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Our mission:

Bringing employers and researchers together to produce robust science and evidence-based work of practical value whose application will contribute to the right of people at work to be 'healthy, motivated and at work'.

BOHRF raises and deploys funds for:

- occupational health research of practical value
- practical guidelines based on evidence

to reduce the enormous cost to employers and workers of work-related illnesses in the UK.

In 2001, BOHRF established close links with the Faculty of Occupational Medicine whilst remaining an independent charity. The Faculty has established a Research Committee to identify scientifically robust research proposals, which attempt to answer questions that will assist the development of evidence-based occupational health practice. This Committee advises and influences decision-making bodies, grant awarding bodies (including BOHRF), private industry and the public sector on research needs and priorities.

Our policy and strategy are determined by our Trustees, who are also responsible for reviewing our risk management controls.

This project was underwritten by BOHRF thanks to corporate sponsor donations. Subsequently, generous project funding was received from almost all sectors having workers exposed to causes of occupational asthma at work.

Brian Kazer
Chief Executive

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PURPOSE

The purpose of these guidelines is to assist the Health & Safety Commission's and Health & Safety Executive's aim to reduce the incidence of asthma caused by substances at work by 30% by 2010.

The intent of the guidelines is to improve the prevention, identification and management of occupational asthma in primary care and in occupational health settings by providing evidence-based recommendations on which future practice and management can be based. It is also intended that information aimed at safety representatives, workers and managers will provide practical guidance for action. Summaries of the evidence-based recommendations for general practice, occupational health and for managers, workers and safety representatives appear in the appendices of this publication and are also available separately.

SCOPE

The guidelines are aimed at doctors and nurses working in general practice, occupational health and respiratory medicine and at employers, safety representatives and workers who may be exposed to substances at work that can cause asthma. The guidelines focus on interventions that might be considered appropriate for health practitioners and employers to implement and they supplement other guidelines that are available for the clinical management of adult asthma.

The guidelines consist of *evidence statements* with ratings of the strength of that evidence and associated references, *recommendations* with ratings of the strength of evidence behind the recommendation and *good practice points* where evidence is lacking.

The guidelines do not intend to provide a list of the several hundred agents known to cause asthma. New causes of occupational asthma are reported regularly and such information is available elsewhere. Neither do they discuss non-occupational asthma except insofar as reviewing the evidence as to whether pre-existing asthma or a history of asthma are risk factors for developing occupational asthma.

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

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1 P R E F A C E

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. The inflammation results in hyper-responsiveness of the airways to many stimuli e.g. cold air, cigarette smoke, exercise, etc and in the clinical setting to methacholine and histamine. Symptoms include wheeze, cough, shortness of breath and chest tightness and are often worse at night or in the early morning.

Asthma is common, affecting adults and children of all ages. It is especially prevalent in the UK, where 4% of adults report asthma¹. Adult asthma may be a continuation of childhood asthma, reactivation of quiescent childhood asthma or new-onset asthma. Between a third and two-thirds of adult asthmatic patients develop asthma for the first time during working years^{2,3,4}.

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, and
- *occupational asthma* i.e. adult asthma caused by workplace exposure and not by factors outside of the workplace. Occupational asthma can occur in workers with or without prior asthma.

Occupational asthma can be subdivided into:

- *allergic occupational asthma* characterised by a latency period between first exposure to a respiratory sensitiser at work and the development of symptoms, and
- *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.

Workplace agents that induce asthma through an allergic mechanism can be broadly divided into those of high and low molecular weight. The former are usually proteins and appear to act through a type I, IgE associated hypersensitivity. Whilst some low molecular weight chemicals are associated with the development of specific IgE antibodies, this is not the case for the majority.

Occupational factors account for 9-15% of cases of asthma in adults of working age⁵. Almost 90% of cases of occupational asthma are of the allergic type^{2,6,7,8,9,10} and therefore this is the focus of this evidence review. The term *occupational asthma* is used throughout the guidelines to mean allergic *occupational asthma* unless specified otherwise.

Occupational asthma is the most frequently reported work-related respiratory disease in many countries, including the UK⁸. The Health and Safety Executive (HSE) estimate that 1,500 to 3,000 people develop occupational asthma each year. This rises to 7,000 cases a year if work-aggravated asthma is included.

The disease may leave people severely disabled having to take early retirement, while many others have to change jobs to avoid contact with the substance which caused their asthma. HSE estimates that the costs to society of new cases of occupational asthma are up to £1.1bn over 10 years.

Occupational asthma is unique in that it is the only type of asthma that is readily preventable. Prevention depends on the effective control of exposure to respiratory sensitisers in the workplace. Occupational asthma has important long-term adverse health and economic consequences. Although symptoms may resolve completely with early diagnosis and early removal from exposure, many patients fail to recover even when completely removed from exposure. In rare cases, occupational asthma has been fatal. Thus prevention is the most important factor in reducing the impact of occupational asthma on individual workers and on society at large.

Evidence-based guidelines are becoming the benchmarks for practice in many areas of health care and the process used to prepare such guidelines is well established. This evidence review and the recommendations derived from it concentrate on interventions and outcomes. The aim is to provide a robust approach to the prevention, identification and management of occupational asthma, based on and using the best available medical evidence.

Anthony Newman Taylor and Paul Nicholson
Chairman and Deputy Chairman of the Research Working Group

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2 EVIDENCE REVIEW METHODS

Introduction

This evidence review concerns the occupational health aspects of the prevention, identification and management of occupational asthma. The review began with a systematic search for all published, methodologically sound and original scientific studies. The methodology of the review may be best summarised as systematic searching plus rating of the strength of the evidence plus a narrative overview by agreement between two experienced and independently minded reviewers.

Literature searches

The literature was searched using standard methods. MEDLINE and EMBASE were searched systematically from 1966 and 1974 respectively to the end of June 2004 for relevant articles published in all languages, using a number of search terms including:

- occupational asthma
- agents known to cause occupational asthma, asthmagens

Additional searching included; personal bibliographies, selected internet searches, citation tracking, scanning of relevant journals in the field and papers known to be 'in press' at the end of June 2004.

More than 2,500 titles and abstracts were considered. Narrative reviews were excluded. Abstracts were reviewed independently by two reviewers to identify papers to be requested for review. 474 papers were obtained and independently critically appraised and assessed for methodological quality, using a standard proforma. Where reviewers disagreed about the score of the paper or its relevance to this research, they discussed it to reach resolution. Where resolution was not achieved, a third reviewer was involved. At this stage, further references were excluded and pertinent data from the remaining 223 papers were entered into an evidence table. The main conclusions are described in the evidence table. This table was reviewed in order to formulate evidence statements and recommendations.

Evidence statements

Criteria for grading evidence and recommendations are designed principally to guide inferences about the effects of treatment. Other hierarchies are needed to answer questions about aetiology, diagnosis, disease frequency and prognosis¹, the areas in which most research into occupational asthma has been focused. Since there are few systematic reviews and randomised controlled trials, there is scarce level 1 evidence as defined by the revised Scottish Intercollegiate Guidelines Network (SIGN) grading system (2000). To overcome this limitation we graded the strength of evidence for each statement using both the SIGN system and the Royal College of General Practitioners (RCGP) three star system (1995) as modified in the Swedish Council on Technology Assessment in Health Care report for scientific studies and the BOHRF Occupational Health Guidelines for the Management of Low Back Pain at Work.

¹ Glasziou P, Vandenbroucke J, Chalmers. Assessing the quality of research. *BMJ*, 2004; 328: 39-41.

(RCGP) three star system

*** Strong evidence – provided by generally consistent findings in multiple, high quality scientific studies.

** Moderate evidence – provided by generally consistent findings in fewer, smaller or lower quality scientific studies.

* Limited or contradictory evidence – provided by one scientific study or inconsistent findings in multiple scientific studies.

- No scientific evidence – based on clinical studies, theoretical considerations and/or clinical consensus.

As there are very few randomised controlled trials and since these do not apply to health surveillance, susceptibility to disease or the sensitivity and specificity of screening and diagnostic procedures in occupational asthma, high quality scientific studies were taken to be major epidemiological surveys and prospective cohort studies. Other, scientifically weaker, studies included retrospective, cross-sectional or uncontrolled cohort studies and case series.

Revised SIGN grading system

Levels of evidence

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

Evidence linking is to the most comprehensive and most recent source available. Where possible this is to a systematic review, which should include all of the earlier, original studies in that area. Direct reference to original studies is made where there is no systematic review, where they are not included in the review(s), or where they are necessary to support an important point.

Clinical judgement is necessary when using evidence statements to guide decision-making. Weak evidence statements on a particular issue or effect do not necessarily mean that it is untrue or unimportant but may simply reflect insufficient evidence.

Recommendations

The guidelines include recommendations followed by an evidence statement or set of evidence statements. Recommendations are written as far as possible in precise, behaviourally specific terms ². They are graded according to the modified RCGP three star system (1995) and the revised SIGN grading system for recommendations (2000).

Revised SIGN grading system

Grades of recommendation

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+

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 .

² Michie S, Johnston M. Changing clinical behaviour by making guidelines specific. *BMJ*, 2004; 328: 343-345.

3 EVIDENCE LINKED STATEMENTS

A Background

Occupational asthma is the most frequently reported occupational respiratory disorder in westernised industrialised populations (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 (Brehl 2003, Hnizdo 2001).

What is the frequency of occupational asthma?

There are no complete registries for reporting occupational diseases such as occupational asthma and the true frequency of the disease is not known. Under-reporting is likely and 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. The incidence of occupationally associated asthma varies 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 demonstrated an attributable risk of 9% whilst the 12 highest scoring studies demonstrated an attributable risk of 15% (Blanc 1999). Another review of 21 studies similarly demonstrated an attributable risk of 15% (Balmes 2003).

A1 *** SIGN 2++ Occupational factors are estimated to account for 9-15% of cases of asthma in adults of working age, including new onset or recurrent disease.

(Balmes 2003, Blanc 1999)

A2 *** SIGN 2++ The annual population incidence of occupationally related asthma ranges from an estimated 12 to 170 cases per million workers with an estimated mean of 47 cases per million workers.

(Ameille 2003, Blanc 1999, Karjalainen 2000, Meredith 1991)

A3 * SIGN 3 The population incidence of occupational asthma may be underestimated by as much as 50%.

(de Bono 1999)

A4 * SIGN 3 The reported incidence of occupational asthma has not decreased in recent years.

(Cortona 2001, Meyer 2001, Reijula 1996)

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.

A5 *** SIGN 2++ The most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.

(Ameille 2003, Brhel 2003, Cortona 2001, Gannon 1993a, Hnizdo 2001, McDonald 2000, Meredith 1991, Meyer 1999, Sallie 1994, Toren 1999)

A6 *** SIGN 2++ The workers most commonly reported to surveillance schemes of occupational asthma include paint sprayers, bakers and pastry makers, nurses, chemical workers, animal handlers, welders, food processing workers and timber workers.

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

A7 ** SIGN 2+ The workers reported from population studies to be at increased risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastics and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, waiters, cleaners, painters, plastic workers, dental workers and laboratory technicians.

(Jaakkola 2003, Johnson 2000, Kogevinas 1996, Kogevinas 1999)

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.

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

A direct relationship between occupational asthma and allergen exposure at work has been demonstrated with acid anhydrides (Grammer 1994, Liss 1993), cimetidine (Coultts 1984), colophony (Burge 1981), enzymes (Cathcart 1997, Cullinan 2000, Juniper 1997, Vanhanen 1997, Weill 1971), green coffee and castor bean (Osterman 1982), flour allergens (Brisman 2000, Cullinan 1994, Cullinan 2001 Heederik 2001, Houba 1998, Musk 1989), crab (Ortega 2001), isocyanates (Meredith 2000, Petsonk 2000, Tarlo 1997a), laboratory animal allergens (Cullinan 1999, Kruize 1997, Platts-Mills 1987), piperazine (Hagmar 1984), platinum salts (Calverley 1995), prawns (McSharry 1994) 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 (Houba 1996, Nieuwenhuijsen 1999, Vanhanen 1997), laboratory animals (Heederik 1999) and platinum salts (Merget 2000).

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

(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, Juniper 1977, Kruize 1997, Liss 1993, Musk 1989, Ortega 2001, Osterman 1982, McSharry 1994, Meredith 2000, Platts-Mills 1987, Tarlo 1997a, 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. Differences between studies relating to the ascertainment of atopy range 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 i.e., 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 detergent enzymes (Juniper 1984, Weill 1971, Zentner 1997), isocyanates (Meredith 2000, Ucgun 1998) laboratory and other animals (Agrup 1986, Botham 1987, Cockcroft 1981, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Jeal 2003, 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, Talini 2002) and some reactive dyes (Docker 1987).

Other studies have demonstrated no such association between atopy and occupational asthma due to exposure to cork (Winck 2004), isocyanates (Butcher 1977, Cullen 1996, Petsonk 2000), detergent enzymes (Cullinan 2000), 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, where possible, 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, 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, Prichard 1984), laboratory animals (Cullinan 1999), crab (Cartier 1984), prawn (McSharry 1994) and acid anhydrides (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, Baur 1998a, Botham 1987, Cullinan 1999, De Zotti 1997, DeZotti 2000, Droste 2003, Gautrin 2001a, Gautrin 2001b, Jeal 2003, Juniper 1984, Krakowiak 2002, Kruize 1997, Platts-Mills 1987, Sjostedt 1989, Sjostedt 1993, Talini 2002, Venables 1988a, Weill 1971, Zentner 1997)

Is there a genetic predisposition for developing occupational asthma?

That only a proportion of workers develop occupational asthma despite similar exposures, suggests an underlying genetic susceptibility to occupational asthma. A number of studies have examined the

role of genes coding for Class I or II human leukocyte antigen (HLA) and respiratory anti-oxidant expression in occupational asthma attributed to isocyanates (Balboni 1996, Beghe 2004, Bernstein 1997, Bignon 1994, Mapp 2000, Mapp 2002, Piirila 2001, Rihs 1997), complex platinum salts (Newman Taylor 1999), western red cedar (Horne 2000), acid anhydrides (Young 1995) and laboratory animal proteins (Sjostedt 1996, Jeal 2003). Most studies were based on small sample sizes and the findings are either inconsistent or unreplicated.

A10 ** SIGN 2- Genetic polymorphisms that code for human leukocyte antigen class II genes or respiratory anti-oxidant mechanisms may predispose to occupational asthma for a number of agents. (Balboni 1996, Bignon 1994, Horne 2000, Jeal 2003, Mapp 2000, Mapp 2002)

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), salmon (Douglas 1995) and snow crab (Cartier 1984). One study demonstrated a dose-dependent effect (Venables 1989a).

Smoking has been identified to increase the risk of sensitisation in only a few studies with exposure to green coffee and castor bean (Osterman 1982, Romano 1995), platinum salts (Baker 1990, Merget 2000, Niezborala 1996), prawn (McSharry1994); and flour (De Zotti 1994).

The role of cigarette smoking is unclear for asthma due to exposure to acid anhydrides, enzymes and laboratory animals. Some studies have shown an increased risk of laboratory animal asthma in smokers (Cullinan 1999, Krakowiak 1997, Venables 1988a), whereas others have shown no effect (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 (Venables 1985a) correlation with specific IgE. Similar conflicting evidence is available for detergent enzymes (Johnsen 1997, 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).

A11 ** SIGN 2+ Cigarette smoking can increase the risk of developing occupational asthma with some sensitising agents. (Calverley 1995, Cartier 1984, Cullen 1996, Douglas 1995, Meredith 2000, Niezborala 1996, Ucgun 1998, Venables 1989a)

Is occupational rhinitis a risk factor for developing occupational asthma?

Rhinitis and asthma frequently occur together. There is epidemiological evidence from the general population of a strong association between the development of asthma and a previous history of either allergic or perennial rhinitis. Occupational rhinitis is purported to be a risk factor for the development of occupational asthma, especially for high-molecular-weight sensitisers. 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.

Rates of co-morbid rhinitis or rhino-conjunctivitis of between 45% and 90% have been reported in subjects suffering from IgE associated occupational asthma attributed to acid anhydrides (Grammer 2002a, Wernfors 1986), laboratory animals (Cullinan 1999, Gautrin 2001a, Gautrin 2001b), snow crab (Cartier 1984) and wheat flour (Houba 1998). The intensity of nasal symptoms appears to be significantly more pronounced in the case of HMW agents (Malo 1997).

A 12 ** SIGN 2+ Occupational rhinitis and occupational asthma frequently occur as co-morbid conditions in IgE associated occupational asthma.

(Cartier 1984, Cortona 2001, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Grammer 2002a, Houba 1998, Malo 1997, Wernfors 1986)

A13 ** SIGN 2+ Rhino-conjunctivitis is more likely to appear before the onset of IgE associated occupational asthma.

(Cortona 2001, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Grammer 2002a, Karjalainen 2003, Malo 1997)

A14 * SIGN 2- The risk of developing occupational asthma is highest in the year after the onset of occupational rhinitis.

(Cortona 2001, Karjalainen 2003)

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, Kim 1999, Munoz 2003), the risk of occupational asthma appears to be highest soon after first exposure to laboratory animal allergens (Agrup 1986, Cullinan 1999, Gautrin 2001a, Gautrin 2001b, Krakowiak 1997, Platts-Mills 1987), isocyanates (Venables 1985b), platinum salts (Calverley 1995, Niezborala 1996, Venables 1989a) and azodicarbonamide (Slovak 1981).

A15 ** 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, Johnsen 1997, Krakowiak 1997, Niezborala 1996, Platts-Mills 1987, Slovak 1981, Venables 1989a).

B Prevention of occupational asthma

Primary prevention aims to prevent the onset of disease, often by reducing or eliminating exposure to the agent in the workplace. Secondary prevention aims to detect disease at an early or pre-symptomatic stage for example by health surveillance. Tertiary prevention aims to prevent worsening symptoms by early recognition and early removal from exposure and is considered later under the management of an identified case of occupational asthma.

The most effective means of control is to prevent exposure altogether either by substituting the agent with a less harmful material or by engineering and hygiene measures. Respiratory protection 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, worker education and training and stringent health surveillance

Is the incidence of occupational asthma reduced by controlling exposure?

There is extensive evidence of a direct relationship between occupational asthma and allergen exposure (page 12). Further studies have explored the effect of reducing exposure on the incidence of occupational asthma. That reduced exposure leads to fewer cases of occupational asthma has been demonstrated with acid anhydrides (Drexler 1999, Liss 1993), detergent enzymes (Cathcart 1997, Juniper 1977), isocyanates (Tarlo 1997a), laboratory animals (Botham 1987, Fisher 1998) and latex (Allmers 2002, Levy 1999, Tarlo 2001).

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, Tarlo 1997a, Tarlo 2001)

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, genetic predisposition and sensitisation to occupational allergens lack sufficient sensitivity and specificity for these 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, Renstrom 1994, Slovak 1981, Venables 1988b)

It is noted later (page 25) that the likelihood of improvement or resolution of symptoms of occupational asthma is greater in workers who are removed from exposure completely. 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.

B4 * SIGN 3 A previous history of asthma is not significantly associated with occupational asthma.

(Cockcroft 1981, Gautrin 2001a)

Does health surveillance prevent occupational asthma?

Periodic health surveillance for occupational asthma aims to identify sensitised workers or cases of asthma at an early and reversible stage of the disease. Very few, and no concurrent comparison studies have been reported of the efficacy of health surveillance in occupational asthma. The only study from which valid conclusions can be drawn is of isocyanate workers in Canada, in whom 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 authors of the report recognised that the improved outcome in the isocyanate workers might, at least in part, be attributable to the concomitant reduction in isocyanate exposure.

B5 * 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.

(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. Very 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 (Gordon 1997, Stenton 1993).

B6 * SIGN 3 Screening questionnaires may lead to an underestimate of the prevalence of asthmatic symptoms.

(Gordon 1997, Stenton 1993)

There have been few small studies of case identification of occupational asthma through surveillance of workers at risk. In one study all true cases of occupational asthma were identified by questionnaire. Spirometry identified many false positives due to poor inspiratory effort and no additional cases of asthma (Kraw 1999). In another study spirometry detected one case of occupational asthma in addition to the two cases identified by questionnaire (Bernstein 1993).

B7 * SIGN 3 Spirometry detects few cases of occupational asthma that would not otherwise be detected by respiratory questionnaire.

(Bernstein 1993, Kraw 1999)

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). Tests for specific IgE to isocyanates are insensitive (about 70% false negative rate) but specific (Tee 1998). 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 and blood sampling of exposed workers to conduct immunological tests is feasible in the workplace.

(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. The best screening question to ask is 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. Occupational asthma can be present when tests of lung function are normal, making these less useful in screening for occupational asthma. Asthmatic symptoms improving away from work can produce false positive diagnoses, so further validation of occupational asthma is needed. The diagnosis is made most easily before exposures or treatments are modified. Serial measurement of peak expiratory flow is the most available initial investigation. When done and interpreted to validated standards there are very few false positive results, but about 20% are false negatives. Skin prick tests or blood tests for specific IgE are available for most high molecular weight allergens, 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 the gold standard diagnostic test. The availability of centres with expertise and facilities for specific provocation testing is very limited in the UK and the test is time-consuming. Specific provocation is indicated particularly when the precise cause of the occupational asthma is unclear, but this knowledge is needed for the management of an employee.

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

The sensitivity of asthma symptoms has high sensitivity but lower specificity, whereas the question "have you been told by a doctor that you have asthma" has a high specificity but low sensitivity (Schlunssen 2004). Asthma symptoms better on days away from work derived from questionnaires have a sensitivity of 58-100% for validated occupational asthma. The sensitivity was below 90% in only one study from Quebec. The sensitivity was 100% in only one study of five latex-exposed nurses. The most common symptoms used were wheeze and shortness of breath. No cases of occupational asthma due to latex were asymptomatic (two studies). The Quebec study showed some improvement in sensitivity to 66% when symptoms improved on holiday. Work-related asthma symptoms were common in those with negative specific challenge tests, the specificity of the questionnaires ranged from 45-100%, 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 have a high sensitivity, but relatively low specificity for occupational asthma.

(Baur 1998b, Cote 1993, 1990 Malo 1991, Merget 1988, Vandenplas 1995a, Vandenplas 2001)

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

There are fewer studies with expert medical histories than questionnaires. The symptoms of occupational asthma 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. Expert histories have poor specificity compared with specific challenge testing.

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, Malo 1997, 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 are no good studies comparing across shift changes with specific challenge testing. Such testing is unlikely to be either sensitive or specific 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 spirometry 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. In one case-control study of day-shift workers in a factory with many cases of colophony asthma, a fall in FEV1 of >10% post-shift was found in 5% of asymptomatic workers and 32% of those with work-related asthma symptoms.

C3 * Sign 3 Pre- to post-shift changes in lung function cannot be recommended for the validation or exclusion of occupational asthma.

(Burge 1979a, Burge 1979b)

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

Six publications describe small case series of consecutive patients attending specialist clinics. Three describe workplace surveys, in the context of research studies, with lower frequencies of daily recordings. Publication bias is probable, particularly in the latter group. In four clinical series and each of the workforce populations acceptable records were returned by over 70% of subjects.

C4 ** SIGN 3 Acceptable peak flow series can be obtained in around two-thirds of those in whom a diagnosis of occupational asthma is being considered.

(Cote 1990, Cote 1993, Henneberger 1991, Hollander 1998, Leroyer 1998, Malo 1995, Quirce 1995, Redlich 2001, Revsbech 1989)

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

A single case series of 74 patients attending a specialist clinic reports the highest combination of sensitivity and specificity with a measurement frequency of at least four readings a day. Less frequent readings produced a higher specificity but lower sensitivity.

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

(Malo 1993a)

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

Six of seven series report high levels of agreement (averaging 80%) between expert assessors with kappa values of at least 0.6. 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 high level of agreement between expert interpretations of serial peak flow records.

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

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

Eight case series report direct and blinded comparisons of serial peak flow measurement and either specific bronchial provocation testing (five studies) or an expert diagnosis (three studies) based on a combination of other types of evidence. Some cases are reported in more than one publication. Reported sensitivities and (particularly) specificities are consistently high: averaging 80% and 90% respectively.

C7 ** SIGN 3 The sensitivity and specificity of serial peak flow measurements are high in the diagnosis of occupational asthma

(Bright 2001, Burge 1982a, Cote 1990, Cote 1993, Leroyer 1998, Liss 1991, Malo 1993a, Perrin 1992)

Are statistical or computed methods of peak flow assessment as accurate as expert interpretation in the diagnosis of occupational asthma?

Three case series compare visual inspection of peak flow records by experts with a variety of statistical indices of the same records. In two, visual inspection gave higher values of sensitivity and specificity; in the third an index derived from maximum values away from work and minimum values at work produced a slightly higher value for sensitivity than did visual inspection. Other statistical indices used in the same report were less sensitive and specific than visual inspection.

Just one computed method of analysis has been reported. The analysis was calibrated using the diagnostic opinion of a single expert and in cases whose occupational asthma was, for the most part, attributable to low molecular weight agents. A sensitivity of 75% and a specificity of 94% for 67 records (32 cases of occupational asthma) were reported.

C8 ** SIGN 3 Statistical analysis of serial peak flow measurements is of limited diagnostic value compared to expert interpretation

(Cote 1993, Leroyer 1998, Perrin 1992)

C9 ** SIGN 2+ Computed analysis of peak flow records has good diagnostic performance

(Gannon 1996, Baldwin 2002)

What are the sensitivity and the specificity of a normal measurement of non-specific reactivity while at work in the diagnosis of occupational asthma?

Studies of non-specific reactivity are confounded by different methods used, different cut-offs for normality and the interval between last occupational exposure and the performance of the test (increasing time may allow recovery of initial hyper-reactors). There are however a large number of studies using different methods from many centres showing that non-specific bronchial hyper-reactivity may be normal in 5-40% of specific challenge positive workers. Testing with higher concentrations of methacholine or histamine at which some non-asthmatics react reduces the number of non-reacting occupational asthmatics, but still leaves some non-reactors. One study showed no additional benefit of non-specific bronchial reactivity measurement over and above a history and specific IgE to inhaled antigens. A normal test of non-specific reactivity is not sufficiently specific to exclude occupational asthma in clinical practice.

C10 *** SIGN 2++ A large number of concordant studies from different centres using different methodologies demonstrated that increased non-specific reactivity is often found in workers with occupational asthma. There are however many reports of normal methacholine or histamine reactivity within 24 hours of exposure in workers with confirmed occupational asthma.

(Anees 2002, Baur 1998b, Brisman 2003, Burge 1982a, Cartier 1989, Hargreave 1984, Koskela 2003, Lemiere 2000, Lin 1995, Malo 1991, Merget 1991, Merget 1996, Moscato 1991, Perrin 1992, Ricciardi 2003, Tarlo 1991, Vandenplas 1995a, Vandenplas 2001)

What are the sensitivity and the specificity of changes in non-specific reactivity at work and away from work in the diagnosis of validated cases 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%.

C11 ** SIGN 2- Changes in non-specific reactivity at and away from work alone have only moderate sensitivity and specificity for diagnosis.

(Cote 1990, Perrin 1992, Tarlo 1991)

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

Paired measurements of non-specific reactivity 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 who were there at the time.

C12 * SIGN 3 Paired measurements of non-specific reactivity may be achieved in the workplace. (El-Zein 2003, Tarlo 1991)

What are the sensitivity and the specificity of specific IgE testing in the diagnosis of validated cases of occupational asthma?

The production of specific IgE antibody may be detected by skin prick or serological tests. The respective sensitivities and specificities of the ability of these tests to detect specific IgE vary between allergens but in any case are dependent on the setting of positive cut-offs. Blood testing for specific serum IgE may not be as sensitive as skin prick testing (Park 2001) but may be useful if skin testing cannot be performed. The presence of specific IgE confirms sensitisation to an agent at work, but alone does not confirm the presence of occupational asthma, nor necessarily its cause. In this sense there is a high false positive rate although, with high molecular weight agents, few false negatives. The power of testing for specific IgE is to exclude an allergen as a cause of a worker's asthma.

Specific IgE is an insensitive but specific test for isocyanate-induced occupational asthma (Tee 1998) although this is to some extent dependent on the time since last exposure. A small study reported greater sensitivity for MDI (83%) than TDI (27%) (Pezzini 1984).

C13 **SIGN2+ Both skin prick and serological tests are highly sensitive for detecting specific IgE and occupational asthma caused by most high molecular weight agents, but are not specific for diagnosing asthma. (Platts-Mills 1987, Vandenplas 1995a)

C14 **SIGN2+ Both skin prick and serological tests are sensitive for detecting specific IgE and occupational asthma caused by acid anhydrides and some reactive dyes; but have a lower specificity for diagnosing asthma. (Baur 1995, Grammer 1998, Howe 1983, Park 1989, Park 2001)

C15 **SIGN2+ Skin prick tests are highly sensitive but less specific for occupational asthma caused by complex platinum salts. (Merget, 1988, Merget 1991, Merget 1996)

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

(Burge 1979a, Burge 1979b, Cartier 1989, Lin 1995, Moscato 1991)

C16 - SIGN 4 Carefully controlled specific challenges come closest to a gold standard test for some agents causing occupational asthma.

C17 - SIGN 4 A negative test in a worker with otherwise good evidence of occupational asthma is not sufficient to exclude the diagnosis.

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 workers are exposed. Studies in this area are open to considerable bias through subject selection.

What is the prognosis of occupational asthma?

Generally, occupational asthma is reported to have a poor prognosis and to be likely to persist and deteriorate unless identified early and managed effectively.

D1 *** SIGN 2+ The symptoms and functional impairment of occupational asthma caused by various agents may persist for many years after avoidance of further exposure to the causative agent.
(Allard 1989, Barker 1998, Chan-Yeung 1982, Chan-Yeung 1987, Hudson 1985, Lemiere 1996, Lozewicz 1987, Mapp 1988, Marabini 1994, Merget 1994, Moller 1986, Munoz 2003, O'Donnell 1989, Padoan 2003, Paggiaro 1984, Paggiaro 1993, Pisati 1993, Rosenberg 1987, Tarlo 1995, Vandenplas 2002, Venables 1987, Venables 1989b)

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 have no further exposure to the causative agent.
(Burge 1982b, Chan-Yeung 1982, Merget 1999, Moscato 1999, Pisati 1993, Rosenberg 1987, Tarlo 1997b, Valentino 1994, Valentino 2002, 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, Park 1997, Piirila 2000, Pisati 1993, Tarlo 1995, Tarlo 1997b, 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, Rosenberg 1987, Ross 1998, Tarlo 1997b)

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. If it is possible to relocate the worker to low or occasional exposure work areas, he or she should remain under increased medical surveillance. Where present, specific IgE can be monitored although this has not been shown to affect 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 1982b, Douglas 1995, Grammer 1993, Grammer 2000, Merget 1999, Pisati 1993, Rosenberg 1987)

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.

D7 * 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) or may not (Cannon 1995, Labanois 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, Labanois 2002).

D8 ** SIGN 2- Approximately one third of workers with occupational asthma are unemployed up to 6 years after diagnosis.

(Ameille 1997, Axon 1995, Cannon 1995, Gannon 1993b, Larbanois 2002, Marabini 1993, Ross 1998, Vandenplas 2002, Venables 1989b)

D9 ** SIGN 2- Workers with occupational asthma suffer financially.

(Ameille 1997, Axon 1995, Bernstein 2003, Gannon 1993b, Larbanois 2002, 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.

D10 - SIGN 4 Systems that incorporate retraining may be more effective than those that do not.

(Ameille 1997, Malo 1993b)

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.

D11 * SIGN 1+ Inhaled corticosteroids used after cessation of exposure may provide small clinical benefits to workers with occupational asthma.

(Malo 1996)

4 PRINCIPAL RECOMMENDATIONS FOR OCCUPATIONAL HEALTH MANAGEMENT

- 1 Employers, health and safety personnel and health practitioners should be aware that at least 1 in 10 cases of new or recurrent asthma in adult life are attributable to occupation. *** SIGN A**

*** SIGN 2++ Occupational factors are estimated to account for 9-15% of cases of asthma in adults of working age, including new onset or recurrent disease.

- 2 Employers and their health and safety personnel should be aware of the very large number of agents known to cause occupational asthma and the risk of exposure to such agents. ** SIGN B**

*** SIGN 2++ The most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust.

- 3 Employers and their health and safety personnel should be aware that the major determinant of risk for the development of occupational asthma is the level of exposure to its causes. ** SIGN B**

*** SIGN 2++ The risk of sensitisation and occupational asthma is increased by higher exposures to many workplace agents.

- 4 Health practitioners should not use poorly discriminating factors - such as atopy, family or personal history of asthma, cigarette smoking and HLA phenotype - which increase individual susceptibility to exposure 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.

* SIGN 3 A previous history of asthma is not significantly associated with occupational asthma.

- 5 Employers should implement programmes to prevent (i.e. reduce the incidence of) occupational asthma by removing or reducing exposure to its causes through elimination or substitution and where this is not possible, by effective control of exposure. ** 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.

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

- 6 Employers and their health and safety personnel should ensure that when respiratory protective equipment is worn, the appropriate type is used and maintained, fit testing is performed and workers understand how to wear, remove and replace their respiratory protective equipment.** * SIGN D
- * SIGN 3 The use of respiratory protective equipment reduces the incidence of, but does not completely prevent, occupational asthma.
- 7 Employers and their health and safety personnel should 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.
- 8 Employers and their health and safety personnel should be aware that for many causes the risk of developing occupational asthma is greatest during the early years of exposure.** ** SIGN C
- ** 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.
- 9 Employers and their health and safety personnel should provide regular health surveillance to workers where a risk of occupational asthma is identified. Surveillance should include a respiratory questionnaire enquiring about work-related upper and lower respiratory symptoms, with additional functional and immunological tests, where appropriate.** ** SIGN C
- ** 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.
- 10 Health practitioners should provide workers at risk of occupational asthma with health surveillance at least annually and more frequently in the first two years of exposure.** ** SIGN C
- ** 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.

- 11 Health practitioners should 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 C**
- ** SIGN 2+ Occupational rhinitis and occupational asthma frequently occur as co-morbid conditions in the case of IgE associated occupational asthma.
- ** SIGN 2+ Rhino-conjunctivitis 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.
- 12 Health practitioners should provide more frequent health surveillance to any workers who have pre-existing asthma to detect any evidence of deterioration.**
- 13 Health practitioners should consider the use of skin prick or serological tests as part of the health surveillance of workers exposed to agents that cause IgE associated occupational asthma to assess the effectiveness of the control of exposure and the risk of occupational asthma among workers.**
- ** SIGN 2+ Skin prick testing and blood sampling of exposed workers to conduct immunological tests is feasible in the workplace.
- 14 Health practitioners should 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 2++ Occupational factors are estimated to account for 9-15% of cases of asthma in adults of working age, including new onset or recurrent disease.
- *** SIGN 2++ The workers most commonly reported from surveillance schemes reported of occupational asthma include bakers and pastry makers, paint sprayers, nurses, chemical workers, animal handlers, food processing workers, timber workers and welders.
- ** SIGN 2+ The workers reported from population studies to be at increased risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastics and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, waiters, cleaners, painters, plastic workers, dental workers and laboratory technicians.
- *** 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 occupational asthma.

- 15 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.**
- 16 Health practitioners should be aware that the prognosis of occupational asthma is improved by early identification and early avoidance of further exposure to its cause.** **** SIGN B**
- ** 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.
- 17 Health practitioners who suspect a worker of having occupational asthma should make an early referral to a physician with expertise in occupational asthma.**
- 18 Health practitioners who suspect a worker of having occupational asthma should arrange for workers to perform serial peak flow measurements at least four times a day.** **** SIGN D**
- ** SIGN 3** 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.
- ** SIGN 3** There is high level of agreement between expert interpretations of serial peak flow records.
- ** SIGN 3** The sensitivity and specificity of serial peak flow measurements are high in the diagnosis of occupational asthma.
- 19 Physicians should confirm a diagnosis of occupational asthma supported 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 B**
- ** 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 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.

20 Employers and their health and safety personnel should ensure that measures are taken to ensure that workers diagnosed as having occupational asthma avoid further exposure to its cause in the workplace. ** SIGN B

** SIGN 2+ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who are removed from exposure completely.

** 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, however, there is contradictory evidence from other studies, which show that redeployment does not lead to improvement in symptoms or prevent deterioration of symptoms.

21 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.

22 Health practitioners should enquire about pre-existing occupational asthma to agents that job applicants might be exposed to in their new job and advise affected applicants that they are not fit to undertake this work. ** SIGN B

** SIGN 2+ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who are removed from exposure completely.

** 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, however, there is contradictory evidence from other studies, which show that redeployment does not lead to improvement in symptoms or prevent deterioration of symptoms.

5 EVIDENCE TABLES

* Original authors' main conclusions from Abstract, Results and Discussion. (*Present reviewers' comments in brackets and italics*)

Authors	Type of study	Original authors' main conclusions *
Agrup et al. 1986	Cross-sectional	Of 19 people with laboratory animal allergy symptoms & positive animal tests, 68% had a history of atopic dermatitis, rhinitis or asthma before they started work or reacted to one or more allergens in the standard battery. Atopic features were present in 3/11 (27%) people with animal related symptoms but with negative animal RAST & skin tests. Of the 30 with no animal related symptoms, 20% had a history of atopic disease or a positive reaction to a standard test or both. Atopy was commoner among those with positive tests to laboratory animal allergens. Smoking habits did not differ significantly. (<i>The first symptoms appeared after a mean latent period of 2.3 years</i>).
Allard et al. 1989	Case series	Follow up assessments made on average 2.3 years & 5.8 years after removal from the workplace, with mean duration of exposure before symptoms 6.3 months. Authors conclude that except for 3 subjects, all were still symptomatic at both follow ups even after > 4 years, the need for medication did not diminish, nor did airway obstruction & hyper-responsiveness improve in this group of subjects with occupational asthma long after exposure ended.
Allmers et al. 2002	Cross-sectional	Study assesses the effects of intervention to reduce the incidence of natural rubber latex (NRL) allergy in personnel working in health care facilities by switching to powder-free NRL gloves. Despite the effect of increased recognition of NRL allergies, 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 occupational allergies caused by NRL in Germany on a nationwide scale. Results clearly indicate that primary prevention of occupational NRL allergies can be achieved if these straightforward & practical interventions are properly carried out & maintained.
Ameille et al. 1997	Case series	Patients with occupational asthma were reviewed on average 3.1 years after the diagnosis. At time of review, 44% of patients had left their previous job & 25% were currently unemployed. 32% remained exposed to the offending agents in the same job. 46 percent of the 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 occupational asthma. The authors conclude that occupational asthma results in severe socio-economic consequences.
Ameille et al. 2003	Reporting scheme	New cases of occupational asthma were collected by a national surveillance programme, based on voluntary reporting & a network of occupational & chest physicians. In 1996-99 the mean annual rate of occupational asthma was 24/million. Rates in men were higher than in women (27/million versus 19/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 occupational asthma were found in bakers & pastry makers (683/million). The authors conclude that the relevance of the programme is confirmed by the annual reproducibility of the results & consistency with other surveillance programmes.
Anees et al. 2002	Case series	Study aimed to determine sputum cellular profile of workers with occupational asthma induced by low molecular agents & to relate this to physiological measures of airway obstruction. Despite having work-related deterioration in peak expiratory flow (PEF), many workers with occupational asthma show low degree of within day diurnal variability atypical of non-OA. Authors conclude that asthma caused by low molecular weight agents can be separated into eosinophilic & non-eosinophilic patho-physiological variants with latter predominating (24/38 had no eosinophils on sputum induction). Both groups had evidence of sputum neutrophilia. Sputum eosinophilia was associated with more severe disease & greater bronchodilator reversibility but no difference in PEF response to work exposure.

Axon et al. 1995	Case series	Study aimed to determine the differences between patients with occupational asthma & those with non-occupational asthma, 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 occupational asthma & one for those with cryptogenic & environmental asthma. The age of onset was significantly higher for those with occupational asthma (42.6 vs 20.7 years). Significantly more subjects with occupational asthma reported improvement on holiday, whereas no significant difference was found in the numbers reporting worsening of symptoms on workdays. Those with occupational asthma were less likely to report seasonal variation in symptoms, exacerbation by allergies, pets & stress, or a family history of asthma. Subjects with occupational asthma were more likely to become unemployed (50% vs 3%). Recognition of some of these features in a patient's history may help in the difficult task of differentiating occupational asthma from non-OA, potentially avoiding the need for exhaustive investigations in some patients.
Baker et al. 1990	Case-control	Study aimed to determine respiratory & dermatological effects of platinum salts sensitisation among workers in a secondary refinery of precious metals. Platinum salts sensitisation was not associated with atopic tendency as measured by sensitivity to common aeroallergens, but was strongly associated with cigarette smoking status. The findings indicate that cigarette smoking may be a risk factor for the development of platinum salts allergy.
Balboni et al. 1996	Case-control	The authors suggest genetic susceptibility for isocyanate occupational asthma, as evaluation of HLA class II gene products in toluene di-isocyanate-induced asthma cases showed a positive association with HLA-DQB1 * 0503 & a negative association with HLA-DQB1 * 0501 alleles, which differed at residue 57 for a single amino acid, i.e. aspartic acid in DQB1 * 0503 & valine in DQB1 * 0501.
Baldwin et al. 2002	Case series	Oasys-2 is a validated diagnostic aid for occupational asthma that interprets peak expiratory flow (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 of occupational PEF records, which may lead to inconsistencies in diagnosis of occupational asthma (experts underscore versus OASYS). There is a need for objective scoring system, which removes human variability, such as that provided by OASYS-2.
Balmes et al. 2003	Systematic review	A review of the published literature regarding the magnitude of the population attributable risk (PAR) for the occupational contribution of asthma has been conducted for this statement. 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 or calculated PAR% range from 4% to 58%, with a median value of 15%.
Barker et al. 1998	Case series	Subjects continued to have respiratory symptoms & bronchial hyper-responsiveness despite avoidance of exposure for 12 years & a progressive fall in IgE.
Bar-Sela et al. 1984	Case-control	16 poultry workers with poultry house-related rhinitis and/or asthma 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; only in these individuals could immediate wheal-and-flare reactions to poultry antigens be detected. 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 demonstrable IgE antibody-mediated reaction suggests a relationship between the two.
Baur & Czuppon, 1995	Case series	9 anhydride workers, who complained of various respiratory symptoms, were studied. 4/9 had immediate-type skin prick test (SPT) responses to one or more conjugates & had elevated IgE concentrations in addition to 2 other workers. 3/6 of six nasal challenges & 4/9 bronchial challenges resulted in positive responses. All but one of the positive nasal or bronchial test responses were associated with elevated IgE levels. The 7 positive challenge test results included 5 positive 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. 1998a	Case series	Study aimed to evaluate 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 & inhalative challenge test responses was significant. However, approximately 29% of the bakers with respiratory symptoms showed no sensitisation to these bakery allergens, whereas 32% of the sensitized bakers in the screening group had no workplace-related symptoms. Atopic status defined by skin prick test 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. Further methods are required to objectively assume irritative patho-mechanisms. Authors conclude that findings indicate the necessity for an improved primary prevention of exposure to inhalative noxae in bakeries.
Baur et al. 1998b	Case series	Methacholine challenge (MC) was performed in 229 subjects with suspected occupational asthma. They were also subjected to specific challenge tests, questionnaire, & interviewed by an experienced physician. Study aimed to investigate whether MC and/or occupational asthma case history are reliable predictors of specific challenge test outcomes. MC results are only moderately associated with workplace-related asthma case histories whereas positive outcomes of challenges with occupational agents are well correlated with positive MC results plus occupational asthma case histories. Authors conclude that in most cases, occupational asthma is combined with bronchial hyper-responsiveness (BHR) & workplace-related asthmatic symptoms. In subjects with a positive occupational asthma case history, a negative MC test result can almost rule out a positive specific challenge test result. Hence, the MC test can reduce performance of the laborious specific challenge test.
Beghe et al. 2004	Case-control	Study aimed to investigate the role of genetic factors in the development of toluene di-isocyanate (TDI)-induced asthma. The distribution of human leukocyte antigen (HLA) class I genes & of tumour necrosis factor (TNF)-alpha A-308G polymorphism was analysed in 142 patients with TDI-induced asthma & in 50 asymptomatic exposed subjects. Neither the distribution of HLA class I antigens nor the distribution of TNF-alpha A-308G polymorphism was different between patients with TDI-induced asthma & asymptomatic exposed subjects suggesting that HLA class I antigens & TNF-alpha A-308G are not associated with susceptibility or resistance to the development of TDI-induced asthma.
Bernstein et al. 1993	Cross-sectional	A study of 243 workers exposed to diphenylmethane di-isocyanate (MDI) was conducted in a plant that had been designed to minimize MDI. On the basis of questionnaire responses, diagnoses were derived that included occupational asthma; non-OA; work-related & non-work-related rhinitis; & lower respiratory irritant responses. PEFV values were abnormal in 3/9 workers with occupational asthma, in 2/4 with non-OA, & in 2/23 case control subjects. A significant association was found between peak flow rate variability & a questionnaire asthma diagnosis. Physicians confirmed 3 cases of occupational asthma, one of which in symptom-free control worker). In all 3 cases asthma symptoms remitted after the worker left the workplace. On the basis of these cases, specific work activities associated with exposure to MDI were identified & corrective measures were instituted. Strict control & monitoring of ambient MDI exposure was associated with a low prevalence of specific sensitisation to MDI & a lower than expected prevalence of occupational asthma.
Bernstein et al. 1997	Case referent	Di-isocyanates are the most common cause of occupational asthma induced by low-molecular-weight chemicals. The disease appears to be immunologically mediated but is independent of IgE antibody synthesis. An underlying genetic susceptibility is suggested by the fact that the disease only develops in approximately 5-10% of exposed workers. Study aimed to determine whether disease susceptibility is influenced by HLA & T-cell receptor V beta gene segment usage. Lymphocytes from workers with di-isocyanate-induced occupational asthma had significantly decreased V beta 1 & V beta 5 gene segment expression before in vitro exposure to di-isocyanates, compared with control groups. Percent V beta 1 & V beta 5 gene segment expression was selectively increased when peripheral blood mononuclear cells were stimulated in vitro with di-isocyanate-conjugated proteins. Low-resolution HLA class II phenotyping revealed no significant differences in the distribution of HLA-DR or HLA-DQ alleles between di-isocyanate-induced occupational asthma & control groups. These findings are consistent with a hypothesis that antigen-specific T-cell subpopulations may be sequestered in the lungs of workers with di-isocyanate-induced occupational asthma & clonally expand after further exposure to di-isocyanates.

Bernstein et al. 2003	Case series	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.
Bignon et al. 1994	Case-control	DQB1*0503 & allelic combination DQB1*0201/0301 were associated with susceptibility to isocyanate occupational asthma, whereas DQB1*0501 & DQA1*0101-DQB1*0501-DR conferred significant protection in exposed, healthy control subjects. Although a group of asthmatic subjects was not examined to rule out an association between HLA & asthma per se., the frequency of DR4 haplotype was lower than in atopic historical controls & similar to that in study controls.
Blanc & Toren 1999	Systematic review	43 attributable risk estimates were obtained from 19 different countries. The median value for the attributable risk of occupational asthma 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 occupational asthma varied widely among countries from a low of 1.2 to a high of 17.4 per 100,000 person-years. The highest rate was observed in Finland. The median incidence of occupational asthma is 4.7 cases per 100,000 person-years. Assuming an incidence for all asthma among adults of working age of 100 per 100,000 person-years, the estimated median attributable risk is 5%.
Botham et al. 1987	Cohort	The pattern of incidence of allergy to laboratory animals was studied prospectively in 383 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.
Brhel, 2003	Surveillance scheme	Presents the profile of occupational respiratory diseases in Czech Republic. In a retrospective study, the author analyses structure, causes, occurrence, & trends of occupational diseases. Between 1996 & 2000, a total of 2,127 new cases were recorded, of which 62.0% were pneumoconioses caused by dust containing free silica, 21.0% were occupational asthma or allergic rhinitis & the rest were divided between lung cancer (10.0%), asbestos-related disorders (4.4%) & variety of other respiratory diseases (2.7%). During the period of the investigations, the decreasing trend of occupational respiratory diseases, which began in 1992, has continued. 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.
Bright et al. 2001	Case series	268 serial peak expiratory flow (PEF) records made by workers with possible occupational asthma were divided into 4 sets. The first 2 were development sets & sets 3 & 4 were "gold standard" sets where the diagnosis had been made independently. Set 3 was used to set cut-off for occupational effect, the sensitivity & specificity for the combined model was determined from the fourth set. The fourth set 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 positively for work-related changes in PEF than the expert. The sensitivity of OASYS-3 was better than OASYS-2 (82% & 75% respectively) for an equivalent specificity (94%). The sensitivity of the human expert was 100% with a specificity of 93%. OASYS-3 provides an objective method of interpreting serial PEF records with sensitivity & specificity approaching that of a human expert.
Brisman et al. 2000	Cohort	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.

Brisman et al. 2003	Case-control	89 subjects (25 asthmatics, 20 rhinitics & 44 controls) underwent skin prick tests (SPTs) with common allergens, flours, fungal alpha-amylase & the storage mite <i>L. destructor</i> . 7 asthmatics & 8 rhinitics reported onset of disease during bakery work. Flour SPTs were positive in 43% of asthmatics or rhinitics versus 16% of referents. The positive predictive value of sensitisation to flour or alpha-amylase in relation to a clinical diagnosis of asthma or rhinitis was 71%. Sensitisation to <i>L. destructor</i> was rare. Authors conclude that bakers' asthma is associated with sensitisation to flour and/or alpha-amylase, atopy taken into account. Indices of airway inflammation were of low predictive value for detecting bakers' asthma or rhinitis in this study.
Brooks, 1981	Cohort	Presumptive diagnosis of occupational asthma was defined on both physiologic & clinical criteria as an observed decline in FEV1 of greater than 10% from the Monday pre-shift value compared to one or more subsequent tests during any of the following 3 days exposure period & a positive clinical history. Occupational asthma was diagnosed in 10 workers. A dose dependent relationship between total western red cedar dust level & prevalence of asthma was noted with employees in jobs with the greatest dust exposure.
Burge et al. 1979a	Case series	Peak expiratory flow rate (PEFR) 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 PEFR records correlate well with BPT & provide a suitable alternative for the diagnosis of mild to moderate occupational asthma.
Burge et al. 1979b	Case series	Peak expiratory flow rate (PEFR) 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 work-related asthma made from subsequent work exposure was compared with the results of bronchial provocation testing & a subjective assessment of peak flow 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.
Burge et al. 1981	Cross-sectional	The 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 three grades of exposure with median levels of 1.92 mg/m ³ (6 subjects), 0.02 mg/m ³ (14 subjects), & less than 0.01 mg/m ³ (68 subjects). All but 2 workers in the first 2 groups, & 90% of a random sample of the last group, were studied. Occupational asthma 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. Survey suggests that sensitisation will not be prevented unless exposure is kept well below present threshold limit value.
Burge, 1982a	Case series	39 electronics workers with occupational asthma were divided into 3 groups & were investigated & followed up 1-4 years later. 20 had left work after their initial diagnosis, 8 had been moved to alternative work within their original factories, & 11 were thought to have asthma unrelated to colophony exposure as they failed to react to colophony at presentation. Histamine reactivity had returned to normal in half the workers who had left their original factories, but in only one worker who had moved within her original factory suggesting that indirect exposure at work was sufficient to delay recovery of histamine reactivity. Only 2 of the 20 affected workers who had left their original factories were symptom free on follow-up, & most had a considerable reduction in their quality of life by continuing asthma.
Burge, 1982b	Case series	Histamine reactivity 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 & bronchial reactivity. Only 2/20 affected workers who had left factory were symptom free, & most had considerable reduction in quality of life by continuing asthma.
Butcher et al. 1977	Cohort	Workers at a toluene-di-isocyanate (TDI) manufacturing plant were studied longitudinally to determine the effects of the chemical on their health. Workers reporting increased lower respiratory symptoms were from the non-smoker group. Immunologic studies showed development of positive skin test to a TDI-human serum albumin conjugate by some persons & an increasing incidence of TDI-specific IgE antibodies as measured by a RAST test. However, there was no correlation between positive TDI inhalation challenge & total IgE concentration or atopic status.

Calverley et al. 1995	Cohort	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 positive skin prick test whereas 10 were symptomatic but had negative skin prick tests. Positive responses to platinum salt skin prick test had a 100% positive predictive value for symptoms & signs of PSS if exposure continued. Risk of sensitisation was about eight times greater for smokers than non-smokers, & six times greater for high exposure than low exposure. Authors concluded that smoking & intensity of exposure were definitely associated with development of PSS & that logical recommendations would be employment of non-smokers, & continued reduction in platinum salts in air in work areas.
Cannon & Cullinan, 1995	Cross-sectional	Earnings adversely affected in all categories – 30% of those with occupational asthma or work-exacerbated asthma reported more losing more than 40% of income. Compared to non-work-related asthma, those with occupational & work-related asthma report greater difficulty in finding new work & higher proportions had changed or suffered disruption to their jobs. <i>(Of the 225 subjects, 113 had occupational asthma, 37 had work-exacerbated asthma & 75 had asthma unrelated to work).</i>
Cartier et al. 1984	Cohort	The prevalence of occupational asthma was studied in 2 snow crab-processing industries. Before the 1982 season, all except 10/313 employees were investigated by a questionnaire, skin prick tests 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 occupational asthma in the previous seasons) by specific inhalation challenges in 33 subjects and/or a combination of monitoring of peak expiratory flow rates & significant changes in bronchial responsiveness to histamine as well as in spirometry after reappearance of symptoms on return to work. Positive skin tests to crab and, to a lesser degree, smoking history but not atopy were related to the presence of occupational asthma. A high prevalence of rhino-conjunctivitis (35/46) & urticaria (16/46) was also documented in the affected individuals.
Cartier et al. 1989	Cross-sectional	The sera of 62/65 workers referred for specific inhalation challenges (SIC) with isocyanates were analysed for the presence of specific antibodies to the relevant isocyanate. SIC were positive in 29 subjects, & were more often positive in those subjects with increased non-specific bronchial responsiveness. 29 subjects demonstrated increased levels of specific IgE and/or IgG antibodies 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 positive challenges had increased levels of specific IgG, whereas 25/33 subjects (76%) with negative challenges had normal levels of antibodies.
Cathcart et al. 1997	Cohort	Workers from five locations in the United Kingdom 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. <i>Study shows correlation between airborne concentrations of enzyme & incidence of asthma in UK soap & detergent industry over 20 years.</i>
Chan-Yeung et al. 1982	Case series	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.
Chan-Yeung et al. 1987	Case series	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 non-specific bronchial hyper-responsiveness 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.

Cockcroft et al. 1981a	Cross-sectional	An association significant at the 2% level was found between skin test 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-related asthma. 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.
Cortona et al. 2001	Case series	A study on occupational rhinitis & asthma diagnosed in 7 occupational health institutes was performed. 141 cases of rhinitis & 281 cases of asthma due to sensitisation to occupational agents were analyzed & their clinical characteristics, aetiology, diagnostic methods & associated allergic diseases were determined. In this population the most frequent agents of occupational rhinitis were wheat flour & latex, whereas those of occupational asthma were latex & isocyanate. More than half of the subjects had more than one clinical manifestation of allergy. In 92/281 asthmatic patients, rhinitis was the first clinical manifestation, particularly in subjects sensitized to high molecular weight substances, & preceded, asthma by 12 months as a mean. Specific bronchial provocation tests were useful for the diagnosis of asthma in 153 of asthmatic patients & 45 of them had an isolated late bronchial reaction following the specific stimulus. At diagnosis 61 subjects (21.7%) had FEV1 < 80% of predicted; factors associated to ventilatory impairment were sensitisation to high molecular weight substances, duration of exposure to the sensitizing agent, persistence of exposure after onset of symptoms.
Cote et al. 1990	Case series	The diagnosis of red cedar asthma is usually confirmed by a specific challenge with plicatic acid. Study aimed to determine the sensitivity & specificity of two other diagnostic tests, prolonged recording expiratory flow rate (PEFR) & measurement of bronchial responsiveness (provocative dose of methacholine causing a 20% fall in FEV1 [PC ₂₀ methacholine]). 23 patients with suspected cedar asthma recorded PEFR during 2 weeks away from work & 3 weeks at work. Plicatic acid challenge test was performed at the end of the study; 14 patients reacted, whereas 9 patients did not. Using the plicatic acid challenge test as the gold standard, the sensitivity & specificity of PEFR recordings were 86% & 89%; changes in PC ₂₀ , 62% & 78%; & 93% & 45% for a positive clinical history. The combination of PEFR & clinical history revealed 100% sensitivity with 45% specificity. Combination of PEFR & PC ₂₀ did not improve the diagnostic accuracy.
Cote et al. 1993	Case series	Peak expiratory flow rates (PEF) are often used to confirm diagnosis of occupational asthma. Study compared the diagnostic value of a qualitative assessment of change in PEF with objective measures of change in PEF & the results of a specific inhalation challenge 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 a challenge test 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 asthma as diagnosed by the specific challenge test. Authors conclude that qualitative assessment of PEF is a good diagnostic test for cedar asthma.
Coutts et al. 1984	Cross-sectional	We issued a questionnaire & performed skin prick tests & spirometry on 3 groups of employees defined according to exposure. 13 (62%) of the 21 patients exposed daily, 4 (21%) of the 19 exposed more than once a week, & 3 (20%) of the 15 exposed less than 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. χ^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	Cross-sectional	Survey of 23 autobody shops aimed to determine the feasibility of clinical epidemiological studies. Among 102 workers, there was a high rate of airway symptoms consistent with occupational asthma (19.6%). Symptoms were most prevalent among 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. Occupational asthma symptoms were found 3 times more frequently among painting shop-floor workers & dedicated painters who did not use a positive 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. There was no clear association between these findings & either questionnaire responses or exposure classification. Overall, the survey suggests that there is a high prevalence of airway symptoms among workers in autobody shops, at least in part due to work-related asthma. However, there is need for both methodological & substantive research in this setting to document rates of occupational asthma & to develop a scientific basis for its effective control.
Cullinan et al. 1994	Cross-sectional	344 employees exposed to flour in bakeries or mills in 7 sites were assessed by self completed questionnaire, & sensitisation measured by the response to skin prick tests, 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. Positive skin test 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	Case-control	Case-referent analysis of newly employed laboratory animal workers. Cases comprised persons developing symptoms of laboratory animal allergy or a positive skin prick test to rat urinary allergens; each was matched with up to two asymptomatic referents. Subjects were assigned to categories of exposure based on measurements of airborne rat urinary allergens. Of the cases, 80% reported that their symptoms started within 2 years of employment. A gradient of increasing odd ratios (OR) for the development of any such symptom across exposure categories was found; for respiratory symptoms & skin test 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 skin test reaction. Allergen exposure was confirmed as the most important determinant of laboratory animal allergy. 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. <i>(31% of subjects with new chest symptoms reported these without other symptoms, whereas 45% had eye/nose & 35% had skin symptom).</i>
Cullinan et al. 2000	Cross-sectional	Occupational & health information was collected by questionnaire from employees & 342 employees were given skin-prick tests. Results indicate a very high rate of enzyme-related sensitisation & asthma in the factory, leading to an estimate of 50 cases of occupational asthma in the current workforce, in addition to the six index cases. Enzyme sensitisation & work-related respiratory symptoms were positively 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	Cohort	Study aimed to estimate the incidence of specific IgE sensitisation & allergic respiratory symptoms among UK bakery & flour mill workers & also 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 cases per 100 person years (py), respectively. Fewer employees developed positive skin prick tests to flour (2.2 cases per 100 py) or alpha-amylase (2.5 cases per 100 py). There were clear relationships between the risks of developing work-related symptoms or a positive skin prick test & three categories of estimated exposure to total dust or flour aeroallergen. Atopic employees were more likely to develop a positive skin prick test-but not work-related symptoms. These findings were unaffected by age, sex or cigarette smoking.

de Bono & Hudsmith, 1999	Cross-sectional	Study looked at general practice notes of asthmatics to assess overall load of occupational asthma in the community. 86% of patients with adult onset asthma studied had at least one occupation recorded in their notes. 32% of these were in jobs known to be significant causes of occupational asthma, yet a potential link between occupation & symptoms had only been recorded in 18% of patients in these jobs. Overall 4% of the patients with adult onset asthma had been given a diagnosis of occupational asthma although in nearly half these cases, a general practitioner & not a specialist had made the diagnosis.
De Zotti et al. 1994	Cross-sectional	A survey was carried out on respiratory symptoms & skin prick test 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; work-related asthma was reported by 11 (4.9%). Personal atopy was significantly associated with skin sensitisation 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. Authors conclude that there is still a significant risk of allergic respiratory disease among Italian bakers. Atopy must be regarded as an important predisposing factor for the onset of symptoms at work. The data confirm that for effective prevention, greater care should be taken not only in limiting environmental exposure, but also in identifying susceptible people.
De Zotti et al. 1997	Cross-sectional	Study investigated the prevalence of atopy & sensitisation to wheat flour/alpha amylase in group of trainee bakers & in group of trainee graphic artists as controls. The follow-up was performed 6 months later only among trainee bakers. Trainee bakers & controls were similar with respect to age, number of smokers, atopy, & detection of serum IgE (RAST) & IgG specific to wheat flour. Positive skin prick test to wheat flour (4%) & alpha amylase (1%) were found only among trainee bakers. 4 students (4.4%) complained of respiratory symptoms when working with wheat flour. At the 6-month follow up, 6.6% of the trainee bakers complained of work-related symptoms (WRS): 3.3% had persistent symptoms, 3.3% were new cases & 1.1% had become asymptomatic. 5 cases (5.5%) were skin positive to wheat flour or alpha amylase, but only one was unchanged, while 4.4% were new cases & 3.3% turned negative. None of these changes was statistically significant. The trainee bakers complaining of WRS at the baseline or at follow-up (7 cases, when 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 skin positive to the occupational allergens (8 cases) showed prevalences of personal atopy & atopy by prick test significantly higher than trainee bakers skin negative to wheat flour or alpha amylase. Authors conclude that these results emphasize the important role of personal atopy as a predisposing factor in the development of occupational disease among trainee bakers.
De Zotti et al. 2000	Cohort	Study aimed to investigate the occurrence of work-related respiratory symptoms & to assess the effect of atopy in 125 trainee bakers. At the baseline examination, 4 students complained of respiratory symptoms (cough & rhinitis) when working with flours & 4 were skin positive 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 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 skin prick test is useful for identifying subjects with allergic disease, but should not be used to exclude non-symptomatic atopic people from bakery work.

Di Stefano et al. 1999	Case series	Reports series of 24 healthcare workers with respiratory symptoms suggestive of occupational asthma due to glutaraldehyde exposure. The history of asthmatic symptoms was investigated with peak expiratory flow rate (PEFR) monitoring, & in 8 subjects, the specific bronchial provocation test (SBPT) was applied as reference standard for diagnosis of occupational asthma. 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 SBPT, the diagnosis of occupational asthma was confirmed by a positive reaction. In 13/16 remaining workers, the serial PEFR monitoring showed a work-related effect. In 3 workers, there was no physiological confirmation of occupational asthma. Measurements of specific IgE antibodies to glutaraldehyde-modified proteins were positive in seven patients (29.1%) according to a cut-off value of 0.88% RAST binding. The presence of atopy to common environmental allergens & smoking was not associated with specific IgE positivity. Authors conclude that report indicates the importance of glutaraldehyde as an occupational hazard among exposed health-care workers. Intervention in the workplace, training of personnel handling this chemical, & accurate health surveillance may reduce the risk of developing occupational asthma due to glutaraldehyde.
Docker et al. 1987	Cohort	A questionnaire survey of 414 workers handling reactive dyes showed that over 15% had work-related respiratory or nasal symptoms. 49 employees with symptoms were referred to chest clinics for detailed assessment. In 19 subjects, the symptoms were attributed to an irritant response whereas in 24, symptoms were attributed to an allergic reaction to a specific agent. A radioallergosorbent test (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. It seems possible that the relatively high proportion of atopics among those experiencing irritant reaction reflects the increased bronchial responsiveness in atopics as compared with the non-atopic population. Atopy may also predispose to specific IgE antibody production to reactive dyes; specific IgE was identified in 81% of those with 'allergic' symptoms but only 37% of those with irritant symptoms.
Douglas et al. 1995	Cross-sectional	Within 3 months of the opening of a salmon-processing plant in the UK, some workers complained of symptoms suggestive of occupational asthma. A survey of all 291 employees identified 24 (8.2%) with occupational asthma. The employees worked near machines, which generated respirable aerosols containing salmon-serum proteins. The IgE response to these proteins was associated with occupational asthma, with increasing severity of symptoms, & with working distance from the aerosol source. The main factor which predisposed to IgE-antibody 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 occupational asthma.
Drexler et al. 1999	Cross-sectional	An investigation with 110 workers exposed to hexahydrophthalic acid anhydride (HHPA) & methyltetrahydrophthalic acid anhydride (MTHPA) was carried out in July 1991 & in December 1991, the hygiene conditions at the plant were improved. In November 1995 a second investigation of 84 people was performed. The relative risk of people sensitised in 1991 of leaving the plant between 1991 & 1995 was 2.6 compared with people without any sign of sensitisation. The percentage of people identified as sensitised in 1991, who were still working at the plant & came to the second investigation, was higher than for people without evidence of sensitisation. 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 positive effect on the symptoms in sensitised people.

Droste et al. 2003	Cross-sectional	Study aimed to estimate the risk among bakery workers of respiratory & allergic disorders relative to that of a reference group of workers without a particular occupational exposure. A random sample of 246 bakers was compared with a reference population of 251 workers from a petrochemical plant in the same region. On average, bakery workers did not more often have skin test positivity than reference workers. However, bakery workers had a strongly increased risk of sensitisation to specific bakery allergens, whereas their risks of positive skin tests 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.
El-Zein et al. 2003	Cohort	Study aimed to determine the incidence of probable occupational asthma (OA), bronchial obstruction & hyper-responsiveness among 286 student welders. Non-specific bronchial reactivity was measurable in 194/204 individuals who were present. There were also individuals who developed non-specific bronchial reactivity 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%).
Fisher et al. 1998	Cohort	In an effort to prevent LAA, a comprehensive program to reduce exposure to environmental allergens was developed in a major pharmaceutical company. The program included education, engineering controls, administrative controls, use of personal protective equipment, & medical surveillance & was surveyed for 5 years. After instituting this program, authors found that the prevalence of LAA ranged from 12%-22% & that 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	Cross-sectional	A study of 2800 workers employed in 3 factories covering 11 years of operation showed that 2344 workers had sufficient lung function data to meet the operational criteria & these were analysed in 3 separate groups. Spirometry & prick tests for specific skin reactions to standardised enzyme were performed at six monthly intervals for the first 6 years of the study & then annually. The lung function of the factory groups was analysed for the effects of working in the detergent industry, the degree of exposure to enzymes, skin prick test positivity to enzymes, atopy, & smoking. Exposure to the enzyme allergen has had no significant long-term effect on the lung function of the detergent workers. A higher proportion of atopics than non-atopics became skin test positive to the allergen & more smokers than non-smokers were sensitised. The overall lung function of detergent workers showed 39 ml/year loss in FEV1 on the 11 year longitudinal study.
Gannon & Burge 1993a	Cohort	A surveillance scheme of physicians likely to see cases of occupational asthma. A recognised incidence of 43 new cases per million general workers per year was detected. Specific occupational incidences varied from 1833 per million paint sprayers to 8 per million clerks. Agents to which workers were exposed at the time of diagnosis were well recognised (isocyanates 20.4%, flour 8.5%, colophony 8.3%). The most commonly used method of diagnosis was serial peak expiratory flow (PEF) measurement. Its use varied (specialist unit 72%, general chest physicians 50%, compensation board 48%). Other methods of diagnosis were used only infrequently outside the specialist unit. Twenty eight per cent 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. (<i>Occupational groups most affected included: paint sprayers, rubber & plastics workers, electroplaters, foundry core makers & moulders, bakery workers</i>).
Gannon et al 1993b	Case series	Workers still exposed – median loss of income due to occupational asthma was 35%. Those removed from exposure were worse off financially - median loss 54% of income. Statutory compensation & that obtained from common law suits did not match the loss of earnings due to development of occupational asthma. Removal from exposure after diagnosis with occupational asthma 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.

Gannon et al. 1996	Case series	Serial peak expiratory flow (PEF) measurement is usually the most appropriate first step in the confirmation of occupational asthma. A computer assisted diagnostic aid (OASYS-2) has been developed. 268 PEF records were collected from workers attending clinic for investigation of suspected occupational asthma & from workers participating in a study of respiratory symptoms in a postal sorting office, & were divided into 2 development sets & two gold 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 occupational asthma 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 clinical practice (<i>mostly low molecular weight agents</i>).
Gautrin et al. 2001a	Cohort	Pre-exposure host characteristics & the school attended were compared between cases & all cohort subjects not meeting the criteria for probable occupational asthma. Twenty-eight apprentices satisfied the definition for 'probable occupational asthma', i.e., onset of immediate skin reactivity to > 1 occupational inhalant & > 3.2-fold decrease in the provocative concentration causing a 20% reduction in FEV1 (PC ₂₀). The incidence of 'probable occupational asthma' was 2.7%. Baseline immediate skin reactivity to pets (rate ratio [RR] 4.1, 95% & bronchial responsiveness (PC ₂₀ > 32 versus PC ₂₀ > 32 mg/ ml) (RR = 2.5) were associated with an increased risk of probable occupational asthma; a lower FEV1 had an apparent, protective effect (RR = 0.58). Authors conclude that apprentices in animal health show a high incidence of probable occupational asthma, & that pre-exposure airway calibre & responsiveness as well as sensitisation to pets are associated with an increased risk. In the comparison of probable occupational asthma cases with subjects with incident sensitisation & no decrease in bronchial responsiveness, only immediate skin reaction to pets was significantly associated with the risk of probable occupational asthma, & a lower FEV1 had an apparent protective effect for the incidence of probable occupational asthma. In the third comparison, atopy, immediate skin reaction to pets, & rhinitis on contact with pets significantly increased the risk of developing probable occupational asthma, whereas having a lower FEV1 was associated with a decreased risk. Of 78 apprentices identified prospectively as developing immunological sensitisation, 36.9% developed probable occupational asthma; therefore, the development of IgE-dependent immunological sensitisation results in a high risk of having probable occupational asthma in the case of animal-derived allergens. This study adds some evidence that asthma is not a risk factor for the incidence of 'probable occupational asthma', & also suggests that having a high FEV1 does not preclude the development of 'probable occupational asthma'.
Gautrin et al. 2001b	Cohort	Study describes the time-course of the incidence of work-related symptoms, skin reactivity & occupational rhino-conjunctivitis (RC) & occupational asthma & assesses the predictive value of skin testing & RC symptoms in apprentices exposed to laboratory animals, in a 3-4-yr programme. Apprentices at five institutions were assessed prospectively with questionnaire, skin-testing with animal-derived allergens, spirometry & airway responsiveness. Depending on the school, students were seen 8, 20, 32 & 44 months after starting the programme. The positive predictive values (PPVs) of skin 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 occupational asthma was 11.4%. Sensitisation, symptoms & diseases occurred maximally in the first 2-3 yrs after starting exposure to laboratory animals. Skin reactivity to work-related allergens & rhino-conjunctivitis symptoms have low positive predictive values.
Gordon & Curran, 1997	Cross-sectional	A questionnaire was issued to 362 flour-exposed workers in a large bakery. The respiratory screening questionnaire identified 68 workers with respiratory symptoms. Of these, 21 proceeded to full assessment. A diagnosis of asthma was made in 5 cases, one of which was bakers' asthma. In addition, 11 workers not reporting any symptoms by questionnaire were referred to clinic & five 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 & Shaugnessy, 1993	Case series	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. (Most employees had been transferred to low exposure jobs for more than 5 years. All had moderate – severe symptoms at diagnosis).

Grammer et al. 1994	Cross-sectional	Study aimed to identify risk factors for development of immunologically mediated respiratory disease in workers exposed to hexahydrophthalic anhydride (HHPA). Of 57 employees in a workplace molding operation utilising HHPA, 7 had both IgE- & IgG-mediated disease, whereas 9 had only IgE-mediated disease. Although neither smoking, age, nor race were 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	Case series	Study aimed to identify risk factors for development of immunologically mediated disease in workers with respiratory symptoms associated with exposure to hexahydrophthalic anhydride (HHPA). Of the 33 employees with respiratory symptoms, 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. A larger sample would have rendered atopy a statistically significant risk factor (assuming effect replication). However, as expected, elevated levels of specific antibodies were statistically & clinically significant risk factors. Development of one type of immunologically mediated disease was highly predictive of development of the other type. In HHPA-exposed employees with respiratory symptoms, development of immunologically mediated respiratory disease is most closely associated with presence of specific IgE or IgG antibodies. Neither race, age, smoking status, atopy, nor exposure levels emerged as significant risk factors in this symptomatic study population.
Grammer et al. 1998	Cohort	Study aimed to define the utility of serum antibody against trimellitic anhydride (TMA) in predicting development of TMA-asthma. In 1990, 181 subjects exposed to TMA for at least 1 year were studied clinically & immunologically. 119 subjects were then followed for 5 years. Of 16 individuals with IgE against TMA in 1990, 3 had immediate asthma & another 6 developed asthma during the follow-up. Of 165 individuals without IgE against TMA, none had immediate asthma in 1990 & only 1 of 102 individuals followed-up developed asthma. Of 44 subjects with IgG against TMA, 6 had immunologic respiratory disease in 1990 & 2 more developed it during follow-up. Of 137 subjects 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 subjects who have/will develop immunological respiratory disease due to TMA exposure. The absence of antibody is a potent negative predictor.
Grammer et al. 2000	Case series	Employees with trimellitic anhydride-induced immunologic lung disease were studied after they had been 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.
Grammer et al. 2002a	Case series	Individuals with occupational asthma may also report symptoms of rhinitis or conjunctivitis. Study aimed to investigate the prevalence of rhinitis & conjunctivitis in subjects with occupational asthma as a result of trimellitic anhydride (TMA) & also to evaluate the onset of rhinitis & conjunctivitis symptoms as compared with the occupational asthma symptoms. 25 consecutive employees with TMA-induced asthma were studied; each of them had participated in an annual surveillance program in which they were queried about rhinitis, conjunctivitis, & other respiratory symptoms. 22/25 (88%) reported rhinitis symptoms whereas 17/25 (68%) reported conjunctivitis symptoms. In 17/22 (77%) individuals with rhinitis & asthma, the rhinitis symptoms preceded the asthma symptoms. In 14/17 (82%) individuals with conjunctivitis, those symptoms preceded the asthma symptoms. The mean time periods for the onset of rhinitis & asthma were 1.8 years & 2.6 years respectively. In summary, symptoms of rhinitis & conjunctivitis are common in subjects with occupational asthma because of TMA & often precede the respiratory symptoms.
Grammer et al. 2002b	Cohort	Study aimed to determine whether the use of respiratory protective equipment would reduce the incidence of occupational asthma due to exposure to hexahydrophthalic anhydride (HHPA) in 66 newly hired individuals. Subjects were evaluated annually for development of positive antibody to HHPA & occupational, immunologic respiratory disease, including occupational asthma. With use of respiratory protective equipment, the rate of developing an occupational immunologic respiratory disease was reduced from approximately 10 to 2% per year. Occupational asthma developed in only three individuals, & they were all in the higher exposure category. Authors conclude that respiratory protective equipment can reduce the incidence of occupational immunologic respiratory disease, including occupational asthma, in employees exposed to HHPA.

Greenberg et al. 1970	Cohort	In a survey of 121 workers exposed to dusts containing derivatives of bacillus subtilis, mainly proteolytic enzymes, skin tests showed evidence of sensitisation was higher among atopic subjects – 16/25 (61%) than among non-atopic subjects – 32/96 (33%). Reduced ventilatory capacity was found in 44% of sensitised workers compared with 14% of those not sensitised. <i>(A selection of common allergens was tested & the reactions to these extracts were used as the criteria for classifying subjects as atopic & non-atopic).</i>
Hagmar et al. 1984	Cohort	This study showed a strong exposure-response relationship as to frequency of work-related airway symptoms indicating asthma. In the most exposed group, about a third of the workers had experienced such symptoms. There was also an association between piperazine exposure & chronic bronchitis.
Hargreave et al. 1984	Case report	Authors report a patient with presumed occupational asthma caused by exposure to toluene di-isocyanate (TDI). Variable airflow obstruction measured by peak flow rates (PFR), & symptoms of asthma reversed by salbutamol, occurred after natural exposure to TDI when methacholine bronchial responsiveness was well into the non-asthmatic range. The asthma occurred at the end of, or just after work, suggesting late asthmatic response. When the patient stopped work, asthma & increased diurnal variation of PFR recurred spontaneously until methacholine responsiveness returned into the normal range. Observations indicate that asthma can occur at a time when methacholine bronchial responsiveness is normal, providing the stimulus is strong enough. They further demonstrate that the magnitude & ease of bronchoconstriction relates to the degree of methacholine responsiveness.
Heederik et al. 1999	Cross-sectional	Data from 3 cross-sectional studies in The Netherlands, the United Kingdom, & Sweden were used. Selection criteria were harmonized, resulting in a study population of 650 animal laboratory workers (60.6% female) with less than 4 years of exposure. 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 worked with rats per week, 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 & Houba 2001	Quantitative risk assessment	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).
Henneberger et al. 1991	Case series	Study aimed to identify the strengths & limitations of using portable peak flow meters to document suspected cases of occupational asthma 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 peak flow meters. For each of the 14 subjects who were successfully tested, the PEFR 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 peak flow measurements to document occupational asthma 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.
Hnizdo et al. 2001	Reporting scheme	Describes the objectives & programme of the nationwide Surveillance of Work-related & Occupational Respiratory Diseases in South Africa scheme (SORDSA). Summarises results obtained for the reporting of occupational asthma in South Africa in the first two years of SORDSA's establishment, ending in October 1998. 225 cases of occupational asthma (6.9%). Concludes that the results from the initial phase show that despite some limitations, SORDSA has the potential to obtain useful data on the industries, agents & occupations causing occupational asthma in this country.

Hollander et al. 1998	Cross-sectional	Study aimed to study relationship between allergic symptoms due to working with rats & variability & changes in peak expiratory flow (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 rate 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. In addition, workers with asthmatic symptoms were also more likely to have higher PEF variability than workers without asthmatic symptoms. Diurnal variation was unhelpful in separating occupational asthma from others. No difference in diurnal variation was observed on animal days from other days. Authors conclude that the peak expiratory flow of workers who reported asthmatic symptoms due to working with rats decreased significantly on days working with laboratory animals.
Horne et al. 2000	Case-control	Patients with red cedar asthma had a higher frequency of HLA DQB1*0603 & DQB1*0302 alleles compared to a group of healthy exposed control subjects & a reduced frequency of DQB1*0501 allele. The frequency of the DRB1*0401-DQB1* 0302 haplotype was increased & the DRB1*0101-DQB1*0501 haplotype was reduced. Authors suggest that genetic factors such as human leukocyte antigen class II antigens may be associated with susceptibility or resistance to development of red cedar asthma.
Houba et al. 1996	Cross-sectional	Workers were categorized according to job history & amylase exposure levels of their jobs. 25% had work-related symptoms, 9% had positive skin prick test 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 positive association was observed between positive skin prick & work-related symptoms. Overall authors conclude that a strong & positive relationship is shown between alpha-amylase allergen exposure levels & specific sensitisation in bakery workers.
Houba et al. 1998	Cross-sectional	Study was conducted among workers from 21 bakeries to study relationship between wheat allergen exposure & wheat sensitisation & work-related allergic symptoms. A strong & positive 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 the presence of specific IgE to common allergens. Indicators of smoking habits were not related to work-related respiratory symptoms. The existence of exposure-sensitisation gradients suggests that work-related sensitisation risk will be negligible when exposure levels will be reduced to average exposure concentration of 0.2 µg/m ³ wheat allergen or approximately 0.5 mg/m ³ inhalable dust during a work shift.
Howe et al. 1983	Cohort	We describe seven women with asthma induced by occupational exposure to an acid anhydride, tetrachlorophthalic anhydride (TCPA), an epoxy resin hardening agent. Inhalation tests with TCPA at atmospheric concentrations of less than one tenth of a manufacturer's recommended exposure limit provoked asthmatic reactions in the four women tested. None had evidence of pre-test bronchial hyper-reactivity. Immediate skin prick test reactions were elicited in the seven subjects by a conjugate of TCPA with human serum albumin (TCPA-HSA) but not in others tested. Specific IgE antibody levels to TCPA-HSA, measured by radioallergosorbent test scores, were significantly elevated in the seven, but not in TCPA-exposed & unexposed comparison groups. These results imply that occupational asthma caused by TCPA is an allergic reaction mediated by specific IgE antibody.
Hudson et al. 1985	Case series	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. Authors infer that the nature of the product responsible for the reaction may play a role & also the type of asthmatic reaction documented at the time of diagnosis through specific inhalation challenge could influence the prognosis. Conclude that subjects with occupational asthma caused by various agents can remain symptomatic of asthma & demonstrate a persistence of bronchial obstruction & hyper-excitability for prolonged periods after cessation of exposure.

Jaakola et al. 2003	Case-control	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 men's 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.
Jeal et al. 2003	Cross-sectional	Figures suggest that approximately 40% of occupational asthma 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. Sensitised individuals were twice as likely to be HLA-DRβ1*07-positive & half as likely to be HLA-DRβ*03 positive. HLA-DRβ1*07 was also, & more strongly independently associated with work-related chest symptoms. Among employees similarly exposed to rats in their work, those who developed symptomatic sensitisation to rat urinary protein are nearly 4 times as likely to be HLA-DRβ1*07-positive as those who remained unsensitised & asymptomatic.
Johnsen et al. 1997	Cohort	Study aimed to investigate the risk of enzyme sensitisation & clinical allergy in workers exposed to enzymes. 8.8% developed clinical enzyme allergy during the first 3 years of employment. The risk declined during the period. The frequency of enzyme sensitisation, expressed as RAST values > 0.5 SU, was 36%, & the frequency of significant RAST values > or = 2 SU was 8%. Ranking diagnoses of enzyme allergy by severity, the frequency of asthma was 5.3%, rhinitis 3.0%, & urticaria 0.6%. Half of the cases occurred within the first 15 months of exposure. The risk of symptomatic allergy & sensitisation to enzymes, expressed as increasing RAST value were significantly increased in smokers. A positive skin prick test at the pre-employment examination did not predispose to clinical enzyme allergy. Likewise, clinical allergy at the pre-employment examination did not predispose to clinical enzyme allergy or sensitisation. Smoking was an independent risk factor for clinical enzyme allergy. Atopic predisposition at the time of engagement was not a significant risk factor for enzyme allergy. This could be due to various selection mechanisms.
Johnson et al. 2000	Cohort	A randomly selected population completed an initial questionnaire, of whom 2,974 (39% response rate) attended the laboratory & completed supplementary questionnaires. Of these latter individuals, 383 had asthma & of these 166 had adult-onset asthma. Asthma was defined as physician-diagnosed asthma, & adult-onset asthma was defined as a first attack at age 15 yr or older. Several methods for estimating occupational asthma were used: (1) reporting of a high-risk job (occupation & industry) for occupational asthma at the time of asthma onset (Probable occupational asthma); (2) reporting of exposure to a substance that may cause occupational asthma (Possible occupational asthma) while not in a high-risk job at the time of asthma onset; & (3) combination of the population attributable risk for high-risk jobs & exposures. Of the individuals with adult-onset asthma, 27 fulfilled the criteria for 'Probable occupational asthma' & 33 for 'Possible occupational asthma'. The percentages of the attendee population with 'Probable occupational asthma' or 'Possible occupational asthma' were 16.3% & 19%, respectively. The percentage with 'Probable' & 'Possible' occupational asthma was 36.1% of all cases of adult-onset asthma. Nursing, baking, hairdressing & chemical, rubber, or plastics processing were common occupations in the 'Probable occupational asthma' group.
Juniper et al. 1977	Cross-sectional	Previous findings that atopics were more likely than non-atopics to become skin prick test positive to a standardised enzymes reagent have been confirmed. An atopic was defined as having a history of atopy (e.g. infantile eczema, asthma, hayfever) and/or a positive skin prick test to one or more common allergens. For non-atopics, 40% of employees with high exposure became skin prick test positive to enzymes versus 9.5% of those with medium exposure & 4.5% of those with intermittent exposure. For atopics, 75% of employees with high exposure became skin prick test positive to enzymes versus 20% of those with intermittent exposure. A reduction in the level of enzyme exposure led to a reduction in the level of sensitisation & respiratory symptoms. (However, no evidence of significant differences in change per annum in FEV1 as percentage between the positive & negative skin prick test employees in any group. Therefore it is significant that atopics are more likely to become sensitised but there is no evidence that this results in changes in lung function).

Juniper & Roberts 1984	Cohort	The 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. 62/1642 subjects experienced enzyme asthma with higher incidence in atopics.
Karjalainen et al. 2000	Cohort	The mean annual incidence rate for occupational asthma was 17.4 cases/100,000 employed workers. The incidence rate 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 occupational asthma occurs in farmers – high exposure since cattle are kept in cow houses for 5-8 months of the year). Authors conclude that estimation of occupation & industry-specific incidence rates forms the basis for successful prevention of occupational asthma, but necessitates collection of data over several years from well-established surveillance systems.
Karjalainen et al. 2002	Cohort	Results showed a significantly increased risk of work-related asthma 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	Cross-sectional	Authors found a clearly elevated risk of asthma among patients with occupational rhinitis (OR) compared with patients with other occupational diseases. (96% of persons had the same job title at time of onset of OR & occupational asthma). The risk of asthma was especially high during the year following notification. 11.6% of OR patients developed occupational asthma 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 OR to occupational asthma = 31 months. (3,637 non asthmatic OR patients from Finnish Register of Occupational Disease. Referents = 31,457 non-occupational asthma non-OR occupational disease cases 1988 through 1999. Study end 31 Dec 2001).
Kim et al. 1999	Case series	The purpose of this study was to evaluate clinical & immunologic characteristics of citrus red mite (CRM, Panonychus citri)-induced occupational asthma. 16 cases of CRM-induced occupational asthma among farmers cultivating citrus fruits were encountered & asthmatic attacks corresponded closely with their work on citrus farms. The mean duration of the latent period was 12.9 (range 7 to 20) years. Fifteen of the 16 complained of recurrent nasal symptoms, which had developed at an earlier time than the asthmatic symptoms. They showed strong positive reactions to CRM extract on skin prick test & had high serum specific IgE antibody against CRM. Skin prick test with common inhalant allergens revealed that 10 had an isolated positive response to CRM with negative results to common inhalant allergens in their environment.
Kogevinas et al. 1996	Case-control	The causes & derived estimates of the risk of asthma attributable to occupational exposures were examined as part of the EC Respiratory Health Survey, in a randomly selected population of five areas of Spain. Bronchial reactivity was determined in 1,797 subjects & atopy in 2,164. Twenty-one occupational sets were defined using information on current occupation, or in subjects reporting change of occupation due to respiratory problems, their occupation at that time. The highest risk of asthma was observed for laboratory technicians, spray painters, bakers, plastics & rubber workers, welders, & cleaners. The risk of asthma attributed to occupational exposures after adjusting for age, sex, residence, & smoking status was 5.0% when asthma was defined as "bronchial reactivity & a report of wheezing or whistling in the chest during the last 12 mo," & 6.7% when asthma was defined as "bronchial reactivity & a report of asthma-related symptoms or medication." Estimates of the attributable risk for adult onset asthma were higher. Authors conclude that occupational exposures constitute a substantial cause of asthma in the young adult Spanish population.
Kogevinas et al. 1999	Cross-sectional	The causes & derived estimates of the risk of asthma attributable to occupational exposures were assessed in people randomly selected from the general population of 26 areas in 12 industrialised countries. The highest risk of asthma, defined as bronchial hyper-responsiveness & reported asthma symptoms or medication were shown for farmers odds ratio [OR] =2.62, painters OR=2.34, plastic workers OR = 2.2, cleaners OR = 1.97, spray painters OR = 1.96 & agricultural workers OR = 1.79. The most consistent results across countries were shown for farmers & cleaners. Excess asthma risk was associated with high exposure to biological dusts, mineral dusts, & gases & fumes. The proportion of asthma among young adults attributed to occupation was 5%-10%.

Kor et al. 2001	Surveillance	Since 1990, occupational asthma has overtaken silicosis & asbestosis as the most common occupational lung disease in Singapore. Since the first notified case of occupational asthma in 1983, a total of 90 cases were confirmed as on 31st December 1999. Of the 90 cases, 19 were females & 71 were males. There were 48 Chinese, 22 Malays, 14 Indians & 6 of other ethnic origins. The mean age at diagnosis was 35.8 +/- 9.3 yrs & the 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. Occupational asthma is a condition associated with disability in the workplace & may still be largely under-reported.
Koskela et al. 2003	Cohort	37 dairy farmers with suspected occupational asthma due to bovine allergens were studied to identify which tests would be useful in selecting patients for a specific inhalation challenge with bovine dander allergens. The sensitivity & specificity of bovine allergen IgE was studied. It appeared that the skin prick allergen was a homemade one & the IgE assay was a Pharmacia unicap. The specific IgE assay had a sensitivity of 9/11 & a specificity of 100%. The skin prick test (at more than 3 mm) had a sensitivity of 11/11 & a specificity of 13/26. There was no additional benefit from measuring the histamine PC ₂₀ or exhaled NO compared with specific challenge test. The clinical history had poor predictive value (specificity 13/36). Authors did however comment that a positive history & a positive specific IgE was sufficient to make the diagnosis.
Krakowiak et al. 1997	Cross-sectional	Laboratory animal allergy develops within first years of exposure; atopy & smoking predispose to laboratory animal sensitisation & to a development of bronchial asthma & allergic rhinitis. (<i>Acute episodes of dyspnoea classified as asthma found in 8 subjects. In all cases, development of symptoms was concurrent with nasal symptoms</i>).
Krakowiak et al. 2002	Cross-sectional	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 positive skin prick tests (SPT) 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 positive to feather allergens & in the serum of 12 subjects with SPTs positive to fur allergens. Rhinitis & asthma were reported by atopic subjects more often than by non-atopic subjects. Occupational asthma due to feathers was diagnosed in 2% of zoo workers, & to fur in 10% of subjects working in contact with birds & furred animals. Authors conclude that results suggest that occupational asthma caused by feathers is very rare in contrast to asthma caused by animal fur. Atopy predisposes to the development of allergic diseases caused by animal fur & feathers.
Kraw & Tarlo, 1999	Cohort	The surveillance questionnaire in this study was sensitive but not specific. Spirometry did not result in detection of asthma in any patients who denied respiratory symptoms. Nevertheless 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. In companies where workers are more fearful of losing their job, there may be less honest completion of health questionnaires & an objective tests such as spirometry may have been more beneficial in such a setting.
Kruize et al. 1997	Cohort	Aimed to study the role of exposure, atopy & smoking in the development of LAA. Study showed that both non-atopic & atopic people seemed to have an increased risk related to exposure intensity when exposed to laboratory animal allergens. Atopic people developed LAA earlier & in more severe forms (asthma) than non-atopics (13% v 6%). The mean time until development of symptoms of LAA was about 109 months in non-atopic people, & 45 months in atopic people. This time until development of first symptoms was also longer than previously reported. More people with asthmatic symptoms 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 less than two hours a 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.
Larbanois et al. 2002	Case-control	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).
Laoprasert et al. 1998	Cohort	Study investigated acceptable latex aeroallergen concentrations below which latex-sensitive health care workers do not experience symptoms & to study the effect of high-efficiency particle arrest (HEPA)-filtered laminar flow helmets in preventing latex-induced symptoms. 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.

Lemiere et al. 1996	Case series	After removal from exposure to the offending agent (mean duration of exposure after onset of symptoms before removal 6 years, follow up assessments on average 3.3 years after removal from exposure), 60% of subjects showed a decrease but a persistence of specific bronchial responsiveness to high & low molecular weight agents. 63% of subjects with occupational asthma to high molecular weight agents had a decrease in specific IgE levels. Significant improvement in non-specific bronchial reactivity (NSBR) in 47% of subjects was observed & all subjects reported symptomatic improvement - 2 were asymptomatic.
Lemiere et al. 2000	Case series	16 workers with occupational asthma caused by the high-molecular-weight-agents flour, psyllium & guar gum were re-exposed to assess their current specific bronchial reactivity (SBR) to the sensitisers (removed from exposure for a mean period of 5.7 years). Concludes that SBR to such agents persists in most cases (11/16) despite a normalisation of NSBR, & that this persistence is associated with a persistence of specific immunisation to the agent. IgE significantly decreased & at lower level at time of second challenge in those not experiencing an asthmatic reaction.
Leroyer et al. 1998	Case series	Peak expiratory flow (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 occupational asthma. 20 subjects referred for possible occupational asthma 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 positive 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 occupational asthma.
Levy et al. 1999	Cohort	The use of powder free protein poor NRL gloves in place of powdered protein rich NRL gloves may reduce the development of sensitisation to latex.
Lin et al. 1995	Case series	Specific challenge tests with a suspected allergen in the workplace are standard to confirm the diagnosis of asthma. 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 positive 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.
Liss et al. 1991	Cross-sectional	Objective criteria for interpretation of peak expiratory flow rate readings were assessed in 50 patients evaluated for suspected occupational asthma who had at least two weeks of PEF readings & an objective diagnosis based on other investigations. The prevalence of occupational asthma was 36 percent. Peak flows were interpreted by two observers blinded to other results. Criteria for a PEF interpretation of occupational asthma were as follow: diurnal variation greater than or equal to 20 percent 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 percent for OA; specificity for no asthma was 53 percent. Excluding those with greater than or equal to 20 percent variation on only one day sensitivity improved to 93 percent for OA, & specificity to 77 percent. There was an acceptable level of inter-observer variation (kappa 62 to 83 percent). We conclude that simple objective criteria for PEF interpretation can be developed with acceptable inter-observer variation.
Liss et al. 1993	Cross-sectional	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 occupational asthma among newly hired workers at the plant. A high prevalence of respiratory symptoms was reported. 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.
Lozewicz & Assoufi, 1987	Case series	At 4-year follow-up, 82% of subjects continued to have respiratory symptoms & approximately half of these required treatment at least once a week, indicating a significant proportion of those with isocyanate-induced asthma are likely to have persisting symptoms for at least several years after exposure is avoided. FEV1 & FVC at follow-up were similar to values obtained at diagnosis. (Mean duration of symptomatic exposure was 2.7 years. No difference observed between those who were relocated within the factory & those who left the factory).

Maghni et al. 2004	Case series	Study hypothesized that persistence of asthma in subjects with occupational asthma after the end of exposure could be explained by presence of airway inflammation that can be documented even years after cessation of exposure. Study showed that lack of improvement in airway responsiveness in subjects with occupational asthma after removal from exposure is associated with the magnitude 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. In the latest follow up from the group, study showed that 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 differences is that the current work did not show significant differences in outcome according to the nature of the agent (high vs. low molecular weight), whereas author's previous work showed a tendency for subjects with occupational asthma due to low molecular weight agents to experience a more satisfactory outcome. Study concludes that failure to improve after cessation of exposure to an agent causing occupational asthma is associated with airway inflammation at follow-up.
Malo et al. 1991	Cross-sectional	Study assessed accuracy of a diagnosis of occupational asthma made upon basis of an open medical questionnaire. 162 subjects were referred to clinic & assessed because their physicians thought their asthma might be work-related. They filled in a questionnaire & then underwent objective assessment with specific inhalation challenges (72), monitoring of peak expiratory flow rates for periods at work & away from work (29), or both (61). 75 subjects (46%) were shown to have occupational asthma. Symptoms alone (type & timing) did not provide a satisfactory differentiation between those subjects with & without occupational asthma. Positive predictive value of questionnaire diagnosis of occupational asthma found to be low (63%) but negative predictive value higher (83%). Therefore, if questionnaire suggests diagnosis of occupational asthma, then >50% chance that the diagnosis is correct. The clinical history taken by physicians with experience in occupational asthma is not a satisfactory diagnostic tool & the presence or worsening of symptoms at work & improvement during weekends & holidays was not conclusively linked with occupational asthma. Normal bronchial hyper-reactivity was observed in 12/75 with proven occupational asthma. Study suggests that an open medical questionnaire is not a satisfactory means of diagnosing occupational asthma.
Malo et al. 1993a	Case control	Peak expiratory flow (PEF) rate recording was carried out in 74 subjects referred for possible occupational asthma, to determine the optimum number of recordings required per day to determine the best between-reader & within-reader reproducibility & sensitivity to specificity ratio. Specific inhalation challenges performed in a hospital laboratory or at the workplace (positive 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). (<i>Almost all low molecular weight agents</i>).
Malo et al. 1993b	Economic analysis	Authors conclude that for subjects with occupational asthma 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. 1995	Cross-sectional	Serial assessment of peak expiratory flow (PEF) rates has been advocated as a sensitive & specific means of investigating occupational asthma. It has been raised that some subjects do not accurately report their values; however, the availability of instruments that assess & store PEF results now make it possible to estimate compliance & accuracy of results. 21 subjects consecutively investigated for occupational asthma 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. (Compliance with PEF recording less in those patients referred for compensation purposes).

Malo et al. 1996	Meta-analysis	Compliance with & honesty in Peak expiratory flow (PEF) monitoring are factors that affect the interpretation of PEF recordings, both within & between reader reproducibility. If occupational asthma diagnosis relies on PEF interpretation, then should use monitors that store data. 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).
Malo et al. 1997	Case series	Study aimed to assess the prevalence, severity & timing of symptoms of rhino-conjunctivitis in association with occupational asthma. Specific inhalation challenges confirmed the diagnosis of occupational asthma in 40 subjects. Symptoms of rhinitis were reported at some time by 37/40 subjects, & conjunctivitis by 29/40 subjects. The prevalence of symptoms was not different for high & low molecular weight (HMW, LMW) agents, although rhinitis was more intense for HMW. There were significantly fewer subjects with occupational asthma due to LMW agents, with rhinitis appearing before asthma. Authors conclude, symptoms of rhino-conjunctivitis are often associated with occupational asthma. Rhinitis is less pronounced in case of LMW agents, but more often appears before occupational asthma in the case of HMW agents
Mapp et al. 1988	Case series	Subjects with occupational asthma due to Toluene di-isocyanate (TDI) exposure were examined. Average duration of exposure to isocyanates ranged 3-41 years, Average follow-up interval of 10 months. 62.9% of subjects showed positive TDI inhalation challenge even following removal from exposure. 22% lost sensitisation to TDI following removal from exposure. Respiratory symptoms, isocyanates sensitisation, & airway hyper-responsiveness to methacholine may persist after removal from occupational exposure to TDI. The type of asthmatic reaction & the severity of the reaction may be important factors for the persistence or the remission of the disease.
Mapp et al. 2000	Case-control	Frequencies of DQA1*0104 & DQB1*0503 were significantly increased in asthmatics compared with asymptomatic controls. DQA1*0101 & DQB1*0501 were significantly increased in asymptomatic controls. No significant difference was found in distribution of DRB1 alleles between asthmatics & controls. Results suggest role for HLA class II genes in conferring susceptibility or resistance to occupational asthma.
Mapp et al. 2002	Case-control	The phenotype of the disease was characterized by using detailed clinical history, lung volumes, airway responsiveness to methacholine, & airway responsiveness to toluene di-isocyanate (TDI). In patients exposed to TDI for 10 or more years, the frequency of the GSTP1 Val/Val genotype was lower in subjects who had asthma (odds ratio, 0.23). Similarly, the frequency of this genotype was significantly lower in subjects with evidence of moderate-to-severe airway hyper-responsiveness to methacholine compared with the frequency in subjects with normal or mild hyper-responsiveness. Data suggest that homozygosity for the GSTP1*Val allele confers protection against TDI-induced asthma & airway hyper-responsiveness. This view is supported by the finding that the protective effect increases in proportion to the duration of exposure to TDI.
Marabini et al. 1993	Case series	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 occupational asthma. 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).
Marabini et al. 1994	Case series	In the group of patients with Toluene di-isocyanate (TDI) related asthma, there was a clear tendency for the asthma to become chronic, regardless of continuation of exposure. Average follow-up period was 6.8 years (SD 0.6). 70% of subjects were 'no longer exposed' to TDI & 14.3% of this group were asymptomatic. No differences observed in symptom prevalence or lung function between exposed or non-exposed subjects. Significant decreases observed in FVC in both groups at follow-up.

McDonald, 2000	Reporting scheme	Data described 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 United Kingdom. Occupational asthma accounted for 25% cases each year. Except for laboratory technicians all other occupations with average annual rates per 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.
McSharry et al. 1994	Case-control	Raised levels of serum IgE antibodies to prawn antigens were found in 15/26 seafood factory process workers with respiratory symptoms & in 1/26 case-matched asymptomatic controls. Raised IgG antibody 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 & with a history of cigarette smoking. 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.
Meijer et al. 2002	Cohort	Study aimed to develop & validate a diagnostic rule to predict sensitisation in laboratory animal workers. Baseline data from 551 laboratory animal workers participating in an ongoing cohort study, bridging a period of 3 years, were used for diagnostic research. Data from 472 workers participating in the first period of the study represented the derivation set & data from 79 workers, participating during the second period, represented the validation set. Serum samples were analysed for specific IgE antibodies against common & laboratory animal allergens, & questionnaire items, exposure determinants, IgE serology, skin prick tests (SPTs), & lung function tests were analysed. Asthmatic symptoms, (work-related) allergic symptoms, sex, occupational exposure to rats, & a positive SPT to common allergens, showed the best performance in discriminating workers at high or at low risk of being sensitised. Authors concluded that high & low risk categories for work-related sensitisation could be distinguished from simple questionnaire data & SPT results. The method can easily be applied in occupational medical practice & may markedly increase the efficiency of occupational health surveillance in laboratory animal workers as well as other workers exposed to high molecular weight allergens.
Meredith et al. 1991	Reporting scheme	The SWORD surveillance scheme uses systematic reporting from physicians to provide a picture of the incidence of occupational respiratory disease in the United Kingdom. 26% of total reported cases were of occupational asthma. The most commonly identified agents causing asthma were isocyanates, flour/grain dusts, wood dust & solder flux. The authors report an overall incidence of 22/million/yr.
Meredith et al. 2000	Case-control	No difference in peak exposures between cases & referents was found, but time weighted average exposures at the time of onset for asthma were higher for cases. The odds of occupational asthma 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. Occupational asthma was associated with a pre-employment history of "atopic illness" (odds ratio 3.5). (Methods of confirming diagnoses were not consistent between two plants & between patients – varied from history alone to specific IgE to 4x daily PEFR. Not best methodology for recording peak i.e. used personal monitors. Asthma, hayfever & eczema were used to indicate atopy. Measured peak exposures were 15-20 minute peaks rather than true peaks).
Merget et al. 1988	Cross-sectional	Anamnestic & immunological 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 platinum 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 positive cutaneous reaction to platinum salts. Total serum IgE was higher in groups A & D than other groups, however platinum salt-specific IgE was higher in group A. Histamine release with platinum salts was found in all groups & was highest in atopic controls. Authors conclude that neither histamine release from basophils with platinum salts, nor RAST for the detection of platinum salt-specific IgE are helpful in the diagnosis of platinum salt allergy.

Merget et al. 1991	Case series	Diagnosis of occupational asthma is based upon a history of work-related symptoms & positive skin prick test (SPT) with platinum salts. Bronchial provocation tests (BPT) have not been performed in epidemiological studies because the SPT is believed to be highly specific & sensitive. Study assesses use of SPT & BPT with methacholine & platinum salt. 27 of 35 workers, who were referred to our clinic with work-related symptoms & 9 control subjects with bronchial hyper-reactivity, underwent a SPT & BPT with methacholine & platinum salt. 22 workers had a positive BPT, 4 of which had a negative SPT. It is concluded that BPT with platinum salts should be performed on workers with work-related symptoms but negative SPT with platinum salts. (<i>Loss of SPT positivity with removal from exposure observed</i>).
Merget et al. 1994	Case series	Both non-specific & specific bronchial responsiveness do not decrease after removal from exposure in immediate-type asthma caused by platinum salts.
Merget et al. 1996	Cross-sectional	Study aimed to assess the quantitative association of bronchial responsiveness to methacholine (MCh) & platinum salts (Pt) in workers with Pt-induced occupational asthma. 57 subjects with Pt-induced asthma underwent skin prick tests with Pt & bronchial challenge with MCh. 5/57 had normal bronchial responsiveness (BHR) in platinum asthma (12%). There was no univariate correlation between BHR to MCh & Pt, but there was a correlation between skin reactivity to Pt & BHR to Pt. Authors conclude that there is moderate association between BHR to Pt & skin reactivity to Pt. There is no association between methacholine responsiveness & BHR to allergen in Pt-induced occupational asthma.
Merget & Schulte, 1999	Cross-sectional	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 occupational asthma 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.
Merget et al. 2000	Cohort	11.3% & 2% study population developed positive platinum salts skin prick test in high & low exposure groups respectively. Development of symptoms was associated with exposure. Smoking was significant predictor of positive platinum salts skin prick test, estimated relative risk 3.9. Atopy or bronchial hyper-responsiveness were not significant predictors.
Meyer et al. 1999	Reporting scheme	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 occupational asthma. The most commonly identified agents causing asthma in 1998 were enzymes, isocyanates, laboratory animals & insects, colophony & fluxes, flour, latex, & glutaraldehyde.
Meyer et al. 2001	Reporting scheme	The SWORD surveillance scheme uses systematic reporting from physicians to provide a picture of the incidence of occupational respiratory disease in the United Kingdom. Analysis of trends over past 8 years shows an increase in mesothelioma, but little change in occupational asthma (26% of cases). (<i>Consistency of observations over 8 years</i>).
Milton et al. 1998	Cohort	A prospective study was conducted of health maintenance organization (HMO) members at risk for asthma. Computerized files, medical records, & telephone interviews were used to identify & characterize asthma cases. Evidence for asthma attributable to occupational exposure was determined from work-related symptoms & workplace exposure. The annual incidence of clinically significant, new-onset asthma was 1.3/1,000, & increased to 3.7/1,000 when cases with reactivation of previously quiescent asthma were included. Criteria for onset of clinically significant asthma attributable to occupational exposure were met by 21% of cases giving an incidence of 71/100,000. The authors conclude that these data suggest the incidence of asthma attributable to occupational exposures is significantly higher than previously reported, & accounts for a sizable proportion of adult-onset asthma.

Moller et al. 1986	Case series	7/12 cases, Toluene di-isocyanate (TDI) asthma was documented by a positive inhalation challenge 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 positive methacholine or cold air challenge prior to study. The one TDI reactor with a negative methacholine challenge had a positive (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 & positive 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 non-specific bronchial hyper-reactivity. The TDI sensitivity may also persist for a long time even in the absence of any additional occupational exposure.
Moscato et al. 1991	Case-control	Study reports the clinical findings & results of inhalation challenge 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 positive TDI inhalation challenge. Most reactors had a dual (30.4%) or a late (41.3%) response & the interval between the last occupational exposure & the specific challenge was significantly shorter in reactors. They also had a significantly higher proportion of positive 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	Case series	At 12 months, 13/25 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 occupational asthma, 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 & Neuhauss, 1998	Case series	Farmers with occupational asthma 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. This shows that the use of respiratory devices in farmers with occupational asthma significantly reduced the degree of bronchial obstruction, but did not provide complete protection.
Munoz et al. 2003	Case series	Immunologic, lung function, & specific bronchial challenge tests (SBCTs) were performed in 8 patients with occupational asthma due to exposure to persulfate salts (3 smokers, 6 presented with rhinitis prior to asthma, & 3 presented with dermatitis). The mean time of exposure to persulfate salts up to diagnosis was 15 years (range 3-27 years), & mean time that had elapsed between symptom onset & diagnosis was 38 months (range 3-120 months). The results of total IgE tests were positive in 6 patients, & the results of skin-prick tests for detection of persulfate salts were positive in 5 of these patients. The results of a SBCT were positive in the 7 patients in whom it was performed. 5 patients avoided exposure to persulfate salts & 3 adopted protective measures following diagnosis. 7/8 patients still had persistent asthma despite avoiding exposure & required treatment for the control of symptoms therefore early diagnosis & prompt removal from exposure are essential. Authors conclude that results suggest that the reliable diagnosis of occupational asthma due to persulfate salts must be based on the specific challenge test until further experience has been acquired. Despite avoiding exposure, patients continued with symptoms & required treatment for the control of symptoms.
Musk et al. 1989	Cross-sectional	A survey of dust exposure, respiratory symptoms, lung function, & response to skin prick tests was conducted in a modern British bakery. All 279 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, bronchial reactivity, & response to skin prick tests 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. The study shows that respiratory symptoms & sensitisation are common, even in a modern bakery.

Newhouse et al. 1970	Cohort	Factory workers making detergents containing Alcalase. 21% of those examined gave a direct positive reaction to prick tests with Alcalase. More than twice as many of the sensitised (to Alcalase) workers compared to the unsensitised workers also reacted to common allergens. 42/57 of workers who were skin prick positive to Alcalase had symptoms of 'acute chest disease.' 75/214 of workers with negative skin prick tests also reported acute chest disease. However, there was a highly significant association between these symptoms & a positive skin reaction to Alcalase. Of the sensitised men, 21.4% had a personal or family history of allergic disease & 65.5% gave positive 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. Authors reported a strong statistical correlation between the positive skin prick test & symptoms.
Newill et al. 1986		Results indicate that the use of the pre-employment screening criteria as determinants for hiring persons to work with laboratory animals is unwarranted especially in view of two observations: (1) the dearth of reliable estimates of the strength of association between the screening criteria & laboratory animal allergy; & (2) the absence of a carefully formulated consensus approach to the problem of allergy to laboratory animals. The authors conclude that the implementation of any occupational 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. Pre-employment screening should be viewed as only one of several possible approaches to the problem of prevention of occupational disease.
Newman Taylor et al. 1999	Cross-sectional	Study investigated the workforce of a large platinum refinery exposed to ammonium hexachloroplatinate (ACP) to test the hypothesis that the development of IgE-associated sensitisation to ACP was influenced by human leukocyte-associated antigen (HLA) phenotype, especially in those with lower ACP exposure. An HLA-DR3 phenotype was more common among cases, & more so in those with low than with high exposure; HLA-DR6 was less common among the cases, an association also stronger in the low-exposure group. Authors conclude that these results provide evidence that HLA phenotype is a significant determinant of sensitisation to complex platinum salts & for the first time show that the strength of this association varies with intensity of exposure to the sensitizing agent. They imply that as exposure-control measures are taken to prevent occupational sensitisation and, by analogy, sensitisation to allergens outside the workplace, disease incidence will increasingly be determined by genetic susceptibility.
Nielsen et al. 2001	Case referent	Study aimed to clarify the exposure-response relationships for the organic acid anhydrides (OAA) hexahydrophthalic & methylhexahydrophthalic anhydrides & the development of specific IgE, IgG antibodies & work-related symptoms in 154 exposed workers & 57 referents. Air levels of the OAA were low & associated with the concentrations of the OAA metabolites in urine. Furthermore, 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. Authors conclude that in spite of the very low OAA levels in the air & metabolites in the urine, there were high & exposure-related risks of specific IgE & IgG sensitisation & of work-related symptoms for the eyes, nose (especially bleeding), & lower airways.
Nieuwenhuijsen et al. 1999	Cross-sectional	Study describes relationship between exposure to alpha-amylase & sensitisation to fungal alpha-amylase. 495 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, & were skin prick tested 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. Authors conclude that study suggests exposure to alpha-amylase is a considerable health risk in British bakeries & flour mills. A small proportion of workers are exposed to alpha-amylase at concentrations that result in high rates of sensitisation. A reduction in exposure to alpha-amylase is likely to reduce this risk.

Niezborala & Garnier, 1996	Cohort	A cohort study was conducted on 77 workers who were not atopic on skin prick tests to three common allergens at the time of recruitment. 18 workers developed a positive result on skin tests & 23 developed symptoms, including all 18 subjects with positive skin tests (incidence of positive skin tests & 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 positive skin tests & 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	Case reports	Study aimed to assess the efficacy of dust respirators in preventing asthma attacks in patients with buckwheat flour/wheat flour-induced occupational asthma. The effect of the work environment was examined in 2 patients with occupational asthma 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. Peak expiratory flow rate (PEFR) decreased by 44% 7 hours after leaving the work environment, showing only a positive 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 respiratory. 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.
O'Donnell et al. 1989	Case series	Occupational asthma related to work in potlines in an aluminum smelter has been diagnosed on clinical criteria in 57 workers. About half were regular tobacco smokers but atopy was uncommon. There was a wide range in the time for which each had been employed prior to development of symptoms, but the average was about 20 months. 34 showed non-specific bronchial hyper-reactivity to methacholine. At annual reviews over a period of 5 years following transfer to other work at the smelter, the majority improved in symptoms in 1-2 years & bronchial hyperreactivity returned to normal. However, over the subsequent 3 years, deterioration, not limited to tobacco smokers or atopic subjects, has occurred in some subjects.
Ortega et al. 2001	Cohort	During crab-processing season, asthma-like symptoms developed in 26% of study participants. Only 9% of those with new asthma-like symptoms were IgE-sensitised to crab at the end of the season. Among the crab-processing jobs, 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	Cohort	Study I comprised 50 selected cases (25 had work-related symptoms & 25 had not). Prick tests & RAST investigations with different factory dust extracts were performed. Study II was a cross-sectional study of 129 workers who were prick-tested with one factory dust extract & with castor bean (CB). 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 the other workers 8 were probably sensitised (27%). These findings support the statement that the risk of sensitisation is greater the stronger the exposure. Study 2: Of the 28 workers with positive skin prick tests, 22 (79%) were smokers while of the 101 with negative skin prick tests 48 (47%) were smokers. The total frequency of sensitisation was 31% among smokers & 10% among non-smokers. The difference was greater the longer the duration of employment. Predisposing factors to developing sensitisation were atopic status, degree & length of exposure, & smoking habits.
Padoan et al. 2003	Case series	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.

Paggiaro et al. 1984	Case series	27 asthmatic & 20 non-asthmatic subjects were followed up 2 years after first examination. 15/27 asthmatics who continued exposure showed significant decrease in FEV1 & bronchial hyper-responsiveness & symptoms of chronic bronchitis. Non-asthmatics showed significant decrease of pulmonary function without changes in bronchial hyper-responsiveness. Conclude that stopping exposure to Toluene di-isocyanate (TDI) frequently did not produce an improvement of the TDI bronchial asthma, but in many cases symptoms of bronchoconstriction & bronchial hyper-responsiveness persist or may get worse. On the other hand, persistence of the occupational exposure causes a more rapid decline of the respiratory function.
Paggiaro et al. 1993	Case series	Subjects with Toluene di-isocyanate (TDI) -induced asthma were studied over an average follow-up period of 48 months. At least 1 year after diagnosis, a specific bronchial responsiveness test with TDI was repeated. A significant positive correlation between months of follow-up & provocative dose inducing a 20 percent fall in FEV1 (PD ₂₀ FEV1) methacholine was observed in 5/16 subjects. In most subjects, non-specific bronchial hyper-responsiveness did not change. 9/16 became non-responsive to TDI at follow-up examination, but only 3 of these showed a significant increase in PD ₂₀ FEV1 methacholine. 7/16 were still responsive to TDI. Study confirms long-term persistence of asthmatic symptoms & which non-specific bronchial hyper-responsiveness in asthma due to TDI after cessation of occupational exposure. Recovery from TDI-induced asthma can occur & only after long-term work cessation. Non-specific bronchial hyper-responsiveness to methacholine can persist even in absence of bronchial hyper-responsiveness to TDI, suggesting permanent chronic damage to mechanisms controlling airway tone.
Park et al. 1989	Case series	Paper reports 9 cases of immediate type occupational asthma to reactive dyes in one dye industry. All patients had had asthmatic symptoms, 4 had had rhinitis & they had worked for 6 to 25 months. Skin prick tests with reactive dyes were positive & bronchoprovocation tests also produced immediate or dual types of bronchoconstriction. Radioallergosorbent test (RAST) technique with nitrocellulose filter paper as a solid phase 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 & Nahm, 1997	Case series	Subjects were given anti-asthmatics, recommended to avoid exposure to Toluene di-isocyanate (TDI), & were monitored for 2 years (mean follow-up 12 months). 17/35 recovered completely, 11 showed significant improvement & 7 remained stable. No effect of age or 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 airway hyper-responsiveness, & the presence of specific IgE antibodies to TDI-human serum albumin conjugate.
Park et al. 2001	Case-control	Study aimed to evaluate the clinical validation of skin prick tests (SPT) & measurement of specific IgE to vinyl sulphone reactive dyes by enzyme linked immunosorbent assay (ELISA). 42 patients with occupational asthma from reactive dyes, 93 asymptomatic factory workers & 16 unexposed controls were enrolled. None of the unexposed controls had a positive response to SPTs. The sensitivity (76.2% v 53.7%), specificity (91.4% v 86.0%), positive predictive value (80.0% v 62.9%), & negative predictive value (89.5% v 80.8%) of SPTs were higher than those of ELISAs. In 4 patients with occupational asthma from reactive dyes & 8 control subjects exposed to reactive dye, IgE specific to reactive dye conjugated to human serum albumin was detected with ELISA even though they showed negative skin reactivity. 6 patients completely avoided the reactive dye for a mean (SD) 27.8 (10.3) months, IgE specific to reactive dyes decreased in all six patients during this time. Authors conclude that both SPTs & detection of IgE specific to reactive dye in serum samples could be valuable for screening, diagnosis, & monitoring occupational asthma resulting from exposure to reactive dyes. These two tests would complement each other.
Perrin et al. 1992	Case series	Peak expiratory flow rates (PEFR) was assessed every 2 h in 61 subjects referred for occupational asthma during a period away from work for at least 2 weeks. 3 experienced readers interpreted graphs of PEFR & PC20 values blindly. There was complete agreement among the experts in 54/61 cases. 25/61 subjects (41%) had positive specific inhalation challenge (SIC). The best index for comparing results of PEFR with SIC was the visual analysis of PEFR with sensitivity & specificity of 81% & 74%. Authors conclude that visual analysis of PEFR is an interesting tool for investigating occupational asthma, although sensitivity & specificity values do not seem satisfactory enough to warrant using it alone. (12 occupational asthma cases had normal BHR).

Petsonk et al. 2000	Cohort	Study evaluated respiratory health in workers using methylene diphenyl di-isocyanate (MDI) at a new wood products 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 skin prick tests to common aeroallergens. Authors conclude that to prevent asthma symptoms among workers, careful control of respiratory tract exposures associated with liquid MDI is important, especially during cleanup activities. Strict limitation of skin contact with di-isocyanates may also be necessary.
Pezzini et al. 1984	Case series	A specific IgE-mediated response was evaluated in 28 workers exposed to TDI or MDI, with diagnosis of occupational asthma & positive 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.
Piirila et al. 2000	Case series	Study carried out on average 10 years after diagnosis. 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 (HDI)-induced asthma was associated with a better outcome than diphenylmethane di-isocyanate (MDI) & toluene di-isocyanate (TDI)-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. 2001	Case referent	Only 5-10% of di-isocyanate-exposed workers develop asthma, suggestive of an underlying genetic susceptibility. Study aimed to examine whether polymorphisms in the GSTM1, GSTM3, GSTP1 & GSTT1 genes modify allergic responses to di-isocyanate exposure. The study population consisted of 182 di-isocyanate exposed workers, 109 diagnosed with di-isocyanate-induced asthma & 73 without asthma. Lack of the GSTM1 gene (null genotype) was associated with a 1.89-fold risk of di-isocyanate-induced asthma. Moreover, among the asthma patients, the GSTM1 null genotype was associated with lack of di-isocyanate-specific IgE antibodies & with late reaction in the specific bronchial provocation test. Similarly, GSTM3 AA genotype was related to late reaction in the specific bronchial provocation test. The GSTP1 Val/Val genotype, on the other hand, was related to high total IgE levels. The most remarkable effect was seen for the combination of GSTM1 null & the GSTM3 AA genotype, which was strongly associated with lack of di-isocyanate-specific IgE antibodies & with late reaction in the bronchial provocation test. Authors conclude that these results suggest, for the first time, that the polymorphic GSTs, especially the mu class GSTs, play an important role in inception of ill effects related to occupational exposure to di-isocyanates.

Pisati et al. 1993	Case series	<p>Patients with toluene di-isocyanate (TDI)-occupational asthma 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 & PD₁₅ methacholine & significant increases in the severity of symptom score & requirement for medication. Group B showed significantly less severe symptoms & a threefold increase in PD₁₅ 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 occupational asthma 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.</p>
Platts-Mills et al. 1987	Cross-sectional	<p>IgG & IgE antibodies 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 antibodies & positive skin tests. There was also a close correlation between reported asthmatic reactions & serum IgE antibody 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 antibody but were also present in 30% of asymptomatic individuals. The incidence & quantity of IgG antibody correlated with the degree of exposure to animals but not with the length of exposure in years. Authors conclude that IgE antibody responses to rat urinary allergen are an important cause of occupational disease. The results for IgG antibody suggest that their prevalence represents a marker for the degree of exposure to rat proteins.</p>
Prichard et al. 1984	Cross-sectional	<p>A total of 176 bakers & 24 subjects employed as bread slicers & wrappers were studied to examine the effect of occupational category on respiratory symptoms, ventilatory capacity, non-specific bronchial reactivity, & prick skin test responses to wheat & common allergens. Bakers had a greater prevalence of attacks of wheeze & dyspnoea & more frequently considered that work affected their chests than did slicers & wrappers. Bakers with a history of asthma with onset since starting work in a bakery had a greater prevalence of chronic cough & sputum, increased bronchial reactivity, & positive prick skin test responses to wheat & common allergens than other bakers. There was a significant association between the frequency of positive prick skin tests to wheat & common allergens, suggesting that prior atopy facilitates sensitisation to cereal antigens. The frequency of positive prick skin responses to common allergens, however, declined with increasing baking duration whereas the frequency of positive skin responses 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 positive prick skin test 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.</p>

Provencher et al. 1997	Surveillance scheme	Study evaluated the feasibility of implementing physician based surveillance system of occupational respiratory diseases (PROPULSE) in Quebec. Chest physicians were asked to report suspected new cases of occupational respiratory diseases & assess whether the condition was related to work & then categorise as highly likely, likely, & unlikely. Of the 161 physicians initially approached, 68% participated. Physicians rated 48% of suspected cases as highly likely, 29% as likely, & 20% as unlikely. The most often reported diagnosis was asthma (63%). The high proportion of cases of asthma probably reflects the increasing importance of this disease but may also reflect the different patterns of reporting among physicians with different expertise. The distribution of cases by diagnostic category is quite different between the PROPULSE system & that of the Workers Compensation Board (annual mean number of compensated cases during four year period). Asthma & allergic alveolitis are more frequent in PROPULSE, reactive airways dysfunction syndrome is about the same in both systems, & other diseases are more frequent among compensated cases. 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.
Quirce et al. 1995	Case series	Study aimed to assess reliability of peak expiratory flow (PEF) monitoring in 17 subjects referred for suspected occupational asthma. 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 peak flow meters for assessment of work-relatedness of asthma has limitations & is not reliable.
Redlich & Stowe, 2001	Cross-sectional	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. 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.
Reijula et al. 1996	Reporting scheme	Between 1986 & 1993 the annual incidence of occupational asthma increased by 70% 227-386 (equally in men & women). Proportion of newly identified occupational asthma from all new cases of asthma was 4.8%, with over half attributed to farming & bakery work.
Renstrom et al. 1994	Cohort	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.
Revsbech & Andersen, 1989	Cross-sectional	Diurnal variation (DV) in peak expiratory flow rate (PEFR) was studied among 132 workers who accomplished 3 daily PEFR measurements for 3 weeks. DV was calculated as difference between highest & lowest PEFR as percentage of the mean PEFR on each day. Median for the whole group was 5.9%. DV was higher among smokers & workers with work-related pulmonary symptoms. Analysis of variance showed that only age & smoking had a significant effect on DV. 12 workers had abnormally high DV, of whom 7 showed no signs of obstructive respiratory disease by spirometry. If only a single spirometric test had been performed the tentative diagnosis of bronchial asthma could have been missed in these 7 workers.

Ricciardi et al. 2003		Study aimed to improve understanding of the pathogenesis of occupational asthma induced by iroko wood dust & looked at the sensitivity & specificity of skin prick tests, RASTS & intra-dermal tests & peak flows & non-specific bronchial reactivity to iroko asthma. It was found that skin prick testing is an insensitive test for the diagnosis of occupational asthma (0/9). Intra-dermal iroko allergen has a sensitivity of 4/9. Peak flows all showed a 20% reduction at work in those with occupational asthma (100% sensitive). All were tested against a gold standard specific challenge test. The histories were 100% sensitive & abnormal non-specific reactivity was 100% sensitive. Paper shows the lack of use of skin prick testing in iroko asthma & the diagnostic sensitive 100% with peak flow records.
Rihs et al. 1997	Case-series	Results indicate that there is no evidence for a significant involvement of HLA class II alleles in the development of isocyanate occupational asthma.
Romano et al. 1995	Cross-sectional	Study aimed to assess the prevalence of allergic respiratory symptoms & of sensitisation to both green coffee beans & castor bean in the whole workforce of a coffee manufacturing plant, & to consider the effect of smoking & atopy. A questionnaire on oculo-rhinitis & asthma was administered & skin-prick tests 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 skin 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.
Rosenberg & Garnier, 1987	Case series	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 exposure to the sensitiser & bronchial responsiveness at diagnosis.
Ross & Mcdonald, 1998	Case series	Chest physicians were better able than occupational physicians to follow progress of patients who had left their jobs. 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.
Sallie et al. 1994	Reporting scheme	The SWORD surveillance scheme uses systematic reporting from physicians to provide a picture of the incidence of occupational respiratory disease in the United Kingdom. 40% of cases (1000 annually) are of occupational asthma or inhalation accidents occupational asthma related to a wide range of agents in many occupations.
Schlunssen et al. 2004	Cohort	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 bronchial hyper-responsiveness or bronchodilator induced reversibility or increased peak expiratory flow 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%.
Sjostedt et al. 1989	Cohort	Family history of allergy, raised total serum IgE & positive skin prick tests against common environmental allergens were pre-disposing factors for the development of laboratory animal allergy.
Sjostedt et al. 1993	Cross-sectional	In a 5-year follow-up study of 88 animal exposed laboratory technicians, the incidence of laboratory animal allergy (LAA), lung function, & the development of allergy test reactivity were investigated. Only 2 individuals developed test positive LAA rhinitis during the follow-up period. Furthermore, 1 subject who had previously had LAA rhinitis developed LAA asthma. In the remaining subjects the results of skin prick tests against laboratory animals & environmental allergens, total serum IgE levels, & lung function were unchanged. Atopy defined as parental & childhood allergy, raised total serum IgE levels, & positive skin prick tests against non-animal environmental allergens & non-laboratory animals were risk indicators for development of test positive 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.

Sjostedt et al. 1996	Case-control	Human leukocyte antigens & possible associations with occupational allergy to laboratory animals & atopy indicators were studied in 97 laboratory animal workers with airway symptoms & 27 symptom free workers, as well as in a population reference group of 123 blood donors in good health. 7 HLA antigens (HLA-A9, -B5, -B12, -B16, -DR4, -DR5, & -Drw6) suggested possible associations with symptoms and/or atopy indicators but only the HLA-B16 differences remained statistically significant. HLA-B16 was elevated in symptom-free subjects compared to the population reference group & in subjects with serum IgE < 10 kU/L. Subjects with serum IgE > 100 kU/L & sensitized against environmental and/or laboratory animals, including LAA asthmatics, lacked HLA-B16. Authors suggest that HLA-B16 or an immunosuppressive gene linked to HLA-B16 reduce the risk of producing IgE antibodies against animal protein allergens.
Slovak et al. 1981	Cohort	A prevalence study of occupational asthma was carried out by questionnaire in 1980 among a group of 151 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 the patients developed asthma within 3 months of first exposure & 75% developed it within the first year. Additional symptoms included rhinitis 29% & conjunctivitis 25%. Re-exposure caused repetition & worsening of symptoms. Immediate removal from further exposure resulted in rapid cessation of symptoms without further recurrence. 7 of 13 sensitised individuals who were still exposed 3 months after the onset of disease developed prolonged airways hyperreactivity to common environmental irritants.
Slovak et al. 1985	Case series	Helmet respirator would appear to be a valuable adjunct in the management of occupational asthma in those that opt to remain in exposure. However, they should be monitored carefully & regularly to ensure that their respiratory function has not deteriorated. Objective evidence of good protection was obtained in 6/8 asthmatics.
Stenton et al. 1993	Cross-sectional	Shipyards 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 per cent 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
Taivainen et al. 1998	Case series	Study investigated the value of powered dust respirator helmets in the treatment of 33 farmers with occupational asthma (24 with occupational asthma induced by cow dander or grains, 2 with other forms of atopic asthma, & 7 with non-atopic asthma) for 1 year. Morning & evening peak expiratory flow rates & daily symptoms of the subjects were monitored for 3 months without the use of the helmet & for 10 months with the helmet. Objective evidence of protection was obtained for farmers with occupational asthma. The morning peak flow rate increased & the variation in daily peak flow rate & the symptoms of cow-barn rhinitis diminished significantly during the helmet period. Authors conclude that results suggest that especially dairy farmers with occupational asthma benefit from the use of a powered dust respirator helmet.
Talini et al. 2002	Cross-sectional	Study aimed to detect new cases of flour-induced occupational asthma, by means of step-by-step approach (questionnaire, pulmonary function tests, skin prick tests & challenge tests). This stepwise approach to clinical diagnosis of occupational asthma allowed detection of small number of cases of previously undiagnosed flour induced occupational asthma (6 cases detected in sample of 297 exposed subjects). Poor correlation between skin prick test to flour & positive bronchial challenge test to flour was observed.
Tarlo & Broder, 1991	Case series	Study assessed the feasibility & results of different investigations using a consistent approach to 154 patients referred to clinic for possible occupational asthma. A positive skin test to a workplace allergen (14%), positive peak flow workplace changes (12%), improvement in methacholine response on holiday (9%), and/or positive specific challenge testing (14%) supported the diagnosis of occupational asthma in 61 subjects (39% of total referrals). 51 of these were related to a workplace sensitizer & 10 to a presumed irritant occupational asthma was excluded in 48 subjects (31%) who had normal methacholine responsiveness within 24 hours of work (22% of 54 subjects), peak flow readings no worse at work than on holidays (14% of total referrals) and/or negative specific challenge 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. 1995	Case series	Retrospective study of 609 claims submitted to Ontario Workers Compensation Board (WCB, 1984-1988). Study to assess determinants of outcome of WCB accepted claims at permanent disability assessments. The WCB decision reached was occupational asthma 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 occupational asthma & to an irritant in 67% with AA. Of 200 occupational asthma 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. 1997a	Cross-sectional	Identifies Ontario cases of isocyanate-induced occupational asthma & 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 occupational asthma claims have higher isocyanate exposures than those without claims.
Tarlo & Banks, 1997b	Case series	A better outcome in occupational asthma induced by isocyanates was associated with early diagnosis & early removal from isocyanates after the onset of asthma. (Better outcome may also relate to the shorter latency of occupational asthma induced by isocyanates). Outcome at a mean of 1.9 years was significantly better in those with a mandatory health surveillance programme.
Tarlo et al. 2000	Case-series	Fifty-one patients reported at their initial visit that their asthma was worse at work & was not worse on weekends or holidays off work (<i>i.e.</i> , 16% of the adult-onset employed asthmatics, 12% of all the adult-onset asthmatic subjects, & 7% of all the adult asthmatics in the clinic). A retrospective chart review of the 51 patients reporting worsened asthma at work indicated probable sensitizer-induced occupational asthma in 8 patients, based on history, exposure to a recognized respiratory sensitizer, & at least one positive objective test supporting occupational asthma. Twenty-five of the 51 asthmatic subjects whose asthma was worse at work likely had work aggravation of underlying asthma, a determination that was based on their recorded history of transient worsening at work & workplace exposure to recognized respiratory aggravating factors, but had no identified or likely workplace.
Tarlo et al. 2001	Case series	Change in glove to lower protein, powder free natural rubber latex (NRL) glove reduces NRL allergy in employees. 2 of the 3 nurses with occupational asthma were able to return to work. Reduction of new onset of NRL-related occupational asthma & also workers with previously diagnoses NRL-occupational asthma were able to continue working in a hospital setting.
Tarlo et al, 2002	Assessment	A medical surveillance programme was introduced into Ontario for workers exposed to diisocyanates in 1983, but no mandated surveillance programme is in effect in this province for other occupational respiratory sensitizers. This study assesses changes in incidence & severity of compensated claims for occupational asthma (OA) due to diisocyanates compared with other causes, which have occurred since the introduction of this surveillance programme. New claims for OA compensated by the Ontario Workers' Compensation Board (WCB) between 1980 & 1993 were retrospectively reviewed. Numbers of claims for OA induced by diisocyanates ranged from 9-15/year in 1980-83, increased up to 55-58 claims/year in 1988-90, then fell to 19-20 claims/year by 1992-93. By contrast yearly numbers of claims for OA due to other causes increased up to 1985-87 then remained relatively stable. Duration of symptoms for OA induced by diisocyanates was shorter than for other claims & there were fewer hospital admissions among those with OA induced by diisocyanates than among those with OA induced by other causes. Occupational asthma 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 diisocyanates.

Tee et al. 1998	Case series	58/101 patients referred for investigation were diagnosed as having isocyanate-induced occupational asthma by means of history, serial peak flow records, & bronchial provocation tests (BPT). Specific IgE antibodies 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 positive 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.
Toren et al. 1999	Case-control	Questionnaire information was collected & included occupational exposures & smoking habits. Odds ratios (OR) were calculated for exposure before asthma onset, stratified by sex & age-class. 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%.
Ucgun et al. 1998	Cross-sectional	For determination of the prevalence of occupational asthma among car & furniture painters exposed to isocyanate in the centre of Eskisehir, Turkey, a clinical & epidemiologic prospective study in three phases was done. In the first phase of the study, a modified questionnaire & pulmonary function test (PFT) were done. During the second phase, peak expiratory flow rate (PEFR) was monitored. In the third phase, non specific bronchial provocation tests (NSBPT) with histamine were done. Finally, through questionnaire, typical history, PFT, PEFR monitoring, & NSBPT, 30 workers (9.6%) were diagnosed as having occupational asthma. Smoking habits & atopy in the occupational asthma-diagnosed workers were found to be statistically significantly high in comparison to the other workers. It was concluded that occupational asthma is a common disorder among automobile & furniture painters, & smoking habits & atopy were seen to have a significant effect on occupational asthma occurrence.
Valentino et al. 1994	Case-series	4 subjects were diagnosed as having latex hypersensitivity after skin prick-testing, & immunoglobulin E serum level against latex gave positive results (2 workers presented dermatitis as well as work-related respiratory symptoms, while the other 2 only showed symptoms suggesting occupational asthma). Changes in methacholine responsiveness also took place. In 1 case, an occupational exposure test resulted in a 24% drop in FEV1 value 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.
Valentino et al. 2002	Case series	Subjects followed for mean of 8.4 years. At follow-up, the group removed from exposure showed significant improvement in symptoms, consequent reduction in use of medications & increase in PD ₂₀ (9/37 subjects in this group were asymptomatic). By contrast, the condition of subjects who had remained exposed deteriorated significantly during follow-up in terms of symptoms, pulmonary function parameters, PD ₂₀ & the use of medication.
Vandenplas et al. 1995a	Cross-sectional	A questionnaire & skin-prick tests with latex & common inhalant allergens were administered to 273 of 289 members of the target population. 13/273 subjects showed skin reactivity to latex. No subject had history suggestive of occupational asthma among those who had negative skin tests to latex. A histamine inhalation challenge was then performed on 12 of 13 latex-sensitive subjects (including 5 subjects with a history of occupational asthma). These 12 subjects demonstrated significant bronchial hyper-responsiveness. All underwent specific inhalation challenges with latex gloves & 7 subjects developed a significant bronchial response. Authors conclude that occupational asthma due to latex occurred in 2.5% of hospital employees. Widespread use of latex gloves should therefore be considered a significant risk to the respiratory health of hospital employees.

Vandenplas et al. 1995b	Case series	Using inhalation challenges, the bronchial response to hypoallergenic gloves was evaluated in 8 health care workers with latex-induced asthma. Exposure to hypoallergenic gloves resulted in the absence (in 6 subjects) or a significant reduction (in 2 subjects) of bronchial response. The effects of repeated exposure to hypoallergenic gloves was assessed in 2 subjects who did not demonstrate changes in peak expiratory flow rates & non-specific bronchial responsiveness to histamine. This study on a limited number of patients 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.
Vandenplas et al. 2001	Cross-sectional	Study examined the accuracy of the clinical history, immunologic tests & non-specific bronchial hyper-responsiveness (BHR) in diagnosing latex occupational asthma compared with specific inhalation challenge (SIC). 45 consecutive patients underwent an open medical questionnaire, skin prick testing against latex, measurement of BHR to histamine, & inhalation challenge with latex gloves. The clinical history, skin prick testing against latex, & assessment of non-specific BHR showed high sensitivity but low specificity when compared with the results of the SIC. The clinical history & immunologic tests were the most useful procedures in diagnosing latex occupational asthma, although combining the 2 procedures remained less accurate than SIC. Further examination of the predictive values of available tests is warranted to recommend diagnostic strategies that are specific to the various agents causing occupational asthma.
Vandenplas et al. 2002	Case series	Initial & follow-up visits (median 56 months) of subjects with latex-induced asthma 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). Study suggests that reduction of exposure to latex represents a reasonably safe alternative that should be considered in workers with latex-induced occupational asthma 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.
Vanhanen et al. 1997	Cross-sectional	Study investigated sensitisation to industrial enzymes in Finnish enzyme production & in Finnish laboratories. The skin prick test showed 21 employees (12%) to be sensitized to one or more enzymes. 16 positive persons also 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, likewise, the exposure-response linear trend was statistically significant, & the statistical significance remained after stratification for atopy. Authors conclude that study confirmed that industrial enzymes are potent sensitizers. Sensitisation may even follow minute degrees of exposure, such as among office personnel. Atopics are more susceptible to sensitisation than non-atopics. Non-atopics are also clearly at risk; the demonstrated exposure-response relationship emphasizes the need for & advantages of proper exposure control.
Vedal et al. 1986	Cross-sectional	Data was obtained from 652 workers in a western red-cedar sawmill on symptoms, pulmonary function, immediate skin reactivity to common allergens, non-specific bronchial responsiveness, 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 non-specific bronchial hyper-responsiveness (BHR). Elevation in RAST was associated with BHR. 46% of workers with RAST elevation had BHR 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 & non-specific bronchial hyper-responsiveness are associated in western red-cedar workers & that this association may reflect a causal connection.

Venables et al. 1985a	Cross-sectional	Using a radioallergosorbent test with a tetrachlorophthalic anhydride (TCPA) human serum albumin conjugate, specific IgE antibody was detected in serum from 24 out of 300 factory floor workers exposed to TCPA. Of these 24, 20 (83.3%) were current smokers compared with 133 (48.2%) of 276 without antibody, & there was a weaker association with atopy, defined by skin tests 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 antibody to this hapten protein conjugate. Nasal symptoms were associated with work area but not with specific IgE against TCPA.
Venables et al. 1985b	Cross-sectional	In 1979 a cross-sectional study, which defined occupational asthma in terms of respiratory symptoms, detected 21 people with suggestive symptoms among the 221 studied. All 21 developed their symptoms after 1971, & it was found that in this year a supplier had modified a coating allowing, at the temperatures used in the process, toluene di-isocyanate to be liberated. 2 of the symptomatic subjects were tested by inhalation of the isocyanate & showed asthmatic reactions & other subjects were found to have asthma related to periods spent at work by records of peak expiratory flow rate. 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. 1987	Case series	Subjects were followed up & assessed 4.5 years after last exposure. 6 living patients reported continuing symptoms suggestive of asthma, & 5 who were studied in 1985 demonstrated mild bronchial hyper-responsiveness. All patients reported that they had improved since leaving the factory, but they still reported symptoms. Authors conclude that after avoidance of exposure to tetrachlorophthalic anhydride, concentrations of specific IgE fell & symptoms of asthma improved, however, both were still present 4 years later.
Venables et al. 1988a	Cross-sectional	Four indices of laboratory animal allergy were studied: symptoms suggestive of occupational asthma, symptoms suggestive of any occupational allergy, skin wheals to animal urine extracts, & serum binding in radioallergosorbent tests with urine extracts. Pooled data from the three surveys showed an association between smoking & all indices except radioallergosorbent tests; the association was significant for symptoms of occupational asthma. One of the three surveys consistently showed a stronger association of allergy indices with smoking than with atopy (defined on skin tests with non-animal aeroallergens). Associations with smoking persisted after stratifying by atopic status, suggesting that smoking may be a risk factor for laboratory animal allergy. (The factory where smoking was more strongly associated with allergy than atopy was new, with mean employment duration of 2.6yrs).
Venables et al. 1988b	Cross-sectional	Survey was carried out on workers exposed to laboratory animals. 44% had symptoms in a self-completed questionnaire that were consistent with laboratory animal allergy (LAA) of whom 11% had chest symptoms. LAA chest symptoms were almost 5 times more common in atopic than non-atopic subjects. 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 positive skin tests 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.

Venables et al. 1989a	Cohort	57 workers smoked & 29 were atopic; 22 developed a positive result on skin testing with platinum salts & 49 developed symptoms, including all 22 whose skin test result was positive. Smoking was the only significant predictor of a positive result on skin testing 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 per 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.
Venables et al. 1989b	Case series	Patients interviewed for follow-up of occupational asthma on average 6 years after asthma developed (median time between exposure & occupational asthma 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 were currently unemployed & 40-73% reported limitations in everyday activities.
Weill et al. 1971	Cohort	13/60 had symptoms of 'lower respiratory tract disease,' 11 with wheezing, cough, shortness of breath & chest tightness. No relation between smoking & symptoms of 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 positive skin prick tests were found in the low exposure group versus 53% of the moderate exposure group & 45% in the high exposure group. In plant B, 16% positive skin prick test 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	Cross-sectional	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-positive skin test & in 2 subjects, antibodies were present. 4 out of 25 heavily exposed subjects without asthma had a non-specific bronchial hyperreactivity. 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	Case-control	Study aimed to evaluate allergic sensitisation to <i>Chrysonilia sitophila</i> , <i>Penicillium glabrum</i> , & <i>Trichoderma longibrachiatum</i> in cork workers with asthma. Skin prick tests with common allergens & with 3 fungi were performed on 10 cork workers with asthma & 8 non-exposed asthmatics. Based on serial peak expiratory flow measurements, 5 were classified as having occupational asthma & 5 as having non-occupational asthma. 2/10 patients with occupational exposure & 4/8 of control group showed positive results for skin prick tests for common allergens. All exposed patients had negative skin prick test 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 occupational asthma 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	Cohort	The number of atopics among RAST sensitive individuals is high (38%). The percentage of atopics among all investigated enzyme workers was 4.5%.

Young et al. 1995	Case-referent	Study aimed to determine association between HLA allele frequency & specific IgE antibody to acid anhydride-human serum albumin (AA-HSA) conjugates among acid anhydride workers. 30 cases with radio-allergosorbent test score versus AA-HSA conjugates > 2 were compared with 30 referents without specific IgE selected from the same factory sites as the cases & matched for age, sex, duration of exposure, atopic status, & smoking habit. Authors found a significant excess of HLA-DR3 in the cases with specific IgE to acid anhydrides when compared with the referents (50% versus 14%). The excess of HLA-DR3 was particularly associated with IgE versus trimellitic anhydride, with HLA-DR3 present in 8/11 workers with & in 2/14 referents without IgE. The proportion of HLA-DR3 among the phthalic anhydride workers was not different in those with IgE from their referents. Authors conclude that findings suggest MHC II proteins are an important determinant of the specificity of the IgE response to an inhaled hapten.
Zentner et al. 1997	Case-control	Study investigated 10 sensitized & 10 non-sensitized workers from a pharmaceutical factory who had been exposed to enzymes. 10 non-allergic subjects served as a control group. Titrated skin prick tests (SPT), RAST, & immunoblot studies were performed with all six enzymes. SPT reactivity revealed multiple sensitizations to proteolytic enzymes. Immunoblot studies demonstrated IgG-binding bands in both SPT-positive & -negative workers, indicating exposure to the enzymes, but not in 10 unexposed control subjects. IgE-binding bands of the enzymes were detected only in workers with a positive SPT reaction and/or a positive RAST result. IgG bands were more frequent & the IgG/IgE ratio was increased in workers without allergic complaints compared to symptomatic workers. This might indicate that high levels of specific IgG antibodies to enzymes are associated with an immune response lacking allergic manifestations in spite of IgE-mediated sensitizations to the enzymes. Atopic subjects were at greater risk of developing IgE-mediated sensitization (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.
Zock et al. 1998	Cross-sectional	Expert judgment of peak flow-time graphs provides an important tool to detect occupational asthma. However, the reproducibility of this technique in an open working population is unknown. Agreement between & within 9 experts was studied using peak flow-time graphs of 49 workers. Results suggest that in a "healthy" working population, judgment of peak flow 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.

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Appendix A

OCCUPATIONAL ASTHMA

A Guide for Occupational Physicians and Occupational Health Practitioners

British Occupational Health Research Foundation

Occupational asthma (OA) is thought to be the cause for about 1 in 10 cases of asthma in adults of working age. Many agents have been reported to cause OA and the major determinant of risk for the development of OA is the level of exposure to its causes.

Asthma is characterised by variable airflow limitation and airway hyper-responsiveness. Once sensitised, exposure to very small concentrations of the substance will cause a reaction. The long term effects can be significant in terms of employability. Even if redeployment is possible, employment in lesser skilled jobs and reduction in income are often the outcomes.

This leaflet summarises the results of a recent review of the scientific evidence on OA*. The review sought to answer some of the key questions about the prevention, diagnosis and practical management of this important condition. The information in this leaflet is intended for the use of Occupational Physicians and Occupational Health Nurse Practitioners in planning programmes for the prevention of OA, rather than for medico-legal purposes.

*Guidelines for the prevention, identification & management of Occupational Asthma: Evidence review and recommendations. British Occupational Health Research Foundation. London 2004

What causes OA?

The most frequently reported agents include isocyanates, flour and grain dust, colophony and fluxes, latex, animals, aldehydes and wood dust. However there are many recognised sensitisers (<http://www.hse.gov.uk/asthma/causes.htm#causes>)

Who is most at risk?

The workers reported from population studies to be at increased risk of developing asthma include bakers, food processors, forestry workers, chemical workers, plastics and rubber workers, metal workers, welders, textile workers, electrical and electronic production workers, storage workers, farm workers, waiters, cleaners, painters, plastic workers, dental workers and laboratory technicians

How can it be prevented?

Employers should assess their workplace for known agents and the risk of exposure, which depends on how the substance is being handled. Exposure should be reduced by elimination or substitution. Where this is not possible, then effective control of exposure at source should be implemented. Personal respiratory protective equipment reduces the incidence of, but does not completely prevent OA. When respiratory protective equipment is worn, the employer must ensure that the appropriate type is used and maintained, fit testing is performed and workers understand how to wear, remove and replace it.

It is important that workers are informed about the causes of OA in the workplace and the need to report symptoms as soon as they develop.

What will the worker complain of? Symptoms of asthma of whatever cause, include attacks of wheezing, coughing, chest tightness or shortness of breath. The symptoms can develop immediately after exposure. But sometimes symptoms appear several hours after exposure, possibly at night, and so any link with workplace activities may not be obvious. Other associated conditions are rhinitis (sneezing/runny nose) and/or conjunctivitis (itchy and inflamed red eyes).

What should be done at the pre-employment stage? Prospective employees should be asked about pre-existing asthma caused by sensitisation to substances that they might be exposed to in their new job. If they already have asthma caused by the substance(s), they should be advised that they are not suitable to undertake this work.

A previous history of asthma is not significantly associated with occupational asthma. Poorly discriminating factors such as atopy, family or personal history of asthma, cigarette smoking and HLA phenotype should not be used to exclude individuals from employment.

How often and what type of health surveillance should be done?

As a minimum, a respiratory questionnaire enquiring about work related upper and lower respiratory symptoms should be completed annually.

The OH practitioner should assess the requirement for further health surveillance on the employer's risk assessment, which will depend upon the nature of the substance handled and the likelihood of exposure. Further testing of lung function and referral for immunological blood tests or skin prick testing, which detect sensitisation, may be appropriate.

- For many substances the risk of developing OA is greatest during the early years of exposure. Therefore more frequent surveillance is indicated for the first two years of exposure.
- Workers with pre-existing asthma of any origin should have more frequent surveillance to detect any potential deterioration in lung function
- Workers who develop rhinitis should have increased surveillance, and the workplace exposure should be investigated and reduced.

How do we find out if someone has OA?

Any worker with symptoms of asthma or rhinitis which are new, recurrent or getting worse should be asked about their job and materials and whether the symptoms improve regularly when away from work. It is not unknown for workers to change job or work processes without the knowledge of the OH practitioner, with the possible changes in exposure.

If a worker is suspected of having OA they should be referred without delay to a physician with expertise in OA. This is likely to be an Occupational Health or Respiratory Physician of Consultant status. The diagnosis is likely to be confirmed in approximately half of these individuals.

To assist in the diagnosis of the condition, the worker should be provided with a peak flow meter and asked to note the best of three readings at least four times a day (for three weeks).

Pre and post shift spirometry is not recommended as it is unlikely to be sufficiently sensitive or specific. Physicians should confirm a diagnosis of OA supported by objective criteria (lung function testing, immunological or both) and not on the basis of history alone, because of the potential implications for future employment.

When any one employee develops confirmed OA or Rhinitis the exposure and the presence of symptoms of other workers should be investigated.

What is the best way of managing someone with OA?

The likelihood of improvement or resolution of symptoms is greater in those who have a shorter duration of symptoms and relatively normal lung function at the time of diagnosis. Early identification and early avoidance of further exposure to its cause improves the prognosis of OA.

The pharmacological management of patients with OA should follow the published clinical guidelines, independent of the cause. OH practitioners should encourage the worker to take any medication as prescribed.

When should exposure cease?

Workers diagnosed as having OA should avoid further exposure to its cause in the workplace.

Appendix B

OCCUPATIONAL ASTHMA

A Guide for General Practitioners and Practice Nurses

British Occupational Health Research Foundation

- Occupational asthma accounts for up to 15% of all adult asthma.
- It is the most commonly reported occupational respiratory disorder in westernized industrial countries.
- Generally occupational asthma has a poor prognosis and is likely to persist and deteriorate unless identified and managed early and effectively.

This guide helps you to:

- outline the key recommendations of the first systematic evidence review of the prevention, identification and management of occupational asthma. *The full guidelines are available from the British Occupational Health Research Foundation (BOHRF).*
- increase primary health care professionals' knowledge of occupational asthma and its management.
- encourage early referral because this affords patients the best chance of improvement or cure

About this guide

Occupational asthma is a significant problem within the United Kingdom. The Health and Safety Executive (HSE) estimate that between 1,500 and 3,000 people will develop occupational asthma each year. This guide will help you in your clinical practice to manage occupational asthma. It will increase your knowledge of the differential diagnosis of occupational asthma and its subsequent management. It gives a brief summary of the 2004 occupational asthma guidelines, which are evidence based.

What is occupational asthma?

Occupational asthma is new onset adult asthma caused by exposure to the workplace and not by factors outside of the workplace. Occupational Asthma is subdivided into two groups:

1. Immunologic occupational asthma in which there is a time delay between exposure to a respiratory sensitizer and the development of symptoms;
2. Non- immunologic occupational asthma that typically occurs within a few hours of high concentration exposure to an irritant at work.

Most cases of occupational asthma are of the immunologic type.

Occupational asthma is preventable. Symptoms may resolve completely with early diagnosis and early removal from exposure. Prevention and cure depend upon the effective control of exposure to respiratory sensitisers in the workplace and early diagnosis.

The development of occupational asthma has long term adverse health and economic consequences. In some cases occupational asthma has proven to be fatal.

Who is at risk of developing occupational asthma?

The most commonly reported professions to suffer from occupational asthma are:

Animal Handlers	Nurses
Bakers and Pastry Makers	Paint Sprayers
Chemical Workers	Timber Workers
Food Processing Workers	Welders

What can health professionals do?

Early diagnosis:

Consider the possibility of an occupational asthma diagnosis in all new cases of adult asthma.

Ask each new adult presenting with asthma symptoms or rhinitis about their job and the substances with which they work; referral to a physician with expertise in occupational asthma may be appropriate

if they fall into one of the high risk professions listed. It is important to remember that rhinitis occurring in patients in high risk professions might signal an increased risk of developing occupational asthma within 12 months of the onset of rhinitis.

An improvement in symptoms when away from work has been shown to be a good indicator that occupational asthma may exist. Therefore, ask the following questions:

- When did the symptoms start?
- Do their symptoms vary when not at work?
- Do their symptoms improve when away from work?

Does a long holiday improve their asthma symptoms? (This is more reliable than asking if symptoms increase upon return to work.)

Lung function tests help with diagnosis:

- Measure peak expiratory flow rate at least four times a day, for at least three weeks and analysed by a validated method.
- Serial peak expiratory flow rates carried out according to established protocols and interpreted appropriately will provide few false positive results, but about 30% false negatives.

The diagnosis of occupational asthma should be confirmed by a specialist in this field. However; there are a limited number of centres that can provide such expertise in the UK.

Blood tests for specific IgE to suspected allergens help to identify sensitization, and together with other symptom related evidence will help identify the causative agent.

Prognosis:

Prognosis will improve for many provided they are withdrawn from exposure to the substance provoking their asthma at an early stage. Those workers who remain in the workplace which has induced their asthma are unlikely to improve and symptoms may worsen. Therefore specialist input is essential as early as possible.

Those who have relatively normal lung function at time of diagnosis and shorter duration of symptoms prior to diagnosis will have the greatest improvement.

Management of occupational asthma

Ideally, management involves redeployment to an environment with complete and permanent avoidance of exposure of allergen provoking asthma. However, in practice this may not be possible due to social, economic and personal factors of the individual. If complete avoidance of allergen is not possible, the individual should relocate to an area with less or occasional exposure to the allergen and remain under increased medical surveillance.

Routine management of asthma should follow the already established guidelines for example BTS (2003) "Asthma management guidelines"

Employers may have an occupational health service with whom the primary care team may liaise, with the patients consent.

Further information

British Occupational Health Research Foundation
Health & Safety Executive
General Practice Airways Group
OASYS and Occupational Asthma
BTS / SIGN Guidelines

<http://www.bohrf.org.uk>
<http://www.hse.gov.uk/asthma>
<http://www.gpiag.org>
<http://www.occupationalasthma.com>
<http://www.sign.ac.uk>

Appendix C

OCCUPATIONAL ASTHMA

A guide for Employers, Workers and their Representatives

British Occupational Health Research Foundation

What is asthma?

Asthma is a condition in which inflammation of the lining of the small airways of the lung together with spasms of the muscles around the airways, cause these airways to narrow and reduce airflow both into and out of the lungs. This produces wheezing, shortness of breath, chest tightness, and coughing. Most people with asthma have periodic attacks of symptoms separated by symptom-free periods. Symptoms can be aggravated by cold air and cigarette smoke and are often worse at night or early in the morning.

What is work related asthma?

Asthma is work-related when there is an association between symptoms and work, and can be divided into the following categories:

- *Work aggravated asthma*: pre-existing or new onset asthma worsened by workplace exposure
- *Occupational asthma*: asthma caused by substances inhaled at work, which can be typed as:
 - *Allergic*: where the immune system becomes sensitised to a substance at work. There is a gap between exposure, becoming sensitised and then developing symptoms.
 - *Irritant*: airway dysfunction caused by a reaction to an irritant substance which does not involve the immune system, symptoms develop within a few hours of exposure.

What is the extent of the problem?

Occupational factors account for 9-15% of cases of asthma in adults of working age with almost 90% of those cases being attributed to an allergic response. The substances responsible for this are known as sensitising agents, and many are well known. HSE figures show that 1,500 to 3,000 people develop occupational asthma in the UK every year, rising to 7,000 including work aggravated cases.

In terms of effects on the economy, new cases over a ten-year period cost society £1.1 billion. In terms of human cost, some workers are left severely disabled; causing early retirement with others forced to change jobs. Occupational asthma is readily preventable, and this is based on controlling exposure to sensitising agents.

About this guidance

This guidance is based primarily on findings from medical evidence relating to occupational asthma and agents known to cause asthma (asthmagens). Using good medical evidence to support this type of guidance is essential, in order to decide the policies for the prevention, identification and management of occupational asthma.

There are full guidelines available from the British Occupational Health Research Foundation (BOHRF). These are aimed at a whole range of groups from health professionals to employers, workers and their safety representatives. This brief guide is based primarily on these guidelines and

targets people in the workplace, supporting good occupational health management practices and worker consultation. The guide will be distributed on a global basis.

What do employers, workers and their safety representatives need to know?

At least 1 in 10 cases of new or recurrent asthma in adults are caused by workplace exposure, and these are related to a very large number of substances used at work. The most frequently reported agents include:

- Isocyanates (found in many paints and foams)
- Flour and Grain dust
- Latex
- Aldehydes
- Colophony and Fluxes
- Animals
- Wood Dust, etc.

There are many more substances (agents) that are known to be capable of causing occupational asthma, and these will affect a whole host of occupations. These include *bakery workers, pastry makers, paint sprayers, cleaners, nursing and care staff, catering workers, lab technicians, chemical workers, animal handlers, woodworkers, welders and timber workers* etc.

The risk of developing occupational asthma is connected to the level of exposure to the agents; this means that the chances of developing an allergy to the substance will increase at higher exposure levels. Therefore removing or reducing exposure to the substance will reduce the incidence of the disease.

It is important you address the situation immediately as, sensitisation and occupational asthma are more likely to develop in the first years of exposure.

In addition people develop symptoms of asthma at lower levels than those in which will cause sensitivity, and the quicker they are removed from exposure the more likely a complete recovery is possible. It is extremely important that employees are informed of the causes, risks and symptoms of asthma so they can report them.

What are the symptoms?

Workers should report the following symptoms as soon as they develop, either to occupational health or their GP, and discuss with them about informing their employers.

- Attacks of wheezing, coughing, chest tightness or shortness of breath
- Rhinitis (sneezing, runny nose) and / or
- Conjunctivitis (itchy and inflamed eyes)

The symptoms may develop immediately after exposure, but sometimes may only appear after several hours' exposure. The symptoms of asthma are the same irrespective of whether or not the cause is work. Determining whether the cause is work requires a careful history and objective testing by a doctor with expertise in occupational asthma.

When any one worker develops confirmed occupational asthma or rhinitis, the exposure and presence of symptoms of other workers should be investigated.

What are the solutions?

Eliminating or substituting the sensitising agent is the best control measure. You therefore need to decide if you can use another substance that is not a known sensitiser.

If you need to use the substance then you will need to look at making sure that exposure is effectively controlled. This can be achieved at source for example by using engineering controls such as Local Exhaust Ventilation (LEV). The equipment should be selected carefully, monitored for effectiveness and maintained and inspected regularly.

PPE is the last resort. Respiratory Protective Equipment (RPE) will reduce the incidence of the condition but not prevent it. To achieve optimum effect it has to be of the appropriate type, fit tested, well maintained and training given in wearing, removal, storage and replacement. It must be noted that even brief removal of the RPE will result in a higher risk of becoming sensitised and developing occupational asthma.

Preventing onset of the disease by eliminating or reducing exposure is the primary objective; a secondary method involves detecting early or pre-symptomatic disease.

This incorporates adequate consultation with workers and their representatives, to implement health surveillance combined with education and training. The purpose is to prevent worsening of symptoms by early detection and removal from exposure.

Removal from exposure should not mean loss of job, as a person who develops occupational asthma might be covered by disability legislation. The employer would then be required to make suitable adaptations to ensure that work is available without being exposed to the causative agent. This may involve redeployment to another job or substitution of the hazardous agent.

Health surveillance

Where a risk of occupational asthma is identified health surveillance should be provided. This can detect the disease at an early stage and the outcome is improved in workers who are included in the programme.

There are different types of test used for identification of the disease, and these are available in the full guidelines. Here is a brief insight into some of the relevant tests to give you an idea:

Clinical questionnaires are useful to identify symptoms of wheeze and / or shortness of breath, but will not detect all people with asthma. Lung function tests may identify some cases of asthma not detected by questionnaire, although the disease can be present with normal readings. Skin prick testing and blood sampling may be available to detect antibodies to some asthmagens, which would be present in a sensitised person.

Health surveillance should be completed at least annually and more frequently when risk is highest, i.e.:

- During the first two years of employment in a job where there is a risk of occupational asthma
- For workers with pre-existing asthma of any origin
- For workers who develop rhinitis or conjunctivitis

If it is confirmed that any workers have developed occupational asthma, remedial measures should be implemented to protect them and all other workers.

Medical Confidentiality

Health professionals will perform any clinical tests needed, and will only provide results to employers in general terms regarding the workers fitness for work. It must be noted that health professionals will not provide clinical information to the employer, without the written consent of the person. This also applies to any questionnaire enquiring about symptoms; consent is subject to strict laws on medical confidentiality.

What about New Workers with Asthma

Pre-employment examinations should be approached with care, as little is known about people's susceptibility factors to occupational asthma. The evidence indicates that a previous history of asthma is not significantly associated with occupational asthma. So it should not be used to exclude individuals from employment, unless it is established that the condition was caused by a particular substance(s), and that the person would be exposed to it / them in their new position. If in doubt, seek advice from an occupational health professional.

Rehabilitation

Rehabilitation is an important process, and should be taken up as soon as possible, as delaying will reduce effectiveness.

There is consistent evidence derived from several countries that about one third of workers with occupational asthma are unemployed after diagnosis. This figure remains the same for these sufferers even after six years, showing that rehabilitation programmes for people with this disease need to be implemented. This is because the loss to society as a whole is immense, in terms of:

- Reduced quality of life and functional loss for the sufferer,
- Loss to family, friends and the community from reduced social activity
- Loss of skills and cost to business
- Cost to the tax payer

Early diagnosis and early avoidance of further exposure, either by relocation or substituting the sensitising agent offer best chance of complete recovery.

Remember that involving all concerned parties and working together will greatly increase the chances of successful rehabilitation. In fact a good all round partnership will help reduce the adverse effects of occupational asthma as a whole.