naires are a better predictor of asthma than BHR (or the combination of BHR and symptoms) when compared with a careful clinical diagnosis of asthma (Pekkanen and Pearce, 1999).

RISK FACTORS FOR ALLERGIC RHINITIS AND ASTHMA

Atopic predisposition is an important risk factor for occupational sensitization and the subsequent development of atopic respiratory diseases such as rhinitis and allergic asthma. The atopic predisposition is probably primarily genetically determined, but in addition, modified by events during the further development and maturation of the immune system early in life. In addition to allergen exposure, exposure to 'adjuvant factors,' which actually function as effect modifiers in the relation between allergen exposure and sensitization may be a risk factor, which could explain why not all 'atopic' individuals develop occupational sensitization at the same exposure levels. Evidence for the existence of such adjuvant factors comes mainly from experimental animal studies, while for human populations very few clear data are available. These adjuvant factors can include diet, pre-existing or concomitant disease, and smoking behavior. Particularly with regard to smoking there is no agreement: some studies have found smoking to be a significant risk factor for occupational sensitization, while in others no significant effects were noted, or even negative associations with the prevalence of IgE to common or occupational allergens. Of special relevance for occupational medicine and hygiene are findings suggesting that work-related exposure to fumes, gases, or specific chemicals, for example, may enhance the risk of allergic sensitization to inhaled occupational allergens (Kapsenberg, 1996; Løvik et al., 1996). This may be true for widely varying agents like diesel exhaust particles, formaldehyde, and disinfectants. Table 5-4 gives an overview of potential risk factors for IgE sensitization to occupational allergens.

The most important risk factors for work-related allergic *symptoms* are type I sensitization to an allergen and exposure levels at the workplace (see Table 5-5). Note that, for induction of symptoms, the instantaneous exposure and short-term duration are much more important than for the induction of sensitization. For sensitization, an often prolonged exposure period is required (for sometimes up to several years). The risk of allergic respiratory symptoms further depends on several other parameters like bronchial or nasal hyperreactivity and a number of 'enhancing' factors that are very similar to the factors mentioned as possible 'adjuvants' in Table 5-4. While the presence of bronchial or nasal hyperreactivity enhances the risk of allergen-specific allergic reactions, it should be noted that it can also enhance the risk of (non-allergic) reactions towards non-allergic exposures (e.g., endotoxins) at the workplace. Similarly, 'common atopy' (IgE sensitization against commonly available allergens) is often recognized as a risk factor for symptoms, particularly in the absence of demonstrable IgE sensitization to the specific allergen, but this relationship to atopy is mainly due to its strong association with airway reactivity.

Table 5-4
Risk factors for IgE sensitization to occupational allergens

- *atopic predisposition*: 'atopy' defined by
  - presonal or family history of atopic disease
  - positive skin prick test(s) to common allergen(s)
  - specific IgE to common allergen(s)

- *allergen exposure*
  - high airborne concentrations at workplace
  - high frequency and short-term duration: e.g., job tasks (hrs/weeks)
  - long-term: job duration (yrs)

- '*adjuvant*' *factors*
  - life style factors: diet, smoking
  - history of non-atopic airway disease
  - other occupational exposures:
    e.g., diesel exhaust particles, gases, disinfectants

NB: *For most factors, only circumstantial or partially conclusive evidence is available.*

OCCURRENCE OF ALLERGIC ASTHMA AND RHINITIS

In several countries, occupational respiratory disease registries have been established that can be used to assess the incidence of occupational asthma. However, definition of occupational asthma can be quite different between registries, and may, in some cases, strongly depend on whether employees are compensated for a confirmed diagnosis of occupational asthma. In addition, generally no distinction between allergic and non-allergic asthma is made. Well known registers are: the British Surveillance of Work-related and Occupational Respiratory Disease (SWORD) project and a more intensive scheme for occupational asthma in the West Midlands region known as SHIELD; a Finnish registry maintained by the Finnish Institute of Occupational Health; the U.S. Sentinel Event Notification System for Occupational Risks (SENSOR); as well as several others in Canada and Germany (Meredith and Nordman, 1996). These registries report incidences of occupational asthma ranging from two to 15 cases per 100,000 persons per year (see Table 5-6). However, these incidence rates are likely to be underestimated by at least a factor 2-3 (Meredith, 1993). Interestingly, occupations with exposures to biological agents (animal allergens, enzymes, flour and grain, wood dust, molds, other plants) make up a considerable proportion of all registered occupational asthma cases in various countries (UK, Finland and Canada; reviewed by Meredith and Nordman, 1996). No registries for rhinitis are available.

Table 5-5
Risk factors for work-related allergic symptoms

- *occupational sensitization*:
  - allergen-specific IgE
  - positive skin prick test (SPT)

- *allergen exposure:*
  - high airborne concentrations at workplace
  - high frequency and duration: job tasks (hrs/weeks)

- *non-specific bronchial (or nasal) hyperreactivity*
  - positive BHR test: histamine or metacholine provocation
  - personal history of allergic airway symptoms
  - reported hypersensitivity to exercise, cold air, dust, smoke, etc.

- *atopic predisposition*: 'atopy' defined by
  - personal or family history of atopic disease
  - positive skin prick test(s) to common allergen(s)
  - specific IgE to common allergen(s)

- '*enhancing factors*'
  - concomittant work-related exposures (gases, fumes, disinfectants)
  - smoking, diet, psychosocial stress

NB: *For most factors, only circumstantial or partially conclusive evidence is available.*

Occupational *allergic* asthma and rhinitis can be found in a large variety of occupational settings such as compost facilities, agricultural and related industries, food industry, detergent industry, medical and public health sector, laboratory animal facilities, bio-pesticide industry, etc. Table 5-7 gives an overview of the most important occupational environments (and most relevant allergens) with an increased risk for occupational allergic asthma and rhinitis. However, many more occupations and industrial environments can potentially contribute to the development of allergic airway diseases, and with the introduction of new industries producing or using products of modern biotechnology (that can potentially act as potent allergens) the number of occupational environments with an increased risk for allergic asthma and rhinitis may even grow. Some of the most widely published examples of occupational allergic asthma include bakers asthma (Houba et al., 1998), latex asthma in health care workers due to the widespread use of latex gloves in health care facilities (Poley and Slater, 2000), and asthma in animal care workers in research institutes (Bush et al., 1998). As noted before, asthma inci-

Table 5-6
Incidence of occupational asthma in various countries, and in different years

Country	Incidence (per 100,000)	Reference
UK	2.0	Meredith, 1993
USA (Michigan)	2.9	Rosenmann et al., 1997
UK (West Midlands)	3.0	Gannon et al., 1991
Finland	3.6†	Keskinen et al., 1978
UK	3.7	Meredith et al., 1996
Germany	4.2†	Baur et al., 1998a
UK (West Midlands)	4.3	Gannon et al., 1993
Canada (Quebec)	6.3	Provencher et al., 1997
Sweden	8.1†	Toren, 1996
Finland	8.1†	Vaarannen et al., 1985
Canada (British Columbia)	9.2	Contreras et al., 1994
Finland	15.0†	Kanerva et al., 1994
Finland	15.2†	Nordman, 1994

†Incidence rates are calculated based on registries for the purpose of compensation for occupational diseases.

Table 5-7
Occupational Type I allergens and occupational environments with increased risk for their workers to develop Type I sensitization and respiratory allergy and asthma

Allergen (source)	Occupational environments with increased risk
Molds	Compost facilities, agriculture and related industries
Microbial enzymes	Biotechnology industry and primary enzyme producers
	Food and feed industry, e.g., bakeries
	Detergent industry
Plant proteins:	
- Pollens of 'new' flowers and vegetables	Agri- and horticulture
- Wheat	Bakery industry
- Soy, corn, etc.	Animal feed industry
- Latex proteins	Medical and public health sector, and other occupations where workers regularly use latex gloves
Mammalian proteins	Animal farming and veterinary occupations
	Pet shops
	Laboratory animal facilities
Invertebrate proteins	Agriculture
	Biopesticides industry (moths, spiders, etc.)

dence and prevalence data are available (Table 5-6), however, it is not clear how many of these asthma cases are attributable to allergic responses.

RECOGNITION AND DIAGNOSIS OF OCCUPATIONAL *ALLERGIC* ASTHMA AND RHINITIS

Before a diagnosis of *allergic* asthma or rhinitis can be made it is necessary to establish whether the worker indeed suffers from asthma or rhinitis (regardless of whether it is caused by allergic or non-allergic mechanisms). A second approach is needed to establish whether allergic or non-allergic mechanisms are involved (non-allergic respiratory diseases will be discussed later in this chapter).

How to recognize and diagnose asthma and rhinitis

There are several simple diagnostic tools available that may help to establish an accurate diagnosis of asthma or rhinitis. When studying a group of workers, a questionnaire may be the first choice. Written questionnaires have been the principal instrument for measuring asthma symptom prevalence in community or occupational surveys, and in homogenous populations these have been standardized, validated, and shown to be reproducible (Burney et al., 1989). A number of symptoms, including wheezing, chest tightness, breathlessness, and coughing (with or without sputum), are recognized by physicians as indicative of asthma. Symptoms such as stuffy, runny, irritative nose, sneezing, and itching, burning, watering eyes are indicative of rhinitis. Table 5-8 gives an overview of relevant questions to diagnose respiratory diseases including asthma (based on modified version of the European Community Respiratory Health Survey (ECHRS) questionnaire (Burney et al., 1994)), rhinitis, bronchitis, and organic dust toxic syndrome (ODTS) (bronchitis and ODTS will be discussed later in the section on non-allergic respiratory diseases). Since respiratory diseases such as asthma and rhinitis involve symptoms that occur from time to time rather than the presence or absence of symptoms on a particular day, most questionnaires define ‘current symptoms’ as symptoms at any time in the previous 12 months (or in case the worker has worked less than a year in his or her current occupation, during the time the worker has been employed in his or her current occupation). In addition to symptom reports occurring at any time in the previous 12 months, it is of interest to ask how often these symptoms occur (e.g., daily/almost daily; 1 to 2 times per week; 1 to 2 times per month, never/seldom).

Most of these questions are not specific for work induced asthma, and thus may also detect asthma that is not work-related or work-related exacerbations of pre-existing asthma. Healthy individuals will reply with ‘never/seldom’ on all questions (although many of them may have had at least some asthma symptoms during the previous year), whereas workers with occupational asthma and rhinitis will answer with at least 1 to 2 times per month for most questions. Depending on exposure levels and severity of the disease, symptoms may occur more frequently. When symptoms disappear or lessen during the weekends and holidays, it is a good indication that symptoms are indeed work-related (workers with non-work related asthma or rhinitis will also express similar symptoms, but symptoms usually do not lessen or disappear during weekends and holidays).

Table 5-8
Suggestions for questions to diagnose or recognise occupational respiratory diseases for use in occupational health surveys

Asthma (including both allergic and non-allergic asthma)*
(Based on modified phase I screening questionnaire for the European Community Respiratory Health Survey (ECRHS); Burney et al., 1994)

1. Have you had a wheezing or whistling in your chest at any time in the last 12 months?
   IF 'NO,' GO TO QUESTION 2; IF 'YES,'
1.1 Have you been at all breathless when the wheeze noise was present?
1.2 Have you had this wheezing or whistling when you did not have a cold?
2. Have you had a feeling of tightness in your chest at any time in the last 12 months?
3. Have you had an attack of shortness of breath at any time in the last 12 months?
4. Have you had an attack of coughing at any time in the last 12 months?
5. Have you had an attack of asthma in the last 12 months?
6. Are you currently taking any medicine (including inhalers, aerosols, or tablets) for asthma?

Allergic rhinitis and mucous membrane irritations*

1. Do you have any nasal allergies, including hay fever (applies only to allergic rhinitis)?
2. Have you had one or more of the following symptoms in the last 12 months: stuffy, runny, irritative nose, or sneezing?
3. Have you had itching, burning, or watering eyes in the last 12 months?
4. Have you had dry cough in combination with nose and eye irritations (applies only to MMI)?

Organic dust toxic syndrome (ODTS)*

1.Have you, during the past 12 months, had sudden episodes of flu-like symptoms such as fever, chills, malaise, muscle or joint pains, and felt completely well within 1 to 2 days?

Bronchitis

1. Do you cough up phlegm almost daily for at least part of the year?
   IF 'YES,'
   1.1 How many months a year do you have this cough?
   1.2 How many consecutive years have you had this cough?

** To assess the severity of the disease (asthma, rhinitis, MMI, or ODTS), the worker could be asked how often these symptoms appear (or how often they use medication), e.g., Daily/almost daily; 1 to 2 times per week; 1 to 2 times per month; never/seldom.*

** To assess whether symptoms are work-related, the workers may be asked whether symptoms disappear during weekends and holidays.*

Questionnaires are useful for epidemiological surveys, but are a crude measure in clinical practice. Often a more objective assessment, such as lung function testing using a spirometer, is required to diagnose asthma. Cross-shift lung function tests repeated through the workweek are preferred (e.g., Mondays after a weekend or holiday, Wednesday, and Friday). Cross-shift decrease in forced expiratory flow in one second (FEV_1, a good lung function parameter to assess airway obstruction; see chapter 1 for more details) on workdays is a good indication of asthma. Acute airway obstruction can (instead of measuring FEV_1 using spirometry) also be monitored by measuring peak flow (PEF) using portable peak flow meters. Workers can self-monitor their peak flow during the day for one or more weeks (including the weekends, allowing the assessment of work related patterns). In order to detect occupational asthma, a PEF reading should be performed at least every third hour and during (or shortly after) attacks of wheeze and cough, starting in the morning before work, during the workday, and after work until bedtime. It is imperative that there is a thorough instruction, and that people are informed that missing readings are expected in order to avoid false recordings (Sigsgaard et al., 1994). Although portable peak flow meters are not as accurate as a spirometer, they are an excellent tool in the recognition of occupational asthma since many measures of one individual can be obtained over a long period. In addition, they are cheap and easy to use, making them suitable instruments for surveys among large groups of workers. Peak flow meters have successfully been used in a large number of studies to show work related airway obstruction (both allergic and non-allergic; Hollander et al., 1998; Zock et al., 1998). Repeated nasal peak flow measurements performed by the subjects on themselves can be used to assess an increase in nasal resistance indicating work related rhinitis.

How to diagnose whether symptoms of asthma and rhinitis are type I allergic symptoms

Once it is established that the worker is suffering from asthma or rhinitis, it is important to assess whether the symptoms are induced by allergic (IgE mediated) or non-allergic responses. Recognition of work-related type I or IgE mediated allergic respiratory symptoms such as *allergic* asthma and rhinitis can be based on their typical features as discussed in previous paragraphs. A systematic approach may comprise the following steps:

1. Evaluation of the presence of allergens at the workplace. Are substances handled that have known or suspected allergenic properties? In addition to the well-known bio-allergens (see Table 5-7), attention should be given to the use of 'new' proteins, e.g., recently introduced enzymes or other products of modern biotechnology.

2. Evaluation of the risk of exposure. Is airborne dispersion of allergens, as dust particles or mists, likely, and if so, during which job tasks or work conditions?

3. Are symptoms compatible with typical type I allergy as described for allergic asthma and rhinitis? Do they occur in direct association with possible allergen exposure, i.e., during or shortly after the tasks or other activities identified in step 2?

4. Are workers with symptoms specifically sensitized to the suspected allergen, and is sensitization rare among workers without symptoms? When no *in vivo* or *in vitro* test is available, do workers with symptoms show a typical 'risk profile', including atopy, BHR, and/or a history of allergic respiratory disease?

Diagnostic tools for recognizing occupational type I allergy are summarized in Table 5-9.

For individual patients, the physician's diagnosis of 'occupational type I allergy' is usually based on the combination of symptoms and a positive skin prick test (SPT) or serum IgE test using the occupational allergen. As indicated earlier, this can be very difficult if the allergen has not been specifically identified or isolated for testing. However, for the most common occu-

Table 5-9
Diagnostic tools to assess occupational Type I (IgE-mediated) allergy

- *symptoms*
  - typical symptoms of upper or lower respiratory allergy
  - symptoms during or shortly after work with suspected allergen
- *demonstration of occupational sensitization*
  - serologic IgE test
  - skin prick test (SPT)
- *systematic evaluation of symptoms in time*
  - diaries recording monitoring of symptoms and job tasks
  - PEF recordings
- *allergen-specific provocation*
  - nasal provocation: symptoms, acoustic rhinometry
  - bronchial provocation: lung function, symptoms

pational allergens, test kits for specific IgE in serum or SPT are available commercially. Although these tests can give a good indication, they do not prove or disprove an etiologic role for occupational allergen exposure and sensitization.

If strictly required (e.g., because of workers' compensation), such proof can be provided by a rigorously controlled allergen provocation test, which may be considered as the 'gold standard.' In such a test, respiratory and other symptoms, lung function, etc. are monitored during and after provocation in an exposure chamber with graded doses of aerosolized allergen. This is a procedure that should be performed under strict medical supervision because of the risk of severe anaphylactic reactions, or of life-threatening broncho-obstruction. Alternatively, as noted before, systematic evaluation of symptoms and/or lung function may be performed with the use of diaries and peak flow meters or other devices for self-monitoring of lung function. This approach can be very useful to demonstrate the work- and task-related effects of certain allergenic exposure on the airways.

A third possibility to confirm the diagnosis of allergic asthma or rhinitis is the demonstration of clinical improvement when the worker is away from work. However, if a patient with suspected occupational allergy shows non-specific airway hyperreactivity, and the workplace is also characterized by exposure to dust, fumes, or other irritants, the beneficial effect of absence from work is not necessarily due to reduced allergen exposure but could be related to non-allergens. Thus, clinical improvement after implementation of more specific measures to reduce allergen exposure (e.g., replacement of certain enzyme-containing preparations, technically improved application systems using solutions and no dry powders, closed systems, or improved ventilation at sites of allergen handling) is much stronger evidence, and also allows the worker to continue his or her present job at the same, but improved, occupational environment.

Often, one diagnostic tool will not give a satisfying diagnosis, and more options have to be explored.

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HP) is a generic term used to describe an acute, subacute, or chronic pulmonary condition with delayed febrile systemic symptoms, manifested by an influx of inflammatory cells and the formation of granulomas in the lung parenchyma (Curtis and Schuyler, 1994). HP is also known as Extrinsic Allergic Alveolitis (EAA), and, depending on the specific work environment where the disease has been observed, various other names have been introduced to describe the disease (e.g., farmer's lung, pigeon breeder's lung, mushroom grower's lung, maple bark stripper's disease, etc.). Symptoms characteristic for HP are very similar to those described for non-allergenic organic dust toxic syndrome (ODTS, described later in this chapter). The most important differences between both diseases have been summarized in Table 5-10, and will be discussed in the section on ODTS.