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The 2004 Guidelines Development Group

See page 2.

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Our mission: *'Bringing employers and researchers together to produce research that will contribute to good employee health and performance at work'.*

BOHRF raises and deploys funds for occupational health research of practical value and practical guidelines based on evidence to reduce the enormous cost to employers and workers of work-related illnesses in the UK.

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C O N T E N T S

G U I D E L I N E D E V E L O P M E N T G R O U P S

2009 - 2010

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Dr A J Scott	British Occupational Health Research Foundation

Conflicts of interest: Professor Sherwood Burge co-developed OASYS, a computer based system to anlayse serial peak expiratory flow measurements.

P U R P O S E

The purpose of these guidelines is to help reduce:

- the incidence of occupational asthma by improved prevention, and
- the severity of individual cases of disease by earlier identification and better management.

S C O P E

The full guideline and associated clinical guidance leaflets are aimed at doctors and nurses working in:

- Occupational health
- Respiratory medicine
- Primary care

A further leaflet will provide practical guidance for action aimed at:

- Employers
- Health and safety professionals, safety representatives, and
- Workers at risk of developing occupational asthma

The guidelines focus on interventions that might be considered appropriate for clinicians and employers to implement and supplement other guidelines that are available for the clinical management of asthma.

The guidelines consist of:

- **Evidence statements** with ratings of the strength of evidence and associated references
- **Recommendations** with grades of the strength of evidence behind the recommendations
- **Good practice points** where evidence is lacking.

The guidelines do not intend to provide a list of the hundreds of agents known to cause occupational asthma. Neither do they discuss non-occupational asthma except insofar as reviewing the evidence as to whether pre-existing disease is a risk factor for developing occupational asthma.

Clinicians, employers and workers need to exercise their judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines, taking into account individual circumstances and patients' wishes. Clinical judgement is necessary when using evidence statements to guide decision-making. Limited recommendations on a particular issue or effect do not necessarily mean that it is untrue or unimportant but may simply reflect insufficient evidence.

It is not intended, nor should it be taken to imply, that these guidelines override existing legal obligations. Duties under the UK Health and Safety at Work Act 1974, the Management of Health and Safety at Work Regulations 1999, the Control of Substances Hazardous to Health Regulations 2002, the Disability Discrimination Act 1995 and 2005 and other relevant legislation and guidance must be given due consideration, as should laws relevant to other countries.

E X E C U T I V E S U M M A R Y

These guidelines are intended to help reduce the incidence of occupational asthma. They aim to provide managers, workers and safety and health professionals with evidence based guidance related to the prevention, identification and management of cases.

This systematic review updates the first edition of these guidelines which reviewed the evidence published up to the end of June 2004; extending the systematic review of the evidence to the end of September 2009. The scope was expanded to include two newer diagnostic tests; sputum eosinophilia and exhaled nitric oxide; and explores delays to diagnosis. It includes an additional 90 studies.

Asthma is a condition of chronic inflammation of the airways, characterised by widespread airflow limitation that is reversible, either spontaneously or with treatment over short periods of time. Inflammation results in hyper-responsiveness of the airways to many stimuli e.g. cold air, cigarette smoke, exercise and in the hospital clinic setting to methacholine and histamine. Symptoms include wheeze, cough, shortness of breath and chest tightness often worse at night or in the early morning. Asthma is common, affecting people of all ages. Adult asthma may be a continuation of childhood asthma, reactivation of quiescent childhood asthma or new-onset asthma.

Asthma is "work-related" when there is an association between symptoms and work. The different types of work-related asthma should be distinguished, since the implications to the worker and the occupational health management of the disease differ. *Work-related asthma* includes two distinct categories:

- *work aggravated asthma*, i.e. pre-existing or coincidental new onset adult asthma which is made worse by non-specific factors in the workplace e.g. cold, dry air, dust and fumes
- *occupational asthma* i.e. asthma induced by exposure in the working environment to airborne dusts, vapours or fumes, in workers with or without pre-existing asthma[1].

Occupational asthma can be subdivided into:

- *sensitiser-induced occupational asthma* characterised by a latency period between first exposure to a respiratory sensitiser at work and the development of immunologically-mediated symptoms
- *irritant-induced occupational asthma* that occurs typically within a few hours of a high concentration exposure to an irritant gas, fume or vapour at work.

Substances that induce asthma through an allergic mechanism can be divided into high (HMW) and low molecular weight (LMW) agents. HMW agents are usually proteins and appear to act through a type I, IgE associated hypersensitivity. Whilst some LMW chemicals are associated with the development of specific IgE antibodies, the pathophysiological mechanism for the majority of cases of asthma attributable to LMW chemicals is unclear. For some agents both immunological and non-immunological mecanisms may be involved.

Occupational factors account for about 1 in 6 cases of asthma in adults of working age. Almost 90% of cases of occupational asthma are of the allergic type[2-6] making it the focus of this evidence review. The term *occupational asthma* is used throughout the guidelines to refer to *sensitiser-induced occupational asthma*.

That only a proportion of workers develop occupational asthma despite similar exposures, suggests an underlying genetic susceptibility to occupational asthma. Studies, mostly based on small sample size, have examined the role of genes coding for susceptibility to occupational asthma attributed to various agents. While we reviewed such studies for the 2004 guidelines, risk information as a result of genetic testing is poorly understood and the use of genetic tests in the practice of occupational medicine is unlikely to be ethically justifiable. Therefore we removed discussion of genetic factors from this review.

The level of exposure to a causative agent at work is the major determinant of risk for the development of occupational asthma. A direct relationship between occupational asthma and sensitiser exposure at work has

been demonstrated for many agents, with studies also demonstrating a positive exposure-response relationship for sensitisation. Reducing airborne exposure reduces the incidence of new sensitisations and/or cases of occupational asthma and should be the focus of prevention. The use of respiratory protective equipment is less effective and does not completely prevent occupational asthma.

Personal risk factors include atopy and smoking. Atopy increases the risk of developing occupational asthma caused by exposure to many high molecular weight agents. Cigarette smoking can increase the risk of developing occupational asthma to some sensitising agents. The positive predictive values of these screening criteria are too poorly discriminating for screening out susceptible individuals from employment, particularly in the case of atopy where the trait is highly prevalent in the general population.

It is difficult to dissociate the effects of health surveillance from the effects of other risk management procedures; however, health surveillance can detect occupational asthma at an earlier stage of disease. There is limited evidence that outcome is improved in workers who are included in a health surveillance programme. There is no body of evidence to determine the essential components of a health surveillance programme, although what evidence there is indicates that spirometry detects few cases of occupational asthma that would not otherwise be detected by respiratory questionnaire.

Occupational asthma should be considered in all workers with symptoms of airflow limitation. The diagnosis is an iterative process. Clinicians who assess working adults with asthma need to ask the patient about their job and the materials they work with in order to initiate timely investigations and referral. They should ask whether symptoms improve on days away from work. This is more sensitive than asking whether symptoms are worse at work, as many symptoms deteriorate in the hours after work or during sleep. The sensitivity and specificity of peak expiratory flow records for the diagnosis of occupational asthma depends on the numbers of working weeks, consecutive days at work and readings taken per day Depending on the quality of recorded series, the sensitivity and specificity of serial peak flow measurements can be high in the diagnosis of occupational asthma. Clinicians who suspect a worker of having occupational asthma should arrange for serial peak flow measurements.

Generally, occupational asthma has a poor prognosis, with about 1/3 of workers achieving symptomatic recovery and about 3/4 having persistent non-specific bronchial hyper-reponsiveness. Early diagnosis and early avoidance of further exposure offer the best chance of complete recovery. Workers who remain in the same job and continue to be exposed to the same agent after diagnosis are unlikely to improve and may worsen. Once sensitised, a worker's symptoms may be incited by exposure to extremely low concentrations of a respiratory sensitiser. Respiratory protective equipment is effective only insofar as it is worn when appropriate, that there is a good fit on the face and proper procedures are followed for removal, storage and maintenance. Consequently, air fed helmet respirators may improve or prevent symptoms in some but not all workers who continue to be exposed to the causative agent.

There is consistent evidence that about 1/3 of workers with occupational asthma are unemployed after diagnosis and that loss of employment following a diagnosis of occupational asthma is associated with loss of income. There is a clear need to identify workers who develop occupational asthma at an early stage and yet significant diagnostic delay occurs. Patients typically experience unnecessarily lengthy delays waiting for specialist assessment following presentation in primary care.

1. Francis HC, Prys-Picard CO, Fishwick D, et al. Defining and investigating occupational asthma: a consensus approach. *Occup Environ Med*, 2007; 64: 361-5.
2. Ameille J, Pauli G, Calastreng-Crinquand A, et al. Reported incidence of occupational asthma in France, 1996-99. The ONAP programme. *Occup Environ Med*, 2003; 60: 136-141.
3. Chatkin JM, Tarlo SM, Liss G, et al. The outcome of asthma related to irritant exposures: a comparison of irritant-induced asthma and irritant aggravation of asthma. *Chest,* 1999;116: 1780-1785.
4. Meyer JD, Holt DL, Cherry N, et al. SWORD 98: surveillance of work-related and occupational respiratory disease in the UK. *Occup Med (Lond),* 1999; 49: 485-9.
5. Hnizdo E, Esterhuizen TM, Rees D, et al. Occupational asthma as identified by the Surveillance of Work-related and Occupational Respiratory Diseases programme in South Africa. *Clin Exp Allergy*, 2001; 31: 32-9.
6. Provencher S, Labreche F, De Guire. Physician based surveillance for occupational respiratory diseases: the experience of PROPULSE, Quebec, Canada. *Occup Environ Med*, 1997; 54: 272-6.

KEY RECOMMENDATIONS FOR OCCUPATIONAL HEALTH MANAGEMENT

Employers and their health and safety personnel should:

1 be aware that the major determinant of risk for the development of occupational asthma is the level of exposure to its causes and should implement programmes to remove or reduce exposure to its causes. **** SIGN B**

*** SIGN 2++	The risk of sensitisation and occupational asthma is increased by higher exposures to many workplace agents.
** SIGN 2+	Reducing airborne exposure reduces the incidence of sensitisation and occupational asthma.

2 be aware that respiratory protective equipment does not completely prevent occupational asthma and ensure that when it is worn, the appropriate type is used and maintained, fit testing is performed and workers understand how to wear, remove and replace it. *** SIGN D**

* SIGN 3	The use of respiratory protective equipment reduces the incidence of, but does not completely prevent, occupational asthma.

3 inform workers about any causes of occupational asthma in the workplace and the need to report any relevant symptoms as soon as they develop. **** SIGN D**

** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to diagnosis.
** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have relatively normal lung function at the time of diagnosis.

4 provide workers at risk of occupational asthma with health surveillance at least annually and more frequently in the first years of exposure. **** SIGN D**

** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have relatively normal lung function at the time of diagnosis.
** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to diagnosis.
* SIGN 3	Health surveillance can detect occupational asthma at an earlier stage of disease and outcome is improved in workers who are included in a health surveillance programme.
** SIGN 2+	Sensitisation and occupational asthma are most likely to develop in the first years of exposure for workers exposed to enzymes, complex platinum salts, isocyanates and laboratory animal allergens.

Health practitioners should:

5 not use poorly discriminating factors - such as atopy, cigarette smoking or a family or personal history of asthma which may increase individual susceptibility to occupational asthma for some agents - as a reason to exclude individuals from employment. *** SIGN D**

* SIGN 3	The positive predictive values of screening criteria are too poorly discriminating for screening out potentially susceptible individuals, particularly in the case of atopy where the trait is highly prevalent.

6 enquire about pre-existing occupational asthma to agents that job candidates might be exposed to in their new job and advise affected candidates that they should not undertake this work, if exposure can not be adequately controlled. **** SIGN C**

** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have little or no further exposure to the causative agent.

7 provide more frequent health surveillance to workers who develop rhinitis when working with agents known to cause occupational asthma and ensure that the workplace and working practices are investigated to identify potential causes and implement corrective actions. **** SIGN D**

** SIGN 2+	Occupational rhinitis and occupational asthma frequently occur as co-morbid conditions.
** SIGN 2+	Rhinoconjunctivitis is more likely to appear before the onset of IgE associated occupational asthma.
*** SIGN 2++	The risk of developing occupational asthma is highest in the year after the onset of occupational rhinitis.

8 enquire of any adult patient with new, recurrent or deteriorating symptoms of rhinitis or asthma about their job, the materials with which they work and whether their symptoms improve regularly when away from work. ***** SIGN A**

*** SIGN 1++	Occupational factors are estimated to account for about 1 in 6 cases of asthma in adults of working age, including new onset or recurrent disease.
*** SIGN 2++	The workers most commonly reported to surveillance schemes of occupational asthma include animal handlers, bakers and pastry makers, chemical workers, food processing workers, hairdressers, paint sprayers, nurses and other health professionals, timber workers and welders.
** SIGN 2+	The workers reported from population studies to be at increased risk of developing asthma include bakers, chemical workers, cleaners, cooks, electrical and electronic production workers, farm workers, food processors, forestry workers, healthcare workers, laboratory technicians, mechanics, metal workers, painters, plastics and rubber workers, storage workers, textile workers, waiters, welders and wood workers.
*** SIGN 2++	The most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.
** SIGN 2+	In the clinical setting questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for the validation of occupational asthma.

9 confirm a diagnosis of occupational asthma by objective criteria (functional, immunological, or both) and not on the basis of a compatible history alone because of the potential implications for future employment. **** SIGN C**

** SIGN 2+	In the clinical setting questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday have a high sensitivity, but relatively low specificity for the validation of occupational asthma.
* SIGN 3	Free histories taken by experts have high sensitivity, but their specificity may be lower. These values may be affected by differences in language and populations.
** SIGN 2+	Approximately one third of workers with occupational asthma are unemployed up to 6 years after diagnosis.
** SIGN 2+	Workers with occupational asthma suffer financially.

10 arrange for workers who they suspect to have occupational asthma to perform serial peak flow measurements at least four times a day and for at least three weeks. **** SIGN D**

** SIGN 3	In specialist settings acceptable peak flow series can be obtained in around two thirds of those in whom a diagnosis of occupational asthma is being considered.
* SIGN 3	The diagnostic performance of serial peak flow measurements falls when fewer than four readings a day are made and records are shorter than three weeks.
** SIGN 3	There is high level of agreement between expert interpretations of serial peak flow records.
** SIGN 3	Depending on the quality of the recorded series, the sensitivity and specificity of serial peak flow measurements are high in the diagnosis of occupational asthma.

Employers, their health and safety personnel and health practitioners should:

11 take measures to protect workers diagnosed as having occupational asthma from further exposure to its cause in the workplace. **** SIGN C**

** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who avoid further exposure to the causative agent.
** SIGN 2+	The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to removal from exposure.
* SIGN 3	Redeployment to a low exposure area may lead to improvement or resolution of symptoms or prevent deterioration in some workers, but is not always effective.
** SIGN 2+	Where clinical considerations permit, reduction of exposure may be a useful alternative associated with fewer socio-economic consequences to complete removal from exposure.

GOOD PRACTICE POINTS FOR OCCUPATIONAL HEALTH MANAGEMENT

1	**Health practitioners should assess whether performing skin prick or serological tests as part of the health surveillance of workers exposed to agents that cause IgE associated occupational asthma adds value to assessing the effectiveness of the control of exposure.**	☑
2	**Health practitioners should provide more frequent health surveillance to any workers who have pre-existing asthma to detect any evidence of deterioration.**	☑
3	**Employers and their health and safety personnel should assess exposure in the workplace and enquire of relevant symptoms among the workforce when any one employee develops confirmed occupational rhinitis or occupational asthma; and identify opportunities to institute remedial measures to protect other workers.**	☑
4	**Health practitioners who suspect a worker of having occupational asthma should make an early referral to a physician with expertise in occupational asthma.**	☑
5	**Physicians treating patients with occupational asthma should follow published clinical guidelines for the pharmacological management of patients with asthma in conjunction with recommendations to avoid exposure to the causative agent.**	☑

METHODOLOGY

Scoping questions

The scoping questions were developed by the Research Working Group of 2004 and reviewed by the two external reviewers and the BOHRF Research Committee.

Stakeholder Involvement

Members of the 2004 Research Working Group represented key stakeholder groups, including respiratory medicine, general practice, occupational health, patients, employers and workers at risk. The wide stakeholder group was not involved in the more confined task of updating of the evidence for the 2010 guidelines.

Systematic literature search

The Scientific Secretary performed the literature search of MEDLINE and EMBASE from 1966 and 1974 respectively for original scientific studies. For the first edition of the guidelines the literature was searched to the end of June 2004 using the search terms "occupational asthma" and "asthmagens" and relating to agents known to cause occupational asthma. For the 2010 evidence review the exercise was repeated for articles published from 2004 to the end of September 2009. The literature was searched using the search term "occupational asthma" for relevant articles published in English. The terms "work" AND "asthma" were avoided since experience from the first review confirmed that this was too sensitive and produced numerous irrelevant papers. More evidence emerged since the 2004 review relating to induced sputum and exhaled nitric oxide. The scope of the review was extended to include these investigations in the 2010 review and an additional specific search for relevant papers was performed retrospectively to 1966 for MEDLINE and 1974 for EMBASE.

Review of abstracts

At each review the Scientific Secretary sent abstracts to paired members of the Research Working Group for independent double-blind selection of studies that were thought to merit critical appraisal. Case reports were excluded, as were narrative reviews, except for citation tracking. The Scientific Secretary informed reviewers of the results of the double-blind screening. Reviewers discussed differences and agreed upon full papers to be requested for review, or a third reviewer was used where it was essential to expedite the process.

Critical appraisal of papers

The Scientific Secretary ordered full papers and sent them to paired members of the Research Working Group for independent double-blind critical appraisal and grading of the strength of the evidence depending on the likelihood of bias and confounding. Studies were graded according to by the revised Scottish Intercollegiate Guidelines Network (SIGN) grading system (2000), see Appendix 1. The Scientific Secretary informed reviewers of their paired reviewer and shared the results of the independent critical appraisal. Where reviewers disagreed about the score of the paper or its relevance, they discussed it to reach resolution. Where resolution was not achieved, a third reviewer was involved.

Case reports and narrative reviews were excluded. Other reasons to reject studies included:

- Papers did not address the scoping questions for this project
- Duplicate publication
- Papers were superseded by more recent studies that incorporated the same data
- Studies based on the same cohort
- Studies did not control for bias or confounding

Constructing the evidence tables

The Scientific Secretary entered the scores and summaries for accepted papers provided by the reviewers into evidence tables. These tables were reviewed in order to formulate evidence statements and recommendations. The number of published studies at each stage of the two reviews was as follows:

	To end Jun 2004	Jul 2004 to end Sep 2010
No. of abstracts screened	> 2,500	996
	⇩	⇩
No. of papers critically appraised	474	164
	⇩	⇩
No of papers contributing to the evidence	223	90

Evidence statements

The evidence tables were reviewed to formulate evidence statements. An explicit link was made to the most comprehensive and most recent source supporting the evidence for each evidence statement. Where possible this was to a systematic review, which included all earlier original studies in that area. Direct reference to original studies was made where there was no systematic review, where they were not included in the original review(s), or where they were necessary to support an important point.

Criteria for grading evidence and recommendations commonly regard randomised controlled trials as providing the highest level of evidence. However, such hierarchies are designed principally to guide inferences about the effects of treatment. Since randomised controlled trials do not apply in many areas of occupational medicine e.g. health surveillance, susceptibility to disease or the sensitivity and specificity of screening and diagnostic procedures, there is scarce level 1 evidence as defined by the SIGN grading system. To overcome this limitation we graded the strength of each evidence statement using both the SIGN system (Table 1) and the Royal College of General Practitioners (RCGP) 3 star system modified in 2008 by the Swedish Council on Technology Assessment in Health Care report for scientific studies (Table 2).

Key recommendations

The evidence statements were reviewed to determine key recommendations which were written in precise, behaviourally specific terms. Each recommendation was graded using both the revised SIGN grading system (Table 3) and the modified RCGP 3 star system (Table 2) and linked to the supporting evidence statements. As with NICE guidelines, papers with a 'minus' grade (indicating a high level of bias or confounding) or grade 3 or 4 were only used as a basis for a recommendation where there was a lack of stronger evidence.

Good practice points

The guidelines include good practice points where there is no, and nor is there likely to be, research evidence. They are based on the clinical experience of the research-working group, legal requirement or other consensus and are indicated in the guideline as ☑.

External review

Both the 2004 evidence review and the 2010 evidence review were reviewed independently by external reviewers.

Levels and grades of evidence and recommendations

1++	High quality meta analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1-	Meta analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Table 1: Scottish Intercollegiate Guidelines Network (SIGN) levels of evidence

Evidence grade		Definition
***	Strong	The conclusion is supported by at least two independent studies with high quality, or a good systematic review
**	Moderate	The conclusion is supported by one study with high quality, and at least two studies with medium quality
*	Limited	The conclusion is corroborated by at least two studies with medium quality
	Insufficient	No conclusions can be drawn when there are no studies that meet the criteria for quality
	Contradictory	No conclusions can be drawn when there are studies of the same quality whose finding contradict one another

Table 2: Royal College of General Practitioners (RCGP) 3 star system

High quality scientific studies were taken to be major epidemiological surveys and prospective cohort studies. Medium quality studies included retrospective, cross-sectional or uncontrolled cohort studies and case series.

A	At least one meta analysis, systematic review, or randomised controlled trial rated as 1++, and directly applicable to the target population; or a systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Table 3: Scottish Intercollegiate Guidelines Network (SIGN) grades of recommendation

A Background

Occupational asthma is the most frequently reported occupational respiratory disease in westernised industrialised populations (Elder 2004, Kor 2001, McDonald 2000, Provencher 1997). In countries such as South Africa and the Czech Republic, where mining is common, occupational asthma is the second most prevalent occupational respiratory disorder after pneumoconiosis (Brhel 2003, Hnizdo 2001).

What is the incidence of occupational asthma?

The prevalence of occupational asthma has not been well defined, due partly to inconsistent definitions, diagnostic criteria and variable work settings as well as limited surveillance data. More statistics are available relating to incidence, principally from surveillance schemes. Occupations within which people are likely to work in small enterprises or to be self-employed, and who do not have access to occupational health services and are not referred for specialist opinion, are likely to be under-reported to some schemes. There are no complete registries for reporting occupational diseases such as occupational asthma and the true frequency of the disease is not known. Reports may not differentiate between the various types of work-related asthma. Published frequencies come from surveillance schemes, compensation registries or from epidemiological studies of the relationship between asthma and occupation. Incidence rates of both work-related and occupational asthma vary between countries depending on the methodology of data collection, definition of cases and the predominant work sectors and occupations. A systematic review of 43 risk estimates from 19 countries estimated an attributable risk of 9% or, from the 12 highest quality studies, 15% (Blanc 1999). Another review of 21 studies similarly suggested an attributable risk of 15% (Balmes 2003); and a subsequent systematic analysis yielded an estimate of 16.9% (Toren 2009).

A1 *** SIGN 1++ Occupational factors are estimated to account for about 1 in 6 cases of asthma in adults of working age, including new onset or recurrent disease.

(Balmes 2003, Blanc 1999, Toren 2009)

A2 *** SIGN 2++ The annual population incidence of occupational or work-related related asthma ranges from an estimated 12 to 300 cases per million workers.

(Ameille 2003, Bakerly 2008, Blanc 1999, Elder 2004, Karjalainen 2000, Kogevinas 2007, McDonald 2005, Meredith 1991, Orriols 2005)

In Spain, the frequency of occupational respiratory diseases recorded by a voluntary surveillance system was four times higher than that reported by the compulsory official system (Orriols 2005). In a small UK study of general practice records four out of seven cases of occupational asthma were diagnosed by GPs without evidence of referral to an occupational physician or specialist, suggesting under-reporting to the UK voluntary scheme (de Bono1999).

A3 * SIGN 2+ The incidence of occupational asthma identified by reporting schemes may be significantly underestimated.

(de Bono 1999, Orriols 2005)

Which agents cause occupational asthma and which workers are at risk?

Several hundred agents have been reported to cause occupational asthma and new causes are reported regularly in the medical literature. The predominant causative agents and the jobs most commonly reported to incur high risk reflect variations of economic activity both between and within different countries, methods of data

collection - surveillance schemes and population studies - occupational classifications of workers and different perceptions of whether asthma is occupational or not.

A4 *** SIGN 2++ Overall, the most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes, adhesives, metals, resins and wood dust.

(Ameille 2003, Bakerly 2008, Brhel 2003, Elder 2004, Gannon 1993a, Hnizdo 2001, McDonald 2000, McDonald 2005, Meredith 1991, Meyer 1999, Orriols 2005, Sallie 1994, Toren 1999)

A5 *** SIGN 2++ The workers most commonly reported to surveillance schemes of occupational asthma include animal handlers, bakers and pastry makers, chemical workers, food processing workers, hairdressers, paint sprayers, nurses and other health professionals, timber workers and welders.

(Ameille 2003, Bakerly 2008, Brhel 2003, Gannon 1993a, Karjalainen 2002, McDonald 2000, Meredith 1991, Meyer 1999, Reijula 1996, Sallie 1994)

A6 ** SIGN 2+ The workers reported from population studies to be at increased risk of developing asthma include bakers, chemical workers, cleaners, cooks, electrical and electronic production workers, farm workers, food processors, forestry workers, healthcare workers, laboratory technicians, mechanics, metal workers, painters, plastics and rubber workers, storage workers, textile workers, waiters, welders and wood workers.

(Jaakkola 2003, Johnson 2000, Kogevinas 2007, Krstev 2007, Li 2008)

When are symptoms of occupational asthma most likely to develop?

The latent interval between first exposure and the onset of recognisable symptoms can vary depending on the agent, the management of exposure and biological variability. Whilst the latent interval can extend to many years (Bar-Sela 1984, Cortona 2001, Hannu 2007, Kim 1999, Moscato 2005, Munoz 2003, Smith 2005), the risk of occupational asthma appears to be highest in the first few years of exposure to laboratory animal allergens (Agrup 1986, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Krakowiak 1997, Platts-Mills 1987), isocyanates (Tarlo 1997a, Venables 1985b), platinum salts (Calverley 1995, Niezborala 1996, Venables 1989a) and azodicarbonamide (Slovak 1981).

A7 ** SIGN 2+ Sensitisation and occupational asthma are most likely to develop in the first years of exposure for workers exposed to enzymes, complex platinum salts, isocyanates and laboratory animal allergens.

(Agrup 1986, Calverley 1995, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Gautrin 2008, Johnsen 1997, Krakowiak 1997, Niezborala 1996, Platts-Mills 1987, Slovak 1981, Tarlo 1997a, Venables 1989a).

What are the risk factors for developing occupational asthma?

Most studies of risk factors for occupational asthma are of cross-sectional design. Where a disease is clearly attributable to exposures at work it is likely to result in differential assortment of employees with or without disease both within and out of an occupation or workplace. Cross-sectional analyses of a current workforce may reflect the resulting survivor effects; moreover they are generally incapable of distinguishing cause from effect. As a result, the absence of any perceptible effect of a putative risk factor may be a consequence more of study design, than of reality. There are few published studies of more robust cohort or case-referent study design. Furthermore there is likely to be considerable publication bias in this area. However, four risk factors have been identified for a number of agents including the predisposing factors of atopy and genetic predisposition, the causative factor of exposure to an agent at work and the contributing factor of cigarette smoking.

Very few studies have examined whether a history of asthma is an independent risk factor for the development of occupational asthma. A prospective study of laboratory animal handlers suggested that bronchial hyper-responsiveness (PC_{20} ≤32 versus PC_{20} >32mg/ml) was associated with an increased risk (relative risk=2.5) of probable occupational asthma (Gautrin 2001a). In a cross-sectional survey of animal workers, those with a previous history of asthma were more likely to develop animal-related asthma but this was not examined

independently of atopic status (Cockcroft 1981). There is insufficient evidence to state whether a previous history of asthma is or is not an independent risk factor for the development of occupational asthma.

Is exposure to agents in the workplace a risk factor for developing occupational asthma?

A direct relationship between occupational asthma and sensitiser exposure at work has been demonstrated with acid anhydrides (Grammer 1994, Liss 1993, Nielsen 2006), acrylates (Jaakkola 2007), cimetidine (Coutts 1984), colophony (Burge 1981), enzymes (Brant 2009, Cathcart 1997, Cullinan 2000, Juniper 1997, Vanhanen 1997, Weill 1971), green coffee and castor bean (Osterman 1982), bakery allergens (Brant 2005a, Brisman 2000, Cullinan 1994, Cullinan 2001, Heederik 2001, Houba 1998, Jacob 2008, Musk 1989), flower pollen (Akpinar-Elci 2004) seafood (fish, molluscs, crustacea) (Jeebhay 2008, Kalogeromitros 2006, McSharry 1994, Ortega 2001), isocyanates (Meredith 2000, Petsonk 2000, Pronk 2007, Tarlo 1997b), laboratory animal allergens (Cullinan 1999, Kruize 1997, Platts-Mills 1987), piperazine (Hagmar 1984), platinum salts (Calverley 1995) and western red cedar (Brooks 1981).

Most of these studies have also demonstrated a positive exposure-response relationship for sensitisation. Studies limited to sensitisation, rather than asthma, have demonstrated a relationship with exposure to acid anhydrides (Nielsen 2001), bakery enzymes (Brant 2005a, Houba 1996, Hur 2008, Nieuwenhuijsen 1999, Vanhanen 1997), laboratory animals (Heederik 1999) and platinum salts (Merget 2000).

A8 *** SIGN 2++ The risks of sensitisation and occupational asthma are increased by higher exposures to many workplace agents.

(Akpinar-Elci 2004, Brant 2005a, Brant 2009, Brisman 2000, Brooks 1981, Calverley 1995, Cathcart 1997, Coutts 1984, Cullinan 1994, Cullinan 1999, Cullinan 2000, Cullinan 2001, Grammer 1994, Hagmar 1984, Heederik 2001, Houba 1998, Hur 2008, Jacob 2008, Jeebhay 2008, Juniper 1977, Kalogeromitros 2006, Kruize 1997, Liss 1993, Musk 1989, Ortega 2001, Osterman 1982, McSharry 1994, Meredith 2000, Nielsen 2006, Platts-Mills 1987, Pronk 2007, Tarlo 1997b, Vanhanen 1997, Weill 1971)

Is atopy a risk factor for developing occupational asthma?

Atopy is a state characterised by the propensity to produce specific immunoglobulin IgE on ordinary exposure to common allergens in the subject's environment. Studies differ in their ascertainment of atopy ranging from those that use an immunological test such as skin prick testing to those that rely on a personal or family history of allergic disease (asthma, eczema or hayfever). This can cause inconsistencies between reported observations.

Atopy has been reported to increase the risk of occupational asthma in workers exposed to acid anhydrides (Nielsen 2006), detergent enzymes (Juniper 1984, Weill 1971, Zentner 1997), flower pollen (Akpinar-Elci 2004), isocyanates (Meredith 2000, Ucgun 1998) laboratory and other animals (Agrup 1986, Botham 1987, Cockcroft 1981, Cullinan 1999, Elliott 2005, Gautrin 2001a, Gautrin 2001b, Jeal 2003, Krakowiak 2007, Sjostedt 1989, Sjostedt 1993, Krakowiak 2002, Kruize 1997, Platts-Mills 1987, Venables 1988a), bakery allergens (Baur 1998a, De Zotti 1997, De Zotti 2000, Droste 2003, Houba 1998, Jacobs 2008, Skjold 2008, Talini 2002, Walusiak 2004), fish extracts (Jeebhay 2008) and some reactive dyes (Docker 1987).

Other studies have not demonstrated an association between atopy and occupational asthma due to exposure to cork (Winck 2004), isocyanates (Butcher 1977, Cullen 1996, Petsonk 2000), detergent enzymes (Cullinan 2000, Larsen 2007), glutaraldehyde (Di Stefano 1999), salmon (Douglas 1995), crab (Cartier 1984), hexahydrophthalic anhydride (Grammer 1996), platinum salts (Merget 2000, Venables 1989a) and plicatic acid in western red cedar (Chang-Yeung 1982).

As with exposure, some studies that examined asthma also examined specific sensitisation. Atopy has been associated with an increased risk of sensitisation in workers exposed to various enzymes (Cullinan 2001, Flood 1985, Greenberg 1970, Houba 1996, Juniper 1977, Larsen 2007, Newhouse 1970, Vanhanen 1997, Witmeur 1973, Zentner 1997), green coffee and castor bean (Osterman 1982, Romano 1995), bakery allergens (Baur 1998a, Cullinan 2001, De Zotti 1994, De Zotti 1997, Houba 1998, Heederik 2001, Hur 2008, Jacob 2008, Karkoulias 2007, Prichard 1984, Walusiak

2004), laboratory animals (Cullinan 1999, Jeal 2006), seafood (fish, molluscs, crustacea) (Cartier 1984, Jeebhay 2008, Kalogeromitros 2006, McSharry 1994) and acid anhyrides (Venables 1985a, Nielsen 2001).

A9 *** SIGN 2++ Atopy increases the risk of developing occupational asthma caused by exposure to many high molecular weight agents that induce the production of specific IgE antibodies.

(Agrup 1986, Akpinar-Elci 2004, Baur 1998a, Botham 1987, Cullinan 1999, De Zotti 1997, DeZotti 2000, Droste 2003, Gautrin 2001a, Gautrin 2001b, Jacob 2008, Jeal 2003, Jeebhay 2008, Juniper 1984, Krakowiak 2002, Krakowiak 2007, Kruize 1997, Platts-Mills 1987, Sjostedt 1989, Sjostedt 1993, Talini 2002, Venables 1988a, Walusiak 2004, 1988a, Weill 1971, Zentner 1997)

Is smoking a risk factor for developing occupational asthma?

Smoking has been identified to increase the risk of occupational asthma in workers exposed to: isocyanates (Cullen 1996, Meredith 2000, Ucgun 1998), platinum salts (Calverley 1995, Venables 1989a) and seafood (fish and crustacea) (Cartier 1984, Douglas 1995, Jeebhay 2008). One study demonstrated a dose-dependent effect (Venables 1989a).

Smoking has been identified to increase the risk of sensitisation in studies of exposure to platinum salts (Baker 1990, Merget 2000, Niezborala 1996), seafood (fish and prawn) (Jeebhay 2008, McSharry1994), flour (De Zotti 1994, Karkoulias 2007) and green coffee and castor bean (Osterman 1982, Romano 1995).

The role of cigarette smoking is unclear for asthma due to exposure to laboratory animals, acid anhydrides and enzymes. Some studies have shown an increased risk of laboratory animal asthma in smokers (Cullinan 1999, Krakowiak 1997, Venables 1988a), whereas others have not (Agrup 1986, Gautrin 2001a, Gautrin 2001b, Kruize 1997, Meijer 2002). For exposure to acid anhydrides, studies have demonstrated both negative (Grammer 1996, Liss 1993) and positive (Nielsen 2006, Venables 1985a) correlation with specific IgE or relevant symptoms. Similar conflicting evidence is available for detergent enzymes (Larsen 2007, Weill 1971). Whilst one study demonstrated an increased risk of sensitisation in bakery workers (DeZotti 1994), smoking does not appear to increase the risk of asthma in bakery workers (Baur 1998a, Cullinan 2001, De Zotti 1994, Houba 1998, Jacob 2008).

A10 ** SIGN 2+ Cigarette smoking can increase the risk of developing occupational asthma with some sensitising agents.

(Calverley 1995, Cartier 1984, Cullen 1996, Douglas 1995, Jeebhay 2008, Meredith 2000, Niezborala 1996, Ucgun 1998, Venables 1989a)

Is occupational rhinitis a risk factor for developing occupational asthma?

There is epidemiological evidence from the general population that rhinitis and asthma frequently occur together, possibly as clinical manifestations of a single disorder. Rates of co-morbid rhinitis or rhinoconjunctivitis of between 45% and 100% have been reported in subjects suffering from occupational asthma attributed to various agents including acid anhydrides, bakery allergens, green coffee and castor beans, isocyanates, laboratory animals, lasamide, persulfates, platinum salts, reactive dyes and snow crab (Cartier 1984, Cockcroft 1981, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Grammer 2002a, Gross 1980, Houba 1998, Klusackova 2007, Krakowiak 1997, Moscato 2005, Park 1989, Romano 1995, Tarlo 1997a, Venables 1988a, Venables 1989a, Walusiak 2004, Wernfors 1986). The intensity of nasal symptoms appears to be significantly more pronounced in the case of HMW agents (Malo 1997).

Occupational rhinitis is purported to be a risk factor for the development of occupational asthma, especially for high molecular weight sensitisers (Castano 2009, Karjalainen 2003). One population study reported that occupational rhinitis (defined as work-related symptoms, specific sensitisation to a work substance, positive nasal challenge and exclusion of other causes) carried a crude relative risk of asthma of 4.8 (Karjalainen 2003). The relative risk was highest among farmers and wood workers and the greatest risk of asthma was in the year after rhinitis was reported. A surveillance programme of workers exposed to laboratory animals found that the

probability of experiencing asthma symptoms by the 11th year of follow-up was 36.7% for workers with animal-related rhinoconjunctivitis symptoms and 5.2% for those without allergy symptoms (Elliott 2005).

While in one study symptoms of asthma and rhinitis developed concurrently in all cases (Krakowiak 1997) in others occupational rhinitis preceded occupational asthma in 20% to 75% of subjects (Cortona 2001, Grammer 2002a, Gross 1980, Moscato 2005, Munoz 2003, Storaas 2005, Walusiak 2004). There is some evidence that symptoms of occupational rhinitis are more likely to precede occupational asthma in the case of IgE-associated occupational asthma (Cortona 2001, Malo 1997, Nielsen 2006).

A11 ** SIGN 2+ Occupational rhinitis and occupational asthma frequently occur as co-morbid conditions.

(Cartier 1984, Castano 2009, Cortona 2001, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Grammer 2002a, Gross 1980, Houba 1998, Klusackova 2007, Malo 1997, Moscato 2005, Romano 1995, Venables 1988a, Venables 1989a, Walusiak 2004, Wernfors 1986)

A12 ** SIGN 2+ Rhinoconjunctivitis may precede or coincide with the onset of occupational asthma.

(Cortona 2001, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Grammer 2002a, Gross 1980, Karjalainen 2003, Krakowiak 1997, Malo 1997, Skjold 2008, Storaas 2005, Walusiak 2004)

A13 *** SIGN 2++ The risk of developing occupational asthma is highest in the year after the onset of occupational rhinitis.

(Cortona 2001, Gautrin 2001b, Grammer 2002a, Gross 1980, Karjalainen 2003, Kim 1999, Nielsen 2006, Skjold 2008)

B Prevention of occupational asthma

Primary prevention aims to avert the onset of disease. Secondary prevention aims to detect disease at an early or pre-symptomatic stage for example by health surveillance. Tertiary prevention aims to mitigate the effects of established disease and is considered later under the management of an identified case of occupational asthma. The most effective measure is primary prevention of exposure either by substituting the agent with a less harmful material or by engineering and hygiene measures. Respiratory protective equipment has a role in situations where control at source is not feasible. With any reported study of preventive measures, it is difficult to distinguish the relative effect of one measure against another, since they are usually implemented as a broad programme with many components including, for example, exposure reductions, health surveillance and worker education and training.

Is the incidence of occupational asthma reduced by controlling exposure?

There is extensive evidence of a direct relationship between occupational asthma and exposure to airborne allergens (page 14). Further studies have explored the effect of reducing exposure on the incidence of occupational asthma. That reduced exposure leads to fewer cases of sensitisation and occupational asthma has been demonstrated with acid anhydrides (Drexler 1999, Liss 1993), detergent enzymes (Cathcart 1997, Juniper 1977), laboratory animals (Botham 1987, Fisher 1998) and latex (Allmers 2002, Levy 1999, Saary 2002, Tarlo 2001, Vandenplas 2009).

B1 ** SIGN 2+ Reducing airborne exposure reduces the number of workers who become sensitised and who develop occupational asthma.

(Allmers 2002, Botham 1987, Cathcart 1997, Drexler 1999, Fisher 1998, Juniper 1977, Levy 1999, Liss 1993, Saary 2002, Tarlo 2001, Vandenplas 2009)

Is the incidence of occupational asthma reduced by respiratory protective equipment?

Respiratory protective equipment can only offer protection when it is worn properly, removed safely and either replaced or maintained regularly. Brief periods of respirator removal might permit a transient, yet sufficiently high exposure to sensitise a worker and lead to subsequent development of asthma. Studies in this area are few and small. One observed a significant association between asthma symptoms and even brief removal of respiratory protective equipment (Petsonk 2000). Another study demonstrated that respiratory protection was associated with a reduction in the incidence of newly diagnosed occupational asthma but did not prevent the disease altogether (Grammer 2002b).

B2 * SIGN 3 The use of respiratory protective equipment reduces the incidence of, but does not completely prevent, occupational asthma.

(Cullen 1996, Grammer 2002b, Petsonk 2000)

Do pre-placement examinations prevent occupational asthma?

Pre-placement examinations should be used to establish a baseline for periodic health surveillance rather than to detect and exclude susceptible individuals from high-risk workplaces. Little is known about host susceptibility factors, with the exception of atopy in those exposed predominantly to high molecular weight agents. The efficiency of screening out susceptible job applicants depends, in part, on the frequency of the trait in the general population. Risk markers such as atopy, smoking and genetic predisposition lack sufficient sensitivity and specificity to be used to screen out job applicants.

B3 * SIGN 3 The positive predictive values of screening criteria are too poorly discriminating for screening out potentially susceptible individuals, particularly in the case of atopy where the trait is highly prevalent.

(Cockcroft 1981, De Zotti 2000, Juniper 1984, Newill 1986, Niezborala 1996, Platts-Mills 1987, Renstrom 1994, Slovak 1981, Venables 1988b)

It is noted later (page 26) that the likelihood of improvement or resolution of symptoms of occupational asthma is greater in workers who avoid further exposure to the causative agent. By extrapolation, workers who already suffer from occupational asthma are at risk from further exposure to the same causative agent, whether exposure is in the same workplace or elsewhere.

Does health surveillance prevent occupational asthma?

Periodic health surveillance for occupational asthma aims to identify sensitised workers or cases of asthma at early and reversible stages of disease. Very few, and no concurrent comparison studies have been reported of the efficacy of such surveillance. One study which compared a standard cross-sectional survey with routine surveillance suggests that health surveillance can underestimate the frequency of occupational asthma (Brant 2005b). A UK multi-centre hospital study where most cases (49/57) were not afforded annual health surveillance revealed a mean delay of four years between the onset of symptoms and a confirmed diagnosis (Fishwick 2007). This contrasts with a mean of nine months in those whose symptoms were detected at health surveillance and who attended for subsequent investigations (Mackie 2008). In a study of isocyanate workers in Canada regular health surveillance was linked to a mandatory programme of control of isocyanate exposure at work. Cases of isocyanate-induced asthma were diagnosed sooner after the onset of symptoms, had better lung function and a better outcome than asthma attributed to other workplace agents not subject to the control programme (Tarlo 2002). It is difficult to dissociate the effects of health surveillance from the effects of other risk management procedures and the study authors recognised that the improved outcome in the isocyanate workers might, at least in part, be attributable to the concomitant reduction in isocyanate exposure.

B4 * SIGN 3 Health surveillance can detect occupational asthma at an earlier stage of disease.

(Mackie 2008, Tarlo 2002)

B5 * SIGN 3 Outcome is improved in workers who are included in a health surveillance programme.

(Tarlo 2002)

Methods commonly used in surveillance to identify cases of occupational asthma are respiratory questionnaire, spirometry (to measure FEV1 and FVC) and, where appropriate, identification of specific IgE by skin prick test or serology. Few published reports have evaluated the components of surveillance used in occupational asthma.

There is no generally accepted questionnaire for use in surveillance for occupational asthma. Studies of the value of questionnaires to detect asthma suggest that they are insensitive (Brant 2005b, Gordon 1997, Stenton 1993).

B6 ** SIGN 2++ Screening questionnaires may lead to an underestimate of the prevalence of asthmatic symptoms.

(Brant 2005b, Gordon 1997, Stenton 1993)

Spirometry can identify many false positives due to poor technique (Kraw 1999) and no or few additional cases of asthma that are not identified by questionnaire (Bernstein 1993, Kraw 1999, Mackie 2008). In a health surveillance programme of motor vehicle repair workers no confirmed cases of occupational asthma were identified on the basis of abnormal spirometry alone (Mackie 2008).

B7 ** SIGN 2+ Spirometry detects few cases of occupational asthma that would not otherwise be detected by respiratory questionnaire.

(Bernstein 1993, Kraw 1999, Mackie 2008)

Skin prick tests and serological tests can detect specific IgE in workers who have become sensitised to high molecular weight allergens and a few low molecular weight chemicals (complex platinum salts, acid anhydrides and some reactive dyes). Since IgE sensitisation is related to exposure, measurement of sensitisation rates in working populations can be used as a measure of the effectiveness of the control of exposure. Higher rates of sensitisation in a workforce reflect poor control and an increased risk of occupational rhinitis and/or occupational asthma in workers.

B8 ** SIGN 2+ Skin prick testing or blood sampling of exposed workers to conduct immunological tests is feasible in the workplace.

(Flood 1985, Juniper 1977, Merget 1988, Redlich 2001, Vedal 1986)

B9 ** SIGN 2+ Prospective surveillance for the development of specific IgE antibodies can be used as part of a broader risk management programme to reduce the incidence of occupational asthma.

(Flood 1985, Juniper 1977)

C. Identification and evaluation of a case of occupational asthma in the worker presenting with respiratory symptoms

Occupational asthma should be considered in all workers with symptoms of airflow limitation. Much of the evidence relating to its diagnosis emanates from specialist settings where the prior probability of disease is high; positive predictive values of tests may be lower in other settings. The diagnosis of occupational asthma is an iterative process. Occupational asthma can be present when tests of lung function are normal, making these less useful in screening. Asthmatic symptoms improving away from work can be due to reasons other than occupational asthma, so further validation is needed. The diagnosis is made most easily before exposures or treatments are modified. While the optimal frequency and duration of serial measurement of peak expiratory flow has not been fully established, it is the most available initial investigation. The test does not differentiate occupational from work-exacerbated asthma (Chiry 2007).

Skin prick tests or blood tests for specific IgE are available for most high molecular weight agents, and a few low molecular weight agents but there are few standardised allergens commercially available which limits their use. A positive test denotes sensitisation, which can occur with or without disease. The diagnosis of occupational asthma can usually be made without specific bronchial provocation testing, considered to be a gold standard, but time-consuming diagnostic test. Specific provocation is particularly indicated when the precise cause of occupational asthma is unclear and this knowledge is needed for the management of the individual employee.

What is the sensitivity and specificity of respiratory questionnaires in the diagnosis of occupational asthma?

The presence of symptoms has high sensitivity but lower specificity. The question “have you been told by a doctor that you have asthma?” has a high specificity but low sensitivity (Schlunssen 2004). Asthma symptoms reported at questionnaire to be better on days away from work have a sensitivity of 58-100% for validated occupational asthma. The sensitivity was below 90% in two studies, one from Quebec (Malo 1991) and one international study including workers from Quebec (Vandenplas 2005); the sensitivity was 100% in one study of five latex-exposed nurses. The most common symptoms reported were wheeze and shortness of breath. The Quebec study showed some improvement in sensitivity (to 66%) when symptoms were reported to improve on holiday. Work-related asthma symptoms were common in those with negative specific challenge tests; the specificity of questionnaires ranges from 45-100%, in only one small study being over 70%.

C1 ** SIGN 2+ In the clinical setting questionnaires that identify symptoms of wheeze and/or shortness of breath which improve on days away from work or on holiday can have a high sensitivity, but relatively low specificity in the diagnosis of occupational asthma.

(Baur 1998b, Cote 1990, Malo 1991, Merget 1988, Vandenplas 1995a, Vandenplas 2001, Vandenplas 2005)

What are the sensitivity and the specificity of an expert medical history and examination in the diagnosis of occupational asthma?

There are fewer studies with expert medical histories than questionnaires. The symptoms of occupational asthma, aside from their work-relatedness, are indistinguishable from those of non-occupational asthma. Asking about deterioration at work was an insensitive method of making the diagnosis of occupational asthma (sensitivity 42% in one small study). Seasonal variation was more common in non-occupational asthma. Two experts from Quebec achieved sensitivities of 83% and 95%, substantially more than obtained by the same group from different patients by questionnaire.

C2 * SIGN 3 Free histories taken by experts have high sensitivity, but their specificity may be lower.

(Axon 1995, Baur 1998b, Koskela 2003, Malo 1991, Ricciardi 2003, Vandenplas 2001)

What are the sensitivity and the specificity of pre and post shift changes in lung function in the diagnosis of occupational asthma?

There is one study comparing across shift changes with specific challenge testing showing a sensitivity of 50% and specificity of 91% for dayshift workers (Park 2009). The results of such testing is confounded since measures of airflow obstruction, such as FEV1 or PEF, have a diurnal variation in most normal workers that is increased in most asthmatics. Furthermore, pre- and post-shift measurements are unhelpful in the case of workers who suffer delayed responses after leaving work or with those who have prolonged bronchoconstriction that extends into the next work shift.

C3 * SIGN 3 Pre to post shift changes in lung function can have high specificity, but have low sensitivity for the validation of occupational asthma.

(Burge 1979a, Burge 1979b, Park 2009)

What is the feasibility of obtaining serial measurements of peak flow in workers suspected of having occupational asthma?

Studies performed among patients attending specialist clinics and in workplace surveys in the context of research studies, showed that acceptable records were returned by over 70% of subjects. In a study assessing the quality of diagnostic procedures among patients referred to the Finnish Institute of Occupational Health with a suspicion of occupational asthma, the quality of serial PEF measurements was sufficient in 52% (Sauni 2009). Serial PEF measurements were performed significantly more often by occupational physicians (56%) and chest physicians (59%) compared to other health units (23%) (Sauni 2009).

C4 *** SIGN 2++ In specialist settings acceptable peak flow series can be obtained in around two thirds of those in whom a diagnosis of occupational asthma is being considered.

(Chiry 2007, Cote 1993, Eifan 2005, Girard 2004, Hannu 2007, Henneberger 1991, Hollander 1998, Huggins 2005, Leroyer 1998, Malo 1995, Minov 2007, Moore 2009a, Munoz 2004, Quirce 1995, Redlich 2001, Revsbech 1989, Sauni 2009)

What are the minimum criteria for serial measurements of peak flow to maintain a high degree of diagnostic accuracy?

Using expert opinion of plotted records, a case series of 74 patients attending a specialist clinic reported the highest combination of sensitivity and specificity with a measurement frequency of at least four readings a day (Malo 1993a). Less frequent readings produced a higher specificity but lower sensitivity. More frequent measurements over longer periods with good adherence to the test increase sensitivity. One study showed that minimum criteria for optimal sensitivity/specificity using computerised interpretation were at least four readings a day, at least three consecutive workdays in each work period and at least three complexes (about three weeks) (Anees 2004).

C5 * SIGN 3 The diagnostic performance of serial peak flow measurements falls when fewer than four readings a day are made and records are shorter than three weeks.

(Anees 2004, Malo 1993a)

Can experts agree on the interpretation of serial measurements of peak flow in the diagnosis of occupational asthma?

Most studies report high levels of agreement (averaging 80%) between expert assessors with kappa values of at least 0.6, exceptions being two series from Canada (Chiry 2007, Girard 2004). A single series, where non-expert assessors were used, reports a much lower level of inter-observer agreement. Three series report levels of intra-

observer agreement over two occasions. A high level of repeatability was reported in two. The third used non-expert assessors.

C6 * SIGN 3 There is moderate agreement between expert interpretations of serial peak flow records.

(Baldwin 2002, Leroyer 1998, Liss 1991, Malo 1996a, Malo 1993a, Perrin 1992, Zock 1998)

What are the sensitivity and specificity of serial measurements of peak flow in the diagnosis of occupational asthma?

A meta-analysis of five studies which examined ***both*** sensitivity and specificity of serial peak flow measurements compared to specific bronchial provocation testing as a reference standard provided pooled estimates of 63.6% and 77.2% respectively (Beach 2005). The authors of the meta-analysis additionally reported one study of workers exposed to a low molecular weight agent (86.7% sensitivity and 90% specificity), two studies reporting only sensitivity (pooled estimate 56.2%) and one study of exposure to a high molecular weight agent reporting only sensitivity (100%) that did not contribute to the pooled estimate. A further study in which 11 out of 20 patients underwent specific bronchial provocation testing reported higher sensitivities of 73-82% and specificities of 89-100% (LeRoyer 1998). Subsequent studies have produced broadly similar findings (Chiry 2007, Hannu 2007, Park 2009).

C7 *** SIGN 1++ Depending on the quality of recorded series, the sensitivity and specificity of serial peak flow measurements can be high for the diagnosis of occupational asthma

(Beach 2005, Chiry 2007, Hannu 2007, Leroyer 1998, Park 2009)

How well do computer-based analyses of peak flow assessment perform in the diagnosis of occupational asthma?

Just one computer-based method of analysis has been reported, mostly from one centre. Compared with a variety of independent diagnostic methods, sensitivities of 68-79% and specificities of 94-100% were reported (Bright 2001, Gannon 1996, Moore 2009a, Moore 2009b). Experience in Canada reported lower values in comparison to specific bronchial provocation tests; sensitivity 35% and specificity 65% (Girard 2004) and suggested that it did not help clinicians distinguish occupational from work-exacerbated asthma (Chiry 2007).

C8 * SIGN 3 Computer-based analyses of peak flow records may be helpful in the diagnosis of occupational asthma

(Gannon 1996, Baldwin 2002, Moore 2009a, Moore 2009b)

What are the sensitivity and the specificity of a single measurement of non-specific reactivity in the diagnosis of occupational asthma?

A meta-analysis provided pooled estimates of sensitivity and specificity of single measurements of non-specific bronchial reactivity compared to specific bronchial provocation testing as a reference standard (Beach 2005). Among the 37 studies that investigated patients exposed to low molecular weight agents, 24 reported both sensitivity and specificity. The pooled estimate of sensitivity was 66.7% (95% confidence interval [CI]: 58.4 to 74.0%) and of specificity was 63.9% (95% CI: 56.1 to 71.0%). Pooled estimates for studies that reported only sensitivity were higher (n=13; 76.6%; 95% CI: 59.0 to 88.2%). 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% (95% CI: 67.7 to 87.6%) and for specificity was 51.3% (95% CI: 35.2 to 67.2%). The estimated sensitivity in the five studies reporting only these data was similar (75.5%; 95% CI: 56.4 to 88.1%). Nine studies reported results for various suspected agents of differing molecular weights; five reporting both sensitivity and specificity. The pooled estimate of sensitivity was 83.7% (95% CI: 66.8 to 92.9%) and specificity was 48.4% (95% CI: 25.9 to

71.6%). Sensitivity was lower in the three studies reporting only this value (43.7%; 95% CI: 10.9 to 83.0%). Subsequent studies have produced broadly similar findings (Maghni 2004, Moscato 2005, Piirila 2008, Yacoub 2007).

C9 *** SIGN 1++ A single measurement of non-specific reactivity has only moderate specificity and sensitivity for the validation of occupational asthma.
(Beach 2005, Maghni 2004, Moscato 2005, Piirila 2008, Yacoub 2007)

What are the sensitivity and the specificity of changes in non-specific reactivity at work and away from work in the diagnosis of occupational asthma?

Three studies were identified where pre and post exposure measurements were attempted. One did not investigate workers further when the at-work reactivity was normal, limiting its interpretation. Using a 3.2 fold change in reactivity (the 95% confidence interval for between test reproducibility), one study found a sensitivity of 48% and a specificity of 64%. Reducing the required change to twofold increased the sensitivity to 67%, reducing specificity to 54%. A smaller study with 14 workers with occupational asthma showed a sensitivity of 62% and specificity of 78%. A further study of workers investigated by specific challenge in Canada showed similar differences in reactivity among challenge positive and challenge negative workers.

C10 * SIGN 3 Changes in non-specific reactivity at and away from work alone have only moderate sensitivity and specificity for diagnosis.
(Cote 1990, Girard 2004, Perrin 1992, Tarlo 1991)

What is the feasibility of obtaining paired measurements of non-specific reactivity at and away from work?

Several studies have shown that paired measurements of non-specific reactivity at and away from work are feasible. Paired measurements were possible in 27/54 workers in whom the tests were considered indicated in one study. In another study measurements were made in 194/204 apprentice welders.

C11 * SIGN 3 Paired measurements of non-specific reactivity may be achieved in the workplace.
(El-Zein 2003, Girard 2004. Tarlo 1991)

What are the sensitivities and the specificities of specific IgE testing in the diagnosis of validated cases of occupational asthma?

The respective sensitivities and specificities of the ability of skin prick or serological tests to detect specific IgE vary between allergens and depend on the setting of positive cut-offs. The sensitivities and specificities of serum specific IgE antibodies to low molecular weight agents depends on whether the antibodies have been properly characterized and the availability of appropriate hapten-conjugates. The presence of specific IgE confirms sensitisation, but alone does not confirm the presence of occupational asthma, nor necessarily its cause.

A meta-analysis provided pooled estimates of the sensitivities and specificities of specific skin prick tests and serum specific IgE compared to specific bronchial provocation tests (Beach 2005). For skin prick tests to low molecular weight agents, five studies reported both sensitivity and specificity, the pooled estimates being 73% and 86% respectively. Sensitivity was 52% in eleven studies reporting only this result. For high molecular weight agents, sixteen studies reported both sensitivity and specificity and ten studies reported only sensitivity, the pooled estimate of sensitivity was 81% and of specificity was 60%. For specific IgE, the pooled estimates of sensitivity and specificity were 31% and of 89% respectively for various low molecular weight agents based on eleven studies reporting both, and 36% sensitivity from ten studies reporting only sensitivity. Sensitivity was higher in studies where high molecular weight agents were examined; pooled estimates of sensitivity and specificity were 74% and of 79% respectively based on nine studies reporting both, and 82% sensitivity from nine studies reporting only sensitivity.

C12 *** SIGN1++ Both skin prick and serological tests are sensitive for detecting specific IgE and occupational asthma caused by most high molecular weight agents but are not specific for diagnosing asthma.

(Baur 2005a, Beach 2005, Jeal 2006, Platts-Mills 1987, van Kampen 2008)

C13 *** SIGN1++ Overall, both skin prick and serological tests are less sensitive for detecting specific IgE and occupational asthma caused by low molecular weight agents and while specificity may be higher they are not specific for diagnosing asthma.

(Baur 1995, Beach 2005, Grammer 1998, Park 1989, Pezzini 1984, Pronk 2007, Tee 1998)

What are the sensitivity and the specificity of specific bronchial provocation testing while at work, and after removal from work, in the diagnosis of occupational asthma

Specific provocation challenges are usually used as the gold standard for occupational asthma diagnosis making assessments of their diagnostic validity difficult. There is a lack of standardised methods for many occupational agents. There is evidence that the threshold exposure increases with time since last exposure, making the tests less sensitive after prolonged absence from work. There are individuals who have been shown to have non-specific reactions to specific challenges at concentrations likely to be found in the workplace and negative specific challenges in workers with otherwise good evidence of occupational asthma when challenge concentrations are confined to levels below occupational exposure standards.

(Baur 2005a, Burge 1979a, Burge 1979b, Cartier 1989, Girard 2004, Lin 1995, Moscato 1991, Munoz 2004, Rioux 2008)

C14 - SIGN 4 Carefully controlled specific challenges come closest to a gold standard test for some agents causing occupational asthma.

Newer diagnostic tests include assessments of airway inflammation by measuring exhaled nitric oxide eNO or counts of eosinophils and neutrophils performed on sputum induced by inhaling nebulised hypertonic saline.

What is the diagnostic value of measurement of exhaled nitric oxide?

The measurement of exhaled nitric oxide produced by inflammatory and epithelial cells in the respiratory tract, is non-invasive, and has been studied extensively in non-occupational asthma. It has not been fully validated as an effective diagnostic test for occupational asthma. Exhaled nitric oxide is increased in other inflammatory lung disorders; levels are lower in persons who smoke and in those who are using inhaled corticosteroids.

Most of the occupational studies have measured exhaled nitric oxide in relation to specific challenge testing. Some studies have demonstrated significant increases in exhaled nitric oxide some hours after positive specific challenge showing rhinitis or asthma (Baur 2005a, Baur 2005b, Barbinova 2006, Piipari 2002).

Exhaled nitric oxide measured before specific challenge has not been shown to predict the challenge result (Hewett 2008, Campbell 2007, Barbinova 2006, Baur 2005a, Piipari 2002). A few studies have measured exhaled nitric oxide in the workplace; and one used FeNO as a measure of exposure control in a group of farmers with occupational asthma (Dressel 2007, Dressel 2009).

C15 * SIGN 3 The role of exhaled nitric oxide measurements in the diagnosis of occupational asthma is not established

(Baur 2005a, Baur 2005b, Barbinova 2006, Piipari 2002)

C16 * SIGN 3 In the clinical setting a normal exhaled nitric oxide does not exclude a diagnosis of occupational asthma

(Baur 2005a, Baur 2005b, Barbinova 2006, Piipari 2002)

What is the diagnostic value of sputum eosinophilia in the diagnosis of validated cases of occupational asthma?

Eosinophilic bronchial inflammation can be assessed by cell counts in fresh sputum, induced by inhaling hypertonic saline. Most studies have investigated changes in sputum eosinophilia after specific challenge, increased levels being found in around 70% of positive challenges (Lemiere 2000, Lemiere 2001) and some negative challenges (Obata 1999). A meta-analysis provided pooled estimates for the sensitivity and specificity of eosinophilia, but included studies that measured eosinophil counts from sputum, blood, or broncho-alveolar lavage (Beach 2005). Studies have shown some workers with occupational asthma have normal levels of sputum eosinophilia prior to challenge (Lemiere 2001, Moscato 2005, Obata 1999, Yacoub 2007). An increase of 1% in sputum eosinophils related to occupational exposure has been suggested as a diagnostic method for occupational asthma (Girard 2004), with a retrospective sensitivity of 65% and specificity of 76%. Using a 2% cut-off the sensitivity was 52% and specificity 80%. Induced sputum has also been studied related to usual workplace exposure and the percentages of eosinophils increased in those with occupational asthma (Lemiere 1999).

C17 * SIGN 3 The measurement of sputum eosinophils may be helpful in the diagnosis of occupational asthma

(Alvarez 2001, Girard 2004, Krakowiak 2005, Lemiere 2001, Maestrelli 1994, Obata 1999)

C18 * SIGN 3 In the clinical setting the absence of sputum eosinophilia does not exclude a diagnosis of occupational asthma

(Anees 2002, Lemiere 2001, Moscato 2005, Obata 1999, Yacoub 2007)

D Management principles for the worker confirmed to have occupational asthma

The outcome of interventions made after a confirmed diagnosis of occupational asthma may depend on a number of factors, including the age of the worker at the time of diagnosis and the agent to which employees are exposed. Studies in this area are open to considerable bias through subject selection.

What is the prognosis of occupational asthma?

A meta-analysis of 39 studies (25 of low molecular weight agents, four of high molecular weight agents and 10 of various agents) reported outcomes after avoidance of exposure to the causative agent. Rates of complete symptomatic recovery varied between 0% and 100%, with a pooled estimate of 32% (Rachiotis 2006). The pooled prevalence of persistent non-specific bronchial hyper-reponsiveness was 73% (Rachiotis 2006). Other and subsequent studies suggest that, generally, occupational asthma has a poor prognosis and is likely to persist and deteriorate unless identified early and managed effectively (Brant 2006, Hannu 2007, Klusackova 2006, Klusackova 2007, Labrecque 2006, Leira 2005, Moller 1986, Park 2006, Piirila 2005, Piirila 2008, Park 2007, Pisati 2007, Tarlo 1995, Venables 1989b). Most of the data are derived from studies of clinic populations in whom outcomes may be poorer than is generally the case.

D1 *** SIGN 1++ The symptoms and functional impairment of occupational asthma may persist for many years after avoidance of further exposure to the causative agent.

(Rachiotis 2006)

Which factors increase the probability of a favourable prognosis after a diagnosis of occupational asthma?

Complete avoidance of exposure may or may not improve symptoms and bronchial hyper-responsiveness. Both the duration of continued exposure following the onset of symptoms and the severity of asthma at diagnosis may be important determinants of outcome. Early diagnosis and early avoidance of further exposure, either by relocation of the worker or substitution of the hazard offer the best chance of complete recovery. Workers who remain in the same job and continue to be exposed to the same causative agent after diagnosis are unlikely to improve and symptoms may worsen.

D2 *** SIGN 2++ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who avoid further exposure to the causative agent.

(Burge 1982, Chan-Yeung 1982, Gautrin 2008, Merget 1999, Moscato 1999, NHSPlus 2008, Park 2006, Pisati 1993, Rosenberg 1987, Tarlo 1997a, Valentino 1994, Vandenplas 1995b)

D3 ** SIGN 2+ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have relatively normal lung function at the time of diagnosis.

(Chan-Yeung 1982, Chan-Yeung 1987, Maghni 2004, Park 1997, Tarlo 1995, Padoan 2003, Rosenberg 1987)

D4 ** SIGN 2+ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to diagnosis.

(Chan-Yeung 1982, Descatha 2007, Park 1997, Piirila 2000, Pisati 1993, Tarlo 1995, Tarlo 1997a, Park 2006, Park 2007, Pisati 2007, Rosenberg 1987, Ross 1998)

D5 ** SIGN 2+ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who have shorter duration of symptoms prior to avoidance of exposure.

(Hudson 1985, Park 1997, Piirila 2000, Pisati 2007, Rosenberg 1987, Ross 1998, Tarlo 1997a)

What evidence is there for benefit of redeployment within the same workplace?

Ideally, complete and permanent avoidance of exposure is the mainstay of management. In practice, workers may reject this advice for social or financial reasons. In employees with latex-induced asthma, the use of powder-free, low protein latex gloves by colleagues reduces symptoms and indices of severity in the affected employee to a similar degree as the use of non-latex gloves by colleagues (NHS Plus 2008). Whether the employee remains in the same workplace with adjustments or is relocated to low or occasional exposure work areas, he or she should remain under increased medical surveillance. Where present, specific IgE levels can be monitored since these decline with cessation of exposure, although there are no studies relating this to outcome.

D6 * SIGN 3 Redeployment to a low exposure area may lead to improvement or resolution of symptoms or prevent deterioration in some workers, but is not always effective.
(Burge 1982, Douglas 1995, Grammer 1993, Grammer 2000, Merget 1999, Pisati 1993, Rosenberg 1987)

D7 ** SIGN 2+ Where clinical considerations permit, reduction of exposure may be a useful alternative associated with fewer socio-economic consequences to complete removal from exposure.
(NHS Plus 2008)

What evidence is there for the benefit of the enhanced use of respiratory protective equipment?

Once sensitised, a worker's symptoms may be incited by exposure to extremely low concentrations of a respiratory sensitiser. Respiratory protective equipment is effective only insofar as it is worn when appropriate, that there is a good fit on the face and proper procedures are followed for removal, storage and maintenance. The few studies that investigate the effectiveness of respiratory protective equipment are limited to small studies in provocation chambers or limited case reports. There are no large studies of long-term outcome.

D8 * SIGN 3 Air fed helmet respirators may improve or prevent symptoms in some but not all workers who continue to be exposed to the causative agent.
(Laoprasert 1998, Muller-Wening 1998, Obase 2000, Pisati 1993, Slovak 1985, Taivainen 1998)

What is the impact of occupational asthma on employment?

There is consistent evidence derived from clinical and workforce case series in a limited number of countries that about one third of workers with occupational asthma are unemployed after diagnosis. The risk may (Axon 1995, Goe 2004) or may not (Cannon 1995, Labarnois 2002) be higher than among other adult asthmatics although this has been examined in only three studies. The risk of unemployment may fall with increasing time after diagnosis (Ross 1998). There is consistent evidence that loss of employment following a diagnosis of occupational asthma is associated with loss of income. In comparison with other adult asthmatics those whose disease is related to work may find employment more difficult (Cannon 1995, Labarnois 2002) and their financial loss may be greater (Santos 2007). Those employees who are relocated to jobs without exposure to the causative agent are more likely to remain in employment and are unlikely to leave those jobs because of their asthma (Dimich-Ward 2007). In the case of health workers with occupational asthma from latex, reduction of exposure may be a reasonable, safe alternative to removal from exposure and is associated with fewer socioeconomic consequences (Vandenplas 2002).

D9 ** SIGN 2+ Approximately one third of workers with occupational asthma are unemployed up to six years after diagnosis.
(Ameille 1997, Axon 1995, Brant 2006, Cannon 1995, Gannon 1993b, Larbanois 2002, Marabini 1993, Ross 1998, Vandenplas 2002, Venables 1989b)

D10 ** SIGN 2+ Workers with occupational asthma suffer financially.
(Ameille 1997, Axon 1995, Bernstein 2003, Gannon 1993b, Larbanois 2002, Marabini 1993, Moscato 1999, Santos 2007, Vandenplas 2002)

What is the effectiveness of compensation being directed towards rehabilitation?

There are no studies that have made direct comparisons between different systems of rehabilitation either under different jurisdictions or within the same jurisdiction at different times.

D11 - SIGN 4 Systems that incorporate retraining may be more effective than those that do not.
(Ameille 1997, Malo 1993b, Piirila 2005)

What is the effect of inhaled corticosteroids on recovery from occupational asthma?

A single small randomised-controlled trial has examined the effect of inhaled corticosteroids on the recovery from occupational asthma after cessation of exposure. Small but statistically significant improvements in some symptoms, peak flow and quality of life were reported.

D12 * SIGN 1+ Inhaled corticosteroids used after cessation of exposure may provide specific clinical benefits to workers with occupational asthma.
(Malo 1996b)

What is the average time between the onset of symptoms and the diagnosis of occupational asthma?

In Italy among hairdressers, the mean duration of symptoms before diagnosis in an allergy centre was reported to be 1.5 years. Experience elsewhere reveals longer delays. A small case series in Spain revealed a mean delay of 38 months (range 3-120 months). In a study in Alberta, Canada the mean time to diagnosis was 4.9 years (3.4 years excluding four outliers). On average, patients waited 7.4 months before discussing the work-relation of symptoms with a physician. The main (self-reported) reasons for delay were lack of enquiry about work-relatedness by the general practitioner (41%) and fear of losing work time (37%). Reported increases in time during secondary care were related to difficulties associated with completion of investigations (35%). Lower education level ($p = 0.04$) and household income ($p = 0.03$) were significantly associated with an increased time to diagnosis (Poonai 2005). In a study in Ontario, the median time to a final diagnosis of occupational asthma after the onset of symptoms was four yrs (Santos 2007). Similarly a study in the UK revealed that patients experienced a mean delay for assessment in secondary care of four years (range 1-27 years) following presentation in primary care (Fishwick 2007). Conversely where patients in the UK have access to an occupational health service, the mean time from health surveillance to confirmed diagnosis among those who completed further investigations was nine months (range 6-12 months), although only 20% of surveillance failures completed investigation (Mackie 2008). In Finland where the median time from the beginning of symptoms to the final diagnosis was 3.2 years, time from the diagnosis of asthma to confirmation of an occupational cause accounted for half of the delay (Sauni 2009).

D13 ** SIGN 3 Lengthy diagnostic delay occurs for patients with occupational asthma
(Fishwick 2007, Moscato 2005, Munoz 2003, Poonai 2005, Santos 2007, Sauni 2009)

E V I D E N C E T A B L E S

ABBREVIATIONS

BHR = bronchial hyper-responsiveness	CI = confidence interval	FeNO = exhaled nitric oxide	HMW = high molecular weight	LAA = laboratory animal allergy
LMW = low molecular weight	OA = occupational asthma	OR = odds ratio	ORh = occupational rhinitis	PEF = peak expiratory flow
NSBR = non-specific bronchial hyper-reactivity	RAST = radioallergosorbent test	SIC = specific inhalation challenge	SPT = skin prick test	WRA = work-related asthma

EVIDENCE TABLE A

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Agrup et al	1986	49	Cross-sectional	2+	Of 19 people with LAA symptoms & +ve animal tests, 68% had a prior history of eczema, rhinitis or asthma or reacted to ≥1 standard allergens. Atopic features were present in 3/11 (27%) with LAAsymptoms & -ve animal RAST/SPTs. Of 30 with no LAA symptoms, 20% had a history of atopic disease &/or a +ve reaction to a standard test. Atopy was commoner among those with +ve tests to laboratory animal allergens. Smoking habits did not differ significantly. First symptoms appeared after a mean latent period of 2.3 years.
Akpinar et al	2004	128	Cross-sectional	2+	Excess risk of "WRA-like symptoms" among Turkish florists was associated with high work intensity (OR, 7.3; 95% CI, 1.1 to 51.8) & long work duration (OR, 5.1; 95% CI, 1.2 to 21.6). Florists with WRA-like symptoms were 5.9 times more likely (95% CI, 1.4 to 24.3) to have a +ve SPT response to flower mix allergen. Excess risk for "WRA-like symptoms" among those with allergic rhinitis (OR, 13.2; 95% CI, 3.1 to 56.4) & conjunctivitis (OR, 8.4; 95% CI, 2.4 to 29.2).
Allmers et al	2002	5101	Cross-sectional	2+	Study assesses the effects of intervention to reduce the incidence of natural rubber latex (NRL) allergy in healthcare workers by switching to powder-free NRL gloves. Education about NRL allergies in health care facilities combined with the introduction of powder-free gloves with reduced protein levels has been associated with a decline in the number of suspected cases of NRL allergies in Germany. Results indicate that primary prevention of occupational NRL allergies can be achieved if these interventions are properly carried out & maintained.
Ameille et al	2003	2178	Reporting scheme	2++	New cases of OA were collected by a national surveillance programme, based on voluntary reporting by occupational & chest physicians. In 1996-99 the mean annual rate of OA was 24/million. The most frequently incriminated agents were flour (20%), isocyanates (14%), latex (7%), aldehydes (6%), persulfate salts (6%), & wood dusts (4%). The highest risks of OA were found in bakers & pastry makers (683/million).
Baker et al	1990	136	Case control	2+	Study aimed to determine effects of platinum salt sensitisation among workers in a precious metals refinery. Platinum salts sensitisation was not associated with atopy as measured by sensitivity to common aeroallergens, but was strongly associated with cigarette smoking status. Cigarette smoking may be a risk factor for the development of platinum salts allergy.
Bakerly et al	2008	1461	Reporting scheme	2+	Annual incidence of OA was 42/million of working population (95% CI = 37-45). All cases fulfilled the criteria for hypersensitivity induced OA. OA was most frequently reported in welders (9%) & healthcare workers (9%). Isocyanates were the commonest offending agents responsible for 21% of reports followed by metal working fluids (MWFs) (11%), adhesives (7%), chrome (7%), latex (6%) & glutaraldehyde (6%). Flour was suspected in 5% of cases while laboratory animals in 1%. Professions most affected were welders, health professionals, moulders, vehicle spray painters, metal making & treating operatives, labourers & cleaners, bakers & flour confectioners, assemblers, metalworking operatives, woodworkers, chemical process operatives & food processors.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Balmes et al	2003	NA	Meta-analysis	1+	A review regarding the magnitude of the population attributable risk (PAR) for the occupational contribution of asthma. All articles published before January 2000 that included PAR% or presented data from which PAR% could be calculated were included in the review. 21 articles were identified in which PAR% due to occupational factors was either reported or data presented from which it could be calculated. The reported of calculated PAR% range from 4% to 58%, with a median value of 15%.
Bar-Sela et al	1984	44	Case-control	2+	16 poultry workers with ORh and/or OA were evaluated. 16 age & sex matched atopic subjects who were not occupationally exposed to poultry & 12 asymptomatic veterinarians with occupational exposure to poultry were controls. Rhinitis & asthma developed only in symptomatic poultry workers after exposure to poultry. The elapsed time between the initial poultry exposure & the onset of poultry house-related symptoms averaged 10 yr. The association between respiratory symptoms temporally related to poultry house exposure & the IgE antibody-mediated reaction suggests a relationship between the two.
Baur et al	1998a	193	Case series	3	Study evaluated the frequency of work-related symptoms & the clinical relevance of sensitisation to allergens in 89 bakers participating in a screening study & 104 bakers filing a claim for compensation. Most frequently, bakers with workplace-related respiratory symptoms showed sensitisation to wheat flour (64%), rye flour (52%), soybean flour (25%), & alpha-amylase (21%). The correlation between these sensitisations & asthma case history & SIC was significant. Approximately 29% of bakers with respiratory symptoms showed no sensitisation to bakery allergens & 32% of the sensitized bakers in the screening group had no work-related symptoms. Atopic status defined by SPT sensitisation to common allergens or elevated total IgE levels was found to be a risk factor for the development of sensitisation to bakery allergens & respiratory symptoms. However, there is evidence for an increased frequency of elevated total IgE as the result of occupational allergen exposure because respective findings were observed in bakers without symptoms.
Blanc et al	1999	-	Meta-analysis	1+	43 attributable risk estimates were obtained from 19 countries. Median value for attributable risk of OA was 9% & 15% when using studies of highest quality. Occupational factors are associated with about 1 in 10 cases of adult asthma, including new onset disease & reactivation of pre-existing asthma. The estimated incidence of OA varied widely among countries from a low of 1.2 to a high of 17.4/100,000 person-years. The highest rate was observed in Finland. The median incidence of OA is 4.7 cases/100,000 person-years. Assuming an incidence for all asthma among adults of working age of 100/100,000 person-years, the estimated median attributable risk is 5%.
Botham et al	1987	383	Cohort	2+	The pattern of incidence of LAA was studied prospectively in individuals occupationally exposed to rodents & to rabbits. The reduction in the incidence of the disease coincided with the introduction of a site order & code of practice for working with animals & an education programme designed to focus awareness on the problem.
Brant et al	2005a	239	Cross-sectional	2++	Cross-sectional survey of supermarket bakers. Symptoms & sensitisation related to exposure by job category & air measurements. Dust exposure GM 1.2mg/m^3 for bakers with questionnaire plus IgE diagnosed asthma in 9%; lower in less exposed. Only 25% of those with work-related chest symptoms had +ve IgE, more commonly with wheat than amylase.
Brant et al	2009	135	Case-referent	2++	New cases of respiratory disease were ascertained by examination of occupational health records & matched to referents. Personal exposures to airborne protease were estimated from >12 000 measurements. There were clear relationships between estimated protease exposure & both lower & upper respiratory disease. After control for age, sex & smoking, OR of lower respiratory disease was significantly elevated (1.98, 95% CI 1.04 to 3.79) in employees working in jobs in the highest quartile of protease exposure (geometric mean 7.9ng.m^{-3}). For employees with upper respiratory disease, risk was significantly elevated at a lower level of estimated protease exposure (geometric mean 2.3ng.m^{-3}). Highest annual incidence of chest disease was between 24-36 months after starting employment, 74% occurring in first 4 yrs. Median length of employment before the onset of symptoms was 31 months for chest symptoms & 37 months for eye/nose symptoms.
Brhel	2003	2127	Surveillance scheme	2+	Between 1996 & 2000 62.0% of new cases were pneumoconioses caused by dust containing free silica, 21.0% were OA or ORh & the rest were divided between lung cancer (10.0%), asbestos-related disorders (4.4%) & variety of other respiratory diseases (2.7%). Flours, animal epithelia & isocyanates have been identified as the main causes with bakers, food processors, farm workers, health care workers, textile workers, plastics processors, welders, paint sprayers & chemical processors being the main occupations at risk.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Brisman et al	2000	2923	Cohort	2+	Study of incidence rates of asthma & rhinitis in bakers. Risk of asthma seemed to be increased at inhalable dust concentrations during dough making or bread forming, whereas the risk of rhinitis was increased at lower concentrations indicating an increased risk in all bakery job-tasks. The risks seemed to be less dependent on the cumulative exposure dust than the inhalable dust concentrations at time of disease onset. Current exposure of > 3mg/m^3 was associated with an increased risk of asthma.
Brooks	1981	10	Cross-sectional	2++	Presumptive diagnosis of OA was diagnosed defined on physiologic & clinical criteria (observed decline in FEV1 > 10%) from the Monday pre-shift value compared to subsequent tests in 1 of the following 3 days exposure period & a +ve clinical history. A dose dependent relationship between western red cedar dust level & prevalence of OA was noted.
Burge et al	1981	88	Cross-sectional	2++	Prevalence of work-related wheeze & breathlessness was measured in factory employees manufacturing flux-cored solder containing colophony. Measurement of colophony in the breathing zone defined 3 grades of exposure. OA was present in 21% of the higher 2 exposure groups & 4% of the lowest exposure group. Mean values of FEV1 & FVC fell with increasing exposure. Total IgM levels were higher in the solder manufacturers than in unexposed controls.
Butcher et al	1977	166	Cohort	2+	Workers at a toluene-di-isocyanate (TDI) manufacturing plant were studied. Workers reporting increased lower respiratory symptoms were from the non-smoker group. Immunologic studies showed development of +ve SPT to a TDI-human serum albumin conjugate by some persons & an increasing incidence of TDI-specific IgE antibodies as measured by a RAST test. There was no correlation between +ve TDI SIC & total IgE concentration or atopic status.
Calverley et al	1995	78	Cohort	2+	Study aimed to measure the incidence of platinum salt sensitivity (PSS) in refinery workers & examine the influence of smoking & exposure to platinum salts or sensitisation. After 24 months, 32/78 (41%) subjects had been diagnosed with PSS, 22 of whom had +ve SPT whereas 10 were symptomatic but had -ve SPTs. +ve responses to platinum salt SPT had a 100% +ve predictive value for symptoms & signs of PSS if exposure continued. Risk of sensitisation was about eight times greater for smokers than non-smokers, & 6 times greater for high exposure than low exposure. Authors concluded that smoking & intensity of exposure were definitely associated with development of PSS.
Cartier et al	1984	303	Cohort	2++	Before the 1982 season, 303/313 employees in 2 snow crab-processing industries were investigated by questionnaire, SPTs with common allergens, crab & crab-boiling water extracts, & spirometry. Diagnosis was confirmed in 46 (15.6%) workers (including 33/64 subjects with a history highly suggestive of OA in the previous seasons) by SIC in 33 subjects and/or a combination of monitoring of PEF rates & significant changes in bronchial responsiveness to histamine as well as in spirometry after reappearance of symptoms on return to work. +ve SPTs to crab and, to a lesser degree, smoking history, but not atopy were related to the presence of OA. A high prevalence of rhinoconjunctivitis (35/46) & urticaria (16/46) was also documented in affected individuals.
Castano et al	2009	43	Case series	3	ORh often coexists with OA, & can be studied objectively during SIC. Rhinitis is rare in LMW group. Long duration of symptomatic exposure before challenge (mean >4 years). No data on timing of onset of rhinitis vs asthma. Additional finding; NSBR >16mg/ml in 39%.
Cathcart et al	1997	731	Cohort	2++	Workers from 5 locations in the UK were subject to respiratory health surveillance including lung function testing over a period of 4-20 years. Exposure groups were defined by job history. Significantly different rates of fall in FEV1 & FVC with time were found by geographical location & by smoking habit, but there were no consistent trends with enzyme exposure between plants.
Cockcroft et al	1981	213	Cross-sectional	2++	An association significant at the 2% level was found between SPT atopic status & asthma from animal contact. Subjects with a previous history of asthma were not significantly more likely to develop symptoms from animal contact but were more likely to develop OA. The authors conclude that excluding atopic individuals will not solve the problem, & screening new entrants is unlikely to be successful in view of the long average exposure period before symptoms develop & the fact that skin reactivity to animal extracts is rarely present without symptoms. All 42 subjects with asthma also had rhinitis.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Cortona et al	2001	422	Case series	3	A study on ORh & OA diagnosed in 7 occupational health institutes was performed. 141 cases of ORh & 281 cases of OA due to sensitisation. The most frequent agents of ORh were wheat flour & latex, whereas those of OA were latex & isocyanate. More than half of the subjects had more than one clinical manifestation of allergy. In 92/281 OA patients, ORh was the first clinical manifestation, particularly in subjects sensitized to HMW substances, & preceded, asthma by 12 months as a mean.
Coutts et al	1984	55	Cross-sectional	2++	Questionnaire, SPTs & spirometry were applied to 3 groups of workers in a cimetidine manufacturing plant defined according to exposure. 13/21 (62%) exposed daily, 4/19 (21%) exposed more than once a week & 3/15 (20%) of those exposed < once a week had work-related respiratory symptoms. Of 8 subjects with symptoms of the lower respiratory tract, 7 were in the group exposed most often. x^2 testing for linear trend showed a strong relation between the proportion affected in each group & the frequency of exposure to dust ($p<0.001$).
Cullen et al	1996	102	Cross-sectional	2++	Survey of 23 autobody shops ahowed there was a high rate of symptoms consistent with OA (19.6%). Symptoms were most prevalent in those with the greatest opportunity for exposure (dedicated spray painters) & least among office workers. Atopy was not associated with risk while smoking seemed to correlate with symptoms. OA symptoms were found 3 times more frequently among painting shop-floor workers & dedicated painters who did not use a +ve pressure ventilator (23.4%) than among those who did (8.3%), but the difference was not statistically significant. Regular use of air-supplied respirators appeared to be associated with lower risk among workers who painted.
Cullinan et al	1994	344	Cross-sectional	2++	344 employees exposed to flour in bakeries or mills in 7 sites were assessed by self completed questionnaire, & sensitisation measured by the response to SPTs, were related to intensity of exposure both to total dust & to flour aeroallergen. Among 264 previously unexposed subjects, work-related symptoms (which started after first employment at site) were related to exposure intensity, especially when exposure was expressed in terms of flour aeroallergen. The relations with eye/nose & skin symptoms were independent of atopic status & cigarette smoking. +ve SPT responses to mixed flour & to alpha amylase were also more frequent with increasing exposure intensity, although this was confounded by atopic status. There was only a weak association between symptoms & specific sensitisation.
Cullinan et al	1999	342	Case-refernt	2++	Cases were persons developing symptoms of LAA or a +ve SPT to rat urinary allergens; each was matched with up to 2 asymptomatic referents. Subjects were assigned to categories of exposure based on measurements of airborne rat urinary allergens. Of the cases, 80% reported that symptoms started within 2 years of employment. A gradient of increasing ORs for the development of any such symptom across exposure categories was found; for respiratory symptoms & SPT reactions the ORs for subjects in the highest exposure category were lower than those in intermediate categories. Atopy increased the OR of most outcomes, as did cigarette smoking, although there was no evidence of a relationship between smoking & the development of a specific SPT reaction. Allergen exposure was confirmed as the most important determinant of LAA. Increased risk among atopic subjects but no statistically significant interaction between atopic status & allergen exposure. The OR associated with allergen exposure were generally higher than those for atopic status. The median length of employment before the onset of new work-related chest symptoms was 18 months compared to 12 months for eye & nose symptoms. (31% of subjects with new chest symptoms reported these without other symptoms, 45% had eye/nose & 35% had skin symptom).
Cullinan et al	2000	342	Cross-sectional	2+	Occupational & health information was collected by questionnaire and SPTs. Results indicate a very high rate of enzyme-related sensitisation & asthma in the factory, leading to an estimate of 50 cases of OA, in addition to 6 index cases. Enzyme sensitisation & work-related respiratory symptoms were +vely correlated with airborne enzyme exposure. Authors conclude that enzyme encapsulation, the existing method of controlling occupational exposure to enzymes in the detergent industry, is insufficient by itself to prevent enzyme-induced allergy & asthma.
Cullinan et al	2001	300	Cohort	2++	Estimates the incidence of specific IgE sensitisation & allergic respiratory symptoms among UK bakery & flour mill workers & to examine the roles of flour aeroallergen & total dust exposures in determining these outcomes. Incidence rates for work-related eye/nose & chest symptoms were 11.8 & 4.1/100 person years, respectively. Fewer employees developed +ve SPTs to flour (2.2 cases/100 person years) or alpha-amylase (2.5/100/person years). There were clear relationships between the risks of developing work-related symptoms or a +ve SPT & 3 categories of estimated exposure to total dust or flour aeroallergen. Atopic employees were more likely to develop a +ve SPT-but not work-related symptoms. These findings were unaffected by age, sex or cigarette smoking.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
de Bono et al	1999	182	Cross-sectional	2++	Study of general practice notes of asthmatics to assess overall load of OA in the community. 86% of patients with adult onset asthma studied had at least 1 occupation recorded in their notes. 32% of these were in jobs known to be significant causes of OA, yet a potential link between occupation & symptoms had only been recorded in 18% of such patients. Overall 4% of the patients with adult onset asthma had been given a diagnosis of OA although in nearly half these cases, a general practitioner & not a specialist had made the diagnosis.
De Zotti et al	1994	226	Cross-sectional	2+	A survey was carried out on respiratory symptoms & SPT responses to common allergens, storage mites, & occupational allergens among bakers & pastry makers. Atopy was present in 54 workers & 42 workers reported allergic respiratory symptoms at work; WRA was reported by 11 (4.9%). Personal atopy was significantly associated with +ve SPT to occupational allergens & more than 50% of the symptomatic subjects at work were atopic. The risk of work-related respiratory symptoms was associated with sensitisation to wheat or alpha-amylase, & with atopy, but not with sensitisation to storage mites, work seniority, or smoking habit.
De Zotti et al	1997	90 (& 80 controls)	Case-referent	2+	Studied a group of trainee bakers & a group of trainee graphic artists as controls. Follow-up was performed 6 months later among trainee bakers. Trainee bakers & controls were similar with respect to age, number of smokers, atopy, & detection of serum IgE (RAST) & IgG to wheat flour. +ve SPT to wheat (4%) & alpha amylase (1%) were found only among trainee bakers. At follow up, 6.6% of trainee bakers complained of work-related symptoms (WRS): 3.3% were persistent, 3.3% were new cases & 1.1% had become asymptomatic. The trainee bakers complaining of WRS at the baseline or at follow-up (7 cases, compared with the non-symptomatics), showed a higher prevalence of personal atopy & skin sensitisation to occupational allergens; there were no differences, however, with regard to atopy by prick test, IgE levels or the presence of wheat specific IgE & IgG. The trainee bakers SPT +ve to the occupational allergens (8 cases) showed prevalences of personal atopy & atopy by prick test significantly higher than trainee bakers SPT -ve to wheat flour or alpha amylase.
De Zotti et al	2000	125	Cohort	2+	Study aimed to investigate the occurrence of work-related respiratory symptoms & to assess the effect of atopy in trainee bakers. At baseline examination, 4 students complained of respiratory symptoms (cough & rhinitis) when working with flours & 4 were SPT +ve to wheat flour or alpha-amylase. The incidence of work-related respiratory symptoms was 3.4% at 6 months, & the cumulative incidence was 4.8% & 9.0% at 18 & 30 months, respectively. The incidence of skin sensitisation to occupational allergens was 4.6% at 6 months & the cumulative incidence was 4.6% at 18 months & 10.1% at 30 months. Authors concluded that personal history of allergic disease is a predisposing factor for the development of symptoms caused by exposure to wheat flour.
Di Stefano et al	1999	24	Case series	3	Healthcare workers with respiratory symptoms suggestive of OA due to glutaraldehyde were investigated. Work environmental levels of glutaraldehyde were measured from air samples. Specific IgE antibodies to glutaraldehyde were measured with a series of glutaraldehyde modified proteins. In the 8 workers who underwent SIC, the diagnosis of OA was confirmed by a +ve reaction. In 13/16 remaining workers, the serial PEF monitoring showed a work-related effect. In 3 workers, there was no physiological confirmation of OA. Measurements of specific IgE antibodies to glutaraldehyde-modified proteins were +ve in seven patients (29.1%). The presence of atopy to common environmental allergens & smoking was not associated with specific IgE positivity.
Docker et al	1987	414	Cohort	2+	A questionnaire survey of workers handling reactive dyes showed that >15% had work-related respiratory or nasal symptoms. 49 workers with symptoms were referred to chest clinics. In 19, symptoms were attributed to an irritant response & in 24 to an allergic reaction to a specific agent. RAST screen containing the most commonly used reactive dyes was used to detect specific IgE. 68% of those with irritant reactions & 86% of those with 'allergic' reactions were atopic.
Douglas et al	1995	291	Cross-sectional	2+	Within 3 months of the opening of a salmon-processing plant, some workers complained of OA-like symptoms. A survey of all employees identified 24 (8.2%) with OA. The employees worked near machines, which generated respirable aerosols containing salmon proteins. The IgE response to these proteins was associated with OA, with increasing severity of symptoms, & with working distance from the aerosol source. The main factor predisposing to IgE-antibody production & OA was cigarette smoking; atopy & a previous allergic history did not. Affected employees were relocated to low-exposure ares & factory ventilation was improved. 11 showed significant clinical & lung function improvement & continued in employment. 13 who still had symptoms were advised to leave and became symptom-free, regaining normal lung function.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Droste et al	2003	246 (& 251 controls)	Case referent	2+	A random sample of bakers was compared with workers from a petrochemical plant in the same region. Bakery workers did not more often have SPT positivity than reference workers. However, bakery workers had a strongly increased risk of sensitisation to specific bakery allergens, whereas their risks of +ve SPTs to common allergens, including wheat pollen & storage mite, were significantly decreased. Bakery workers had significantly more often respiratory & work-related symptoms. Accordingly, they had lower lung function parameters. Atopy & sensitisation to bakers' allergens were independent & additional risk factors for work-related symptoms.
Elder et al	2004	520	Reporting scheme	2++	The commonest condition was OA (170 cases) for which the most common causative agent was wood dust. Other major causes were dust, isocyanates, paint fumes, thermolysis products, solvents, welding fumes & latex.
Elliott et al	2005	603	Cohort	2++	Laboratory animal workers were followed up for an average of 12 years. Probability of OA by 11 years 0.367 for workers with allergy symptoms & 0.052 for those without allergy symptoms at baseline; rhinitis a risk factor. At completion, 35% of those originally sensitised but not asthmatic developed OA compared with 22.4% who were originally unsensitised.
Flood et al	1985	2344	Cross-sectional	2+	Results from workers in 3 enzyme detergent manufacturing factories covering 11 years of operation were analysed in 3 separate groups. Spirometry & SPTs to standardised enzyme were performed 6 monthly for the first 6 years & then annually. A higher proportion of atopics than non-atopics became SPT +ve to the allergen & more smokers than non-smokers were sensitised.
Gannon et al	1993a	500	Surveillance scheme	2++	A recognised incidence of 43 new cases/million workers/year was detected. Agents to which workers were exposed at the time of diagnosis were well recognised (isocyanates 20.4%, flour 8.5%, colophony 8.3%). 28% of workers were exposed to the suspected causative agent at the time of diagnosis, 38% were either on long-term sickness absence, had retired, or had become unemployed. Occupational groups most affected included: paint sprayers, rubber & plastics workers, electroplaters, foundry core makers & moulders, bakery workers.
Gautrin et al	2001a	373	Cohort	2++	Pre-exposure host characteristics & school attended were compared between cases & all cohort subjects not meeting the criteria for probable OA. 28 apprentices satisfied the definition for 'probable OA', i.e., onset of immediate SPT reactivity to > 1 occupational inhalant & > 3.2-fold decrease in the provocative concentration causing a 20% reduction in FEV1 (PC_{20}). Baseline SPT to pets (rate ratio [RR] 4.1, 95% & bronchial responsiveness ($PC_{20} \leq 32$ versus $PC_{20} > 32$ mg/ ml) (RR = 2.5) were associated with increased risk of probable OA; a lower FEV1 had an apparent protective effect (RR = 0.58). Comparing probable OA cases with subjects with +ve SPT & no decrease in bronchial responsiveness, only +ve SPT to pets was significantly associated with the risk of probable OA, & a lower FEV1 had an apparent protective effect for the incidence of probable OA. In the 3rd comparison, atopy, +ve SPT to pets, & rhinitis on contact with pets significantly increased the risk of developing probable OA, whereas having a lower FEV1 was associated with a decreased risk. Of 78 apprentices identified prospectively as developing immunological sensitisation during the 3 to 4 year prospective study, 36.9% developed probable OA; the development of IgE sensitisation results in a high risk of having probable OA in the case of animal-derived allergens.
Gautrin et al	2001b	373	Cohort	2++	Study describes the time-course of the incidence of work-related symptoms, SPT reactivity & occupational rhinoconjunctivitis (RC) & OA & assesses the predictive value of SPT & RC symptoms in apprentices exposed to laboratory animals in a 3-4 yr programme. Apprentices at 5 institutions were assessed prospectively with questionnaire, SPT with animal-derived allergens, spirometry & airway responsiveness. Depending on the school, students were seen 8, 20, 32 & 44 months after starting the programme. Development of +ve SPT & RC symptoms mainly occurred in the first 2 years after starting exposure, whereas onset of respiratory symptoms was more common in the 2nd & 3rd year. Sensitisation, symptoms & diseases occurred maximally in the first 2-3 yrs after starting exposure to laboratory animals.
Gautrin et al	2008	408	Cohort	2++	Incidence rates of sensitisation & symptoms are lower after entrance to the workforce in comparison to apprenticeship. Symptoms acquired during apprenticeshp remit after starting work in a different job. Follow-up average 7.6 yrs after aprenticeship. New sensitisation 9.7/100 yrs in training, 1.3/100 yrs during subsequent exposed work. 16/20 sensitised during training then not exposed became SPT -ve (18.5/100 yrs). Probable OA 8.3% during training & 3% during later exposure. Incidence of sensitisation reduces with duration of follow-up.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Grammer et al	1993	29	Case series	3	Trimellitic anhydride workers with late asthma & late respiratory systemic syndrome improved clinically & immunologically when moved to lower exposure jobs. Approximately half of the asthma & rhinitis workers improved when moved, whereas the other half continued to be very symptomatic. Elevated levels of specific IgE may be a useful marker in the latter sub-population.
Grammer et al	1994	57	Cross-sectional	2+	7/57 employees in a workplace molding operation utilising hexahydrophthalic anhydride (HHPA) had both IgE- & IgG-mediated disease, whereas 9 had only IgE-mediated disease. Although smoking, age & race were not risk factors for development of immunologically mediated disease, exposure level & specific antibody were. Authors conclude that development of immunologically mediated respiratory disease due to HHPA is most closely associated with exposure level & development of specific IgE or IgG antibodies.
Grammer et al	1996	33	Case series	3	Of employees with respiratory symptoms caused by hexahydrophthalic anhydride 20 had no immunologically mediated disease, 7 had both IgE-mediated & IgG-mediated disease, 5 had IgE-mediated disease only & 1 had IgG-mediated disease only. Elevated levels of specific antibodies were statistically & clinically significant risk factors. Development of 1 type of immunologically mediated disease was highly predictive of development of the other. Race, age, smoking status, atopy & exposure levels did not emerge as significant risk factors.
Grammer et al	2002a	25	Case series	3	Consecutive employees with trimellitic anhydride-induced OA were studied; each participated in an annual surveillance program in which they were queried about respiratory symptoms. 22/25 (88%) reported rhinitis; 17/25 (68%) reported conjunctivitis. In 17/22 (77%) individuals with rhinitis & asthma, rhinitis preceded asthma. In 14/17 (82%) individuals with conjunctivitis, these symptoms preceded asthma. Mean latency for onset of rhinitis & asthma were 1.8 years & 2.6 years respectively.
Greenberg et al	1970	121	Cohort	2+	In a survey of workers exposed to dusts containing Bacillus subtilis derived enzymes, SPTs showed evidence of sensitisation was higher among atopics 16/25 (61%) than among non-atopics 32/96 (33%). Reduced ventilatory capacity was found in 44% of sensitised workers compared with 14% of those not sensitised. (SPT to common allergens was used to classify subjects as atopic & non-atopic).
Gross et al	1980	399	Cross-sectional	2++	LAA allergy was more likely to occur in subjects with previously known allergies, especially to domestic pets, & was most likely to become manifest within a few months of the first exposure. In the group with LAA, nasal symptoms were invariably present & tended to precede pulmonary symptoms, which occurred in half of the group.
Hagmar et al	1984	602	Cohort	2+	A strong exposure-response relationship for the frequency of work-related airway symptoms indicating asthma. In the most exposed group, about 1/3 of workers had experienced such symptoms. There was also an association between piperazine exposure & chronic bronchitis.
Hannu et al	2007	34	Case series	3	Persistent symptoms in Finnish welders with stainless steel asthma render most of them unable to continue at work. +ve challenges to stainless steel welding fumes but SPTs to potassium dichromate & chromium chloride at 1mg/ml universally -ve (sensitivity = 0%). NSBR normal at presentation in 38%. Long latent interval (mean 18 years), peak flow records +ve in 5/8.
Heederik et al	1999	650	Cross-sectional	2++	Data from 3 cross-sectional studies of animal laboratory workers in the Netherlands, UK & Sweden. Air allergen levels were assessed previously & converted on the basis of an interlaboratory allergen analysis comparison. Available sera were analyzed for the presence of specific antibodies against common allergens (house dust mite, cat, dog, & grass & birch pollen) & work-related allergens (rat & mouse urinary proteins). Questionnaire items on work-related respiratory symptoms, hours/week worked with rats, job performed, smoking habits, & sex were used in this analysis. A clear exposure-response relationship was observed for rat urinary allergen exposure & specific IgE antibodies against laboratory animals.
Heederik et al	2001	393	Quantitative risk assessment	2+	Exposure response modelling using classical epidemiological approaches & advanced statistical methods suggested an increased risk of sensitisation with increasing dust & allergen exposure & gave similar "lowest" or "no observed effect levels" (LOEL or NOEL) estimates. When sensitisation plus asthma or rhinitis was considered as critical endpoint, exposure-response relationships were steeper indicating lower LOEL values. Atopics exposed to low levels of wheat allergen had approximately 2-fold increased risk of sensitisation compared with non-exposed atopics. This risk increased with increasing exposure, for atopics & non-atopics.

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Hnizdo et al	2001	3285	Reporting scheme	2++	Reports the results of the 1st 2 years of the Surveillance of Work-related & Occupational Respiratory Diseases in South Africa scheme (SORDSA). 225 cases of OA (6.9%). Latex was the most frequently reported agent for OA, followed by isocyanates & platinum salts. LMW agents accounted for 59.6% of the cases of OA.
Houba et al	1996	178	Cross-sectional	2++	Workers were categorized according to job history & amylase exposure levels of their jobs. 25% had work-related symptoms, 9% had +ve SPT to fungal amylase, 8% amylase-specific IgE. Atopy & amylase exposure appeared to be the most important determinants of skin sensitisation i.e.: prevalence ratio (PR) for atopy 20.8, medium exposure PR = 8.6 & high exposure PR = 15.9. For IgE sensitisation atopy was only significant determinant, PR = 8.3. A +ve association was observed between +ve SPT & work-related symptoms. A strong & +ve relationship is shown between alpha-amylase allergen exposure levels & specific sensitisation in bakery workers.
Houba et al	1998	393	Cross-sectional	2++	Study was conducted among workers from 21 bakeries. A strong & +ve association was found between wheat flour allergen exposure & wheat flour sensitisation. This relationship was steepest & strongest in atopics. In sensitized bakers those with an elevated allergen exposure had more often work-related symptoms. Work-related symptoms were highly prevalent among these bakery workers, ranging from 7% with chest tightness to 21% with rhinitis. Most workers with chest tightness also reported rhinitis (72%). Variables significantly associated with symptoms were atopy, defined either as elevated total IgE or specific IgE to common allergens. Indicators of smoking habits were not related to work-related respiratory symptoms.
Hur et al	2008	392	Cross-sectional	2++	67 bakery workers (17.1%) complained of work-related upper and lower respiratory symptoms. The prevalence of OA based on positive provocations was 1.5%. The sensitization rate to wheat flour was 5.9% by SPT and 6.5% by ELISA, and was closely associated with the presence of atopy and work-related lower respiratory symptoms ($P<0.001$ for both).
Jaakkola et al	2003	521 cases (932 controls)	Case-control	2++	Study assessed the relationship between occupation & risk of developing asthma. The occupations were classified according to potential exposure to asthma-causing inhalants. Asthma risk was increased consistently for both men & women in the chemical, rubber & plastic, & wood & paper industries. Risk in relation to occupation was increased only for men - for bakers & food processors, textile workers, electrical & electronic production workers, laboratory technicians & storage workers. Of the predominantly male occupations, metal & forestry work were the strongest determinants of asthma. For women, asthma risk increased for waiters, cleaners & dental workers. Results suggest an increased asthma risk in both traditional industries & forestry & in several non-industrial occupations.
Jaakkola et al	2007	799	Cross-sectional	2+	A study of female dental assistants in the Helsinki metropolitan area (response rate 87%). Daily use of methacrylates was related to a significantly increased risk of adult-onset asthma (adjusted OR 2.65, 95% CI 1.14-7.24), nasal symptoms (1.37, 1.02-1.84), and work-related cough or phlegm (1.69, 1.08-2.71). Nasal symptoms showed a dose-response relation with increasing years of exposure to methacrylates. Dental assistants with a history of atopic diseases were particularly susceptible to exposure to methacrylates, the adjusted OR for adult asthma being 4.18 (95% CI 1.02-28.55) and for nasal symptoms 2.11 (1.08-4.19).
Jacobs et al	2008	860	Cross-sectional	2++	Dutch craft & industrial bakers with good exposure estimates. Total dust exposure closely related to wheat antigen exposure. Atopy & exposure levels both risk factors for wheat sensitisation, but not smoking in this group with 35% current smokers. Bell shaped sensitisation/exposure curve with peak at about 20-30ug/m^3 wheat. Fall off at higher levels thought to be survivor effect rather than development of tolerance. Poor relationship between work-related symptoms & wheat sensitisation (24/202 with ORh on questionnaire & 37/81 with WRA symptoms.
Jeal et al	2003	1121	Cross-sectional	2+	Figures suggest that approximately 40% of OA in this laboratory animal worker population can be attributed to an HLA-DRβ1*07 phenotype; in comparison, attributable proportions for atopy & daily work in an animal housing facility are 58% & 74% respectively.
Jeal et al	2006	689	Cross-sectional	2++	Cross-sectional study with 89% response rate with questionnaire & specific IgE & IgG4. 11% +ve Rat IgE. RAST related to atopy as a risk factor. Protective effect of IgG4 to rats 2 fold compared with risk of IgE 25 fold. Some evidence that there may be attenuation of the exposure-response relationship at high exposures in laboratory animal workers.

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Jeebhay et al	2008	594	Cross-sectional	2++	The prevalence of probable OA in 2 processing plants was 1.8%. Atopy (OR=3.16) & current smoking (OR=2.37) were associated with sensitisation to fish & with probable OA, atopy (OR=2.17) & smoking (p<0.001) (numbers too small to generate a meaningful OR).
Johnsen et al	1997	1064	Cohort	2++	8.8% of workers exposed to enzymes developed clinical enzyme allergy during first 3 years of employment. Risk declined over the period. Frequency of enzyme sensitisation, expressed as RAST values > 0.5 SU, was 36%, & the frequency of significant RAST values > or = 2 SU = 8%. Frequency of asthma was 5.3%, rhinitis 3.0%, & urticaria 0.6%. Half of cases occurred within the first 15 months exposure. Risk of symptomatic allergy & sensitisation to enzymes, expressed as increasing RAST were significantly increased in smokers. Neither a +ve SPT nor clinical allergy at pre-employment predisposed to clinical enzyme allergy. Smoking was an independent risk factor for clinical enzyme allergy. Atopic predisposition was not a significant risk factor for enzyme allergy.
Johnson et al	2000	2974	Cohort	2+	A randomly selected population completed an initial questionnaire, of whom 2,974 (39% response rate) attended the laboratory & completed supplementary questionnaires. Of these latter, 383 had asthma & of these 166 had adult-onset asthma. Of individuals with adult-onset asthma, 27 met the criteria for 'probable OA' & 33 for 'possible OA'. The percentages of the attendee population with 'probable OA' or 'possible OA' were 16.3% & 19%, respectively. The percentage with 'probable' & 'possible' OA was 36.1% of all cases of adult-onset asthma. Nursing, baking, hairdressing & chemical, rubber, or plastics processing were common occupations in the 'probable OA' group.
Juniper et al	1977	1642	Cross-sectional	2+	Previous findings that atopics were more likely than non-atopics to become SPT +ve to enzymes were confirmed. An atopic was defined as having a history of atopy (e.g. eczema, asthma, hayfever) and/or +ve SPT to ≥1 common allergens. For non-atopics, 40% of workers with high exposure became SPT +ve to enzymes vs 9.5% of those with medium exposure & 4.5% of those with intermittent exposure. For atopics, 75% of workers with high exposure became SPT +ve to enzymes vs 20% of those with intermittent exposure.
Juniper et al	1984	1642	Cohort	2+	62/1642 subjects had OA with higher incidence in atopics.Authors conclude that subjects with previous chest disease should not be exposed to occupational allergens, but that exclusion of asymptomatic atopics from this type of work is probably not justified.
Kalogeromit et al	2006	64 + 60	Case referent	2++	Investigated possible risk factors for sensitisation in seafood processing workers compared with 60 controls. All had SPTs with cod, sardines, shrimp, spiny lobster, crabs, salmon, mussels, & trout & -ve & +ve control. RAST was evaluated in thsoe with +ve SPTs. Atopic status was tested with SPTs to 7 common inhalant allergens. 23/64 workers (35.9%) were SPT +ve to ≥1 of the seafood allergens & the prevalence in the control group was 10% (6/60; OR, 5.049; 95% CI, 1.884-13.533). The prevalence of +ve SPT in allergen species tested in the fishery workers group was shrimp, 12.5%; spiny lobster, 10.9%; mussels, 7.8%; crabs 3.1%; cod, 3.1%; sardines, 1.6%; salmon, 1.6%; & trout, 1.6%. Atopy (p = 0.02), intensity (p = 0.03), & duration of exposure (p = 0.03) were potential risk factors for IgE sensitization.
Karjalainen et al	2000	2602	Reporting scheme	2++	Mean incidence for OA was 17.4/100,000 workers/year. The incidence was highest in bakers, painters & lacquerers, veterinary surgeons, chemical workers, farmers, animal husbandry workers, food manufacturing workers, welders, plastic product workers, butchers & sausage makers, & floor layers. Cases caused by animal epithelia, hairs & secretions or flours, grains, & fodders accounted for 60% of the total (approximately 50% of all OA occurs in farmers – high exposure since cattle are kept in cow houses for 5-8 months of the year).
Karjalainen et al	2002	49575	Reporting scheme	2+	Significantly increased risk of WRA for either men or women in 125 occupations. For men, the risk was highest among bakers, laundry workers, shoemakers & repairers, tanners, pelt dressers, metal plating & coating workers. For women, the risk was highest among shoemakers & repairers, railway & station personnel, jewellery engravers, engine room crew, moulders, round-timber workers, & bakers.
Karjalainen et al	2003	35,094	Reporting scheme	2++	A clearly elevated risk of OA was found among patients with ORh compared with patients with other occupational diseases. (96% of persons had the same job title at time of onset of ORh & OA. The risk of OA was especially high during the year following notification. 11.6% of ORh patients developed OA in the follow up period compared to 3.1% among referents. Crude incidence rate = 19/1000/yr vs 4/1000/year crude relative risk = 4.8. Relative risk varied according to occupation/allergen – highest in farming, laboratory animal work & woodworking. Mean interval ORh to OA = 31 months. (3,637 non asthmatic ORh patients from Finnish Register of Occupational Disease. Referents = 31,457 non-OA non-OR occupational disease cases 1988 through 1999. Study end 31 Dec 2001.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Karkoulias et al	2007	58	Cross-sectional	2+	Investigated sensitization to wheat flour & other baking allergens (oat, barley, & rye flour) in traditional bakers. Atopy was identified by ≥1 +ve SPTs to common aeroallergens. Atopy was a risk factor for sensitisation to flour OR=15.12 (95%CI=2.54-116.65) & to wheat flour OR=8.8 (95%CI 1.44-68.94). An association was also found for current smokers vs never smokers & sensitisation to wheat flour (p=0.018).
Kim et al	1999	16	Case series	3	Asthmatic attacks in farmers with citrus red mite (CRM)-induced OA cultivating citrus fruits corresponded closely with work. Mean latency was 12.9 (range 7 to 20) years. 15/16 complained of recurrent nasal symptoms, which developed earlier than asthma symptoms. They showed strong +ve reactions to CRM extract on SPT & had high serum specific IgE antibody against CRM. SPT with common inhalant allergens revealed that 10 had an isolated +ve response to CRM with -ve results to common inhalant allergens in their environment.
Klusackova et al	2007	5	Case series	3	Patients from a lasamide production line with suspected OA & ORh were examined. Nonspecific & SIC tests were performed to confirm the diagnosis. At follow-up (1-3 years after removal from exposure), all of the tests (except SIC) were repeated. At the 1st hospitalization, nonspecific bronchoprovocation test were +ve for 3 patients. SIC was +ve in 3 patients; symptoms of rhinitis were present in all 5 patients. Several years after removal from exposure to the occupational agents, normalization was not yet complete for all of the patients.
Kogevinas et al	2007	6837	Cohort	2++	In a population of young adults, the annual incidence of OA was 250-300/million. Population at typical risk 10-25%. Risk factors are atopy & parental asthma, but not smoking. High risk exposures include metal working fluid, irritant gasses & fumes, textiles, agricultural & organic particles as well as common specific exposures like cleaning agents, reactive chemicals using isocyanates & hydrised reactive dyes, glues & biocides, latex. High risk jobs were nursing & cleaning & probably baking & spray painting.
Kor et al	2001	90	Surveillance scheme	2++	Since 1990, OA has overtaken silicosis & asbestosis as the commonest occupational lung disease in Singapore. Since the first notified case of OA in 1983, 90 cases (19 female & 71male) were confirmed at the end of 1999. Mean duration of exposure prior to onset of symptoms was 34.9 +/- 57.3 months. The most common causative agent was isocyanates (28 cases, 31%) followed by solder flux (12 cases, 13%) & welding fumes (8 cases, 9%) respectively. 13 (14.4%) workers were assessed to have permanent disability under the Workmen's Compensation Act. OA is a condition associated with disability in the workplace & may still be largely under-reported.
Krakowiak et al	1997	60	Cross-sectional	2+	LAA develops within first years of exposure; atopy & smoking predispose to laboratory animal sensitisation & to a development of bronchial asthma & allergic rhinitis. (Acute episodes of dyspnoea classified as asthma found in 8 subjects. In all cases, development of symptoms was concurrent with nasal symptoms).
Krakowiak et al	2002	68	Cross-sectional	2+	Study aimed to determine the prevalence of respiratory symptoms & immediate hypersensitivity to feather & fur allergens & pulmonary function among 68 zoological garden workers. 45 subjects revealed +ve SPTs with any inhalant allergen. 12 reacted to feather extracts & 18 reacted to animal fur extracts. IgE specific for occupational allergens was seen in the serum of 5 subjects with SPTs +ve to feather allergens & in the serum of 12 subjects with SPTs +ve to fur allergens. OA & ORh were reported by atopic subjects more often than by non-atopic subjects. Atopy predisposes to the development of allergic diseases caused by animal fur & feathers.
Krakowiak et al	2006	88	Cross-sectional	2+	A study of animal shelter workers occupationally exposed to cats & dogs. They responded to a questionnaire concerning the history of exposure to animal allergens & job characteristics & were subjected to SPT to common & occupational allergens, & determination of total serum IgE level & specific IgE. SPT with rat & mouse allergens were also performed. BHR & PEF were measured at work & off work only in workers with work-related symptoms suggestive of OA. The prevalence of OA was 9.1%. The univariate logistic regression analysis revealed a significant role of atopy (sensitisation to grass pollen) for work-related symptoms suggestive of OA.
Krstev et al	2007	1050	Case referent	2+	Cases were 1,050 women who reported a physician-diagnosed asthma as adults. Controls were 4,200 women matched to the cases by year of birth & age at diagnosis. Lifetime occupational histories were obtained. Logistic regression was applied to estimate ORs adjusting for smoking, education, family income, & concurrent chronic bronchitis. Asthma was more prevalent in 3 different production industries for metal products (OR = 1.6, 1.9 & 2.4), ships (OR = 2.6) & in occupations as farm workers (OR = 4.0), laboratory technicians (OR = 2.2), & installation & maintenance workers for weaving & knitting machineries (OR = 2.4; 1.1-5.4).

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Kruize et al	1997	99	Cohort	2+	Study showed that both non-atopic & atopics have an increased risk related to exposure intensity when exposed to laboratory animal allergens. Atopics developed LAA earlier & in more severe forms (asthma) than non-atopics (13% vs 6%). The mean latency for the onset of LAA was about 109 months in non-atopics & 45 months in atopics. More people with asthma were found in the high exposure categories. Time until development of symptoms of LAA was shorter at a higher intensity of exposure, except for those exposed for <2 hours/week. Authors conclude that exposure & atopy are significant predictors of LAA & that the risk of developing LAA remained present for a much longer period (>3 years) than considered before.
Larsen et al	2007	1207	Cohort	2+	Retrospective follow-up study based upon data gathered from health surveillance since 1970. 1207 employees from production & laboratories were included. The risk of sensitisation & allergy was doubled among smokers. Pre-employment atopy was only associated with sensitisation risk. The study found no evidence of an exposure-reponse relationship, probably due to exposure misclassification.
Li et al	2008	25078	Case series	3	Asthma hospitalization records were retrieved at ages >30 years. Among males, increased risks were noted for farmers, mechanics & iron & metal workers, welders, bricklayers, workers in food manufacture, packers, loaders & warehouse workers, waiters & chimney sweeps with prolonged exposures in 2 censuses. For females, increased risks were observed among assistant nurses, religious, juridical & other social science-related workers, drivers, mechanics & iron & metalware workers & wood workers.
Liss et al	1993	52	Cross-sectional	2+	The prevalence of specific IgE was highest in the mold & intermittent groups (54%), in comparison with the coil assembly (25%) & office (0%) groups. After adjusting for smoking status the differences between exposure groups was not significant. Associations were found between the prevalence of TCPA-specific IgE responses & both exposure status & duration of employment. There was a higher prevalence of sensitisation among those who have never smoked & former smokers.
Malo et al	1997	40	Case series	3	Study assessed the prevalence, severity & timing of symptoms of rhinoconjunctivitis in association with OA. SIC confirmed the diagnosis of OA. Rhinitis was reported at some time by 37/40 (92%) & conjunctivitis by 29/40 (72%). Prevalence of symptoms was not different for HMW & LMW agents, although rhinitis was more intense for HMW (19/24 subjects with ≥3 of the following symptoms: runny nose, itchy nose, nasal blockage, & sneezing) than for LMW (5 out of 14 subjects) ($p<0.01$). There were significantly fewer subjects with OA due to LMW agents, with rhinitis appearing before asthma ($p=0.03$). Rhinitis preceded asthma in 14/24 cases related to HMW agents & in 3/14 cases related to LMW agents. Rhinitis & asthma developed concurrently in 9/24 & 9/14 cases of OA.
McDonald, et al	2000	7387	Reporting scheme	2++	Data from 9 years of the SWORD surveillance scheme, which uses systematic reporting from physicians to provide a picture of the incidence of occupational respiratory disease in the UK. OA accounted for 25% cases each year. Except for laboratory technicians all other occupations with average annual rates/million over 100, were concerned with manufacturing & processing that used chemicals metals & organic materials. Increase in proportion of cases attributed to latex & decrease in those attributed to isocyanates.
McDonald et al	2005	-	Reporting scheme	2++	OA was responsible for about 25% of cases of work-related respiratory disease overall, affecting mainly craft related occupations & machinists, & most often attributed to isocyanates, metals, grains, wood dusts, solders, & welding fume. During the 10 year period 1992-2001 there were few changes in level of reported incidence, apart from some decline in OA & inhalation injuries. Even so, the reported incidence of new cases of acute respiratory illness caused by work remains substantial.
McSharry et al	1994	26 (& 26 controls)	Case-control	2+	Raised levels of serum IgE to prawn antigens were found in 15/26 seafood factory process workers with respiratory symptoms & in 1/26 case-matched asymptomatic controls. Raised IgG titres against the same antigens were found in 18 subjects in each symptom grouping. The prawn-specific IgE antibody response was significantly associated with atopy, a history of cigarette smoking & with increasing exposure. Non-atopic non-smokers were unlikely to become sensitized. The titre of the prawn-specific IgE antibody correlated with the duration of exposure & with the duration of symptoms. IgE antibody was produced mainly by smokers, whereas IgG antibody was the predominant antibody produced by non-smokers.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Meijer et al	2002	551	Cohort	2+	Baseline data from laboratory animal workers bridging ove 3 years were used. Data from 472 workers participating in the 1st period of the study represented the derivation set & data from 79 workers, participating during the 2nd period, represented the validation set. Serum samples were analysed for specific IgE against common & laboratory animal allergens & questionnaire items, exposure determinants, IgE serology, SPTs & lung function tests were analysed. Asthmatic symptoms, work-related allergic symptoms, occupational exposure to rats & a +ve SPT to common allergens, showed the best performance in discriminating workers at high or low risk of being sensitised.
Meredith et al	1991	2101	Reporting scheme	2++	The SWORD surveillance scheme uses systematic reporting from physicians to provide a picture of the incidence of occupational respiratory disease in the UK. 26% of total reported cases were of OA. The most commonly identified agents causing asthma were isocyanates, flour/grain dusts, wood dust & solder flux. The workers most at risk included welders, laboratory technicians, metal workers, pastics workers, bakers, painters & sprayers & chemical workers. The authors report an overall incidence of 22/million/yr.
Meredith et al	2000	97	Case-control	2+	No difference in peak exposures between cases & referents was found, but time weighted average exposures at the time of onset for OA were higher for cases. The odds of OA for those for whom estimated exposure to isocyanates was greater than the median concentration for the control group was 3.2 times the odds for those exposed to lower concentrations. OA was associated with a pre-employment history of “atopic illness” (OR 3.5) & less strongly with smoking.
Merget et al	2000	308	Cohort	2++	11.3% & 2% study population developed +ve platinum salts SPT in high & low exposure groups respectively. Development of symptoms was associated with exposure. Smoking was significant predictor of +ve platinum salts SPT, estimated relative risk 3.9. Atopy & BHR were not significant predictors.
Meyer et al	1999	2966	Reporting scheme	2+	The SWORD surveillance scheme uses systematic reporting from physicians to provide a picture of the incidence of occupational respiratory disease in the United Kingdom. 27% of total reported cases were of OA. The most commonly identified agents causing asthma in 1998 were enzymes, isocyanates, laboratory animals & insects, colophony & fluxes, flour, latex, & glutaraldehyde.
Moscato et al	2005	47	Case series	3	On the basis of SIC, 24 hairdressers were diagnosed with OA (51.1%), due to persulfate salts in 21 (87.5%), permanent hair dyes in 2 (8.3%), & latex in 1 (4.2%). 13 also received a diagnosis of ORh due to persulfate salts in 11 (84.6%) & to paraphenylenediamine in 2 (15.4%). Patients with persulfate OA had a long period of exposure to bleaching agents, a long latent period between the start of exposure & the onset of symptoms. SPT with ammonium persulfate in a subset of patients gave -ve results. The +ve SIC in some workers, the latent period between the onset of exposure & the onset of symptoms, the type of SIC response, & the association of asthma with other diseases such as dermatitis & rhinitis suggest an immunologic mechanism that remains to be elucidated.
Munoz et al	2003	8	Case series	3	Immunologic, lung function & SIC were performed in cases of OA due to persulfate salts in a factory manufacturing hair bleach products - 6 presented with rhinitis prior to OA. The mean time of exposure to persulfate salts up to diagnosis was 15 years (range 3-27 years).
Musk et al	1989	279	Cross-sectional	2+	A survey of dust exposure, respiratory symptoms, lung function, & response to SPTs was conducted in a modern British bakery. All participants completed a self-administered questionnaire on symptoms & their relation to work. Of the participants in the main exposure group, 35% reported chest symptoms which in 13% were work-related. The corresponding figures for nasal symptoms were 38% & 19%. Symptoms, lung function, BHR, & response to SPTs were related to current or past exposure to dust using logistic or linear regression analysis as appropriate. Exposure rank was significantly associated with most of the response variables studied.
Newhouse et al	1970	271	Cross-sectional	2++	Among detergent factory workers, 21% of those examined were SPT to Alcalase. More than twice as many sensitised workers vs non-sensitised workers also reacted to common allergens. 42/57 of workers who were SPT +ve to Alcalase had symptoms of ‘acute chest disease.’ 75/214 of workers with -ve SPTs also reported acute chest disease. However, there was a highly significant association between these symptoms & a +ve SPT to Alcalase. Of the sensitised men, 21.4% had a personal or family history of allergic disease & 65.5% gave +ve responses to prick tests with one or more of the common allergens. For the men who were not sensitive to the enzyme, 9.5% gave a personal or family history of allergic disease & 21.4% were sensitive to one of the common allergens.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Nielsen et al	2001	211	Case referent	2+	Study to clarify the exposure-response relationships for the organic acid anhydrides (OAA) hexahydrophthalic & methylhexahydrophthalic anhydrides & the development of specific IgE, IgG & work-related symptoms in 154 exposed workers & 57 referents. For the exposed workers, there were high prevalences of sensitisation (IgE 22%, IgG 21%), which correlated with the exposure. Neither atopy nor smoking increased this risk significantly. Work-related symptoms were more prevalent among the exposed workers than among the referents.
Nielsen et al	2006	146	Cohort	2++	Prospective cohort of Swedish acid anhydride exposed workers in whom the annual incidence of work-related chest symptoms (one third sensitised) was 31.1000person years even at exposures <10mcg/mg; rates of follow-up unclear. Laryngeal symptoms the first sign in some with an average latency of months, nasal symptoms 7 months, eyes 11 months & lower respiratory symptoms 16 months. Sensitivity for specific IgE for lower respiratory tract symptoms 33%.
Nieuwjenhuijsen et al	1999	495	Cross-sectional	2+	Personal flour dust samples were taken in 7 British bakeries & flour mills & analysed for alpha-amylase. Workers filled out questionnaires on work-related symptoms, smoking history, & work history, & had SPT with common allergens & fungal alpha-amylase to assess sensitisation. Exposure to alpha-amylase showed only a moderate correlation with concentrations of dust & flour aeroallergen. Results also showed a relation between exposure to alpha-amylase & sensitisation to fungal alpha-amylase. Atopic subjects had an increased risk of sensitisation, but this was not significant.
Orriols et al	2006	359	Reporting Scheme	2+	102/142 (74%) physicians approached who were all seeing patients with occupational respiratory diseases participated. 359 cases were reported, of which asthma (48.5%), was the most common. The most frequent suspected agents were isocyanates (15.5%), persulfates (12.1%), cleaning products (8.6%), wood dust (8%), flour (7.5%) & latex (6.9%). The frequency of occupational respiratory diseases recorded by this voluntary surveillance system was four times higher than that reported by the compulsory official system.
Ortega et al	2001	107	Cohort	2+	During crab-processing season, asthma-like symptoms developed in 26% of participants. Only 9% of those with new asthma-like symptoms were IgE-sensitised to crab at the end of the season. Workers with high exposure work i.e. butchering & degilling workers had the highest incidence of respiratory symptoms. Both personal & process-related factors appear to affect the development of respiratory symptoms in crab-processing workers. In univariate analysis for associated factors, a statistically significant association with family history of allergies & elevated eosinophil cationic protein was found. Smoking did not reach statistical significance.
Osterman et al	1982	50 & 129	Cohort & cross-sectional	2+	Study I comprised 50 selected cases (25 had work-related symptoms & 25 had not). SPT & RAST with different factory dust extracts were performed. Study II was a cross-sectional study of 129 workers who had SPT with 1 factory dust extract & with castor bean. Study 1: 12 were atopics: 9 (40%) of sensitised workers & 3 (10%) of the non-sensitised. Among the raw coffee workers, 14 were sensitised to coffee or castor bean (67%) & among other workers 8 were probably sensitised (27%). Findings support the statement that the risk of sensitisation is greater the stronger the exposure. Study 2: Of the 28 workers with +ve SPTs, 22 (79%) were smokers; of the 101 with -ve SPTs 48 (47%) were smokers. Frequency of sensitisation was 31% among smokers & 10% among non-smokers. Difference was greater the longer the duration of employment. Predisposing factors to sensitisation were atopic status, degree & length of exposure, & smoking.
Park et al	1989	9	Case series	3	All patients had had OA symptoms to reactive dyes, 4 had had ORh & had worked for 6 to 25 months. SPTs with reactive dyes were +ve & broncho-provocation tests produced immediate or dual types of bronchoconstriction. RAST was used to detect specific IgE to 4 reactive dye-human serum albumin conjugates. High specific IgE binding was found in 8 asthmatic workers compared with 13 -ve controls. RAST inhibition test revealed that there was no immunological cross-reactivity between 4 reactive dyes.
Petsonk et al	2000	214	Cohort	2+	Study evaluated respiratory health in workers using methylene diphenyl di-isocyanate (MDI) at a new wood product manufacturing plant designed to minimise worker exposure. New-onset asthma-like symptoms were reported in 15/56 workers in areas with the highest potential for exposure versus 0/43 workers in the lowest potential exposure areas. In high exposure areas, new-onset asthma-like symptoms developed in 47% of workers who had noted MDI skin staining versus 19% without skin stains. Working around & cleaning up liquid MDI represented a significant risk for asthma-like symptoms in both current smokers & non-smokers. Asthma-like symptoms were associated with variable airflow limitation & specific IgE to MDI-albumin but not with SPTs to common aeroallergens.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Platts-Mills et al	1987	179	Cross-sectional	2+	IgG & IgE to a purified rat urinary allergen in sera were measured in 179 laboratory workers of whom 30 reported symptoms on exposure to rats. The incidence & quantity of IgG correlated with the degree of exposure to animals but not with the length of exposure in years. The mean time before symptoms developed was approximately 2.5 years. Handlers (approx 8hrs/day) had a greater incidence than heavy users (approx 2hrs/day). There was an increased incidence of asthma among atopic individuals as judged by +ve SPTs to other allergens. However, in order to exclude 66% of workers who developed asthma, it would have been necessary to exclude 71 individuals who had +ve SPTs to inhalant allergens. Rejecting the 41 individuals a history of inhalant allergy & +ve SPTs would only have avoided 50% of the cases of asthma & 33% of cases of rhinitis. Most atopic individuals did not develop allergic symptoms or specific IgE.
Prichard et al	1984	200	Cross-sectional	2+	Bakers & subjects employed as bread slicers & wrappers were studied. Bakers had a greater prevalence of attacks of wheeze & dyspnoea & more frequently considered that work affected their chests than did slicers & wrappers. There was a significant association between the frequency of +ve prick SPTs to wheat & common allergens, suggesting that prior atopy facilitates sensitisation to cereal antigens. The frequency of +ve SPTs to common allergens, however, declined with increasing baking duration whereas the frequency of +ve SPTs to wheat increased with increasing baking duration, suggesting that subjects who were sensitised to common allergens were leaving the industry whereas subjects who stayed in the industry increased their risk of developing sensitisation to wheat. Oven handlers had a greater prevalence of attacks of wheeze & dyspnoea & more frequently considered that work affected their chests than either dough makers or general bakers. They also had a greater prevalence of +ve prick SPT responses to wheat than dough makers or general bakers. Oven handlers also had a lower mean standardised casual FEV1 than either general bakers or dough makers. Thus oven handlers appear to have a greater risk of developing respiratory allergy & airflow obstruction than bakers in other occupational categories.
Pronk et al	2007	581	Cross-sectional	2++	Work-related respiratory symptoms in a cross-sectional study of Dutch spray painters were related to an extensive set of isocyanate exposure measurements. Chest tightness & specific IgE sensitisation (which was rare) were associated with current exposure. 67% response rate in individual workplaces, but only 10-30% workplaces took part. Questionnaire diagnosis of OA required symptoms to occur during or shortly after work (rather than improve on days away from work).
Provencher et al	1997	161	Surveillance scheme	2++	Physician based surveillance system of occupational respiratory diseases (PROPULSE) in Quebec. The most often reported diagnosis was asthma (63%). The most frequent sensitising agents reported for asthma were the same in both systems (isocyanates, flour, & wood dust). Other main causes were farm & laboratory animals, plastic, additives & rubber & welding fumes Authors conclude that physician based reporting procedure can be implemented as part of surveillance system to supplement data from other sources.
Reijula et al	1996	2623	Reporting scheme	2++	Between 1986 & 1993 the annual incidence of OA increased by 70% (equally in men & women). Proportion of newly identified OA from all new cases of asthma was 4.8%, with over half attributed to farming & bakery work.
Romano et al	1995	211	Cross-sectional	2++	Study assessed the prevalence of allergic respiratory symptoms & sensitisation to both green coffee beans & castor bean in the workforce of a coffee manufacturing plant. A questionnaire on oculo-rhinitis & asthma was administered & SPTs for green coffee beans, castor bean & 15 common inhalant allergens were carried out on 211 workers. 10% of workers complained of oculo-rhinitis alone & 16% of asthma (nearly always associated with oculo-rhinitis). Evidence of sensitisation to occupational allergens was more common in smokers, with a more than twofold increase in relative risk. The strong association between SPT positivity to common & occupational allergens suggests that atopy acts as an enhancing host factor towards occupational sensitisation. Authors concluded that findings indicated that castor bean is the major cause of occupational sensitisation among coffee workers, whereas smoking & atopy act as enhancing factors.
Sallie et al	1994	1000	Reporting scheme	2++	40% of cases (1000) reported annually to the UK SWORD surveillance scheme are of OA or inhalation accidents OA related to a wide range of agents in many occupations. The commonest substances reported as casusing OA included: isocyanates, flour & grain, wood dust, laboratory animals, aldehydes & amines. Workers most at risk included spray painters, bakers, chemical process workers, nurses, laboratory workers, woodworkers & foam & plastic processors.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Sjostedt et al	1989	101	Cohort	2+	Family history of allergy, raised total serum IgE & +ve SPTs against common environmental allergens were pre-disposing factors for the development of LAA.
Sjostedt et al	1993	88	Cross-sectional	2+	5-year follow-up study of laboratory animal workes. 2 individuals developed test +ve LAA rhinitis during the follow-up period. Furthermore, 1 subject who had previously had LAA rhinitis developed LAA asthma. Atopy defined as parental & childhood allergy, raised total serum IgE levels, & +ve SPTs against common allergens & non-laboratory animals were risk indicators for development of test +ve LAA asthma. The low incidence of LAA during the 5-year follow-up is interpreted as a result of an early LAA development in atopic subjects.
Skjold et al	2008	114	Cohort	2++	The incidence of work-related nasal & chest symptoms in these apprentice bakers was 22.1 & 10.0/100 person years respectively & higher in those who were atopic. Neither outcome was commonly associated with evidence of specific IgE sensitisation. OA definition required methacholine PC20 <1440ug, 1/87 reaching 20 months had OA. Many developed new symptoms but these unrelated to wheat sensitisation. Mean times for new rhinitis 237 days, lower respirotory symptoms 374 days & wheat sensitisation 477 days. Main conclusion, rhinitis occurs sooner than asthma symptoms, most work-related symptoms without wheat sensitisation
Slovak et al	1981	151	Cohort	2++	A prevalence study of OA was carried out by questionnaire in workers who had been exposed to azodicarbonamide dust in the process of its manufacture. 28 (18.5%) people without previous asthma gave a history of episodes of late onset asthma after exposure to azodicarbonamide. Over half developed asthma within 3 months of 1st exposure & 75% developed it within the 1st year. Additional symptoms included rhinitis 29% & conjunctivitis 25%.
Smith et al	2005	90	Case series	3	Data on the latent period for symptomatic sensitization, resulting in either OA or ORh, were obtained from an in-house health surveillance programme in a single large organization. Over a period of 10 years, 90 employees were identified with symptoms attributable to sensitization. The mean latent period was 7.3 years, with 3 employees describing the onset of symptoms in their first year of exposure.
Storaas et al	2005	197	Cross-sectional	3	Employees in 6 bakeries were interviewed and completed a questionnaire. SPT was performed, total and specific IgE were determined. Prevalence of ORh varied between 23% and 50%, depending on the criteria used. The occurrence of nasal symptoms preceded the development of lower airway symptoms. ORh, both IgE- and non-IgE-mediated, was associated with asthma symptoms. Commonest causes of sensitization (20%) were storage mites. Storage mite sensitization was related to occupational rhinitis and work exposure.
Talini et al	2002	297	Cross-sectional	2+	Millers & bakers were examined by questionnaire, pulmonary function tests & SPTs to common allergens & to wheat flour dust extracts. 82 subjects who showed asthma-like symptoms in the questionnaire and/or low forced expiratory volume in 1 sec (FEV1) were selected for methacholine challenge; hyperreactive subjects underwent SIC with flour dust. 6 were diagnosed as having flour-induced OA. Atopy & SPT sensitivity to flour was partially related to the response to flour bronchial challenge.
Tarlo et al	1997a	223	Cross-sectional	2+	Identifies Ontario cases of isocyanate-induced OA & the companies at which they worked. Compares levels of isocyanate concentrations measured at 20 case companies with non-case companies based on air samples. Results provide some evidence that facilities having OA claims have higher isocyanate exposures than those without claims.
Tarlo et al	1997b	235	Case series	3	74% of patients with isocyanate induced OA had work-related nasal symptoms, a significantly lower proportion than in other OA. About 50% of those who developed OA did so within the first 3 years of exposure.
Toren et al	1999	1780	Nested case-referent	2+	Questionnaire information was collected, including work exposures & smoking habits. The highest risks for asthma were associated with exposure to grain dust (OR = 4.2) & flour dust (OR = 2.80). Among males, significantly increased risks were observed after exposure to flour dust, welding fumes, man-made mineral fibres, & solvents. Among females, increased risks for asthma were associated with exposures to paper dust & textile dust. In logistic regression models controlling for age, smoking, sex & interacting exposures, increased risks were seen for welding fumes (OR = 2.0), man-made mineral fibres (OR = 2.6) & solvents (OR = 2.2). The fraction of asthma attributed to occupational exposures after adjusting for sex, smoking & age was 11%.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Toren et al	2009	-	Meta-analysis	1+	Authors searched Pub Med from June 1999 through December 2007 & identified 6 longitudinal general population-based studies; 3 case-control studies & 8 cross-sectional analyses from 7 general population-based samples. They added 10 estimates prior to 1999 included in a previous review. The longitudinal studies indicate that 16.3% of all adult-onset asthma is caused by occupational exposures. In an overall synthesis of all included studies the overall median PAR value was 17.6%.
Ucgun et al	1998	312	Cross-sectional	2+	A clinical & epidemiologic prospective study in 3 phases was done among car & furniture painters exposed to isocyanate in Turkey. In the 1st phase of the study, a modified questionnaire & pulmonary function test (PFT) were done. During the 2nd phase PEF was monitored. In the 3rd phase, histamine NSBR tests were done. 30 workers (9.6%) were diagnosed as having OA. Smoking habits & atopy in the OA-diagnosed workers were found to be statistically significantly high in comparison to the other workers.
Vanhanen et al	1997	173	Cross-sectional	2+	Study in Finnish enzyme production & laboratories. The SPT showed 21 employees (12%) to be sensitized to ≥1 enzymes. 16 +ve persons had specific IgE. Atopy was distinctly associated with enzyme sensitisation. An exposure-response relationship was found for enzyme sensitisation & for respiratory symptoms during work. For sensitisation, the exposure-response linear trend was statistically significant. It weakened but remained statistically significant after stratification for atopy. For symptoms, the exposure-response linear trend was statistically significant & the statistical significance remained after stratification for atopy. Atopics are more susceptible to sensitisation than non-atopics. Non-atopics are also at risk; the exposure-response relationship emphasizes the need for proper exposure control.
Venables et al	1985a	329	Cross-sectional	2++	Using RAST with a tetrachlorophthalic anhydride (TCPA) human serum albumin conjugate, specific IgE was detected in 24/300 factory workers exposed to TCPA. 20/24 (83.3%) were current smokers compared with 133/276 (48.2%) without antibody. There was a weaker association with atopy, defined by SPTs with common allergens. Smoking & atopy interacted, the prevalence of antibody being 16.1% in atopic smokers, 11.7% in non-atopic smokers, 8.3% in atopic non-smokers, & nil in non-atopic non-smokers. Smoking may predispose to, & interact with atopy in, the production of specific IgE to this hapten protein conjugate. Nasal symptoms were associated with work area but not with specific IgE against TCPA.
Venables et al	1985b	221	Cross-sectional	2++	21/221 developed symptoms after 1971. In this year a supplier had modified a coating allowing, at the temperatures used in the process, liberating toluene di-isocyanate (TDI). 2 symptomatic subjects were tested by inhalation of TDI & showed asthmatic reactions. Others were found to have asthma related to work by PEF records. Over half the 21 had a symptom free latent period after first exposure of three years or less, a pattern not seen in other subjects with respiratory symptoms. After the isocyanate had been removed from the process 17 of these subjects became asymptomatic or improved; a greater proportion than in other subjects with respiratory symptoms.
Venables et al	1988a	296	Cross-sectional	2++	This study examined data from 3 surveys of workers exposed to laboratory animals. 4 indices were studied: symptoms suggestive of OA, symptoms suggestive of any occupational allergy, +ve SPT to animal urine extracts & serum binding in RAST with urine extracts. Pooled data from the 3 surveys showed an association between smoking & all indices except RAST; the association was significant for symptoms of OA. 1 of the 3 surveys consistently showed a stronger association of allergy indices with smoking than with atopy (defined as SPTs to common aeroallergens). Associations with smoking persisted after stratifying by atopic status, suggesting that smoking may be a risk factor for LAA. (The factory where smoking was more strongly associated with allergy than atopy was new; mean employment duration 2.6yrs).
Venables et al	1989a	91	Cohort	2+	Smoking was the only significant predictor of a +ve result on SPT with platinum salts & its effect was greater than that of atopy; the estimated relative risks when both were included in the regression model were: smokers versus non-smokers 5.05 & atopic versus non-atopic 2.29. Number of cigarettes smoked/day was the only significant predictor of respiratory symptoms. Smokers were at increased risk of sensitisation by platinum salts & had an increased risk of occupational allergy. Smoking pre-dated allergy, the association was strong & there was a suggestion of a dose-dependent gradient, observations that are consistent with a causal relationship. The risk for atopy was smaller than that for smoking & was not significant after taking account of smoking. People with a history of allergy were not employed in the refinery & thus a few highly susceptible atopic subjects may have been excluded, leading to underestimation of the risk from atopy. Of the 15 subjects with chest symptoms, 14 also had eye/nose symptoms.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Weill et al	1971	60	Cohort	2+	13/60 had symptoms of 'lower respiratory disease,' 11 with wheezing, cough, shortness of breath & chest tightness. No relation between smoking & symptoms or exposure level & symptoms was observed. Symptomatic individuals were more likely to have an atopic history – 43% of symptomatic individuals were atopic versus 19% of asymptomatic individuals. In plant A, no +ve SPTs were found in the low exposure group versus 53% of the moderate exposure group & 45% in the high exposure group. In plant B, 16% +ve SPT reactions were found in the low exposure group, versus 35% of the moderate exposure group & 52% in the high exposure group.
Wernfors et al	1986	118	Cross-sectional	2+	Out of 118 workers exposed to phthalic anhydride (PA) dust for 2 months or more in 4 plants producing alkyd and/or polyunsaturated polyester resins, 28 suffered from work-related rhinitis, 13 from chronic productive bronchitis & 21 from work-associated asthma. Asthma was mostly of the late type & in 48% bronchial symptoms were preceded by rhinitis. Rhinitis was present in only 19% of non-asthmatics. 3 out of 11 asthmatics had a PA-+ve SPT & in 2 subjects, antibodies were present. 4 out of 25 heavily exposed subjects without asthma had a NSBR. Chronic productive bronchitis was common & was more prevalent among former workers than among present employees, indicating a selection of non-reacting subjects in the plant.
Winck et al	2004	18	Case-control	2+	Study aimed to evaluate allergic sensitisation to *Chrysonilia sitophila, Penicillium glabrum*, & *Trichoderma longibrachiatum* in cork workers with asthma. SPTs with common allergens & with 3 fungi were performed on 10 cork workers with asthma & 8 non-exposed asthmatics. Based on serial PEF measurements, 5 were classified as having OA & 5 as having non-OA. 2/10 patients with occupational exposure & 4/8 of control group showed +ve results for SPTs for common allergens. All exposed patients had -ve SPT results for the fungal extracts. In patients with asthma & occupational exposure, immunoblotting results confirmed the absence of specific IgE. However, specific IgG4 was present in some cases. Authors conclude that atopy does not seem to characterise OA in cork workers. Despite their long exposure to moulds, no evidence of IgE sensitisation was found to the 3 most prevalent cork fungi in patients with OA, which points to the search for other causative agents, such as cork chemical compounds or contaminants.
Witmeur et al	1973	355	Cross-sectional	2++	The number of atopics among RAST sensitive individuals is high (38%). The percentage of atopics among all investigated enzyme workers was 4.5%.
Zentner et al	1997	10 + 10	Case-control	2+	Study investigated 10 sensitized & 10 non-sensitised workers from a pharmaceutical factory who had been exposed to enzymes. 10 non-allergic subjects served as a control group. Titrated SPTs (SPT), RAST, & immunoblot studies were performed with all six enzymes. SPT reactivity revealed multiple sensitisations to proteolytic enzymes. Immunoblot studies demonstrated IgG-binding bands in both SPT +ve & -negative workers, indicating exposure to the enzymes, but not in 10 unexposed control subjects. Atopic subjects were at greater risk of developing IgE-mediated sensitisation (7/10) & allergic symptoms to enzymes (5/7). However, even without risk of atopy, IgE-mediated hypersensitivity occurred in a few subjects (3/13) exposed to enzymes by inhalation for prolonged periods of time

EVIDENCE TABLE B

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Bernstein et al	1993	243	Cross-sectional	2+	Study of workers exposed to diphenylmethane di-isocyanate (MDI) in a plant designed to minimize exposure. On the basis of questionnaire responses, diagnoses were derived that included OA; non-OA; work-related & non-work-related rhinitis; & lower respiratory irritant responses. A significant association was found between PEF variability & a questionnaire asthma diagnosis. Physicians confirmed 3 cases of OA. 1 possible case was a symptom-free maintenance worker who reported no symptoms on questionnaire or when examined by a physician, but who had impaired FEV1 that improved by 16% after bronchodilator treatment. In all 3 cases OA symptoms remitted after the worker left the workplace.
Botham et al	1987	383	Cohort	2+	The pattern of incidence of allergy to laboratory animals was studied prospectively in individuals occupationally exposed to rodents & to rabbits. The reduction in the incidence of the disease coincided with the introduction of a site order & code of practice for working with animals & an education programme designed to focus awareness on the problem.
Brant et al	2005b	3000	Cohort & Cross-sectional	++	A supermarket company with 324 in-store bakeries conducted a 3 stage health surveillance programme. The 1st stage involved the administration of a simple respiratory questionnaire. If chest symptoms were present a 2nd questionnaire focusing on their work relationship was administered. If +ve a blood sample was requested to measure specific IgE to flour & fungal alpha-amylase. The results were compared to an independent cross-sectional survey of employees in 20 of the company's stores. The prevalence of employees who reported "any respiratory symptoms" was higher at survey than at surveillance (64% vs 22%). Surveillance estimated that 1% of bakery employees had work related symptoms with specific IgE, compared with 4% in the cross-sectional survey. Comparison with a standard cross-sectional survey suggests that routine surveillance can underestimate burden of OA.
Cathcart et al	1997	731	Cohort	2++	Workers from 5 locations in the UK were subject to respiratory health surveillance including lung function testing over a period of 4-20 years. Study shows correlation between airborne concentrations of enzyme & incidence of asthma in UK soap & detergent industry over 20 years.
Cockcroft et al	1981	213	Cross-sectional	2++	An association significant at the 2% level was found between SPT atopic status & asthma from animal contact. Subjects with a previous history of asthma were not significantly more likely to develop symptoms from animal contact but were more likely to develop animal WRA. The authors conclude that excluding atopic individuals will not solve the problem, & screening new entrants is unlikely to be successful in view of the long average exposure period before symptoms develop & the fact that SPT reactivity to animal extracts is rarely present without symptoms.
Cullen et al	1996	102	Cross-sectional	2++	Survey of 23 autobody shops. There was a high rate of airway symptoms consistent with OA (19.6%). Symptoms were most prevalent among those with the greatest opportunity for exposure (dedicated spray painters) & least among office workers. Smoking seemed to correlate with symptoms. OA symptoms were found 3 times more frequently among painting shop-floor workers & dedicated painters who did not use a +ve pressure ventilator (23.4%) than among those who used it (8.3%), but the difference was not statistically significant. Regular use of air-supplied respirators appeared to be associated with lower risk among workers who painted part- or full-time. Due to limited compliance, only 2 demonstrated unequivocal evidence of labile airways; 2 others demonstrated lesser changes consistent with an occupational effect on flow rates.
De Zotti et al	2000	125	Cohort	2+	Study aimed to investigate the occurrence of work-related respiratory symptoms & to assess the effect of atopy in trainee bakers. Authors conclude that personal history of allergic disease is a predisposing factor for the development of symptoms caused by exposure to wheat flour & may be a criterion of unsuitability for starting a career as a baker. Atopy based on the SPT is useful for identifying subjects with allergic disease, but should not be used to exclude non-symptomatic atopic people from bakery work.
Drexler et al	1999	110	Cross-sectional	2++	An investigation of workers exposed to hexahydrophthalic acid anhydride (HHPA) & methyltetrahydrophthalic acid anhydride (MTHPA) when hygiene conditions at the plant were improved. In November 1995 a second investigation of 84 people was performed. Of the 6 people with clinically relevant sensitisation confirmed by a challenge test in 1991, 5 were still at their workplace. From 1991 they were only exposed to MTHPA at a reduced concentration & all of them reported fewer symptoms than in 1991. Authors concluded that in cross-sectional studies there is a selection bias with a risk of underestimating the incidence of allergic diseases. The results further suggest that the improved hygiene conditions probably had a +ve effect on the symptoms in sensitised people.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Fisher et al	1998	159	Cohort	2+	A comprehensive programme to reduce exposure to laboratory animal allergens was developed in a pharmaceutical company (education, engineering controls, administrative controls, use of personal protective equipment & medical surveillance) & was surveyed for 5 years. After instituting the programme, authors the prevalence of LAA ranged from 12%-22% & the incidence was reduced to zero during the last 2 years of observation. Authors conclude that LAA is preventable through the implementation of a comprehensive effort to reduce exposure to allergens.
Flood et al	1985	2344	Cross-sectional	2+	Results from enzyme detergent workers employed in 3 factories were analysed in 3 separate groups. Spirometry & SPTs to standardised enzyme were performed 6 monthly for the first 6 years & then annually. The large reduction in enzyme dust levels coincided with a drop in the incidence of +ve SPTs to enzymes among new employees & among atopics.
Gautrin et al	2001b	373	Cohort	2++	Study describes in apprentices exposed to laboratory animals, in a 3-4-yr programme. Apprentices at 5 institutions were assessed prospectively with questionnaire, SPT with animal-derived allergens, spirometry & airway responsiveness. Depending on the school, students were seen 8, 20, 32 & 44 months after starting the programme. The +ve predictive values (PPVs) of SPT reactivity to work-related allergens for the development of work-related RC & respiratory symptoms were 30% & 9.0%, respectively, while the PPV of work-related RC for the development of OA was 11.4%. Both SPT reactivity to work-related allergens & rhinoconjunctivitis symptoms have low +ve predictive values.
Gordon, et al	1997	362	Cross-sectional	2+	A questionnaire was issued to flour-exposed workers in a large bakery. The questionnaire identified 68 workers with respiratory symptoms. Of these, 21 proceeded to full assessment. A diagnosis of asthma was made in 5 cases, 1 of which was bakers' asthma. 11 workers not reporting any symptoms by questionnaire were referred to clinic & 5 were diagnosed as having asthma. Authors conclude that screening questionnaires may lead to an underestimate of the prevalence of asthmatic symptoms & as such should not be used alone in workplace screening.
Grammer et al	2002b	66	Cohort	2+	Study aimed to determine whether the use of respiratory protective equipment (RPE) would reduce the incidence of OA due to exposure to hexahydrophthalic anhydride (HHPA) in newly hired individuals. Subjects were evaluated annually for development of +ve antibody to HHPA & occupational, immunologic respiratory disease, including OA. With use of RPE, the rate of developing an occupational immunologic respiratory disease was reduced from approximately 10 to 2% / year. OA developed in only 3 individuals (all in the higher exposure category). Authors conclude that RPE can reduce the incidence of occupational immunologic respiratory disease, including OA, in employees exposed to HHPA.
Juniper et al	1977	1642	Cross-sectional	2+	Reduction in the in the level of enzyme exposure led to a reduction in the level of sensitisation & respiratory symptoms. However, no evidence of significant differences in annual change in FEV1 as percentage between the +ve & -ve SPT employees in any group.
Kraw et al	1999	39	Cohort	2+	The surveillance questionnaire in this study was sensitive but not specific. Spirometry did not detect asthma in any patients who denied respiratory symptoms. It remains possible that workers may have been more honest in admitting symptoms on the questionnaire, knowing that an objective breathing test was also being performed.
Levy et al	1999	275	Cohort	2+	Use of powder free protein poor NRL gloves in place of powdered protein rich NRL gloves may reduce the development of sensitisation to NRL.
Liss et al	1993	52	Cross-sectional	2+	The prevalence of specific IgE was highest in the mold & intermittent groups (54%), in comparison with the coil assembly (25%) & office (0%) groups. Since ventilation was installed & tetrachlorophthalic anhydride (TCPA) exposures reduced to less than 0.1 mg/m^3, there was a marked decrease in symptoms & no new cases of OA among newly hired workers at the plant.
Mackie et al	2008	92	Case series	3	Analysis of respiratory questionnaire & spirometry results during 1995-2000 & more detailed assessment of the outcome of possible OA cases between 1998 & 2000. Approximately 3700 employees had health surveillance each year. 27% required further assessment; information on 92 employees who were referred to their GP for further assessment was examined. None of these was recommended for GP review on the basis of abnormal spirometry alone. In 8 cases (9%) there was a combination of abnormal spirometry & +ve history & in the other 84 cases (91%) abnormal history only. Half failed to see their GP & of those referred to a specialist only 63% attended. Of 20 employees who did see a specialist, 9 (45%) were diagnosed as having OA due to isocyanates, indicating a mean annual incidence rate of 0.79/1000 workers identified by surveillance. The mean time from health surveillance to confirmed diagnosis was 9 months (range 6-12 months).

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Merget et al	1988	56	Cross-sectional	2++	Data of platinum (Pt) refinery workers were compared (group A: workers with work-related symptoms (8); group B: workers with symptoms not clearly work-related (9); group C: asymptomatic workers (13) & controls (group D: atopics (10); group E: non-atopics (16). Exposure to Pt salt was higher in group A than in groups B or C. All subjects of group A & 3 workers of group B, but none of the workers of the other groups, showed a +ve SPT to Pt salts. Total serum IgE was higher in groups A & D than other groups, however Pt salt-specific IgE was higher in group A. Histamine release with Pt salts was found in all groups & was highest in atopic controls. Neither histamine release from basophils with Pt salts, nor RAST to detect Pt salt-specific IgE were helpful in the diagnosis of Pt salt allergy.
Moscato et al	2005	47	Case series	3	All exposed & symptomatic. NSBR at baseline in 12/21 challenge +ve workers (sensitivity 57%), measured mean 3 days (1-45) after last exposure. Average latency from first exposure to symptoms 7 years. Rhinitis preceeded asthma in 4/21, rhinitis developed simultaneously with asthma in 7/21, 10/21 with OA did not have rhinitis. Rhinitis therefore not a very useful early symptom in this group. 0/14 challenge +ve workers had +ve SPT to freshly prepared ammonium persulphate at 1 & 5%. Patch tests to ammonium persulphate +ve in 9 with contact dermatitis. Sputum eosinophilia defined as >3%. Sensitivity for OA versus challenge 70% (7/10) & specificity 73% (3/11 +ve), measurements pre challenge. Also states stop-resume test +ve in 13/23 challenge negative workers.
Newill et al	1986	1600	Other	2++	Results indicate that the use of the pre-employment screening criteria as determinants for hiring laboratory animal workers is unwarranted especially in view of: (1) the dearth of reliable estimates of the strength of association between the screening criteria & LAA; & (2) the absence of a carefully formulated consensus approach to the problem of LAA. Authors conclude that the implementation of a screening program should be preceded by careful evaluation of its risks & benefits by all groups involved, that any potential medical benefits of screening should outweigh its disadvantages or hazards, & that a clearly developed policy on the use of results of the screening programme should be established.
Petsonk et al	2000	214	Cohort	2+	Study evaluated respiratory health in workers using methylene diphenyl di-isocyanate (MDI) at a new wood product manufacturing plant designed to minimise worker exposure. Respiratory protection (RPE) included +ve pressure air-supplied hoods in the areas of greatest concern, & air-purifying negative pressure RPEs in other areas. Workers were asked if they used the required RPE when potentially exposed to MDI, & whether they briefly removed the RPE at any time while potential exposed. New-onset asthma-like symptoms were reported in 15/56 workers in areas with the highest potential for exposure versus 0/43 workers in the lowest potential exposure areas. New onset asthma symptoms were significantly more prevalent among workers who indicated that they had briefly removed RPE, than among individuals who reported never doing this. Among workers who subsequently indicated briefly removing their RPE at work, 18% had met the case definition; in contrast, of the individuals who reported they never removed their respirators, none had started out with asthma symptoms ($p = 0.05$).
Platts-Mills et al	1987	179	Cross-sectional	2++	IgG & IgE to a purified rat urinary allergen in sera were measured in 179 laboratory workers of whom 30 reported symptoms on exposure to rats. In order to exclude 66% of workers who developed asthma, it would have been necessary to exclude 71 individuals who had +ve SPTs to inhalant allergens. Rejecting the 41 individuals a history of inhalant allergy and +ve SPTs would only have avoided 50% of the cases of asthma and 33% of cases of rhinitis. Most atopic individuals did not develop allergic symptoms or specific IgE.
Redlich & Stowe	2001	75	Cross-sectional	2+	Study aimed to characterize effects of di-isocyanate exposures on auto body shop workers. No overt cases of clinically apparent di-isocyanate asthma were identified based on spirometry, methacholine challenge, peak flows, & symptoms. HDI-specific IgE was detected in 2 workers. HDI-specific lymphocyte proliferation, increased methacholine responsiveness, & symptoms of chest tightness/ shortness of breath were more common in most heavily HDI-exposed workers. Findings demonstrate the presence of HDI-specific immune responses in a large proportion of healthy HDI-exposed workers.
Renstrom et al	1994	225	Cohort	2+	In a prospective study of laboratory technicians, selected indicators of allergy & atopy were studied in an attempt to determine predictors of laboratory-animal allergy (LAA). From results it does not seem likely that refusing to employ atopic subjects in animal work will prevent the development of LAA. Preventing atopic subjects from animal work would only have reduced the 9 sensitised and/or symptomatic subjects to 7. Preventing subjects with total IgE levels >100 kU/l from working with animals would have reduced the number of subjects developing LAA to 2 instead of 9. On the other hand, 8 non-reactive subjects (after this study) would also have been excluded from such work.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Saary et al	2002	97 + 131	Cross-sectional	2++	A study using a questionnaire & SPTs to NRL extract. 97 subjects completed the questionnaire & underwent SPTs in 2000; compared with 131 subjects in 1995. Percentages of subjects reporting asthma symptoms, rhinitis or conjunctivitis within minutes of NRL exposure were 4% & 7% respectively in 2000; & in 1995 were 7% (P = not significant), 13% (P = not significant). Of 97 subjects who underwent SPTs, 3 (3%) had +ve SPT responses to NRL in 2000; compared with 13 (10%) of 131 subjects in 1995 (P =.03). The results suggest a preventive effect on NRL allergy in dental students from the change to low-protein/powder-free NRL gloves in the dental school.
Slovak et al	1981	151	Cohort	2+	A study was carried out by questionnaire in 1980 among a group of workers who had been exposed to azodicarbonamide dust in the process of its manufacture. Atopics were not selected out at pre-employment. Identical proportions (48%) were found among sensitised & un-sensitised asymptomatic workers. It is unlikely that atopy is predictive of predisposition to azodicarbonamide sensitivity. Author concluded that it seemed timely to reconsider the value of the widespread occupational medical practice of automatically excluding atopics from work with lung sensitisers.
Stenton et al	1993	1126	Cross-sectional	2+	Shipyard workers & job applicants completed an asthma questionnaire, & also underwent measurements of ventilatory lung function (FEV1, FEV1/FVC & PEFR) & airway responsiveness. The questionnaire symptoms (wheeze, chest tightness, undue coughing or abnormal breathlessness) had a low (28%) sensitivity for detecting definite or possible asthmatic activity & a specificity of only 73%. The sensitivity of the ventilatory function tests (any one abnormal) was also low at 21% with a specificity of 92%. When the FEV1 < 80 % predicted criterion was considered separately, its sensitivity was 11% & its specificity was 98%. Results illustrate that caution is needed when interpreting the results of questionnaires & measurements of ventilatory lung function in the diagnosis of asthma among working populations
Vandenplas et al	2009	195	Compensation Register	2+	Incident cases of NRL-induced OA were identified through a retrospective review of claims submitted to the Workers' Compensation Board to December 2004. Categorized by the year of asthma onset, the incident cases of definite & probable NRL-induced OA markedly decreased from 1999 onwards. 88/300 hospitals (29.3%) returned completed questionnaires. Among those responding, the use of powdered NRL gloves fell from 80.9% in 1989 to 17.9% in 2004. Powdered NRL gloves were predominantly substituted with NRL-free gloves, especially in the case of non-sterile procedures. These national compensation-based data confirm that a persistent decline in the incidence of NRL-induced OA has occurred since late 1990s. This downward trend has temporally been associated with a decreasing usage of powdered NRL, further supporting a beneficial role of changes in glove policies. There may have been a reduction in the allergen content of gloves as part of manufacturing improvements.
Vedal et al	1986	652	Cross-sectional	2++	Data was obtained from 652 workers in a western red-cedar sawmill on symptoms, pulmonary function, immediate SPT reactivity to common allergens, NSBR, total IgE level, & sensitisation to plicatic acid conjugated with human serum albumin as measured by RAST. 7% of workers had an elevated RAST, & 20% had NSBR. Elevation in RAST was associated with NSBR. 46% of workers with RAST elevation had NSBR compared to 18% in workers with no RAST elevation. BHR was associated with increased prevalence of respiratory symptoms as well as with lower levels of pulmonary function. Authors conclude that plicatic acid-specific IgE & NSBR are associated in western red-cedar workers & that this association may reflect a causal connection.
Venables et al	1988b	138	Cross-sectional	2+	Survey was carried out on workers exposed to laboratory animals. 44% had symptoms in a self-completed questionnaire that were consistent with LAA of whom 11% had chest symptoms. LAA chest symptoms were almost 5 times more common in atopic than non-atopic subjects (20% versus 4%). A +ve SPT to animal urine was associated with atopy versus non-atopics (23% versus 5%) & with LAA chest symptoms. Although not statistically significant, there was an inverse relationship between duration of employment & LAA chest symptoms suggesting selection of affected people out of employment with animals. As atopy is common in the general population it is difficult to justify excluding atopic subjects from employment with animals, but atopic subjects who develop +ve SPTs to animal allergens may be at particular risk of chest symptoms & could be identified during employment & advised on risk. Regular screening at least provides useful information on the scale of the LAA within an organisation & in conjunction with occupational histories may point to particular working areas or practices that should be modified. There was a suggestion in these results of an association between LAA chest symptoms & current smoking.

EVIDENCE TABLE C

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Allmers et al	2000	27	Case series	3	No clear relationship between FeNO changes & bronchial reposnse to SIC was observed in patients challenged with latex (n=18) or with MDI (n=9)
Alvarez et al	2001	3	Case series	3	Carried out SPT with common and occupational allergens and with oilseed rape (OSR) extract. Total and specific serum IgE levels were measured. The patients underwent SIC. The day before and 24 h after SIC, the methacholine (M)-BPT and induced sputum were performed. OSR sensitization (skin tests and specific serum IgE) was detected in all 3 patients. The OSR-BPT elicited early responses in 2 subjects. Methacholine sensitivity, sputum eosinophils, and sputum ECP levels increased 24 h after the SIC in all the patients. NSBR can be normal with +ve SIC.
Anees et al	2002	38	Case series	3	Study of sputum cellular profile of workers with OA induced by LMW agents & to relate this to physiological measures of airway obstruction. Despite work-related deterioration in PEF, many workers with OA show low within day diurnal variability atypical of non-OA. Authors conclude that LMW OA can be either eosinophilic or non-eosinophilic with latter predominating (24/38). Sputum eosinophilia was associated with more severe disease & greater bronchodilator reversibility but no difference in PEF response to work exposure. Sputum eosinophilia observed in 37% of 38 patients with OA; the presence of eosinophilia was unrelated to the causative agent, the duration of exposure, atopy or treatment.
Anees et al	2004	141	Case series	3	Identified minimum quantity requirements for best results for Oasys discriminant analysis. If ≥2.5 weeks, ≥3 consecutive workdays & ≥4 readings/day, then sensitivity 78.1% & specificity 91.8% against independent diagnoses. For lesser quantity records sensitivity 63.6% & specificity 83.3%. High quality PEF records have a higher sensitivity & specificity
Axon et al	1995	30	Case series	3	Study aimed to determine the differences between patients with OA & those with non-OA at 2 clinics. Significantly more subjects with OA reported improvement on holiday, whereas no significant difference was found for worsening of symptoms on workdays. Those with OA were less likely to report seasonal variation in symptoms, exacerbation by allergies, pets & stress, or a family history of asthma. Recognition of some of these features in a patient's history may help in the difficult task of differentiating OA from non-OA.
Baldwin et al	2002	24	Case series	3	OASYS-2 is a diagnostic aid for OA that interprets PEF records. Study aimed to assess level of agreement between expert clinicians interpreting serial PEF measurements in relation to work exposure & to compare the responses given by OASYS-2. Considerable variation in agreement was seen in expert interpretation, which may lead to inconsistencies in diagnosis of OA (experts underscore versus OASYS). There is a need for objective scoring system, which removes human variability, such as that provided by OASYS-2.
Barbinova et al	2006	55	Case series	3	A rise of 50% or more in baseline FeNO following SIC with diisocyanates was observed both in patients with a +ve challenge response & in those with NSBR whose challenge response was negative. The combination of NSBR & an increase in FeNO may indicate a high risk of subsequent OA
Baur et al	1995	9	Case series	3	Anhydride workers, who complained of various respiratory symptoms, were studied. 4/9 had +ve SPT responses to ≥1 conjugates & had elevated IgE concentrations in addition to 2 other workers. 3/6 of six nasal challenges & 4/9 bronchial challenges resulted in +ve responses. All but one of the +ve nasal or bronchial test responses were associated with elevated IgE levels. The 7 +ve challenge test results included 5 +ve SPT. In all but 2 of the subjects with negative challenge test results, no specific IgE could be detected. In these 2 subjects the negative results were associated with low levels of IgE, & in one, with the absence of asthma. Anhydrides investigated in this study can induce IgE-mediated hypersensitivity, which can be diagnosed by using the respective human serum albumin in estimation of specific IgE & in skin, nasal & bronchial challenge tests. Estimation of IgE was demonstrated to be more sensitive than SPT.
Baur et al	1998b	229	Case series	3	Methacholine challenge (MC) was performed in subjects with suspected OA. They were also subjected to SIC, questionnaire & interviewed by an experienced physician. Study aimed to investigate whether MC and/or OA case history are reliable predictors of SIC outcomes. MC results are only moderately associated with WRA case histories whereas +ve outcomes of challenges with occupational agents are well correlated with +ve MC results plus OA case histories. Authors conclude that in most cases, OA is combined with BHR & WRA symptoms. In subjects with a +ve OA case history, a -ve MC test result can almost rule out a +ve SIC test result. Hence, the MC test can reduce performance of the laborious SIC.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Baur et al	2005 (a)	45	Case series	3	Case series of healthcare workers with latex exposure. FeNO measured before & after SIC. 16/20 challenge +ve rhinitis had +ve latex IgE, +ve in 1/11 with asthma. Baseline FeNO >9.5 ppb in 7/13 with OA, 8/20 with ORh & 2/12 without disease. >50% increase in FeNO seen at 20-60 mins post challenge in 12/31 (39%) sensitised & 10/14 (71%) non sensitised. FeNO not helpful at baseline or <1 hour post challenge. Specificity & sensitivity of a 50% eNO increase after 22 h in responders were 100 and 56%, respectively. FeNO did not increase the diagnostic validity of SIC over & above standard physiological measures. The latex antigen identified all those with OA & 80% of those with ORh.
Baur et al	2005 (b)	22	Case series	3	Challenges in workers with suspected isocyanate asthma (unclear what criteria were required for inclusion). All exposed, but not clear how recently. 3/5 challenge +ve workers has +ve MDI/HAS IgE (>0.35kU/l with Pharmacia CAP). FeNO measured at 100ml/sec (twice standard rate) normal values said to be <7.7 ppb. Sensitivity for FeNO >7.7 at baseline 4/5 (80%); specificity 8/17 (47%). FeNO increased >30% in 4/5 challenge +ve & 7/17 challenge negative. Does not support the use of FeNO for the diagnosis of OA
Beach, et al	2005	-	Meta-analysis	1++	Estimated pooled sensitivities & specificities for several tests compared to SIC. For NSBR tests, 24 studies reported sensitivity & specificity, with pooled estimates of 66.7% (95% CI: 58.4 to 74.0%) & 63.9 % (95% CI: 56.1 to 71.0%) resp. Pooled estimate from 13 studies reporting only sensitivity was 76.6 % (95% CI: 59.0 to 88.2%). 13 studies reported results for HMW agents, 10 reported sensitivity & specificity with pooled estimates of 79.3% (95% CI: 67.7 to 87.6%) & 51.3% (95% CI: 35.2 to 67.2%) resp. The estimated sensitivity in 5 studies reporting only this data was 75.5 % (95% CI: 56.4 to 88.1%). For agents of differing molecular weights, 5 studies reported sensitivity & specificity. The pooled estimate of sensitivity was 83.7 % (95% CI: 66.8 to 92.9 %) & specificity was 48.4% (95% CI: 25.9 to 71.6%). Sensitivity 43.7% (95% CI: 10.9 to 83.0%) in 3 studies reporting only this value. For serial PEFR 5 studies investigated mixed agents & reported both sensitivity & specificity, with pooled estimates of 63.6 % (95% CI: 43.4 to 79.9%) & 77.2% (95% CI: 66.5 to 85.2 %) resp. One study of a LMW agent reported 86.7 % (95% CI: 59.5 to 96.6%) sensitivity & 90 % (95% CI: 53.3 to 98.6 %) specificity. 2 other studies only reported sensitivity with a pooled estimate of 56.2% (95% CI: 17.2 to 88.8%). 1 study of a HMW agent reported 100% (95% CI: 56.6 to 100%) sensitivity. For SPT to LMW agents, 5 studies reported both sensitivity & specificity, with pooled estimates of 72.9% (95% CI: 59.7 to 83.0%) & 86.2% (95% CI: 77.4 to 91.9%) resp. Sensitivity 51.8 %; 95% CI: 28.5 to 74.4 %) in 11 studies reporting only this result. 16 studies reported sensitivity & specificity for SPT for HMW agents, with pooled estimates of 80.6% (95% CI: 69.8 to 88.1%) & 59.6% (95% CI: 41.7 to 75.3%) resp. Sensitivity was 80.9%; 95% CI: 60.5 to 92.1%) in 10 studies reporting only that result. 5 studies included patients exposed to various agents, with pooled estimates for sensitivity & specificity of 63.0% (95% CI: 41.5 to 80.3%) & 59.2% (95% CI: 45.4 to 71.7%) resp. 11 studies considering serum specific IgE to LMW agents reported sensitivity & specificity; with pooled estimates of 31.2% (95% CI: 22.9 to 40.8%) & 88.9% (95% CI: 84.7 to 92.1%) resp. 10 studies only reported sensitivity, with a pooled estimate of 35.9% (95% CI: 23.2 to 50.9%). For HMW agents, 9 studies reported sensitivity & specificity with pooled estimates of 73.7% (95% CI: 63.9 to 81.0%) & 79.0% (95% CI: 50.5 to 93.3%) resp. 9 studies reported sensitivity alone with a pooled estimate of 81.7 % (95% CI: 57.8 to 93.5%). 6 studies reported eosinophil counts from sputum, blood, or broncho-alveolar lavage. 3 reported sensitivity & specificity with a pooled estimate of 54.9% (95% CI: 23.7 to 82.7 %) & 72.3% (95% CI: 54.1 to 85.3%) resp; 1 study reported 100% sensitivity only. 2 studies of LMW agents reported sensitivity only with a pooled estimate of 53.1% (95% CI: 10.3 to 91.8%).
Brant et al	2005a	239	Cross-sectional	2++	Symptoms & sensitisation in supermarket bakers related to exposure by job category & air measurements. Dust exposure GM 1.2mg/m^3 for bakers with questionnaire plus IgE diagnosed asthma in 9%; lower in less exposed. Only 25% of those with work-related chest symptoms had +ve IgE, more commonly with wheat than amylase.
Brant et al	2006	45	Case series	3	Follow up of symptomatic workers following a study of 78% (35/45) workers diagnosed with OA to detergent enzymes. 86% reported an improvement in their symptoms, 29% asymptomatic. Estimated half life of specific IgE 20 months.
Bright et al	2001	268	Case series	2+	Serial PEF records made by workers with possible OA were divided into 4 sets; 1 & 2 being development sets & 3 & 4 "gold standard" sets where diagnosis was made independently. Set 3 was used to set cut-off for occupational effect, the sensitivity & specificity for the combined model was determined from set 4, which was also used to determine the sensitivity & specificity of the human expert. The repeatability of the human expert re-scoring the same complexes had a weighted kappa score of 0.71. OASYS-3 was 100% repeatable. Both OASYS-3 & OASYS-2 tended to score records less +vely for work-related changes in PEF than the expert. Sensitivity of OASYS-3 was better than OASYS-2 (82% & 75% resp) for an equivalent specificity (94%). The sensitivity of the human expert was 100% with a specificity of 93%.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Brisman et al	2003	89	Case-control	2+	25 asthmatics, 20 rhinitics & 44 controls underwent SPTs with common allergens, flours, fungal alpha-amylase & the storage mite *L. destructor*. 7 asthmatics & 8 rhinitics reported onset of disease during bakery work. Flour SPTs were +ve in 43% of asthmatics or rhinitics vs 16% of referents. The +ve predictive value of sensitisation to flour or alpha-amylase in relation to a clinical diagnosis of OA or ORh was 71%. Sensitisation to *L. destructor* was rare. Indices of airway inflammation were of low predictive value for detecting bakers' asthma or rhinitis in this study.
Burge et al	1979a	29	Case series	3	PEF was measured in 29 workers with respiratory symptoms exposed to colophony fumes & compared with occupational history & bronchial provocation testing (BPT) in the same workers. The most common pattern is for asthma to increase with each successive working day, sometimes with an equivalent deterioration each working day. Regular recovery patterns taking 1, 2, & 3 days are described. Assessment of these records has shown them to be specific & sensitive. Results of PEF records correlate well with BPT & provide a suitable alternative for the diagnosis of mild to moderate OA.
Burge et al	1979b	23	Case series	3	PEF was recorded in workers with respiratory symptoms who were exposed to isocyanate fumes at work. Each worker was also admitted for bronchial provocation testing to toluene di-isocyanate (TDI) or diphenylmethane di-isocyanate (MDI) fumes or both. A final assessment of WRA made from subsequent work exposure was compared with the results of bronchial provocation testing & a subjective assessment of PEF records. Both techniques were specific & sensitive. Recovery from work-induced asthma was shown to be slow - up to seventy days. Several workers developed a pattern resembling fixed airways obstruction.
Campbell et al	2007	54	Cross-sectional	2+	FeNO using ATS/ERS guidelines. +ve SPT used 3mm wheal as cut off sensitivity 100% against symptoms, specificity 7/11 for rhinitis or asthma, 2/11 for asthma. FeNO measured in all & not related to symptoms or sensitisation. Mean values very low (5.9 +/-0.3 ppb nonsensitised & 6.3 +/-0.5 ppb sensitised despite high level of atopy, sugesting that the offline measurements were not valid. At face value suggests that FeNO measurement at work not helpful in differentiating between sensitised & unsensitised. Establishes lupin flour as a cause of asthma & rhinitits, with +ve SIC.
Cartier et al	1989	62	Cross-sectional	2++	The sera of 62/65 workers referred for SIC with isocyanates were analysed for the presence of specific antibodies to the relevant isocyanate. SIC were +ve in 29 subjects, & were more often +ve in those subjects with increased NSBR. 29 subjects demonstrated increased levels of specific IgE and/or IgG to isocyanates in the absence of antibodies against human serum albumin. Although there was a loose association between the results of SIC & levels of specific IgE, the association was much better with the level of specific IgG. 21/29 subjects (72%) with +ve challenges had increased levels of specific IgG, whereas 25/33 subjects (76%) with negative challenges had normal levels of antibodies.
Castano et al	2009	43	Case series	3	ORh often coexists with OA, & can be studied objectively during SIC. ORh is rare in LMW group. Long duration of symptomatic exposure before challenge (mean >4 years). NSBR >16mg/ml in 39%.
Chiry et al	2007	34	Case series	3	Using visual inspection or a computer programme, clinicians were unable to differentiate occupational from work-exacerbated asthma from serial PEF records alone. Agreement between experts for visual inspection varied (Cohens k 0.27 to 0.7).
Cote et al	1990	23	Case series	3	The diagnosis of red cedar OA is usually confirmed by a SIC with plicatic acid. Study aimed to determine the sensitivity & specificity of two other tests, PEF & measurement of bronchial responsiveness (provocative dose of methacholine causing a 20% fall in FEV1 [PC_{20} methacholine]). Patients with suspected OA recorded PEF during 2 weeks away from work & 3 weeks at work. Plicatic acid SIC was performed at the end of the study; 14 patients reacted; 9 did not. Using the plicatic acid SIC as the gold standard, the sensitivity & specificity of PEF recordings were 86% & 89%; changes in PC_{20}, 62% & 78%; & 93% & 45% for a +ve clinical history. The combination of PEF & clinical history revealed 100% sensitivity with 45% specificity. Combination of PEF & PC_{20} did not improve the diagnostic accuracy.
Cote et al	1993	25	Case series	3	Study compared the diagnostic value of a qualitative assessment of change in PEF with objective measures of change in PEF & the results of a SIC test with plicatic acid. 25 subjects with possible red cedar asthma recorded PEF 6 times a day for 3 weeks at work & for 2 weeks away from work & underwent SIC with plicatic acid at the end of the recording period. Results show that qualitative PEF analysis had sensitivity of 87% & specificity of 90% in confirming red cedar OA as diagnosed by SIC.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Di-Franco et al	1998	48	Case series	3	All had prior +ve SIC, were still exposed & had +ve NSBR. For sputum eosinophils >1% 8/8 HMW OA has sputum eosinophilia, 10/16 LMW & 22/24 non-OA asthmatics. Conclusion in workers with OA & +ve SICs who remain exposed, sputum eosinophis >1% (often within the normal range) seen in all those with HMW OA & 63% of those with LMW OA. The finding of sputum eosinophils <1% does not exclude OA in a currently exposed worker.
Dressel et al.	2007	81 + 24	Case-referent	2+	The short-term effect of an educational intervention in asthmatic farmers was evaluated on the basis of spirometric indices and FeNO. Farmers with OA (n = 81), mostly sensitised against cow dander and storage mites, participated in a 1-day educational programme. Outcome measures were assessed at baseline and after 4-6 weeks, using FeNO, lung function and a questionnaire. Results were compared with those of a control group without intervention (n = 24). In the educational group, the proportion of subjects reporting work-related symptoms was reduced after the intervention. FeNO decreased from a geometric mean of 28.2 to 25.7 ppb, and, in subjects with an elevated (>35 ppb) baseline FeNO (n = 32), from 59.7 to 49.2 ppb. The corresponding changes in the control group were 25.6 versus 27.7 ppb and 49.5 versus 48.1 ppb. Spirometric results were unaltered in both groups. Thus FeNO, a marker of allergic airway inflammation, indicated a beneficial effect of a short-term educational intervention in farmers with OA.
Dressel et al.	2009	43	Case series	3	Study of non-smoking farmers with OA 1 year after an educational intervention (n=43) & 15 (not random) with no educational intervention. Small but significant reduction in FeNO in intervention group (31.5-25ppb) but no change in controls (27.2-30.7ppb). Supports use of FeNO in monitoring intervention.
Eifan et al	2005	72	Cross-sectional	2++	85 apprentice car painters registered for car-painting course during the academic year. 72 actively attending agreed to participate. Asked to do 4 readings / day over 3 weeks. Min of 5 days away from work accepted, with remaining at work. 2 experts reviewed PEFs. Showed OA if deterioration at work compared to rest in 2/3 weeks & daily/weekly variability was ≥20%. 36/72 painters complained of WRA symptoms. 28/36 agreed to do PEFs. 6/28 deemed falsified, 22/28 returned reasonable PEF.
El-Zein et al	2003	194	Cohort	2+	Study aimed to determine the incidence of probable OA, bronchial obstruction & hyper-responsiveness among 286 student welders. NSBR was measurable in 194/204 individuals who were present. There were also individuals who developed NSBR without symptoms. Going from a 3.2 fold change to a 2-fold change did not enhance the sensitivity of looking for changes in reactivity. There were also individuals who lost their reactivity (3.1%) about half as often as those who became reactive (6.7%).
Gannon et al	1996	268	Case series	3	PEF records were collected from workers attending clinic for investigation of suspected OA & from workers participating in a study of respiratory symptoms in a postal sorting office, & were divided into 2 development sets & two 2 standard sets. The latter consisted of records from workers in which a final diagnosis had been reached by a method other than PEF recording. Comparison with gold standard set 1 identified a cut off which proved to have a sensitivity of 75% & a specificity of 94% for an independent diagnosis of OA when applied to gold standard set 2. The performance of OASYS-2 is more specific & approaches the sensitivity of other statistical methods of analysis. The evaluation of a large number of PEF records from workers exposed to different sensitising agents suggests that these results should be robust & should be repeatable in practice.
Gautrin et al	2008	408	Cohort	2++	Incidence rates of sensitisation & symptoms are lower after entrance to the workforce in comparison to apprenticeship. Symptoms acquired during apprenticeship remit after starting work in a different job. Follow up average 7.6 yrs after apprenticeship. New sensitisation 9.7/100 yrs in training, 1.3/100 yrs during subsequent exposed work. 16/20 sensitised during training then not exposed became SPT -ve (18.5/100 yrs). Probable OA 8.3% during training & 3% during later exposure. Prognosis better for no mould sensitisation, no pets, no NSBR at start, no skin symptoms. Nothing on level of sensitisation. Shows sensitisation lost on follow-up at 18.5/100 yrs, incidence reduces with duration of follow-up.
Girard et al	2004	49	Case series	3	Study of workers investigated by SIC in Canada, 45/94 excluded. Unable to perform SIC 9/94, unable to induce sputum 7/94, uninterpretable PEF record 3/49, no induced sputum 1/49. Increase in sputum eosinophils >1% sensitivity 65.2% specificity 76%; Increase in sputum eosinophils >2% sensitivity 52% specificity 80%; Increase in sputum eosinophils >6.4% sensitivity 26.1% specificity 92%; PEF analysis by Oasys performed poorly with sensitivity 34.8% & specificity 65.2%; records may have been of suboptimal quality. Addition of sputum eosinophilia increased sensitivity to 36.4%-50% (specificities 75%-80%). Expert agreement of PEF records poor (Cohens Kappa 0.4-0.6).

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Grammer et al	1998	119	Cohort	2+	Aimed to define the utility of serum antibody against trimellitic anhydride (TMA) in predicting development of OA. In 1990, 181 subjects exposed to TMA for at least 1 year; 119 were followed for 5 years. Of 16 with IgE against TMA in 1990, 3 had immediate asthma & another 6 developed asthma during follow-up. Of 165 individuals without IgE against TMA, none had immediate asthma in 1990 & only 1/102 followed-up developed asthma. Of 44 with IgG against TMA, 6 had immunologic respiratory disease in 1990 & 2 more developed it during follow-up. Of 137 without IgG against TMA, none had an immunologic respiratory disease in 1990 & none developed it. Authors conclude that development of antibody against TMA (IgE & IgG) is predictive of the development immunological respiratory disease; absence of antibody is a potent negative predictor.
Grammer et al	2000	42	Case series	3	Employees with trimellitic anhydride-induced immunologic lung disease were studied after they were moved to low-exposure jobs for more than 1 year. Pulmonary symptoms were obtained by physician-administered questionnaire, immunologic studies were performed using ELISA techniques & spirometry & chest films were obtained annually. Of 42, 36 were asymptomatic with normal spirometry. Only mild intermittent symptoms or mild abnormalities on spirometry were present in the other 6 individuals. Approximately half of the individuals had a decline in antibody titre.
Hannu et al	2007	34	Case series	3	Persistent symptoms in case series of 34 Finnish welders with stainless steel asthma render most of them unable to continue at work. +ve challenges to stainless steel welding fumes but SPTs to potassium dichromate & chromium chloride at 1mg/ml universally negative (sensitivity=0%). NSBR normal at presentation in 38%. Long latent interval (mean 18 years), PEF records +ve in 5/8.
Henneberger et al	1991	26	Case series	3	Study aimed to identify the strengths & limitations of using portable PEF meters to document suspected cases of OA that were reported to a surveillance project. Between May 1988 & January 1990, physicians reported 70 cases voluntarily. Subjects who were still employed in suspected work sites were requested to test themselves for at least 15 days, using portable PEF meters. For each of the 14 subjects who were successfully tested, the PEF data provided valuable information about their asthma-work association. However, a large number of subjects whose cases were reported (56) either could not be tested or were not successfully tested. Authors conclude that the collection of serial PEF measurements to document OA would best be initiated by the treating physician when the patient first sought care, rather than waiting until after the case was reported to the state health department.
Hewitt et al	2008	50	Cohort	2+	Measurements of FeNO and spirometry were obtained at baseline (Friday) and twice-daily following a weekend with no animal contact. 11/50 subjects had work-related symptoms; 2/11 had positive serology for LAA. Baseline FeNO was high (> 150 ppb) in the 2 seropositive subjects and increased progressively during the working week in 1 subject, confirming exposure-driven airway inflammation. In seronegative subjects, mean FeNO levels were 19.8 and 21.7 in the symptomatic and nonsymptomatic groups, respectively, with no significant changes in Fe(NO) over time. Serial FeNO measurements may provide complementary information in the assessment of possible occupational sensitisation. The sensitivity and specificity of this approach to diagnosing occupational asthma requires further evaluation.
Hollander et al	1998	398	Cross-sectional	2++	Study aimed to study relationship between allergic symptoms due to working with rats & variability & changes in PEF. 73% subjects completed PEF readings on at least 9 days, of whom 208 had PEF readings on working days with & without contact with animals. The overall prevalence of allergic symptoms was 17.3%. Asthmatic symptoms were reported by 6.7% & PEF values for these workers decreased significantly on days working with the animals compared to the workers without symptoms. Workers with asthmatic symptoms were more likely to have higher PEF variability than workers without asthmatic symptoms. Diurnal variation was unhelpful in separating OA from others. No difference in diurnal variation was observed on animal days from other days. Authors conclude that the PEF of workers who reported asthmatic symptoms due to working with rats decreased significantly on days working with laboratory animals.
Huggins et al	2005	244	Case series	3	Consecutive new referrals were recruited from a specialized occupational lung disease clinic and requested to carry out serial PEFs for the assessment of suspected OA. Requests to carry out the records were either from written postal instructions or personal instruction from a PEF specialist. Record quality received from other clinicians was also analysed separating those using dedicated occupational forms, and those submitting on graph type forms. The postal return rate was 56% and the personal rate 85%. The number of records fulfilling all the data quality criteria were similar in the postal and personal groups (55 and 59%, respectively). Pre-existing records from other clinics plotted from graph charts (fulfilling all criteria) were only adequate in 23%, compared with 61% adequate for pre-existing records plotted from occupational forms. Failure of the record to contain consecutive work periods of > or =3 workdays was the most common failure.

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Jacobs et al.	2008	860	Cross-sectional	2++	Study of a representative group of Dutch craft & industrial bakers with good exposure estimates. Total dust exposure closely related to wheat exposure (20-30ug/m^3 wheat antigen equivalent to 2mg/m^3 dust), can rely on total dust exposure. Atopy & exposure levels both risk factors for wheat sensitisation, but not smoking in this group with 35% current smokers. Bell shaped sensitisation/exposure curve with peak at about 20-30ug/m^3 wheat. Fall off at higher levels thought to be survivor effect rather than development of tolerance. Poor relationship between work-related symptoms & wheat sensitisation (24/202 with ORh on questionnaire & 37/81 with WRA symptoms. Work-relatedness defined from questionnaire as during work.
Jeal et al	2006	689	Cross-sectional	2++	Survey of employees exposed to rats at work on 6 UK pharmaceutical sites. 689 (89%) provided a blood sample and completed a questionnaire. High exposure to rats is associated with lower rates of specific IgE and symptoms but an increased frequency of high specific IgG and IgG4 production. Specific IgG4 produced together with specific IgE may reduce the risk of developing work-related chest symptoms compared with when specific IgE is produced alone. 11% +ve Rat IgE. RAST related to atopy as a risk factor.
Koskela et al	2003	37	Cohort	2++	Dairy farmers with suspected OA due to bovine allergens were studied to identify which tests were useful in selecting patients for SIC with bovine dander allergens. The specific IgE assay had a sensitivity of 9/11 & a specificity of 100%. The SPT (at > 3 mm) had a sensitivity of 11/11 & a specificity of 13/26. There was no additional benefit from measuring histamine PC_{20} or FeNO compared with SIC. Clinical history had poor predictive value (specificity 13/36). Authors did comment that a +ve history & a +ve specific IgE was sufficient to make the diagnosis.
Krakowiak et al	2005	53	Case series	3	The purpose of the study was to analyze morphological and biochemical changes in induced sputum after provocation with occupational allergens (mixture of flours and grains) in subjects with diagnosed OA. Subjects with OA and healthy volunteers had physical examination, SPTs with common and occupational allergens & spirometry. Specific IgE against common and occupational allergens was also measured. Bronchial inflammation was characterized by the percentage of cells & levels of eosinophil cationic protein (ECP). There was a significant increase in the proportion of eosinophils, basophils, lymphocytes, and in the ECP level in induced sputum of occupational allergics after the specific provocation. Sputum induction is a reliable method for measuring allergen-induced airway inflammation.
Lemiere et al	2000	15	Case series	3	All removed from exposure for some time (1-13 years). 5/13 showed a halving or more of Pc20 post challenge (Change in NSBR >x2 sensitivity 38%). Sputum eosinophils counted at x106/ml (no percentages). No normal values given, but increased in day before +ve challenge (when a mean fall in FEV1 was 7.4 =/- 3.8%) in 14/15. Supports eosinophilia as being common post challenge, can be interpreted as mean 7.4% fall in FEV1 significant. Induced sputum might be used to support a +ve challenge when the fall in FEV1 <10%
Lemiere et al	2001	41	Case series	3	SICs were performed in: 17 subjects with a history consistent with OA with +ve SIC; 14 subjects reporting a history consistent with OA with -ve SIC; and 10 asthmatic subjects with no history of OA. Induced sputum and methacholine challenges were performed at the end of the control day and again at the end of the last day of exposure. There was an increase in median sputum eosinophil numbers in subjects with +ve SICs but not in asthmatic subjects without OA. A combination of > 0.26 10(6)/mL increase in sputum eosinophil numbers and a decrease in the concentration of methacholine inducing a 20% fall in FEV(1) of at least 1.8-fold compared with baseline values predicted a 20% fall in FEV1 in 96% (95% CI, 70%-99%) of patients.
Leroyer et al	1998	20	Case series	3	PEF monitoring is often used to establish relationship between occupational exposure & asthma. FEV1 has been found to be a better physiologic index than PEF in the measurement of airflow obstruction. Study aimed to compare accuracy of serial monitoring of PEF & FEV1 in diagnosis of OA. 20 subjects referred for possible OA were asked to perform serial monitoring of PEF & FEV1. 2 sets of graphs were plotted for both PEF & FEV1 (graphs with best of all values & graphs with best of 2 reproducible values). 11 subjects had a +ve inhalation challenge test. In the case of analysis of the graphs plotted with the best of all values, the sensitivity & specificity of the PEF recording was greater than sensitivity of the FEV1 recording. Authors concluded that unsupervised FEV1 is not more accurate than unsupervised PEF monitoring in the diagnosis of OA.
Lin et al	1995	9	Case series	3	SIC with a suspected allergen in the workplace are standard to confirm the diagnosis of OA. Facilities for sophisticated exposure tests are available only in a few institutions. A pilot study was carried out that used a novel approach for an occupational dust challenge test with a rotahaler. The results showed that a +ve challenge test with a rotahaler to deliver red cedar dust was specific in the diagnosis of red cedar asthma but a negative response could not rule out the diagnosis. The rotahaler has merits of being easy to operate, safe, inexpensive, & readily available.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Liss et al	1991	50	Case-series	3	Objective criteria for interpretation of PEF readings were assessed in patients evaluated for suspected OA who had at least 2 weeks of PEF readings & an objective diagnosis based on other investigations. The prevalence of OA was 36%. PEF records were interpreted by 2 observers blinded to other results. Criteria for a PEF interpretation of OA were as follows: diurnal variation ≥ 20% relatively more frequently or with greater variation on working days than days off work. With the objective diagnoses as the gold standard, the sensitivity of the PEF interpretations was 72% for OA; specificity for no asthma was 5%. Excluding those with ≥20% variation on only one day sensitivity improved to 93% for OA, & specificity to 7%. There was an acceptable level of inter-observer variation (kappa 62 to 83%). Authors conclude that simple objective criteria for PEF interpretation can be developed with acceptable inter-observer variation.
Maestrelli et al	1994	9 + 4	Case referent	2+	9 subjects with OA induced by diisocyanate (DI) and 4 control subjects never exposed to DI were studied. In sensitized subjects eosinophils increased from a median value of 5 (15)% before SIC to 29 (29)% (P = 0.014) and to 30 (31)% (P = 0.031) 8 and 24 h after SIC, respectively. Sputum eosinophilia was observed both in early and late reactors and declined to near to baseline values 48 hr after SIC. Eosinophils in control subjects did not exceed 7% during the study.
Maghni et al	2004	133	Case series	3	NSBR at diagnosis in 4% of 133 patients with OA from a variety of agents. A poor outcome after avoidance of exposure was associated with sputum eosinophilia and/or neutrophilia at follow-up
Malo et al	1991	162	Cross-sectional	2++	Subjects were referred to clinic & assessed because their physicians thought their asthma might be WRA. They filled in a questionnaire & underwent objective assessment with SICs (72), monitoring of PEF for periods at & away from work (29), or both (61). 75 subjects (46%) were shown to have OA. Symptoms alone (type & timing) did not provide a satisfactory differentiation between those subjects with & without OA. +ve predictive value of questionnaire diagnosis of OA found to be low (63%) but negative predictive value higher (83%). Therefore, if questionnaire suggests diagnosis of OA, then >50% chance that the diagnosis is correct. The clinical history taken by physicians with experience in OA is not a satisfactory diagnostic tool & the presence or worsening of symptoms at work & improvement during weekends & holidays was not conclusively linked with OA. Normal BHR was observed in 12/75 with proven OA. Study suggests that an open medical questionnaire is not a satisfactory means of diagnosing OA.
Malo et al	1993a	74	Case control	2++	PEF recording was carried out in subjects referred for possible OA, to determine the optimum number of recordings required/day to determine the best between-reader & within- reader reproducibility & sensitivity to specificity ratio. SICs performed in a hospital laboratory or at the workplace (+ve in 33 subjects & negative in 41) were considered the gold standard. Graphs of PEF recordings were generated in 4 different ways: every 4 hours, 4 times/day, 3 times/day & every morning & evening & were assessed blindly by 3 readers in 3 different centres. Recording PEF every 2 hours results in a slightly more satisfactory agreement between readers & in concordance in terms of sensitivity/specificity than less frequent readings (4 times/day assessment almost as satisfactory).
Malo et al	1995	21	Case series	3	Instruments that assess & store serial PEF results make it possible to estimate compliance & accuracy of results. Subjects investigated for OA were asked to assess their PEF every 2 hours during the day & record the times & values, unaware that the results were being stored. At least 6048 values should have been recorded, but only 4839 were either recorded or stored. Only 49% of recordings were accurate for both value & timing.
Malo et al	1996a	34	Case series	3	Compliance with & honesty in PEF monitoring are factors that affect the interpretation of PEF recordings, both within & between reader reproducibility. If OA diagnosis relies on PEF interpretation, then monitors that store data should be used. Compliance with PEF reduces expert agreement (66% compliance for disagreement, 77% for agreement). Self-reported PEF 3.4% lower at work & 1% higher off work on hand written than data logged readings suggesting manipulation (17/34 legal claims in Canada).
Merget et al	1988	56	Cross-sectional	2++	Data of platinum refinery workers were compared (group A: workers with work-related symptoms (8); group B: workers with symptoms not clearly work-related (9); group C: asymptomatic workers (13) & controls (group D: atopics (10); group E: non-atopics (16). Exposure to Pt salt was higher in group A than in groups B or C. All subjects of group A & 3 workers of group B, but none of the workers of the other groups, showed a +ve cutaneous reaction to platinum salts. Total serum IgE was higher in groups A & D than other groups, however Pt salt-specific IgE was higher in group A. Histamine release with Pt salts was found in all groups & was highest in atopic controls. Authors conclude that neither histamine release from basophils with Pt salts, nor RAST for the detection of Pt salt-specific IgE are helpful in the diagnosis of Pt salt allergy.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Merget et al	1991	36 (27 OA)	Case referent	2++	Study assesses use of SPT & BPT with methacholine & platinum salt. 27/35 workers referred to a clinic with work-related symptoms & 9 control subjects with BHR underwent SPT, methacholine challenge & SIC. 22 workers had a +ve SIC, 4 of which had a negative SPT. It is concluded that SIC with platinum salts should be performed on workers with work-related symptoms but negative SPT with platinum salts.
Merget et al	1996	57	Cross-sectional	2++	Study aimed to assess the quantitative association of NSBR to methacholine (MCh) & platinum salts (Pt) in workers with Pt-induced OA. 57 subjects with Pt-induced asthma underwent SPTs with Pt & bronchial challenge with MCh. 5/57 had normal NSBR in platinum asthma (12%). There was no univariate correlation between BHR to MCh & Pt, but there was a correlation between SPT reactivity to Pt & BHR to Pt. Authors concluded that there is moderate association between SIC to Pt & SPT reactivity to Pt. There is no association between methacholine responsiveness & BHR to allergen in Pt-induced OA.
Minov et al	2007	5	Cross-sectional	2++	Asthmatic (symptoms in last 12 months & +ve histamine) tea exposed workers asked to take 4 readings/day, 2 weeks at work & 2 weekends away from work (+ve record) & 2 work periods separated by at least 10 days (negative). Considered +ve when PEF varied 20% or more during work days as opposed to days off. 5 tea workers diagnosed as asthma. All completed PEFs (no results of quality). 1 subject had work-related PEFs & an 8-fold change in histamine BHR.
Moore et al	2009a	72	Case series	3	Workers with OA symptoms and/or specific IgE to a detergent enzyme were asked to complete 2 hourly PEF measurements for 4 weeks. Outputs from the Oasys programme assessed PEF response. These were then related to the levels of sensitization & current occupational exposure to detergent enzymes. 67/72 workers returned PEF records; 97% were able to return a record with at least 4 readings/day & 87% at least 3 weeks in length. 79% (n = 27) of those with a final diagnosis of OA had peak flow records confirming the disease using Oasys.
Moore et al	2009b	226	Case series	3	The aim of this study was to improve the diagnostic value of computer-based PEF analysis by using the program Oasys-2 to calculate a score from the area between the curves (ABC) of PEF on days at & away from work. Mean 2-hourly PEFs were plotted separately for workdays & rest days for 109 workers with OA & 117 control asthmatics. A score based on the ABC was computed from records containing >or= 4 day shifts, >or= 4 rest days, & >or= 6 readings/day. Patients were randomly classified into two data sets (analysis & test sets). Receiver operator characteristic (ROC) curve analysis determined a cut-off point from set 1 that best identified those with OA, which was then tested in set 2. Logistic regression analysis showed that all ABC PEF scores were significant predictors of OA. ROC curve analysis showed that a difference of 15 L/min/h provided a high specificity without compromising sensitivity in diagnosing OA. Analysis of data set 2 confirmed a specificity of 100% & sensitivity of 72%.
Moscato et al	2005	47	Case series	3	All exposed & symptomatic. NSBR at baseline in 12/21 challenge +ve workers (sensitivity 57%), measured mean 3 days (1-45) after last exposure. Average latency from first exposure to symptoms 7 years. Rhinitis preceeded asthma in 4/21, rhinitis developed simultaneously with asthma in 7/21, 10/21 with OA did not have rhinitis. Rhinitis therefore not a very useful early symptom in this group. 0/14 challenge +ve workers had +ve SPT to freshly prepared ammonium persulphate at 1 & 5%. Patch tests to ammonium persulphate +ve in 9 with contact dermatitis. Sputum eosinophilia defined as >3%. Sensitivity for OA versus challenge 70% (7/10) & specificity 73% (3/11 +ve), measurements pre challenge. Also states stop-resume test +ve in 13/23 challenge negative workers.
Munoz et al	2004	11	Case series	3	SIC possible in 8/11 (2 FEV1 too low, one anaphylactic on SPT), sensitivity when done 100%, specificity7/8, 87.5%). Challenges with potassium persulphate 5-30g diluted in 150g lactose & tipped, persulphate air levels 1-6mg/m^3 during 10 minute tipping exposures. One late reaction in unexposed asthmatic at 30g/150g. NSBR normal in 2/8, sensitivity 75%, specificity 12.5%. 3/8 not currently exposed. Serial PEF records in the 5 still at work, +ve in 4/5 (80%). SPTs at 5% weight/vol: sensitivity 4/8 (50%) specificity 8/8 (100%)
Obata et al	1999	17	Case series	3	14/17 currently exposed, other <3 months away. NSBR <8mg/ml in all challenge +ve & 3/8 challenge negative workers. Prechallenge sputum eosinophils <2% in 3/9 challenge +ve & 5/8 challenge negative. Methacholine increased sputum eosinophils in 2/9 challenge +ve. Post challenge 8-9/9 challenge +ve had sputum eosinophils >2%. Does not support the use of induced sputum eosinophilia in the diagnosis of OA pre-challenge.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Park et al	1989	9	Case series	3	All patients had had OA symptoms to reactive dyes in one dye industry, 4 had had rhinitis & they had worked for 6 to 25 months. SPTs with reactive dyes were +ve & bronchoprovocation tests also produced immediate or dual types of bronchoconstriction. RAST was used to detect specific IgE to 4 reactive dye-human serum albumin conjugates. High specific IgE binding was found in 8 asthmatic workers compared with 13 negative controls. The RAST inhibition test revealed that there was no immunological cross-reactivity between 4 reactive dyes. These results suggested that the mechanism of their asthmatic symptoms was immunological, mostly an IgE-mediate reaction.
Park et al	2009	36 + 44	Case referent	2+	Mean changes in PEF across morning/day shifts were compared between workers with OA, confirmed using SIC, & non-working asthmatics. Individuals were divided into a development set, used to identify the optimum cross-shift change for diagnosing OA, & an evaluation set, used to test the sensitivity & specificity of this value. Comparative analysis of serial PEF records was performed using OASYS-2 computerised system. A cross-shift decrease in PEF of 5 L/min achieved acceptable specificity in the development set. Applied to the evaluation set, this cut-off had a specificity of 90.9% & a sensitivity of 50%. Analysis of serial PEF records using linear discriminant analysis identified OA with a sensitivity of 83.3% & a specificity of 90.9%. Serial analysis using mean work/rest day PEF comparison had a sensitivity of 66.7% & a specificity of 100%. Cross-shift changes in PEF in morning/day-shift workers have poor sensitivity in diagnosing OA & are inferior to serial techniques.
Perrin et al	1992	61	Case series	3	PEF was assessed every 2 hrs in subjects referred for OA during a period away from work for at least 2 weeks. 3 experienced readers interpreted graphs of PEF & PC20 values blindly. There was complete agreement among the experts in 54/61 cases. 25/61 subjects (41%) had +ve SIC. The best index for comparing results of PEF with SIC was the visual analysis of PEF with sensitivity & specificity of 81% & 74%. Authors conclude that visual analysis of PEF is an interesting tool for investigating OA, although sensitivity & specificity values do not seem satisfactory enough to warrant using it alone. (12 OA cases had normal BHR).
Pezzini et al	1984	28	Case series	3	A specific IgE-mediated response was evaluated in workers exposed to TDI or MDI, with diagnosis of OA & +ve to bronchial provocative challenge. The presence of anti-di-isocyanate IgE was observed in 27% of subjects exposed to TDI & 83% of those exposed to MDI, particularly in individuals who experienced an acute massive exposure. An immediate-type response to bronchial provocative test was found in 66% of individuals with specific antibodies. Specific IgE are prevalent (91%) in subjects who developed symptoms before 6 years of exposure to isocyanates. The results suggest an association between the presence of specific IgE, early asthmatic symptoms & heavy episodic exposure.
Piipari et al	2002	40	Case series	3	FeNO measured at 100ml/sec with cut-off at 14.5ppb. No change in FeNO in negative challenges. . Prechallenge FeNO normal in 12/14 +ve challenges. FeNO >30% post challenge in 8/14 +ve challenges. Does not support use of FeNO pre challenge in diagnosis of OA.
Piirila et al	2008	17	Case series	3	NSBR & pulmonary inflammatory markers (but not lung function) improve after cessation of exposure in patients with isocyanate asthma. 24% normal NSBR at presentation.FEV1 declined mean 79 ml/yr with no exosure, inflammation improved. Not possible to separate effect of removal from exposure & ICS treatment. Confirms poor prognosis.
Platts-Mills et al	1987	179	Cross-sectional	2+	IgG & IgE to a purified rat urinary allergen in sera were measured in 179 laboratory workers of whom 30 reported symptoms on exposure to rats. There was a good correlation between IgE & +ve SPTs. There was also a close correlation between reported asthmatic reactions & serum IgE to rat allergen - IgE was present in 12/18 of workers with asthmatic reactions but only 2/135 of workers without symptoms. IgG to rat allergen were present in all sera with IgE but were also present in 30% of asymptomatic individuals. The incidence & quantity of IgG correlated with the degree of exposure to animals but not with the length of exposure in years
Quirce et al	1995	17	Case series	3	Study aimed to assess reliability of PEF monitoring in 17 subjects referred for suspected OA. Subjects were requested to monitor their PEF 6 times daily for 2 weeks at work & at least 10 days away from work, unaware that their readings were stored. Of those who completed the monitoring, only 55.3% of the records were completely accurate in terms of the value & the timing of the measurements, 23.3% were inaccurate either in terms of the recorded value or of the timing of the measurement, & the remainder were fabricated results (not recorded by the Mini-Log). Our results suggest that PEF monitoring using ordinary PEF meters for assessment of work-relatedness of asthma has limitations & is not reliable.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Redlich & Stowe	2001	75	Cross-sectional	2+	No overt cases of clinically apparent di-isocyanate OA in auto body shop workers were identified based on spirometry, methacholine challenge, PEF & symptoms. Hexamethylene di-isocyanate (HDI)-specific lymphocyte proliferation was present in 30% & HDI-specific IgG in 34% of workers, but they were not associated. HDI-specific IgE was detected in 2 workers. HDI-specific lymphocyte proliferation, increased methacholine responsiveness, & symptoms of chest tightness/ shortness of breath were more common in most heavily HDI-exposed workers. Findings demonstrate the presence of HDI-specific immune responses in a large proportion of healthy HDI-exposed workers.
Revsbech et al	1989	139	Case series	3	Diurnal variation (DV) in PEF was studied in 132/139 workers produced an acceptable record of 3 readings/day for at least half of the 3 week period. DV was calculated as difference between highest & lowest PEF as percentage of the mean PEF on each day. Median for the group was 5.9%. DV was higher among smokers & workers with work-related pulmonary symptoms.
Ricciardi et al	2003	29	Case-control	2+	Study aimed to improve understanding of the pathogenesis of OA induced by iroko wood dust & looked at the sensitivity & specificity of SPTs, RASTS & intra-dermal tests & PEF & NSBR to iroko asthma. It was found that SPTs are an insensitive test for the diagnosis of OA (0/9). Intra-dermal iroko allergen has a sensitivity of 4/9. PEFs all showed a 20% reduction at work in those with OA (100% sensitive). All were tested against a gold standard SIC test. The histories were 100% sensitive & abnormal NSBR was 100% sensitive. Paper shows the lack of use of SPT in iroko asthma & the diagnostic sensitive 100% with PEF records.
Sauni et al	2009	150	Case series	3	The quality of diagnostic procedures was assessed by reviewing the files of 150 patients who were referred to the Finnish Institute of Occupational Health in 2003 with a suspicion of an occupational cause of their asthma. The quality indicators used were assessment of workplace exposures, spirometric studies, bronchodilator response, serial workplace measurements of PEF & the time since first symptoms to the final diagnosis. For each indicator, criteria to differentiate between sufficient & insufficient care were developed. Exposure assessments, spirometric studies & bronchodilator responses were performed in 92, 87 & 79% of cases in the total study group, respectively. Workplace measurements of PEF had been performed in 51% of the cases, & the quality of measurements was sufficient in 52%. Workplace exposures had been assessed significantly more often by occupational physicians than in those referred by others. Serial PEF measurements had been performed significantly less often in other health clinics (23%) compared to occupational health services (56%) or respiratory clinics (59%) ($p<0.01$).
Schlunssen et al	2004	302 (& 71 controls)	Cohort	2++	Study aimed to investigate the relation between wood dust exposure & different indices of asthma among 302 woodworkers & 71 non-exposed subjects. There was a tendency to increased risk of asthma among atopic woodworkers compared to atopic non-exposed subjects. Wood dust exposure was associated with asthma, despite a low dust level compared to other studies. Atopy was an important effect modifier in the association between asthma & wood dust exposure. When the golden standard was defined as BHR or bronchodilator induced reversibility or increased PEF variability, the sensitivity of asthma symptoms as defined in this study was 75% with a specificity of 61%. Physician diagnosed asthma had an 85% specificity, but the sensitivity was low, 33%.
Sjaheim et al	2004	45	Case referent	2+	FeNO (& bronchial histology) compared in workers with potroom asthma, in exposed controls & in unexposed asthmatics. No data to calculate sensitivity or specificity of any of the measures. The findings suggest a wide range of eosinohil infiltration & FeNO & support the concept of phenotypes based on these measures.
Smith et al	2007	90	Case series	3	Specific IgE persists (while symptoms improve) 5 years or more after workplace exposure ceases in patients with latex asthma. Cohort of NRL sensitised HCW with many with severe reactions not included in original cohort. Sensitivity of Phadia immunocap IgE for any disease was 53%, when enhanced with Hev b5 62%. Over 56 months of follow-up IgE reduced; reduction less with severe initial reaction, cross-reacting food sensitisation & continuing NRL exposure. Continuing OA reduced from 52.9% of cohort to 5.9%.
Swiercynska et al	2008	42	Case series	3	Bakers, healthcare workers & farmers with specific realistic type challenges to occupational allergens. 17/42 challenge +ve. FeNO correlated with sputum eosinophilia. Eosinophilia in nasal lavage & changes in NSBR were criteria for a +ve challenge. Mean increase in FeNO at 24 hours after challenge but not before. FeNO not corrected for smoking or inhaled corticosteroid use. Paper included latex glove challenges, 1/2 with +ve challenge had latex IgE.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Tarlo et al	1991	154	Case series	3	Study assessed the feasibility & results of different investigations for patients referred to clinic for possible OA. A +ve SPT to a workplace allergen (14%), +ve PEF workplace changes (12%), improvement in methacholine response on holiday (9%), and/or +ve SIC testing (14%) supported the diagnosis of OA in 61 subjects (39% of total referrals). 51 of these were related to a workplace sensitizer & 10 to a presumed irritant OA was excluded in 48 subjects (31%) who had normal methacholine responsiveness within 24 hours of work (22% of 54 subjects), PEF readings no worse at work than on holidays (14% of total referrals) and/or negative SIC testing (10% of total referrals). Insufficient information could be obtained for a diagnosis in the remaining 45 subjects (28%). No single investigation was considered diagnostic in this study.
Tarlo et al	2001	7	Case series	3	Change in gloves to lower protein, powder free natural rubber latex (NRL) gloves reduces NRL allergy in employees. 2 of the 3 nurses with OA were able to return to work. Reduction of new onset of NRL-related OA & also workers with previously diagnoses NRL-OA were able to continue working in a hospital setting.
Tarlo et al	2002	844	Other	2+	A medical surveillance programme was introduced in Ontario for workers exposed to diisocyanates (DI) in 1983, but no mandated surveillance programme is in effect in this province for other asthmagens. This study assessed changes in incidence & severity of compensated OA claims due to DI compared with other causes, which occurred since the introduction of the surveillance programme. New claims for OA compensated by the Workers' Compensation Board (WCB) between 1980 & 1993 were retrospectively reviewed. Numbers of claims for OA induced by DI ranged from 9-15/year in 1980-83, increased to 55-58/year in 1988-90, then fell to 19-20/year by 1992-93. Yearly numbers of claims for OA due to other causes increased up to 1985-87 & remained relatively stable. Duration of symptoms for OA induced by DI was shorter than for other claims & there were fewer hospital admissions among those with OA induced by DI than among those with OA induced by other causes. OA from all causes was diagnosed earlier in claims for 1987-93 compared with 1980-86, & indicators of severity of asthma were also milder in accepted claims during 1987-93 than in earlier claims. Although engineering & industrial hygiene measures may have contributed to these changes, our findings are also consistent with a beneficial contribution from the medical surveillance programme for workers exposed to DI.
Tee et al	1998	58	Case series	3	58/101 patients referred for investigation were diagnosed as having isocyanate-induced OA by means of history, serial PEF records, & bronchial provocation tests (BPT). Specific IgE to isocyanates were measured in all patients by RAST. 20 patients had a RAST ratio of 2 or greater to at least one isocyanate. 13 (28%) of the 46 patients with a +ve BPT response had RAST ratio of 2 or greater, & 9 (20%) had a RAST ratio of 3 or greater. Raising the RAST cut-off from 2 or greater to 3 or greater reduced its sensitivity but increased the specificity of the test to 100%. With a RAST score of 3 or greater, it is wholly specific & therefore diagnostic of isocyanate-induced asthma. The sensitivity of specific IgE measurement is highest when blood is taken less than 30 days from last exposure, which is consistent with the observed half-life (6 months). Measurement of specific IgE to isocyanates is a specific but relatively insensitive test for asthma induced by isocyanates.
van Kampen et al	2008	71	Case series	3	High concentrations of specific IgE are associated with a +ve response to SIC in bakers. Sensitivity compromised by measuring IgE after removal from exposure in 64% (mean .4years). 100% +ve predictive value for a +ve challenge was obtained with a >5mm wheal (wheat) or 4.5mm (rye) & 2.32 ku/l (wheat & 9.64ku/l (rye), suggesting further confirmation with challenge not needed if these present.
Vandenplas et al	1995a	273	Cross-sectional	2++	Questionnaire & SPTs with latex & common inhalant allergens were administered to 273/289 subjects. 13/273 showed SPT reactivity to latex. None of those who had negative SPTs to latex had history suggestive of OA. Histamine inhalation challenge was then performed on 12 of 13 latex-sensitive subjects (including 5 subjects with a history of OA). These 12 subjects demonstrated significant BHR. All underwent SICs with latex gloves & 7 subjects developed a significant bronchial response. Authors conclude that OA due to latex occurred in 2.5% of hospital employees. Widespread use of latex gloves should therefore be considered a significant risk to respiratory health of hospital employees.
Vandenplas et al	2001	45	Cross-sectional	2++	Patients underwent an open medical questionnaire, SPT against latex, measurement of BHR to histamine & SIC with latex gloves. Clinical history, SPTs & assessment of NSBR showed high sensitivity but low specificity compared with SIC. Clinical history & immunologic tests were the most useful procedures in diagnosing latex OA. Combining the 2 procedures remained less accurate than SIC. Further examination of predictive values of tests is warranted to recommend diagnostic strategies that are specific to various agents causing OA.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Vandenplas et al	2005	212	Case series	3	In a hospital setting, symptoms are helpful in predicting OA. Specificity of wheezing at work was 85%, sensitivity 40%. Improvement weekends had a sensitivity of 76% specificity 54%. Improvement during holidays: sensitivity 74% specificity 57%.Loss of voice negatively associated with +ve challenge. Predictive model set up & tested on same population.
Walusiak et al	2004	287	Cohort	2+	Apprentice bakers were examined by questionnaire, SPTs to common & occupational allergens, evaluation of total serum IgE level & specific IgE at 0, 1 year & 2 years after onset of vocational training. Incidence of work-related chest symptoms was 4.2% in 1st year & 8.6% in 2nd year of exposure. Hypersensitivity to occupational allergens developed in 4.6 & 8.2% of subjects, respectively. Incidence of ORh was 8.4% after 1 year & 12.5% after 2 years, & that of OA/cough-variant asthma 6.1 & 8.7%, respectively. Latency period of ORh was 11.6 +/- 7.1 months & chest symptoms 12.9 +/- 5.5 months. Only in 20% of OA cases could ORh be diagnosed a stage earlier. In 21/25 subjects with OA, chronic cough was the sole clinical manifestation. Stepwise logistic regression analysis revealed that +ve SPT to common allergens was a significant risk factor of hypersensitivity to occupational allergens (OR = 10.6, 95% CI 5.27; 21.45), ORh (OR = 3.9, 95% CI 1.71; 9.14) & OA (OR = 7.4, 95% CI 3.01; 18.04). Moreover, +ve SPT to occupational allergens on entry to the training was a significant risk factor of asthma (OR = 6.9, 95% CI 0.93; 51.38). In most subjects who developed OA, rhinitis occurred at the same time as chest symptoms.
Yacoub et al	2007	40	Case series	3	Follow up study of workers with OA confirmed by SIC a mean of 3 years post last exposure; most improved after cessation of exposure; but there is a high prevalence of persistent depression/anxiety. Most subjects had NSBR at diagnosis; 25% had no sputum eosinphilia at diagnosis; persisting eosinophila was the only abnormality in 1/40. Suggests that there is a subset of OA with no increase in sputum eosinophils, & changes in NSBR an insensitive method of diagnosis.
Zock et al	1998	49	Cross-sectional	2+	Expert judgment of PEF-time graphs provides an important tool to detect OA. However, the reproducibility of this technique in an open working population is unknown. Agreement between & within 9 experts was studied using PEF-time graphs of 49 workers. Results suggest that in a "healthy" working population, judgment of PEF graphs is not a favourable method for detection of airway obstruction. If this technique is applied in epidemiological studies, judgment of the graphs should be done by more than one expert.

EVIDENCE TABLE D

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Ameille et al	1997	209	Case series	3	Patients with OA were reviewed on average 3.1 years after the diagnosis. At review, 44% had left their previous job & 25% were currently unemployed. 32% remained exposed to the offending agents in the same job. 46% of patients had suffered a reduction of income. Claims for compensation, size of the company, level of education, & age at the time of diagnosis were significantly associated with a risk for becoming unemployed or having a new employer after the diagnosis of OA. 54% of employees who claimed compensation had to leave their company compared to 22% of employees who did not do so. However the study did not allow the authors to determine whether loss of employment was the cause or consequence of the claim for compensation. The authors conclude that OA results in severe socio-economic consequences & that effort should be made to increase & improve retraining programmes.
Axon et al	1995	26 with OA, 29 with non-OA	Case series	3	Study aimed to determine the differences between patients with OA & those with non-OA, which might help in their diagnosis. Questionnaires were distributed to 30 subjects aged 18-65 years at each of two clinics - one for patients with OA & one for those with cryptogenic & environmental asthma. Subjects with OA were more likely to become unemployed (50% vs 3%).
Bernstein et al	2003	25	Case series	3	Workplace interventions were initiated in 20/25 subjects reporting work aggravated asthma. All had concurrent symptoms of work-related urticaria & rhinitis. 19 workers were switched to non-latex gloves & 18 reported resolution of all symptoms, despite the fact that 12 (66%) continued to work with colleagues who were using powdered natural rubber latex (NRL) gloves. Another healthcare worker (HCW) had a job change that resulted in resolution of both contact urticaria & asthma, although rhinitis symptoms persisted. 4 workers in the asthma group left their jobs because of persistence of symptoms before specific interventions were made. 1 HCW continued to work in the same health care facility without intervention & all NRL associated symptoms persisted. Job changes led to a mean 24% reduction in income.
Brant et al	2006	45	Case series	3	Follow up of symptomatic workers following a cross sectional study of 78% (35/45) workers diagnosed with OA to detergent enzymes. 86% reported an improvement in their symptoms, 29% asymptomatic. Estimated half life of specific IgE 20 months.
Burge	1982	39	Case series	3	NSBR to histamine was measured before SIC in the following groups: 51 workers exposed to toluene di-isocyanate (TDI); 40 workers exposed to diphenylmethane diisocyanate (MDI); 45 electronics workers exposed to colophony fumes & 13 unexposed controls. Finally 38 electronics workers had repeated measurements after moving their place of work. Histamine BHR returned to normal more frequently in those who left work than in those who had moved within their original factories, suggesting that the latter had sufficient indirect exposure to maintain their symptoms & BHR. Only 2/20 affected workers who had left factory were symptom free, & most had considerable reduction in quality of life by continuing asthma.
Cannon, et al	1995	225	Cross-sectional	2+	Patients with WRA, whether initiated or provoked by agents inhaled at work, suffer adverse economic & employment consequences. Earnings adversely affected in all categories – 30% of those with OA or work-exacerbated asthma reported more losing more than 40% of income. Compared to non-WRA, those with occupational & WRA report greater difficulty in finding new work & higher proportions had changed or suffered disruption to their jobs. For many patients, continuing a chosen career, often after many years' training, was not possible. Those in higher socioeconomic groups found it easier to diversify into related careers; skilled manual workers had less opportunity to transfer into equally skilled work & often obtained unskilled work or became unemployed. (Of the 225 subjects, 113 had OA, 37 had work-exacerbated asthma & 75 had asthma unrelated to work).
Chan-Yeung et al	1982	125	Case series	3	50/125 subjects remained in the same job & all had respiratory symptoms. In 75 exposures ceased. Of these, half became asymptomatic. Noted that subjects who became asymptomatic had relatively normal lung function at time of diagnosis. Asthma was often not recognised; it took an average of 2 years after onset of symptoms to reach correct diagnosis. Subjects with shorter duration of exposure & shorter duration of symptoms prior to diagnosis & removal from exposure showed improvement. Early diagnosis & removal from exposure were found to be associated with recovery.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Chan-Yeung et al	1987	232	Case series	3	Subjects observed on average 4 years after diagnosis - 96 continued to work with red cedar, 136 left the industry. Of these, only 55/136 recovered completely whereas 81 were still symptomatic. Those that recovered were younger, had significantly better pulmonary function & a lesser degree of NSBR at time of diagnosis, indicating diagnosis at an earlier stage of the disease. A higher proportion of patients who recovered had late asthmatic reaction on inhalation provocation test at time of diagnosis. All 96 subjects still exposed had respiratory symptoms & required medication. Authors concluded that the most important determinant of favourable outcome is early diagnosis & removal from exposure. Partial removal from exposure did not prevent the decline in lung function.
Descatha et al	2007	229	Case series	3	The severity of OA is related to the duration of symptoms prior to diagnosis but not to agents, smoking, age, atopy or sex. Agents mostly responsible were persulphates, isocyanates & flour.
Dimich-Ward et al	2007	302	Cross-sectional	2++	In the follow-up period for employed subjects (n=185) of those who continued working with western red cedar after diagnosis (n=143), 30.1% remained in exposed jobs, 25.9% switched to jobs without exposure to western red cedar & 16.8% eventually quit their jobs because of their asthma. By comparison, the majority of subjects (73.8%) who began working in unexposed jobs within 1 yr of diagnosis (n=42) remained in their jobs & none quit because of their asthma.
Douglas et al	1995	291	Cross-sectional	2+	Within 3 months of the opening of a salmon-processing plant in the UK, some workers complained of symptoms suggestive of OA. A survey of all employees identified 24 (8.2%) with OA. The employees worked near machines, which generated respirable aerosols containing salmon-serum proteins. The IgE response to these proteins was associated with OA, with increasing severity of symptoms, & with working distance from the aerosol source. The main factor which predisposed to IgE production & asthma was cigarette smoking, whereas atopy & a previous allergic history did not. The affected employees were reallocated to a low-exposure worksite & factory ventilation was improved. 11 showed significant clinical & pulmonary function improvement, & continued in employment. 13 who still had symptoms were advised to leave, thereafter becoming symptom-free, & regaining normal respiratory function. Early recognition of symptoms & prompt action to reduce aerosol exposure avoided the long-term reduction in pulmonary functions often associated with OA.
Dressel et al.	2007	81 + 24	Case-referent	2+	The short-term effect of an educational intervention in asthmatic farmers was evaluated on the basis of spirometric indices and FeNO. Farmers with OA (n = 81), mostly sensitised against cow dander and storage mites, participated in a 1-day educational programme. Outcome measures were assessed at baseline and after 4-6 weeks, using FeNO, lung function and a questionnaire. Results were compared with those of a control group without intervention (n = 24). In the educational group, the proportion of subjects reporting work-related symptoms was reduced after the intervention. FeNO decreased from a geometric mean of 28.2 to 25.7 ppb, and, in subjects with an elevated (>35 ppb) baseline FeNO (n = 32), from 59.7 to 49.2 ppb. The corresponding changes in the control group were 25.6 versus 27.7 ppb and 49.5 versus 48.1 ppb. Spirometric results were unaltered in both groups. Thus FeNO, a marker of allergic airway inflammation, indicated a beneficial effect of a short-term educational intervention in farmers with OA.
Dressel et al.	2007	113	Case series	3	113 farmers with OA in education group compared with non-random group of 24 also with OA not taking part in education programme. Niox Mino used for FeNO, a level of 35ppb was classed as normal. All able to measure FeNO, not all able to measure FEV1. Changes in FeNO seen after education, no change in FEV1. Supports use of FeNO as a measure of intervention in farmers with OA.
Fishwick et al	2007	97	Case series	3	Consecutive patients with suspected OA were recruited from 6 secondary care clinics with an interest in OA. Semi-structured interviews were performed & hospital case notes were reviewed to summarise relevant investigations & diagnosis. 97 patients were recruited, with a mean age of 44.2 years (range 24-64), 51 of whom (53%) had OA confirmed as a diagnosis. Most (96%) had consulted their general practitioner (GP) at least once with work-related respiratory symptoms, although these had been present for a mean of 44.6 months (range 0-320 months) on presentation to secondary care. Patients experienced a mean delay for assessment in secondary care of 4 years (range 1-27 years) following presentation in primary care. Significant diagnostic delay currently occurs for patients with OA in the UK.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Gannon et al	1993b	112	Case series	3	Workers who had a diagnosis of OA made ≥1 year earlier were followed up. 32% remained exposed to the causative agent. 35% were no longer employed, 41% due to unemployment, 44% due to ill health retirement & 15% due to chronic sick leave. Workers still exposed – median loss of income was 35%. Those removed from exposure were worse off financially - median loss 54% of income. Compensation did not match the loss of earnings due to development of OA. Removal from exposure after diagnosis with OA is beneficial in terms of symptoms & lung function, but is associated with a loss of income. Early diagnosis is important for symptomatic improvement after removal from exposure. Inadequate compensation may contribute to the workers' decision to remain exposed after diagnosis.
Gautrin et al	2008	408	Cohort	2++	Symptoms acquired during apprenticeship remit after starting work in a different job. Follow up average 7.6 yrs after apprenticeship. New sensitisation 9.7/100 yrs in training, 1.3/100 yrs during subsequent exposed work. 16/20 sensitised during training then not exposed became SPT -ve (18.5/100 yrs). Probable OA 8.3% during training & 3% during later exposure. Prognosis better for no mould sensitisation, no pets, no NSBR at start, no skin symptoms. Nothing on level of sensitisation. Shows sensitisation lost on follow-up at 18.5/100 yrs, incidence reduces with follow up years.
Goe et al	2004	1101	Reporting Scheme	2++	Those with new onset WRA were twice as likely as those with work-aggravated asthma to have left their company (47% vs 23%).
Grammer et al	1993	29	Case series	3	Trimellitic anhydride workers with late asthma & late respiratory systemic syndrome improved clinically & immunologically when moved to lower exposure jobs. Approximately half of the OA & ORh workers improved when moved, whereas the other half continued to be very symptomatic. Elevated levels of specific IgE may be a useful marker in the latter sub-population.
Hannu et al	2007	34	Case series	3	Persistent symptoms in Finnish welders with stainless steel asthma render most of them unable to continue at work. +ve challenges to stainless steel welding fumes but SPTs to potassium dichromate & chromium chloride at 1mg/ml universally negative (sensitivity=0%). NSBR normal at presentation in 38%. Long latent interval (mean 18 years), peak flow records +ve in 5/8.
Hudson et al	1985	63	Case series	3	63 subjects studied after cessation of exposure (>60months), 49 of whom are still symptomatic. The symptomatic subjects had history of more prolonged exposure after onset of symptoms as compared to respective asymptomatic group. Conclude that subjects with OA caused by various agents can remain symptomatic of asthma & demonstrate a persistence of bronchial obstruction & hyper-excitability for prolonged periods after cessation of exposure.
Klusackova et al	2006	37	Case series	3	Patients with OA attributed to various agents. 57% (n=21) had evidence of BHR at the time of diagnosis. Despite avoidance of exposure, 6.5 years after diagnosis persistent symptoms (86.5%) & BHR (51%) observed; some outcomes (BHR & sputum eosinophilia) worse in those whose asthma had been attributed to HMW agents.
Klusackova et al	2007	5	Case series	3	NSBR & SIC tests were performed in 5 patients from a lasamide production line with suspected OA & ORh to confirm the diagnoses. During the follow-up visit (1-3 years after removal from exposure), all of the tests (except the SIC) were performed again. Several years after removal from exposure to the occupational agents, normalization (with respect to the parameters followed) was not yet complete for all of the patients. Allergic symptoms (despite the removal from occupational allergen exposure) persisted even after several years.
Labrecque et al	2006	79	Cohort	2++	89/105 randomly chosen subjects had complete data at T0 (the time of diagnosis) & 79 were re-evaluated at T2, around 2 years after removal from exposure, for final impairment-disability assessment. At T0 & T2, a clinical examination, spirometry & methacholine challenge, were performed. At T2, 79/89 patients were reassessed (89%). 8 patients were lost to follow up & 2 were too unstable to be reassessed. No statistical difference was observed for spirometry data & antiasthmatic medication use between T0 & T2 (P = 0.11). At T2, 73% of patients were still using short-acting beta2 agonists & 39% inhaled glucocorticoids. FEV1 variation of +/-10% from T0 to T2 occurred in 31 subjects (40%). FEV1 worsened in 14 (18%), remained significantly unchanged in 51 (64%), & improved in 14 (18%). NSBR improved in significantly in 19 (24%); the others remained unchanged. Neither were associated with smoking status (P > 0.05). NSBR was normalized in 9 of 79 (11%) patients. Clinical remission occurred in only four (5%) subjects. These results show the generally poor medical outcome of isocyanate-induced OA.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Laoprasert et al	1998	9	Case-series	3	Investigated latex aeroallergen concentrations below which latex-sensitive healthcare workers do not experience symptoms & to study HEPA-filtered laminar flow helmets in preventing latex-induced symptoms. Under challenge chamber conditions, latex-sensitive health care workers underwent 7 sequential SIC tests by donning & discarding either vinyl gloves (challenge 1), low latex-allergen powder-free gloves (challenge 2), or high latex-allergen powdered gloves (challenges 3 to 7) for up to 1 hour. Volunteers wore a laminar flow helmet during all challenges; HEPA filters in the helmet were in place only during challenges 3 & 4. Flow-volume loops, symptom scores, & latex aeroallergen concentrations were measured before & during each test. During challenges 5 & 6, mean maximum % falls in FEV1 (-16% & -11%, respectively) were significantly greater compared with those measured during challenges 3 & 4 (-3% & -1%, respectively) (P =.03). Mean maximum change from baseline symptom scores during challenges 5 & 6 was significantly higher than that during challenges 3 & 4 (P =.006). During challenges with high latex-allergen gloves, 4 volunteers had reproducible FEV1 falls of 20% or greater at cumulative inhaled latex aeroallergen doses ranging from less than 100 ng to 1500 ng. The laminar flow helmets were effective in reducing latex-induced symptoms. Only 1 volunteer exhibited a fall in FEV1 of 20% or greater after a cumulative inhaled latex aeroallergen dose of less than 100 ng, & no volunteer showed a decline in FEV1 after exposure to powder-free low allergen gloves.
Larbanois et al	2002	157	Case-control	2++	This study investigated the socioeconomic outcomes of subjects who experienced WRA symptoms in the absence of demonstrable OA & to compare these outcomes with those found in subjects with documented OA. Subjects (n=157) who were being investigated for WRA, were surveyed. Of these 86 had OA, ascertained by a +ve SIC, & 71 subjects had a negative SIC response. After a median interval of 43 months (range 12-85 months), the subjects were interviewed to collect information on employment status, income changes, & asthma-related work disability. Asthma-related work disability, defined as any job change or work loss due to asthma, was slightly more common in subjects with OA (72%) than in those with negative SIC (54%). Rates of unemployment were 46% (WRA) & 38% (OA). Rates of income loss were: 59% (WRA) & 62% (OA). Median actual income loss was 22% (OA) & 23% (WRA).
Leira et al	2005	1239	Reporting scheme	2++	Norwegian physicians are obliged to report occupational diseases to the Labour Inspection Authority. Data were collected from the notifications for respiratory disease for the period 1995-1999. A postal questionnaire inquiring into work, respiratory symptoms, smoking & socioeconomic consequences of the disease was sent to 1,239 workers with a physician's diagnosis of obstructive respiratory disease. The response rate to the questionnaire was 81% (1,000 workers of whom 723 had OA). At the time of notification, more than half of the workers had left their original jobs. At the time of this study 2-6 years later, approximately the same proportion of workers had experienced a reduction in income & had received financial compensation; 60-78% were still on asthma medication.
Maghni et al	2004	133	Case series	3	Lack of improvement in airway responsiveness in subjects with OA after removal from exposure was associated with the degree of functional impairment at the time of diagnosis, the time lapse since diagnosis, & presence of an inflammatory influx. Logistic regression showed that baseline PC_{20} & time lapse since diagnosis were significantly associated with PC_{20} values at follow up. Subjects removed from exposure for 5 years or more had a more favourable outcome than those seen at shorter interval. The current study extends those results to 10 years or more. Factors associated with a more favourable outcome were, as in the previous series, time lapse since diagnosis & PC_{20} value at time of diagnosis. The only difference is that current work did not show significant differences in outcome according to high vs. LMW agent. A poor outcome after avoidance of exposure was associated with sputum eosinophilia and/or neutrophilia at follow-up
Malo et al	1993b	134	Economic analysis	2++	Authors conclude that for subjects with OA in Quebec, the mean interval for a medico-legal decision is 8 months, a minority (8%) are still unemployed 2-4 years after being assessed, the quality of life is more affected than control group & the mean cost is close to $CAN 50,000. At 2 years or more after diagnosis, 84% required asthma medication despite no longer being exposed to the causative agent.
Malo et al	1996b	32	Randomised control trial	1+	In a small randomised, crossover, double-blind trial of inhaled corticosteroids (vs. placebo) following the diagnosis of OA small improvements in some symptoms, functional & quality of life measurements were observed during the active treatment period.
Malo et al	2004	80	Case series	3	In selected cases, improvement in NSBR continues for many years after cessation of exposure but is fastest in the first 2.5 years. Recovery unrelated to agent, duration of symptomatic exposure, smoking or treatment at presentation; but better in men, & in those with higher FEV1 & higher PC20 at presentation

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Marabini et al	1993	128	Case series	3	Subjects categorized 'exposed workers', 'unexposed workers' & 'unemployed'. At time of diagnosis, respiratory symptoms were similar in all groups, but at follow-up (51-88 months after diagnosis) use of medication, respiratory symptoms & asthma severity were higher in 'worker exposed' group. Significant differences were found in income at follow-up. Unemployed had the lowest income & working-unexposed subjects also had a significantly lower income, both at diagnosis & during follow-up examination, than working-exposed. After diagnosis 27% changed job, which was associated with a decrease in income & 41% were unemployed. Socioeconomic factors are more important in determining the working status of subjects after a diagnosis of OA. The unemployed were older & had less dependents compared with those working (probably had to continue to work in the same job because they had a large number of dependents).
Merget et al	1999	83	Cross-sectional	2+	83 workers in study: - 9 continued to be exposed (Group A), 16 were transferred within building (Group B), 39 were transferred within plant but different building (Group C) & 19 left the plant (Group D). At median period of about 4 years after diagnosis, asthma symptoms were reported by all subjects still exposed but by only 37/74 after transferral, with no difference being found between groups B, C & D. For the majority of subjects with OA due to platinum salts, transfer to low exposure areas may not be associated with a more unfavourable outcome as compared with complete removal from exposure sources.
Moller et al	1986	7	Case series	3	In 7/12 cases toluene di-isocyanate (TDI) asthma was documented by a +ve SIC to low levels of TDI. 6/7 TDI reactors had persistent respiratory symptoms & required daily treatment even though they had been removed from exposure for as long as 12 years (mean 4.5 years). 4/6 of these TDI reactors had dual bronchospasm & 2/6 had late bronchospasm to less than 20 ppb TDI - all had a +ve methacholine or cold air challenge prior to study. The one TDI reactor with a negative methacholine challenge had a +ve (immediate) bronchospastic response to a TDI challenge performed one week after removal from exposure. 5/12 had negative TDI challenge, two of whom had persistent respiratory symptoms & +ve methacholine challenges at time of TDI inhalation testing. Conclude that respiratory symptoms may persist following long-term removal from occupational exposure to TDI & are associated with NSBR. The TDI sensitivity may also persist for a long time even in the absence of any additional occupational exposure.
Moscato et al	1991	113	Case-control	2+	Study reports the clinical findings & results of SIC with toluene di-isocyanate (TDI) & methacholine in 113 subjects with a history of exposure to TDI & work-related respiratory symptoms. Only some of the subjects (40.7%) had isocyanate asthma, diagnosed by a +ve TDI SIC. Most reactors had a dual (30.4%) or a late (41.3%) response & the interval between the last occupational exposure & the SIC was significantly shorter in reactors. They also had a significantly higher proportion of +ve responses to methacholine & a significantly lower mean PD_{15} FEV1. Authors conclude that methacholine challenge could not identify subjects with TDI- asthma.
Moscato et al	1999	25	Case series	3	At 12 months, 13/25 subjects were removed from exposure (Group A) whereas 12 continued to be exposed (Group B). Immediately after diagnosis, asthma severity improved irrespective of whether patient removed from exposure or continued exposure, probably as a result of better therapeutic regimen. At 12 months re-evaluation, 6/13 were asymptomatic in group A, whereas in group B, all subjects were still symptomatic. In OA, cessation of exposure to the offending agent results in a decrease in asthma severity & in pharmaceutical expenses, but is associated with a deterioration of the individual's socio-economic status. Those removed from exposure suffered 26.6% loss in annual income.
Muller-Wening et al,	1998	26	Case series	3	Farmers with OA were challenged with an exposure to work-related dusts for up to 60 min, resulting in significant increases in airway resistance (Raw), thoracic gas volume (TGV) & specific airway resistance (sRaw) compared to baseline values. After mean period of 21 weeks, the farmers were subjected to a second challenge, but this time wearing a protective respiratory device (RD). Significant increases in Raw, TGV & sRaw were again observed, but were on average 50-80% smaller than increases seen when RDs were not worn. The use of respiratory devices in farmers with OA significantly reduced the degree of bronchial obstruction, but did not provide complete protection.
Munoz et al	2003	8	Case series	3	Immunologic, lung function, & SIC were performed in 8 patients with OA due to exposure to persulfate salts in a factory manufacturing hair bleaching products - 6 presented with rhinitis prior to OA. The mean time that had elapsed between symptom onset & diagnosis was 38 months (range 3-120 months).

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
NHS Plus	2008	-	Systematic Review	2+	Reviewed 3 studies which showed that in employees with latex-induced asthma, personal avoidance of latex gloves, including the use of powder-free, low protein latex gloves by colleagues reduces symptoms & indices of severity in the affected employee to a similar degree as the use of non-latex gloves by colleagues. All but the most severe cases of latex-induced asthma can be managed without the need for redeployment, ill health retirement or termination of employment. Where clinical considerations permit, reduction of exposure may be a useful alternative associated with fewer socio-economic consequences to complete removal from exposure.
Niezborala et al	1996	77	Cohort	2+	A study was conducted on 77 workers who were not atopic on SPTs to 3 common allergens at the time of recruitment. 18 workers developed a +ve result on SPTs & 23 developed symptoms, including all 18 subjects with +ve SPTs (incidence of +ve SPTs & symptoms was highest during the first 2 years of work). Screening atopic subjects with common allergens when they joined the company did not seem to result in a reduction of the incidence of allergy to complex platinum salts. Smoking was a significant predictive factor for both +ve SPTs & symptoms (5.53 times that of non-smokers). Findings confirm that smoking is & that atopy may not be a high risk factor for the development of allergy to complex platinum salts. The high incidence of sensitisation & the available data on the clinical course of sensitised workers show that sensitised workers must be promptly & completely removed from exposure.
Obase et al	2000	2	Case reports	3	Study aimed to assess the efficacy of dust respirators in preventing asthma attacks in patients with buckwheat flour/wheat flour-induced OA. The effect of the work environment was examined in 2 patients with OA with & without the use of a commercially available mask or a dust respirator. In patient 1, environmental exposure resulted in no symptoms during & immediately after work, but coughing, wheezing, & dyspnoea developed after 6 hours. PEF decreased by 44% 7 hours after leaving the work environment, showing only a +ve late asthmatic reaction. In patient 2, environmental exposure resulted in coughing & wheezing 10 minutes after initiation during bread making, & PEFR decreased by 39%. After 7 hours, PEFR decreased by 34%. The environmental provocation tests in both patients were repeated after wearing a commercial respirator. This resulted in a complete suppression of the late asthmatic reaction in patient 1 & of the immediate & late asthmatic reactions in patient 2. Authors conclude that dust respirators are effective in preventing asthma attacks induced by buckwheat flour & wheat flour.
Padoan et al	2003	87	Case series	3	Followed up on average 11 years after removal from exposure. Symptoms occurred in 84.6% of subjects still exposed to toluene di-isocyanate (TDI) & 75% of those removed for < 10years & in 60% of those removed for > 10years. Confirms the poor clinical outcome of TDI-induced asthma. Symptoms & airway hyper-responsiveness improve slowly for >10 years after leaving the workplace. A more favourable prognosis was associated with a better lung function, a lower degree of airway hyper-responsiveness to methacholine at diagnosis & longer interval from cessation of exposure.
Park et al	1997	35	Case series	3	Subjects were given anti-asthmatics, recommended to avoid exposure to toluene di-isocyanate (TDI) & were monitored for 2 years (mean 12 months). 17/35 recovered completely, 11 showed significant improvement & 7 remained stable. No effect of age, exposure duration or specific IGE was noted. Favourable prognosis was associated with short duration of asthmatic symptoms before diagnosis, immediate cessation of exposure after diagnosis, milder degree of BHR, & the presence of specific IgE to TDI-human serum albumin conjugate.
Park et al	2006	26	Case series	3	Methacholine airway hyperresponsiveness (AHR) & lung function were evaluated & compared in 26 patients with reactive dye (RD) OA at the time of diagnosis & after complete avoidance of the causative agents. Patients with continued (n = 13) or remitted (n = 6) AHR were further monitored for up to a mean +/- SD of 8.7 +/- 1.8 years. AHR resolved in 10 (38%) of 26 patients a mean +/- SD of 2.2 +/- 1.3 years after complete avoidance of RDs; however, prebronchodilator forced expiratory volume in 1 second (FEV1) values were not different. Levels of IgE specific to RD-human serum albumin complex were markedly decreased at first follow-up in 5 RD-atopic patients from whom paired serum samples were compared (P = .02). The AHR disappeared in an additional 5 patients & improved in 4 by the second follow-up. The FEV1 values also improved compared with diagnosis & first follow-up levels. Favorable prognosis was associated with early diagnosis of RD-OA & complete avoidance of the causative agent. No association was found with smoking history, latent periods, the presence of RD specific IgE, baseline provocation concentration that caused a decrease in FEV1 of 20%, or FEV1.
Park et al	2007	11	Case series	3	Asthma severity (but neither skin sensitisation nor spirometry) failed to improve after avoidance of exposure for up to an average of 13.7 years in Korean patients with reactive dye asthma. At final assessment 7/11 had sputum eosinophila.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Piirila et al	2000	235	Case series	3	In 1976-1992 245 new cases of OA induced by diisocyanates were diagnosed. Aim was to study the clinical outcome of OA. A questionnaire was sent to the 235 patients alive in 1995, & validated by re-examining clinically 91 of them. The study was carried out on average 10 years after the diagnosis. Of the patients 82% experienced symptoms of asthma, 34% used no medication & 35% were on regular medication. Patients with IgE-mediated asthma had significantly better prognosis than IgE negative patients. It proved to be partly due to shorter exposure & symptomatic periods before diagnosis. Hexamethylene di-isocyanate induced asthma was associated with a better outcome than diphenylmethane di-isocyanate & toluene di-isocyanate induced asthma. Those who continued in their primary work place did not report more symptoms than those working in new work places. Early diagnosis & adequate medical surveillance, including active treatment & swift vocational rehabilitation, are equally essential for the patient's overall prognosis. No association between persistence of symptoms or need of medication with duration of exposure, duration of symptoms before diagnosis or the latency period.
Piirila et al	2008	17	Case series	3	NSBR & pulmonary inflammatory markers (but not lung function) improve after cessation of exposure in patients with isocyanate asthma. 24% normal NSBR at presentation.FEV1 declined mean 79 ml/yr with no exosure, inflammation inproved. Not possible to separate effect of removal from exposure & ICS treatment. Confirms poor prognosis.
Piirila et al	2005	245	Case series	3	Aim was to follow-up the working status & life satisfaction of patients with diisocyanate-induced asthma in 245 cases diagnosed during 1976-1992. A questionnaire was sent out on average 10 (3-19) yr after the diagnosis to the surviving 235 patients. The questionnaire was validated by re-examining 91 of them clinically, & with spirometry, histamine challenge test & peak flow surveillance. Of the 213 responding patients, 14% were unemployed, & for 50% of them unemployment was caused by asthma. Another 17% had an occupational pension & 34% were re-educated. 80% of those retired or unemployed reported that their asthma was the cause.
Pisati et al	1993	60	Case series	3	Patients with toluene di-isocyanate (TDI)-OA were re-evaluated five years after diagnosis. At follow up 17/60 (group A) had relocated to jobs with only occasional exposure to TDI (15 of them used protective respiratory devices). The remaining 43/60 (group B) avoided further inhalation of TDI by moving to another sector. Group A showed a significant decrease in FEV1 & PD_{15} methacholine & significant increases in the severity of symptom score & requirement for medication. Group B showed significantly less severe symptoms & a threefold increase in PD_{15} methacholine (duration of exposure to TDI & of symptoms before the initial diagnosis delineated the patients who recovered from those who did not improve; intermediate values in these features characterised the subjects who improved but did not recover). It is inferred that complete removal from exposure is the only effective way of preventing deterioration in patients with OA due to TDI. Early diagnosis & early removal from exposure after the onset of asthma are important factors for a favourable outcome of the disease. This approach, however, does not necessarily lead to recovery. Persistence of asthma was associated with the duration of exposure to TDI & of symptoms at work before diagnosis. The use of protective devices or treatment was also unable to prevent the worsening of asthmatic symptoms & further damage to the airways.
Pisati et al	2007	25	Case series	3	Aims of this study were to define whether toluene diisocyanate (TDI) BHR persists in subjects with OA after long-term cessation of exposure & the determinants at the time of diagnosis of patients' outcome. 25 nonatopic spray painters with OA due to TDI were re-examined 58 +/- 7 months after removal from exposure. On both examinations, the severity of asthmatic symptoms & the need for antiasthma treatment over the past 12 months were graded & lung function tests, measurement of airway responsiveness to methacholine (PD20), circulating total IgE & TDI-HSA specific IgE, SPTs with common inhalant allergens & SIC with TDI were carried out. 7 subjects were still TDI-reactors & 18 lost reactivity to it. All persistent reactors had still asthma & their symptom score, medication score, FEV1, PD20 and serum IgE were unchanged between assessments. In the 18 subjects no longer responsive to TDI, 8 had still features of asthma: their symptom and medication score had improved significantly, but FEV1, PD20 and serum IgE had not significantly changed. The other 10 patients no longer reactors to TDI were asymptomatic and their PD20 had become normal. The duration of symptomatic exposure to TDI was the only feature at diagnosis that differentiated patients with persistent TDI airway hyper-responsiveness and asthma from those who were no longer responsive to TDI but still asthmatic and those who were no longer responsive to TDI and no longer asthmatic (4 +/- 1.6; 2.1 +/- 0.8; 0.6 +/- 0.3 years, respectively; $p < 0.001$).

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Poonai et al	2005	42	Case series	3	Charts of patients referred to the University Health Network Asthma Centre were reviewed for evaluation of OA, with clinic visits from 1997-2002. 42 patients fulfilling objective OA criteria were administered a structured telephone interview to examine the chronology and nature of health care consultation and reasons for possible delay in diagnosis. The mean time to diagnosis was 4.9 years (3.4 years excluding 4 outliers). On average, patients waited 7.4 months before discussing the work-relation of symptoms with a physician. Main self-reported reasons for delay were lack of enquiry about work relatedness by the primary care physician (41%) and fear of losing work time (37%). Reported increases in time during secondary care were related to difficulties associated with completion of investigations (35%). Lower education level ($p = 0.04$) and household income ($p = 0.03$) were significantly associated with an increased time to diagnosis. Physicians who assess working adults with asthma need to ask pertinent work-related questions when taking a history in order to initiate timely investigations & referral. Socio-economic factors are also associated barriers to early diagnosis of OA.
Rachiotis et al	2007	-	Meta-analysis	1++	Systematic review of prognosis of OA with wide range of recoveries with a pooled estimate of 32%. Poor prognosis with increasing age, better prognosis with the shortest duration of exposure (less than 76 months). Pooled estimate for persisting NSBR at follow up 73% higher among workers exposed to HMW agents. Some evidence that a shorter duration of symptoms is associated with a higher rate of symptomatic recovery.
Rosenberg et al	1987	31	Case series	3	Patients with isocyanate-induced OA were studied 6-54 months after diagnosis. 4 had the same work conditions & unchanged or worse respiratory symptoms; 7 had an alternative job or safer work conditions at the same work-place & suffered from mild to severe symptoms. The remaining 20 subjects were definitely removed from exposure. 50% of those removed from exposure remained symptomatic 19 months after cessation of exposure versus all those who remained in same job with safer conditions/those relocated in same place of work. Of the 20 subjects removed from exposure, 10/20 were asymptomatic - appeared to be younger & to have shorter durations of total & symptomatic exposures. Even modest re-exposure allows the allergic process to continue. In those given new jobs in which the sensitising agent was nearly always absent, excellent clinical & functional improvement was observed. Therefore quality of new work site seems to play a role in evolution of isocyanate-induced asthma. Prognostic factors include duration of symptoms, length of total & symptomatic exposures to the sensitiser & bronchial responsiveness at diagnosis.
Ross et al	1998	1317	Case series	3	Maximum possible follow up ranged from 18 months to 5.5 years. Excluding medico-legal cases almost half of the workers were with the same employer. A further 18% were with a new employer, meaning that about 2/3 continued in employment. 30% were unemployed or medically retired & 6% had retired. Longer exposure both before & after diagnosis was associated with poorer prognosis - patients exposed for year or more after diagnosis recovered from asthma less frequently but were more often employed than those exposed for less than a year. Subjects whose exposure continued only for a few months most often found new employment.
Santos et al	2007	167	Case series	3	This study examined individual & work-related factors associated with longer times to diagnostic milestones among groups with OA & work-exacerbated asthma (WEA). Suspected cases were identified from an occupational lung disease clinic & claimants to the Ontario Workplace Safety & Insurance Board. Questionnaire administration & chart review were undertaken. 80 participants were classified as having sensitizer-induced OA & 87 as having WEA. The reported median time of first suspicion of a diagnosis of WRA was 1 yr for WEA patients & 2 yrs for OA patients. Both groups reported income loss post-diagnosis, which was more pronounced among OA patients. The median time to a final diagnosis of OA after the onset of symptoms was 4 yrs. Factors related to delayed diagnosis of OA in Canada include male sex, single status, low education & higher age. The main delay in seeking attention is from the initial medical contact rather than the worker. The average time from a worker consulting a health professional was one month; the average time from a worker suspecting OA was 8 months.
Sauni et al	2009	150	Case series	3	The median time from the beginning of symptoms to the final diagnosis was 3.2 years, although asthma was diagnosed within 1.2-1.3 years from the beginning of symptoms. Time from the diagnosis of asthma to confirmation on & occupational cause accounted for half of the delay. The performance of serial measurements of PEF at the workplace & the time to diagnosis should be substantially improved.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Slovak et al	1981	151	Cohort	2+	Study was carried out by questionnaire in workers who had been exposed to azodicarbonamide dust in the process of its manufacture. 28 (18.5%) people without previous asthma gave a history of episodes of late onset asthma after exposure to azodicarbonamide. Re-exposure caused repetition & worsening of symptoms. Immediate removal from further exposure resulted in rapid cessation of symptoms without further recurrence. 7/13 sensitised individuals who were still exposed 3 months after the onset of disease developed prolonged BHR to common environmental irritants.
Slovak et al	1985	10	Case series	3	The efficacy of the Racal Airstream helmet respirator in preventing symptoms due to LAA was assessed. 8/10 were established cases of asthma & 2 had severe rhinitis. PEF readings, recorded every 2 hours, were kept for 7 weeks (6 in exposure), together with a symptoms diary. Objective evidence of good protection was obtained in 6/8 eight asthmatic patients; overt asthma was seen in the other 2. Persons with severe local symptoms of rhinitis & conjunctivitis also benefit subjectively from the use of the helmet although symptoms are not completely suppressed. Helmet respirator would appear to be a valuable adjunct in the management of OA in those that opt to remain in exposure. However, they should be monitored carefully & regularly to ensure that their respiratory function has not deteriorated.
Smith et al	2007	90	Case series	3	Specific IgE persists (while symptoms improve) ≥5 years after workplace exposure ceases in patients with latex asthma. Sensitivity of Phadia immunocap IgE for any disease was 53%, when enhanced with Hev b5 62%. Over 56 months follow-up IgE reduced; reduction less with severe initial reaction, cross-reacting food sensitisation & continuing NRL exposure. Continuing OA reduced from 52.9% of cohort to 5.9% (no objective confirmation).
Taivainen et al	1998	33	Case series	3	Investigated the value of powered dust respirator helmets in the treatment of 33 farmers with OA (24 with OA induced by cow dander or grains, 2 with other forms of atopic asthma, & 7 with non-atopic asthma) for 1 year. Morning & evening PEF & daily symptoms were monitored for 3 months without & for 10 months with the helmet. Objective evidence of protection was obtained for farmers with OA. The morning peak flow rate increased & the variation in daily PEF & the symptoms of ORh diminished significantly during the helmet period.
Tarlo et al	1995	609	Case series	3	Study to assess determinants of outcome of Ontario Workers Compensation Board accepted claims at permanent disability assessments. The decision reached was OA in 39% of claims (57% of these attributed to isocyanates). A further 39% were accepted for aggravation of asthma from irritant exposures (AA). Exposure to a known sensitiser occurred in 91% with OA & to an irritant in 67% with AA. Of 200 OA accepted claims reviewed at a mean of 1.9 years later, clearing of asthma occurred in 19% & milder asthma in 47%. At follow-up 54% were unemployed. Outcome was best with early diagnosis & milder impairment of pulmonary function at initial assessment.
Tarlo et al	1997b	235	Case series	3	A better outcome in OA induced by isocyanates was associated with early diagnosis & early removal from isocyanates after the onset of asthma. Outcome at a mean of 1.9 years was significantly better in those with a mandatory health surveillance programme.
Valentino et al	1994	4	Case-series	3	4 subjects were diagnosed as having latex hypersensitivity after SPT & IgE serum level against latex gave +ve results. Changes in methacholine responsiveness also took place. In 1 case, an occupational exposure test resulted in a 24% drop in FEV1 after 25 min of inhalation exposure. At least 1 year after diagnosis, 2 subjects who had been removed completely from latex exposure experienced no further latex-induced symptoms. The other workers, who continued working in the same laboratories using vinyl gloves, now display less severe symptoms but require regular anti-allergy treatment.
Vandenplas et al	1995b	8	Case series	3	Using SIC, bronchial response to hypoallergenic gloves was evaluated in healthcare workers with latex-induced OA. Exposure to hypoallergenic gloves resulted in the absence (in 6 subjects) or a significant reduction (in 2 subjects) of bronchial response. The effect of repeated exposure to hypoallergenic gloves was assessed in 2 subjects who did not demonstrate changes in PEF & NSBR to histamine. This study suggests that the use of hypoallergenic gloves could be an effective means of reducing the risk of asthmatic reactions in health care workers with latex-induced asthma when complete avoidance cannot be achieved.

Author	Year	No. of subjects	Study design	Level of evidence	Authors' main conclusions
Vandenplas et al	2002	36	Case series	3	Initial & follow-up visits (median 56 months) of subjects with latex-induced OA included questionnaire & measurement of PC_{20}. At follow-up, subjects who avoided exposure (16/36), asthma severity had decreased from median score of 8.5 to 3.5 & PC_{20} value increased from 0.4 mg/ml to 2.3 mg/ml. In subjects who reduced their exposure (20/36), asthma severity score improved from 6.5 to 2.5 & PC_{20} values rose from 0.5 mg/ml to 2.4 mg/ml. Cessation of exposure to latex was associated with asthma-related work disability (69%) & loss of income (62%) more frequently than was reduction of exposure (35% & 30%, respectively). Reduction of exposure to latex represents a reasonably safe alternative that should be considered in workers with latex-induced OA when suppression of exposure is not feasible or when the possibilities for non-exposed jobs are limited. Compared with complete removal, reduction of exposure is associated with a substantially lower socio-economic impact.
Venables et al	1989b	79	Case series	3	Patients interviewed for follow-up of OA on average 6 years after asthma developed (median time between exposure & OA symptoms 4 years). 90% felt asthma had improved in parallel with avoidance or reduction in exposure to causative agent. However, 72% still required therapy of some sort & 10% had required hospital admission. 1/3 of patients were currently unemployed & 40-73% reported limitations in everyday activities.
Yacoub et al	2007	40	Case series	3	Follow up study of workers with OA confirmed by SIC; most improved after cessation of exposure; but there is a high prevalence of persistent depression/anxiety. Most subjects had NSBR at diagnosis.

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