OA caused by HMW agents had normal NSBR, not exposed for approximately 5 yrs
Lemiere, 1996	Canada	English	Removed	Mixed (M)	Clinic	Workers with OA due to isocyanate/flour/gum no longer exposed

Table E-5. Description of included studies (Management cohorts review) (continued)

Author, Year	Location	Language of Publication	Intervention Categories	Suspected Agent (molecular weight)	Subject Source	Description of Included Subjects
Lin, 1996	Canada	English	Exposed, removed	Wood dust: cedar (L)	Clinic	Male workers with OA due to western western red cedar diagnosed between 1972-92
Lozewicz, 1987	United Kingdom	English	Reduced, removed	Isocyanates (L)	Clinic	Various workers diagnosed with isocyanate-induced asthma between 1971-79, no exposure approximately 4 yrs
Maghni, 2004	Canada	English	Removed	Mixed (M)	Clinic	Workers with OA due to mixed causes, no longer exposed
Malo, 2004	Canada	English	Removed	Mixed (M)	-	Workers with OA with serial NSBPT measurements at diagnosis and after removal from exposure
Malo, 1994a	Canada	English	Removed	Chemical: chlorine (L)	Clinic	Pipefitters and welders working in a paper mill with bronchial hyperresponsiveness after 3 month exposure to chlorine
Malo, 1993b	Canada	English	Removed	Mixed (M)	Clinic	Workers, mostly exposed to isocyanates, with a confirmed diagnosis of OA and receiving compensation from WBC
Mapp, 1988	Italy	English	Exposed, removed	Isocyanates (L)	-	Lumber workers with OA due to TDI, follow-up approximately 10 mos
Malo, 1988b	Canada	English	Removed	Snow crab (H)	-	Snowcrab workers with OA, no longer exposed, follow-up between 12-64 mos
Marabini, 2003	Italy	English	Exposed	Mixed (M)	Clinic	Carpenters/bakers/farmers/coach worker with OA
Merget, 1999	Germany	English	Exposed, reduced, removed,	Chemical: platinum salts (L)	Workplace	Metal refinery/catalyst production workers with OA due to platinum salts
Meyer, 1977	Germany	German	Removed	Metal dust (L)	Workplace	Workers with metal dust allergy identified in the workplace
Moscato, 1999	Italy	English	Exposed, reduced, removed,	Mixed (M)	Clinic	Workers diagnosed with OA due to mixed causes between 1992-95, follow-up at 12 mos
Munoz, 2003	Spain	English	Protection, removed	Chemical: persulfate (L)	Clinic	Cosmetic factory workers, hairdressers with OA due to persulfate salts
O'Donnell, 1989	New Zealand	English	Exposed	Potroom (L)	Workplace	Smelter workers diagnosed with potroom asthma
Orriols, 1999	Spain	Spanish	Protection, removed	Isocyanates (L)	Clinic	Workers with OA caused by isocyanates
Paggiaro, 1993	Italy	English	Reduced, removed	Isocyanates (L)	Workplace	Furniture manufacturing workers with OA due to TDI

Table E-5. Description of included studies (Management cohorts review) (continued)

Author, Year	Location	Language of Publication	Intervention Categories	Suspected Agent (molecular weight)	Subject Source	Description of Included Subjects
Paggiaro, 1990	Italy	English	Removed	Isocyanates (L)	-	Workers with TDI asthma no longer exposed
Paggiaro, 1984a	Italy	English	Exposed, removed	Isocyanates (L)	-	Furniture manufacturing workers with OA due to TDI
Park, 2002a	Korea	English	Removed	Isocyanates (L)	Clinic	Workers with TDI asthma, no longer exposed >5 yrs
Park, 1994	Korea	English	Removed	Chemical: chromium (L)	Clinic	Workers in metalplating/cement/construction work with OA due to chromium exposure
Perfetti, 1998a	Canada	English	Removed	Mixed (M)	Clinic	Volunteer workers randomly selected from clinic charts diagnosed with OA, mixed causes
Piirila, 1996	Finland	English	Reduced, removed	Chemical: sulfur dioxide (L)	Workplace	Miners accidentally exposed to sulfur dioxide reviewed 13 yrs later
Pisati, 1994	Italy	English	Exposed, removed	Chemical: cobalt (L)	Clinic	Workers with OA due to cobalt diagnosed between 1982-90
Pisati, 1993	Italy	English	Reduced, removed	Isocyanates (L)	Clinic	Workers exposed to paint/varnish/foam diagnosed with TDI asthma between 1980-85
Rosenberg, 1987	France	English	Exposed, protection, reduced, removed	Isocyanates (L)	Clinic	Car spray-painters/foam manufacturers/cabinet makers, etc. with isocyanate-asthma, follow-up 6-54 mos
Ross, 1998	United Kingdom	English	Removed	Mixed (M)	Other	Charts of workers with OA refered to SWORD project
Saetta, 1995	Italy	English	Removed	Isocyanates (L)	-	Workers with OA due to TDI, no longer exposed
Sen, 1998	United Kingdom	English	Removed	Enzymes: fruit (H)	Workplace	Factory workers preparing fruit with OA due to enzymes
Simonsson, 1985	Sweden	English	Exposed, removed	Metal: aluminum fluoride or sulfate (L)	Clinic	Workers from aluminum factories with OA due to aluminum fluoride/sulphate
Slovak, 1985	United Kingdom	English	Protection	Animal/bird: lab animals (H)	Workplace	Lab animal workers diagnosed with OA, still exposed
Smith, 1999	United Kingdom	English	Exposed, reduced	Flour (H)	Other	Workers across flour-using industries with OA
Sulotto, 1989	Italy	Italian	Removed, medications	Mixed (M)	Clinic	Workers with clinically diagnosed OA from various causes
Taivainen, 1998	Finland	English	Protection	Animal/bird: cow dander and grain (H)	Clinic	Farmers with OA due to cow dander or grains

Table E-5. Description of included studies (Management cohorts review) (continued)

Author, Year	Location	Language of Publication	Intervention Categories	Suspected Agent (molecular weight)	Subject Source	Description of Included Subjects
Vandenplas, 2002	Belgium	English	Reduced, removed	Latex (H)	Clinic	Health-care/non-health-care workers with OA due to latex
Venables, 1987	United Kingdom	English	Removed	Chemical: TCPA (L)	Workplace	Female process workers with OA due to TCPA, no longer exposed, follow-up approximately 4.5 yrs
Venables, 1985	United Kingdom	English	Reduced	Isocyanates (L)	Workplace	Various workers in a steel coating plant with OA due to coating vapours

Abbreviations: **H** = high; **HHPA** = hexahydrophthalic anhydride; **L** = low; **M** = mixed; mos = months; **NRL** = natural rubber latex; **NSBPT** = non-specific bronchial provocation; **NSBR** = non-specific bronchial reactivity; **OA** = occupational asthma; **SWORD** = surveillance of work-related occupational respiratory disease; **TCPA** = tetrachlorophthalic anhydride; **TDI** = toluene di-isocyanates; **TMA** = trimellitic anhydride; **WCB** = workers' compensation board; **yr** = year; **yrs** = years

Table E-6. Demographic characteristics of included patients (Management cohorts review)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	% predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	SIC Confirmed OA	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)		
Allard, 1989	28	92.9	46 (11)	60.7	C: 17.9	-	87 (21.3)	0.5 (0.8)	0.3 (0.2)	Yes	-
Ameille, 1997	209	75.1	38 (12)	-	-	-	88 (20)	-	3.7 (5.1)	No	-
Banks, 1990	6	-	-	-	C: 33.3 N: 66.7	0	-	-	-	Yes	-
Barker, 1998	6	0	37 (4.2)	-	-	-	FEV_1: 2.1 (0.2)	-	-	Yes	-
Bernstein, 2003	67	4.5	36.1 (11.5)	82.1	-	-	-	-	4.5 (4.8)	No	No
Burge, 1982a	45	20	49 (6.8)	-	N: 48.9	-	-	-	2.5	Yes	Yes
Gannon, 1993	224	74.1	-	-	C: 12.1 Ex: 21.9 N: 15.6	-	-	-	-	No	-
Gassert, 1998	55	29.1	41.1 (9.8)	-	C: 9.1 Ex: 32.7 N: 58.2	25.5	-	10.7 (6.9)	-	No	-
Gorski, 1999	56	-	38 (9)	-	C: 26.8 Ex: 26.8 N: 46.4	-	-	-	-	No	-
Grammer, 2000	29	89.7	36.5 (8.8)	-	C: 44.8 Ex: 13.8 N: 41.4	-	-	1.1 (5.2)	-	No	-
Grammer, 1996	7	100	37 (4.3)	-	C: 14.3 Ex: 28.6 N: 57.1	-	-	-	-	No	-
Harries, 1979	3	100	41.3 (3.7)	66.7	C: 66.7 Ex: 33.3 N: 0	-	FEV_1: 3 (0.4)	8 (9.6)	2.5 (3.1)	Yes	-
Jyo, 1989	-	-	-	-	-	-	-	-	-	No	-

Table E-6. Demographic characteristics of included patients (Management cohorts review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	% predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	SIC Confirmed OA	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)		
Laoprasert, 1998	11	0	35.5 (6.2)	63.6	C: 0 N: 100	-	-	-	-	No	Yes
Lemiere, 2000	16	68.8	41.3 (9.9)	75	C: 31.3 Ex: 50 N: 18.8	-	99 (14.4)	10.7 (9.5)	-	Yes	Yes
Lemiere, 1996	15	73.3	49.1 (10.4)	53.3	C: 0 Ex: 40 N: 60	-	96 (12)	18.1 (13.6)	6 (5.6)	Yes	-
Lin, 1996	280	100	40.9 (11.2)	27.9	C: 4.6 Ex: 28.2 N: 67.1	-	86.1 (16.7)	6.1 (6.4)	-	Yes	Yes
Lozewicz, 1987	56	83.9	46.1 (9.8)	35.7	C: 21.4 Ex: 41.1 N: 26.8	3.6	82.5 (21.1)	6.5 (7.4)	2.7 (2.1)	Yes	-
Maghni, 2004	133	60.9	43 (12)	59.4	C: 18 Ex: 39.8 N: 42.1	-	84.1 (20.3)	12.1 (10.6)	3.9 (4.7)	No	Yes
Malo, 2004	80	80	42.8 (12.4)	53.8	C: 20 Ex: 37.5 N: 42.5	-	90.2 (16.5)	11.5 (10.7)	3.3 (4.2)	Yes	Yes
Malo, 1994a	20	100	48 (10)	50	C: 55 Ex: 40 N: 5	-	80.4 (19.3)	-	-	No	-
Malo, 1993b	134	76.1	44 (12)	60.4	-	-	91 (20)	-	-	Yes	-
Malo, 1988b	31	9.7	37.1 (12.2)	29	C: 64.5 Ex: 19.4 N: 16.1	-	-	1.1 (0.5)	0.6 (0.4)	Yes	-
Mapp, 1988	35	71.4	34.6 (13.7)	22.9	C: 8.6 Ex: 28.6 N: 62.9	0	-	13.5 (11.3)	3.7	Yes	Yes

Table E-6. Demographic characteristics of included patients (Management cohorts review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	% predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	SIC Confirmed OA	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)		
Marabini, 2003	10	90	49.9 (7)	30	C: 10 Ex: 60 N: 30	-	75.1 (12.6)	24.2 (14.3)	-	Yes	-
Merget, 1999	83	-	38 (10.4)	45.8	C: 51.8 Ex: 22.9 N: 25.3	-	-	-	-	Yes	-
Meyer, 1977	168	-	-	-	-	-	-	-	-	No	-
Moscato, 1999	25	72	34 (9.3)	16	C: 28 Ex: 24 N: 48	-	103 (6.8)	5 (5)	1.8 (1.2)	Yes	Yes
Munoz, 2003	8	0	35 (10.3)	37.5	C: 37.5	0	99.3 (9.9)	14.6 (8.7)	-	Yes	-
O'Donnell, 1989	57	100	31 (6.3)	29.8	C: 50.9	-	-	-	-	No	-
Orriols, 1999	21	81	36.4 (10.9)	23.8	C: 57.1 Ex: 19 N: 23.8	-	80.8 (21)	6.1 (6.9)	-	Yes	-
Paggiaro, 1993	16	68.8	46.7 (9.4)	-	C: 12.5 Ex: 37.5 N: 50	-	81.7 (12.5)	20.7 (8.9)	3.8 (4.1)	Yes	Yes
Paggiaro, 1990	10	80	49.5 (7.4)	-	C: 10 Ex: 50 N: 40	-	82.7 (15.6)	-	4.3 (2.6)	Yes	Yes
Paggiaro, 1984a	27	59.3	50.2 (9.1)	-	C: 29.6 Ex: 0 N: 70.4	-	-	15.5 (10)	-	Yes	-
Park, 2002a	41	-	-	-	-	-	-	22.4 (5.5)	-	Yes	Yes
Park, 1994	3	100	47.3 (9.1)	100	C: 0 Ex: 100 N: 0	-	-	-	-	Yes	-

Table E-6. Demographic characteristics of included patients (Management cohorts review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	% predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	SIC Confirmed OA	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)		
Perfetti, 1998a	99	73.7	43 (12)	59.6	C: 15.2 Ex: 39.4 N: 45.5	-	-	12.5 (11.3)	3.2	Yes	Yes
Piirila, 1996	7	100	26.9 (5.1)	-	C: 57.1 Ex: 0 N: 28.6	-	-	-	-	No	-
Pisati, 1994	9	-	-	-	C: 11.1 Ex: 11.1 N: 77.8	-	-	-	-	Yes	-
Pisati, 1993	60	-	37.3 (11.6)	13.3	C: 15 Ex: 0 N: 85	5	-	15.3 (9.1)	4.4	Yes	Yes
Rosenberg, 1987	31	87.1	35.9 (16.6)	29	C: 19.4	3.2	97 (35.7)	3 (6)	1.4 (2.2)	Yes	-
Ross, 1998	1011	70.6	40.9 (12.3)	-	C: 22.4 Ex: 27.8 N: 40.8	-	-	4 (8.1)	-	No	-
Saetta, 1995	10	50	39.1 (12.8)	20	C: 0 Ex: 0 N: 100	-	98.6 (15)	17.5 (14.5)	3.5 (3.7)	Yes	Yes
Sen, 1998	3	66.7	31.3 (13.3)	100	C: 33.3 Ex: 0 N: 66.7	66.7	-	-	0.5 (0.1)	No	-
Simonsson, 1985	19	100	24 (4.5)	10.5	C: 57.9 Ex: 31.6 N: 10.5	10.5	93 (6)	1.2 (1.3)	-	No	Yes
Slovak, 1985	8	-	-	100	-	-	-	-	-	No	-
Smith, 1999	-	-	-	-	-	-	-	-	-	No	-
Sulotto, 1989	10	50	39 (7.3)	-	C: 70	-	101.6 (9.5)	9.5 (7)	-	Yes	No

Table E-6. Demographic characteristics of included patients (Management cohorts review) (continued)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	% predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	SIC Confirmed OA	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)		
Taivainen, 1998	24	-	-	-	-	-	-	-	-	Yes	-
Vandenplas, 2002	36	11.1	32 (4.4)	63.9	C: 5.6 Ex: 5.6 N: 88.9	30.6	-	-	7.2	Yes	Yes
Venables, 1987	6	0	39 (2.8)	16.7	C: 100	0	-	-	-	Yes	-
Venables, 1985	21	100	41.2	28.6	C: 47.6	-	93	7.7	-	No	-

Abbreviations: **C** = current; **Ex** = ex; **FEV_1** = forced expiratory volume in one second; **N** = never; **OA** = occupational asthma; **SIC** = specific inhalational challenge

Table E-7. Description of interventions and outcomes (Management cohorts review)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Allard, 1989	Removed	Ceased exposure for at least 6 mos	28	NSBPT Pulmonary function Questionnaire	Histamine: PC_{20} FEV_1 FEV_1 Including symptoms, smoking habits, and need for medication
Ameille, 1997	Exposed Protection Reduced Removed	No change Improved ventilation or used appropriate respirator Different job in same workplace Left workplace	20 46 38 85	Questionnaire	Including current working status and financial situation
Banks, 1990	Reduced	Moved to areas with negligable or no exposure	6	NSBPT Pulmonary function Questionnaire	Methacholine: PD_{20} FEV_1 FEV_1 and FVC Including symptoms and smoking habits
Barker, 1998	Removed	All subjects left the factory in 1980	6	NSBPT Pulmonary function Questionnaire Skin prick test Serum specific IgE	Histamine bronchial responsiveness Average daily amplitude (maximum PEFR - minimum PEFR/maximum PEFR) over 28 day period Including symptoms, medication use, and smoking 1% TCPA-HSA RAST
Bernstein, 2003	Exposed Protection Reduced Removed	No intervention initiated Used NRL gloves Transferred Left workplace	1 19 1 4	Skin prick test	Latex
Burge, 1982a	Reduced Removed	Moved within factory, no description of exposure status Changed workplace	9 22	NSBPT Pulmonary function Questionnaire	Histamine reactivity FEV_1 and FVC Including symptoms and medication use
Gannon, 1993	Exposed Removed	Not described Removed from exposure	34 78	Questionnaire	Including symptoms, employment state, and current financial situation
Gassert, 1998	Removed	Removed from exposure	55	Questionnaire	Including symptoms, daily activity, and medication use

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Gorski, 1999	Removed	Changed jobs or stopped working	56	NSBPT Pulmonary function Questionnaire Skin prick test Serum specific IgE	Histamine: PC_{20} FEV_1 FEV_1 Including symptoms and medication use Common allergens and flours RAST
Grammer, 2000	Reduced Removed	Transferred to lower exposure Completely removed from exposure	22 7	Pulmonary function Questionnaire Serum specific IgE Serum specific IgG	Spirometry (not specified) Including type and severity of symptoms Described in text Described in text
Grammer, 1996	Removed	Removed from exposure for at least 1 yr	11	Pulmonary function Questionnaire Serum specific IgE Serum specific IgG	Spirometry (not specified) Including type and severity of symptoms Described in text Described in text
Harries, 1979	Reduced Removed	Changed tasks Moved to a safer location or left industry	1 2	Interview Pulmonary function	Including medication use FEV_1 and FVC
Jyo, 1989	Medications	Immunotherapy	47	Improvement after hyposensitization therapy Serum specific IgE Serum specific IgG	Improvement after hyposensitization therapy RAST RAST
Laoprasert, 1998	Protection	Used NRL gloves and/or helmet filter	11	SIC Symptoms	Latex aeroallergen Not described
Lemiere, 2000	Removed	Removed from exposure	16	Questionnaire SIC Skin prick test Serum specific IgE	Including symptoms, need for medication, and smoking habits Suspected agent Cereals, guar gum, and psyllium RAST
Lemiere, 1996	Removed	No longer exposed after diagnosis	15	Questionnaire SIC Skin prick test Serum specific IgE Serum specific IgG	Including symptoms and need for medication Suspected agent Common inhalants RAST Not described

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	**Description**	**Number of Patients**	**Test**	**Description**
Lin, 1996	Exposed	Continued exposure	158	Pulmonary function[17]	FEV_1
	Removed	Left industry after diagnosis	122	Exhaled nitric oxide[25]	Not reported
				NSBPT[25]	Methacholine: PC_{20} FEV_1
				Questionnaire[25]	Not described
				Sputum cell counts[25]	Eosinophils, neutrophils, epithelial, lymphocytes, and macrophages
				Bronchial lavage[22]	Total cell count and % macrophages, lymphocytes, neutrophils, eosinophils, epithelial cells, degenerated cells, total protein, and albumin
				Interview[20]	Including current work situation
				Skin prick test[20]	Common allergens
				Serum specific IgG[20]	Radial immunodiffusion
	Reduced[18]	Changed jobs resulting in intermittant exposure	42	Serum eosinophil count[19]	Serum eosinophil count
				Bronchial lavage[21]	Including protein, albumin, eosinophils, and neutrophils
Lozewicz, 1987	Reduced	Relocated to another area within the plant	28	NSBPT	Histamine: 10% fall in FEV_1
				Pulmonary function	FEV_1 and FVC
				Questionnaire	Including symptoms and medication use
	Removed	Left workplace	21	SIC	TDI, MDI, HDI, NDI
				Skin prick test	Common allergens
Maghni, 2004	Removed	No longer exposed	133	NSBPT	Methacholine: PC_{20} FEV_1
				Pulmonary function	FEV_1
				Questionnaire	Including exposure status, symptoms, and medication needs
				Sputum cell counts	Eosinophils, neutrophils, IL-8, MPO, and eotaxin
Malo, 2004	Removed	No longer exposed to causal agent	80	NSBPT	Methacholine: PC_{20} FEV_1

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Malo, 1994a	Removed	Not exposed to chlorine during the 1 yr follow-up period	20	Medications NSBPT Pulmonary function	Beta-2-agonist and or inhaled steroids or none Methacholine: PC_{20} FEV_1 FEV_1
Malo, 1993b	Removed	Subjects had left work for at least 2 yrs prior to entering the study	134	Quality of life questionnaire[28] WCB claim data[29] NSBPT [28] Pulmonary function [29] Questionnaire [29]	Asthma quality of life questionnaire Administrative WCB claim data Methacholine: PC_{20} FEV_1 FEV_1 Including symptoms and need for medication
Malo, 1988b	Removed	Removed from exposure since the time of diagnosis	31	NSBPT Pulmonary function Questionnaire Serum specific IgE	Histamine or methacholine: PC_{20} FEV_1 FEV_1 and FVC Including sympoms, need for medication, and smoking habits RAST
Mapp, 1988	Exposed Removed	Not described No longer exposed	5 30	NSBPT Pulmonary function SIC Symptoms	Methacholine: PD_{20} FEV_1 FEV_1 TDI, MDI, HDI, NDI Not described
Marabini, 2003	Exposed	Attempted to reduce exposure (n=7) but none moved to no exposure	10	NSBPT Pulmonary function	Methacholine: PC_{20} FEV_1 FEV_1 and FVC
Merget, 1999	Exposed Reduced Removed	Same workplace Transferred to jobs not directly exposed to irritant Transferred outside of workplace	9 16 19	NSBPT[30] Pulmonary function[30] Questionnaire[30] Skin prick test[30] SIC[31]	Methacholine: PD_{50} sGaw FEV_1 Including symptoms at and away from work and employment status Platinum salts Platinum salts
Meyer, 1977	Removed	Ceased exposure	168	NSBPT	Acetycholine: improved responsiveness

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Moscato, 1999	Exposed	Performed the same task in the same workplace	7	NSBPT	Methacholine: PD_{20} FEV_1
	Reduced	Changed task within workplace and reported intermittent or lower exposure	5	Pulmonary function Questionnaire	PEF for the duration of the study Including symptoms, working conditions, financial condition, and disease related costs
	Removed	Left workplace	7		
Munoz, 2003	Protection	Not described	3	NSBPT	Methacholine: PC_{20} FEV_1
	Removed	All subjects advised to avoid exosure	5	Pulmonary function	Serial PEF 4 times/day for 2 wks on and off work
				SIC Skin prick test	Potassium persulfate Potassium and ammonium persulfate
O'Donnell, 1989	Exposed	Moved within factory, no description of exposure	57	NSBPT	Methacholine: PC_{20} FEV_1
Orriols, 1999	Protection Removed	Not described Avoided casual exposure	4 17	Symptoms	Persistent, worsening, or asymptomatic
Paggiaro, 1993	Reduced	Moved within factory with occasional exposure	7	NSBPT	Methacholine: PD_{20} FEV_1
	Removed	Left industry	9	SIC	TDI
Paggiaro, 1990	Removed	Ceased exposure after diagnosis	10	Bronchial lavage	Total cell count and % macrophages, lymphocytes, neutrophils, and eosinophils
				NSBPT	Methacholine: PD_{15} FEV_1
Paggiaro, 1984a	Exposed	Continued exposure	15	NSBPT Pulmonary function	Bethanechol: 15% drop in FEV_1 FEV_1 and FVC
	Removed	Left workplace	12	SIC Skin prick test	Not described Common allergens
Park, 2002a	Removed	Withdrawn from work to avoid further exposure	41	Serum specific IgE[32]	ELISA
Park, 1994	Removed	Advised to discontinue exposure	3	NSBPT Serum specific IgG[32] NSBPT[33]	Methacholine: PC_{20} FEV_1 ELISA Methacholine: PC_{20} FEV_1

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Perfetti, 1998a	Removed[34]	Subjects removed from exposure >or equal to 5 yrs, and those removed from exposure for <5 yrs	99	NSBPT[34] Pulmonary function[34] Questionnaire[34] Skin prick test[34]	Methacholine: PC_{20} FEV_1 FEV_1 Including current and previous use of inhaled steroids and exposure status Ubiquitous agents
	Reduced[35]	Occasional or reduced levels of exposure (wearing a mask or respirator)	8	Serum specific IgE[35]	EAST
Piirila, 1996	Reduced Removed	Same task after industrial accident (RADS) Retired after industrial accident (RADS)	3 1	Bronchodilatory response Exercise test NSBPT Pulmonary function	Change in FEV_1 5 minutes after 3 puffs of rimiterol hydrobromide Change in PEF after exercise Histamine: percent change in FEV_1 FEV_1 and FVC
Pisati, 1994	Exposed Removed	Not described Moved to another industry	1 8	NSBPT Pulmonary function Questionnaire SIC Skin prick test	Methacholine: PD_{15} FEV_1 FEV_1 and FVC Including exposure status, symptoms, and medication needs Cobalt Common inhalant allergens and patch test to cobalt sulphate
Pisati, 1993	Reduced Removed	Different task with reduced exposure and used protective respiratory device Ceased exposure within 6 mos of diagnosis	17 43	Interview NSBPT Pulmonary function Skin prick test	Including working conditions, symptoms, need for medication, and hospital stays Methacholine: PD_{15} FEV_1 FEV_1 and FVC Common inhalant allergens
Rosenberg, 1987	Exposed Protection Reduced Removed	Unchanged work conditions Efficient masks, ventilation Changed task within workplace Completely removed from exposure	4 3 4 20	NSBPT Pulmonary function Questionnaire	Acetycholine: percent change in FEV_1 FEV_1 and FVC Including work status, symptoms, requirement for medications, and smoking habits

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Ross, 1998	Removed	Not described	1033	Questionnaire	Including symptoms and employment status
Saetta, 1995	Removed	Ceased exposure	10	Bronchoscopy[36] NSBPT[36] SIC[36] Bronchoscopy[37]	Fibroblast counts Methacholine: PD_{20} FEV_1 TDI Basement membrane thickness
Sen, 1998	Removed	Left industry	3	Serum specific IgE Serum specific IgG	RAST RAST
Simonsson, 1985	Exposed Removed	Not described Not described	6 13	NSBPT Pulmonary function SIC	Methacholine: TD_{15} FEV_1 FEV_1 and FVC Aluminium salts
Slovak, 1985	Protection	Helmet respirator and outer protective clothing	10	Pulmonary function Skin prick test	Serial PEF every 2 waking hrs for 7 wks Lab animal allergy
Smith, 1999	Exposed Reduced	Same workplace Different job in same workplace	11 11	Interview	Including symptoms and current job situation
Sulotto, 1989	Removed and medications	Took beclomethasone for 3 to 12 mos after cessation of exposure	10	NSBPT Pulmonary function	Methacholine: PD_{20} FEV_1 FEV_1, FVC, MEF_{50}, MEF_{25}
Taivainen, 1998	Protection	Helmet respirator	26	Pulmonary function Symptoms	Serial PEF: morning and evening Recorded daily on a 4 point scale
Vandenplas, 2002	Reduced Removed	<20 pairs of latex gloves used per wk by co-workers Latex gloves never used	20 16	NSBPT Pulmonary function Questionnaire SIC	Histamine: PC_{20} FEV_1 FEV_1 Including occupational status, smoking habits, symptoms, medication needs, and other allergic reactions Latex gloves
Venables, 1987	Removed	Not described	6	NSBPT Pulmonary function Questionnaire Skin prick test Serum specific IgE	Histamine: PC_{20} FEV_1 FEV_1 Including current respiratory symptoms, medication, and smoking habits. 1% TCPA-HSA RAST

Table E-7. Description of interventions and outcomes (Management cohorts review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Venables, 1985	Reduced	Industrial intervention to reduce TDI levels	21	Pulmonary function Questionnaire	Serial PEF: every 2 waking hrs for 4 wks Including symptoms

Abbreviations: **EAST** = enzyme allergosorbent test; **ELISA** = enzyme-linked immuno sorbent assay; **FEV_1** = forced expiratory volume in one second; **FVC** = forced vital capacity; **HDI** = hexamethylene di-isocyanate; **hrs** = hours; **IL-8** = interleukin-8; **MDI** = diphenylmethane di-isocyanate; **MEF_{25}** = maximal expiratory flow at 25% of vital capacity; **MEF_{50}** = maximal expiratory flow at 50% of vital capacity; **mos** = months; **MPO** = myeloperoxidase; **NDI** = naphthalene di-isocyanate; **NSBPT** = non-specific bronchial provocation; **NRL** = natural rubber latex; **PC_{20}** = provocative concentration causing a 20% drop in FEV_1; **PD_{15}** = provocative dose causing a 15% drop in FEV_1; **PD_{50}** = provocative dose causing a 50% drop in FEV_1; **PEF** = peak expiratory flow; **PEFR** = peak expiratory flow rate; **RADS** = reactive airways dysfunction syndrome; **RAST** = radio allegro sorbent test; **SIC** = specific inhalational challenge; **TCPA-HSA** = tetrachlorophthalic anhydride human serum albumin; **TD_{15}** = threshold dose causing a 15% drop in FEV_1; **TDI** = toluene di-isocyanates; **WCB** = workers' compensation board; **wk** = week; **wks** = weeks; **yr** = year; **yrs** = years

Table E-8. Description of included studies (Management trials review)

Author, Year	Location	Language of Publication	Intervention Categories	Suspected Agent (molecular weight)	Subject Source	Description of Included Subjects
Armentia, 1990	Spain	English	Medications	Flour (H)	-	Bakers and pastry cooks with asthma symptoms due to wheat flour
Crescioli, 1992	Italy	English	Medications	Isocyanates (L)	-	Workers SIC positive to TDI
DeMarzo, 1988	Italy	English	Medications	Isocyanates (L)	-	Workers sensitized to TDI
Fabbri, 1985	Italy	English	Medications	Isocyanates (L)	-	Workers SIC positive to TDI
Maestrelli, 1993	Italy	English	Removed and medications	Isocyanates (L)	-	Workers with OA due to TDI
Malo, 1996	Canada	English	Removed and medications	Mixed (M)	-	Workers with OA due to various causes
Malo, 1994b	Canada	French	Medications	Mixed (M)	-	Workers, mostly exposed to isocyanates, referred to a clinic for exploration of OA
Mapp, 1987	Italy	English	Medications	Isocyanates (L)	Clinic	Workers with OA due to TDI
Moscato, 1985	Italy	English	Medications	Isocyanates (L)	-	Male workers with OA due to TDI
Mueller, 1998	Germany	English	Protection	Straw/grain (U)	-	Dairy/bull breeding farmers with suspected OA
Paggiaro, 1987a	Italy	English	Medications	Isocyanates (L)	-	Workers with OA due to TDI
Vandenplas, 1995a	Belgium	English	Reduced	Latex (H)	-	Healthcare workers with latex glove related asthma
Woitowitz, 1972	Germany	English	Medications	Flour (H)	-	Workers with OA due to flour

Abbreviations: **H** = high; **L** = low; **OA** = occupational asthma; **SIC** = specific inhalational challenge; **TDI** = toluene di-isocyanates; **U** = unknown

Table E-9. Demographic characteristics of included patients (Management trials review)

Author, Year	Number of Patients	Male	Age	Atopic	Smoking Status	History of Asthma	% predicted FEV_1 (unless otherwise stated)	Years of Exposure	Years of Symptoms	SIC Confirmed OA	Current Medication Stopped for Testing
		(%)	mean (SD)	(%)	(%)	(%)	mean (SD)	mean (SD)	mean (SD)		
Armentia, 1990	30	-	34.5 (12.2)	-	-	-	-	12.8 (9.6)	5 (4)	Yes	-
Crescioli, 1992	6	100	42.8 (6.5)	0	C: 0 Ex: 0 N: 100	-	104.5 (10.4)	-	-	Yes	Yes
DeMarzo, 1988	9	88.9	34.7 (10.4)	0	-	-	96.7 (10.4)	-	-	No	Yes
Fabbri, 1985	5	60	39.6 (17.3)	0	C: 0 Ex: 20 N: 80	-	108 (11.7)	-	-	Yes	Yes
Maestrelli, 1993	15	26.7	37.4 (10)	20	-	-	-	12.6 (7.2)	3.4 (-)	Yes	Yes
Malo, 1996	32	68.8	39.3 (12.9)	59.4	C: 21.9 Ex: 9.4 N: 68.8	-	-	9.4 (11)	2.7 (-)	Yes	-
Malo, 1994b	22	63.6	46 (10)	59.1	C: 22.7 Ex: 27.3 N: 50	-	84 (13)	13 (12)	3 (3)	Yes	Yes
Mapp, 1987	24	66.7	35.2 (11.6)	29.2	-	-	-	-	-	Yes	Yes
Moscato, 1985	5	100	29.4 (9)	-	-	-	92.2 (13.8)	-	-	Yes	-
Mueller, 1998	26	69.2	38.6 (11.8)	23.1	C: 38.5	-	FEV_1: 3.5 (1)	34 (14.9)	9.1 (6.8)	Yes	Yes
Paggiaro, 1987a	10	80	48 (8.2)	20	C: 20 Ex: 30 N: 50	-	82.2 (16.2)	-	5.5 (4)	No	Yes
Vandenplas, 1995a	8	12.5	31 (3.7)	62.5	C: 0 Ex: 12.5 N: 87.5	-	98.6 (10.2)	-	-	Yes	-
Woitowitz, 1972	18	100	31.4 (10.2)	-	-	-	-	-	-	Yes	-

Abbreviations: **C** = current; **Ex** = ex; **FEV_1** = forced expiratory volume in one second; **N** = never; **OA** = occupational asthma; **SD** = standard deviation; **SIC** = specific inhalational challenge

Table E-10. Description of interventions and outcomes (Management trials review)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	Description	Number of Patients	Test	Description
Armentia, 1990	Medications	Hyposensitization (immunotherapy) and placebo	26	Hypersensitivity after 20 mos of immunotherapy or placebo	Immune complexes[38] Wheal area[39]; methacholine challenge[39]; serum total IgE[39]; serum specific IgE[39]
Crescioli, 1992	Medications	Theophylline and placebo	6	2 SICs separated by 1 wk: 1 with drug / 1 without	Change in FEV_1 after SIC
DeMarzo, 1988	Medications	High dose beclomethasone, low dose beclomethasone, placebo	9	3 SICs separated by at least 1 wk: for each treatment phase	Change in FEV_1 after SIC
Fabbri, 1985	Medications	Indomethacin and prednisone	5	2 SICs: pre-treatment and 3 days after treatment started	Change in FEV_1 after SIC
Maestrelli, 1993	Removed and medications	Beclomethasone and placebo	15	Hypersensitivity after 5 mos of drug or placebo	Maximum fall in FEV_1 after SIC; PD_{20} FEV1 after methacholine challenge; change in cortisol level
Malo, 1996	Removed and medications	Beclomethasone and placebo	32	Spirometry/hyper-reponsiveness after 12 mos with treatment 1 and 6 mos with treatment 2	Change in pulmonary function; PC_{20} FEV_1 after methacholine challenge; quality of life; and symptoms
Malo, 1994b	Medications	Salbutamol and placebo	25	Change in FEV_1 after SIC	Change in FEV_1 after SIC after administration with salbutomol or placebo to diminish late asthmatic reaction
Mapp, 1987	Medications	Beclomethasone and placebo, thoephylline and placebo, varapamil and placebo, cromolyn and placebo	6, 6, 6, 6	2 SICs separated by at least 1 wk: 1 with drug / 1 without	Change in FEV_1 after SIC
Moscato, 1985	Medications	Nifedipine and placebo	5	2 SICs separated by at least 1 wk: 1 with drug / 1 without	Change in FEV_1 after SIC
Mueller, 1998	Protection	Respirators with P2 filters	26	2 SIC's separated by 21 wks: 1 without respirator / 1 with	Change in airway resistance and thoracic gas volume before and after SIC
Paggiaro, 1987a	Medications	Atropine and placebo	18	2 SICs separated by at least 1 wk: 1 with drug / 1 without	Change in airway resistance and thoracic gas volume before and after SIC

Table E-10. Description of interventions and outcomes (Management trials review) (continued)

Author, Year	Intervention(s)			Outcome(s)	
	Type of Intervention	**Description**	**Number of Patients**	**Test**	**Description**
Vandenplas, 1995a	Reduced	4 types of gloves: Triflex®, low-powdered Triflex®, non-powdered Nutex®, powdered Sensi-Touch®	8	3 SICs with different gloves (all Triflex® then randomized to two of low-powdered Triflex®, non-powdered Nutex®, or powdered Sensi-Touch®)	Maximum fall in FEV_1 after SIC
Woitowitz, 1972	Medications	Fenoterol and placebo	9	SIC after treatment with drug or placebo	Airway resistance

Abbreviations: **FEV_1** = forced expiratory volume in one second; **PC_{20}** = provocative concentration causing a 20% drop in FEV_1; **PD_{20}** = provocative dose causing a 20% drop in FEV_1; **SIC** = specific inhalational challenge; **wk** = week; **wks** = weeks

Table E-11. Methodological quality of included studies (Management cohorts review)

Author, Year	Downs and Black Quality Score	Data Collection	Provided Individual Patient Data	Funding Source
Allard, 1989	16	Prospective	No	Not reported
Ameille, 1997	17	Prospective	No	Not reported
Banks, 1990	17	Prospective	Yes	Government
Barker, 1998	21	Prospective	Yes	Government
Bernstein, 2003	15	Prospective	No	Government
Burge, 1982a	16	Prospective	No	Not reported
Gannon, 1993	19	Prospective	No	Not reported
Gassert, 1998	21	Prospective	No	Government
Gorski, 1999	12	Prospective	No	Not reported
Grammer, 2000	15	Prospective	No	Internal and private
Grammer, 1996	17	Prospective	Yes	Internal
Harries, 1979	17	Prospective	Yes	Not reported
Jyo, 1989	9	Prospective	Yes	Government
Laoprasert, 1998	19	Prospective	Yes	Private and internal
Lemiere, 2000	20	Prospective	Yes	Foundation
Lemiere, 1996	22	Prospective	Yes	Private and other
Lin, 1996	22	Prospective	No	Not reported
Lozewicz, 1987	19	Prospective	No	Not reported

Table E-11. Methodological quality of included studies (Management cohorts review) (continued)

Author, Year	Downs and Black Quality Score	Data Collection	Provided Individual Patient Data	Funding Source
Maghni, 2004	21	Prospective	No	Not reported
Malo, 2004	17	Prospective	No	Not reported
Malo, 1994	18	Prospective	Yes	Government and other
Malo, 1993	14	Prospective	No	Not reported
Malo, 1988	18	Prospective	Yes	Not reported
Mapp, 1988	18	Prospective	Yes	Government and other
Marabini, 2003	18	Prospective	No	Other
Merget, 1999	20	Prospective	No	Not reported
Meyer, 1977	6	Prospective	No	Not reported
Moscato, 1999	22	Prospective	No	Government
Munoz, 2003	19	Prospective	Yes	Not reported
O'Donnell, 1989	13	Prospective	No	Not reported
Orriols, 1999	12	Prospective	No	Not reported
Paggiaro, 1993	16	Prospective	Yes	Government
Paggiaro, 1990	18	Prospective	Yes	Government
Paggiaro, 1984	15	Prospective	Yes	Not reported
Park, 2002	18	Prospective	Yes	Private
Park, 1994	12	Prospective	Yes	Not reported

Table E-11. Methodological quality of included studies (Management cohorts review) (continued)

Author, Year	Downs and Black Quality Score	Data Collection	Provided Individual Patient Data	Funding Source
Perfetti, 1998	19	Prospective	Yes	Foundation
Piirila, 1996	17	Prospective	Yes	Not reported
Pisati, 1994	14	Prospective	Yes	Not reported
Pisati, 1993	18	Prospective	No	Not reported
Rosenberg, 1987	10	Prospective	Yes	Not reported
Ross, 1998	22	Retrospective	No	Government
Saetta, 1995	17	Prospective	Yes	Government
Sen, 1998	13	Prospective	Yes	Not reported
Simonsson, 1985	13	Prospective	Yes	Not reported
Slovak, 1985	9	Prospective	Yes	Not reported
Smith, 1998	12	Prospective	No	Not reported
Sulotto, 1989	10	Prospective	No	Not reported
Taivainen, 1998	21	Prospective	Yes	Not reported
Vandenplas, 2002	22	Prospective	No	Other
Venables, 1987	20	Prospective	Yes	Not reported
Venables, 1985	10	Prospective	No	Not reported

Table E-12. Methodological quality of included studies (Management trials review)

Author, Year	Randomization	Randomization Method	Double Blind	Double Blind Method	Explanation of Withdrawal or Follow-up	Allocation Concealment	Funding
Armentia, 1990	No	Unclear	Yes	Unclear	Adequate	Inadequate	Not reported
Crescioli, 1992	Yes	Unclear	Yes	Unclear	Adequate	Unclear	Government and other
DeMarzo, 1988	Yes	Unclear	Yes	Unclear	Adequate	Unclear	Private and government
Fabbri, 1985	No	Unclear	No	Unclear	Adequate	Inadequate	Private and government
Malo, 1996	Yes	Unclear	Yes	Unclear	Adequate	Adequate	Private and foundation
Malo, 1994	No	Unclear	Yes	Unclear	Adequate	Unclear	Not reported
Mapp, 1987	Yes	Unclear	Yes	Unclear	Adequate	Unclear	Government and foundation
Mastrelli, 1993	Yes	Unclear	Yes	Unclear	Adequate	Unclear	Government
Moscato, 1983	Yes	Unclear	No	Unclear	Adequate	Unclear	Not reported
Muller-Wening, 1998	No	Unclear	No	Unclear	Adequate	Inadequate	Not reported
Paggiaro, 1987	No	Unclear	No	Unclear	Adequate	Inadequate	Government
Vandenplas, 1995	Yes	Unclear	No	Unclear	Adequate	Unclear	Not reported
Woitowitz, 1972	Yes	Unclear	Yes	Unclear	Adequate	Adequate	Not reported

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Diagnosis

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Appendix F: Technical Expert Panel, List of Peer Reviewers, and Translators

Technical Expert Panel

Margaret Coopey
Agency for Healthcare Research and Quality, Washington, United States

Richard Jones
University of Alberta, Edmonton, Canada

Catherine Lemiere
University of Montreal, Montreal, Canada

David Muir
McMaster University, Hamilton, Canada

Susan Tarlo
University of Toronto, Toronto, Canada

Dilini Vethanayagam
University of Alberta, Edmonton, Canada

Peer Reviewers

Ronald Balkissoon
University of Colorado School of Medicine, United States

Sherwood Burge
Birmingham Heartlands Hospital, United Kingdom

Prasant Adhikari
Workers' Compensation Board of Manitoba, Canada

Mark Cullen
Yale University School of Medicine, United States

Paul Cullinan
Royal Brompton Hospital, United Kingdom

Clive Deutscher
Workers' Compensation Board of Alberta, Canada

David Hendrick
University of Newcastle Upon Tyne, United Kingdom

Jean Luc Malo
University of Montreal Medical School, Canada

Phillipa Poole
University of Auckland, New Zealand

Carrie Redlich
Yale University School of Medicine, United States

Olivier Vandenplas
Université Catholique de Louvain, Belgium

Translators

Rudy Bella
Lefarge, Edmonton, Canada

Maurice Blitz
Capital Health, Edmonton, Canada

Anatoly Dobrousin
Capital Health, Edmonton, Canada

Bing Gao
Capital Health, Edmonton, Canada

Walter Kipp
University of Alberta, Edmonton, Canada

Zhi Li
University of Alberta, Edmonton, Canada

Arto Ohinmaa
University of Alberta, Edmonton, Canada

Maria Ospina
University of Alberta, Edmonton, Canada

Rob Polakowski
University of Alberta, Edmonton, Canada

Galina Portmoi
University of Alberta, Edmonton, Canada

Jacques Rizkallah
University of Alberta, Edmonton, Canada

Paul Sperka
University of Alberta, Edmonton, Canada

Appendix G: Quality Analysis of the Diagnostic Occupational Asthma Studies

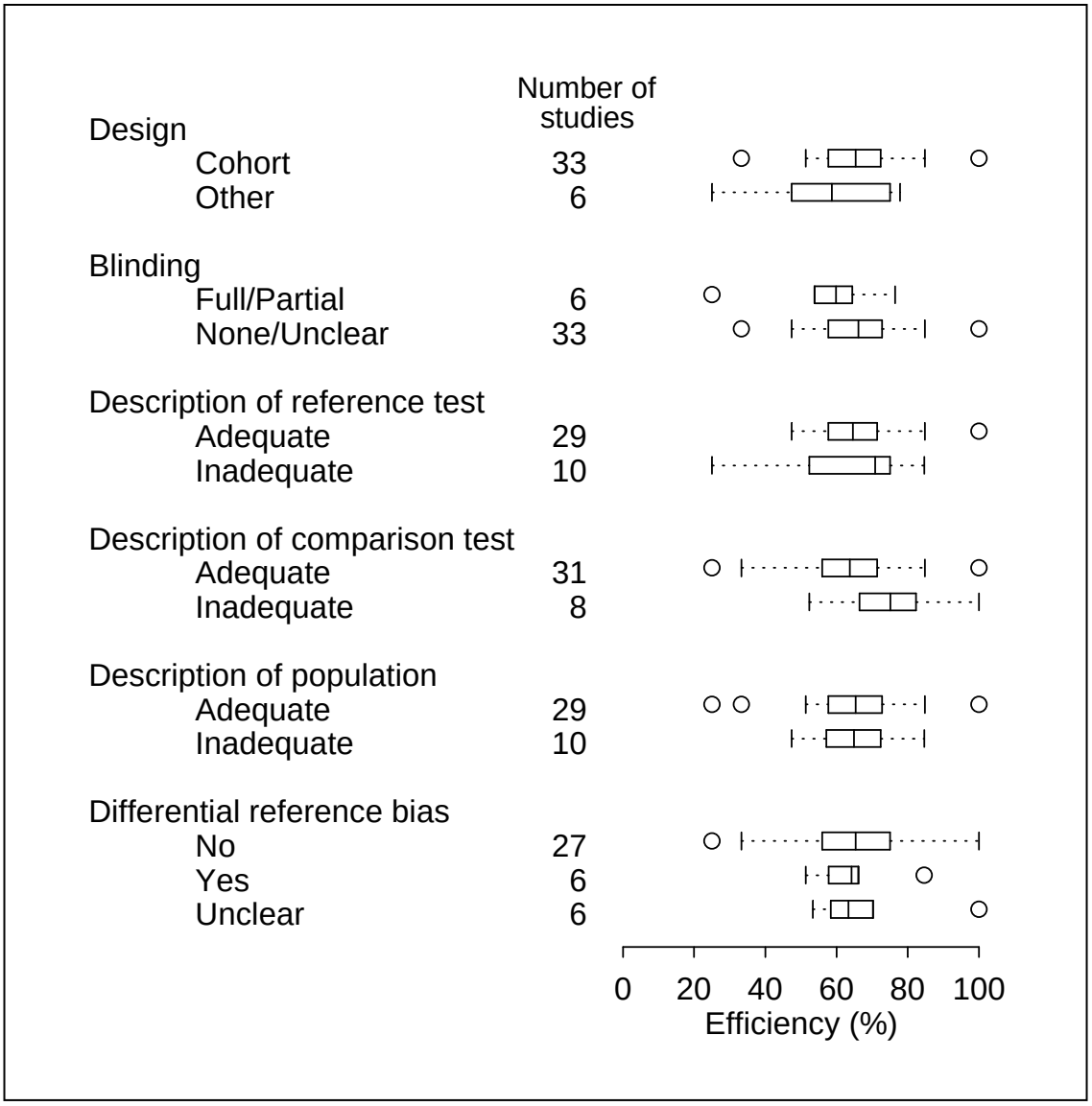
Quality Analysis

For the diagnosis review, the quality of the included studies was low. More formal analyses of the overall quality was attempted to determine the impact study quality on the results. This was evaluated by visual assessment of the distribution of results according to the validated criteria described in the Methods section of the report.

The figures below illustrate the distribution of efficiency (total proportion of correctly identified patients) according the six relevant diagnostic test methodological criteria outlined in the Methods section for single NSBP test compared to SIC for the 39 studies which gave results for both disease positive and disease negative patients. The seventh validated criterion involves the use of a valid reference standard, and our research team considered SIC to be a valid reference standard for these OA studies. Single NSBP test was selected for evaluation from all other options because it was the most frequently reported comparison test.

Our conclusion that the quality of the studies did not impact the results in the review is based on our observation that the distribution of efficiency did not markedly differ depending on any specific quality maker. We also considered sensitivity and specificity alone and reached the same conclusion.

Figure G-1. Distribution of efficiency of tests comparing NSBP test to SIC by diagnostic study quality criteria



Appendix H: Sensitivity and Specificity of Comparison Tests that Used SIC as a Reference Standard

Table H-1: High molecular weight asthmagens
Table H-2: Low molecular weight asthmagens
Table H-3: Mixed/unknown asthmagens

Table H-1. High molecular weight asthmagens

Comparison Test	Number of Studies	Pooled Sensitivity (95% CI)		Pooled Specificity (95% CI)	
NSBP test	10	79.3	(67.7, 87.6)	51.3	(35.2, 67.2)
Specific skin prick test	16	80.6	(69.8, 88.1)	59.6	(41.7, 75.3)
Specific IgE	9	73.3	(63.9, 81.0)	79.0	(50.5, 93.3)
NSBP test combined with					
Specific skin prick test	4	60.6	(21.0, 89.9)	82.5	(54.0, 95.0)
Specific IgE	2	35.6	(1.2, 96.1)	84.6	(48.2, 97.0)
Specific skin prick test and specific IgE	3	65.2	(6.7, 98.0)	74.3	(45.0, 91.0)
Specific skin prick test or specific IgE	3	60.4	(11.8, 94.5)	81.5	(47.8, 95.5)
Serial NSBP test	1	100	(34.2, 100)	100	(20.7, 100)
Clinical diagnosis	2	93.7	(69.3, 99.0)	32.3	(7.5, 73.8)

Table H-2. Low molecular weight asthmagens

Comparison Test	Number of Studies	Pooled Sensitivity (95% CI)		Pooled Specificity (95% CI)	
NSBP test	24	66.7	(58.4, 74.0)	63.9	(56.1, 71.0)
Specific skin prick test	5	72.9	(59.7, 83.0)	86.2	(77.4, 91.9)
Specific IgE	11	31.2	(22.9, 40.8)	88.9	(84.7, 92.1)
NSBP test combined with					
Specific skin prick test	1	100	(74.1, 100)	80.0	(49.0, 94.3)
Specific IgE	1	0	(0, 49.0)	100	(61.0, 100)
Serial NSBP test	2	67.5	(42.6, 85.3)	65.6	(41.1, 84.0)
Serial PFT (usually PEFR)	1	86.7	(59.5, 96.6)	90.0	(53.3, 98.6)
Clinical diagnosis	5	93.6	(85.0, 97.5)	68.9	(54.7, 80.3)

Table H-3. Mixed/Unknown Asthmagens

Comparison Test	Number of Studies	Pooled Sensitivity (95% CI)		Pooled Specificity (95% CI)	
NSBP test	5	83.7	(66.8, 92.9)	48.4	(25.9, 71.6)
Specific skin prick test	5	63.0	(41.5, 80.3)	59.2	(45.4, 71.7)
Specific IgE	2	85.1	(40.3, 98.0)	61.2	(7.0, 97.1)
Serial NSBP test	3	50.0	(35.5, 64.5)	66.8	(53.3, 78.0)
Serial PFT (usually PEFR)	5	63.6	(43.4, 79.9)	77.2	(66.5, 85.2)
Clinical diagnosis	2	95.1	(86.8, 98.3)	47.7	(26.7, 69.7)
Eosinophil counts	3	54.9	(23.7, 82.7)	72.3	(54.1, 85.3)

Abbreviations: CI = confidence interval; **NSBP** = non-specific bronchial provocation; **PFT** = pulmonary function test; **PEFR** = peak expiratory flow rate