

Review article

Occupational asthma

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The respiratory diseases that may be contracted as a consequence of exposure to sensitizing agents in the workplace are rhinitis, asthma, and hypersensitivity pneumonitis. These diseases are mainly allergic in nature, though different immunologic mechanisms may operate. The importance of irritant exposures, however, should not be underestimated. In fact, there is no information on the relative contribution of irritant and immunologic mechanisms, and a possible synergistic effect between them should be considered. Because of the enormous amount of information on these diseases, this article focuses on occupational asthma (OA).

OA has been defined as variable airway narrowing causally related to exposure in the working environment to airborne dusts, gases, vapors, or fumes (1). A more recent definition (2) stated that OA is a disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular environment, and not to stimuli encountered outside the workplace. This includes two main subgroups:

- 1) OA with a latency period, which is the most common type of OA and includes all instances of immunologic asthma
- 2) OA without a latency period, which is best illustrated by irritant-induced asthma or the reactive airways dysfunction syndrome (RADS).

The second form of OA was first described by Brooks et al. (3), and comprehensive reviews have been published (4, 5).

Epidemiology

OA has become the most common form of occupational lung disease in many industrialized countries. OA accounted for 26% of all occupational or work-related respiratory diseases in the UK (6) and for 52% of the cases in British Columbia, Canada (7). However, a few studies have aimed to measure the frequency in the general population of asthma that is attributable to occupation. A survey in the USA showed that 15.4% of all cases of asthma are due to workplace exposure (8). In a population-based study in Spain, the risk of adult onset asthma attributed to occupational exposures was 6–9% (9). The frequency of OA, however, varies among types of industries, and it depends on the physicochemical properties of the inhaled agent, level and duration exposure, host factors, and industrial hygiene practices. Since most current epidemiologic studies of OA are of a cross-sectional nature, estimates of prevalence may be distorted by survivor effects, causing workforce selection. Incomplete ascertainment and reporting are other causes of bias in prevalence rates (10).

Etiopathogenesis

About 250 agents encountered at work have been reported to induce OA in susceptible workers (11, 12), and this number will probably continue to increase as new materials are introduced. These agents can be broken down into three major categories according to their pathogenesis. In some circumstances, several mechanisms may be impli-

Table 1. Common causative agents of OA and occupations at risk

Mechanism	Type of agent	Causative agent	Occupations
Immunologic IgE-dependent	High-molecular-weight agents	Animal urine or dander	Animal handlers, veterinarians
		Cereal and soya flour	Bakers, millers
		Grain dust	Grain-store workers, farmers
		Enzymes	Bakers, pharmaceutical workers
		α-Amylase, cellulase, papain, pepsin, <i>B. subtilis</i> -derived	Pharmaceutical and food workers
		Tropical woods	Detergent industry workers
		Gums (acacia, guar)	Sawmill workers, carpenters
		Psyllium	Printers, carpet manufacturers
		Seafood proteins	Pharmaceutical workers, nurses
		Locusts	Seafood processors
		Chironomids	Laboratory workers, scientists
		Egg proteins	Fish breeders, fishermen
		Casein, lactoserum	Egg-processing workers
		Storage mites	Diary workers, tanners
		Latex	Farmers, Grain-store workers
		Ornamental plants	Health-care workers, manufacturers
		Weeping fig	Plant-releasing workers
		Statice	Florists, gardeners
		Baby's breath	Florists
		Cochineal	Natural dye and food processors
		Henna	Hairdressers
		Castor bean	Oil industry workers, dock workers
		Green coffee bean	Coffee roasters
		Fresh vegetables	Homemakers, horticulturists
Immunologic IgE-dependent	Low-molecular-weight chemicals (haptens)	Acid anhydrides	Plastic, epoxy resin workers
		Platinum salts	Platinum-refinery workers
		Reactive dyes	Textile and dyeing workers
		Chloramine T	Beverage and chemical manufacturers
		Persulfate salts	Hairdressers
Immunologic (cell-mediated?)	Low-molecular-weight chemicals	Diisocyanates	Polyurethane, foundry workers, painters
		Western red cedar	Sawmill workers, carpenters
		Amines	Photographers, shellac workers, chemists
		Colophony	Electronic workers, welders
		Azobisformamide	Plastic, rubber workers
		Diazonium salts	Photocopy paper processors
		Acrylates	Health-care and plastic workers
		Cobalt	Diamond polishers, hard-metal grinders
Nonimmunologic (toxic effect)	Low-molecular-weight chemicals (irritants)	Chlorine	Pulp mill and chemical workers
		Nitrogen oxides	Pyrite workers, miners
		Sulfur dioxide	Spray painters, chemical workers
		Ammonia	Cleaners, chemical workers
		Carboxylic acid	Firemen, policemen
		Sodium fumes	Hospital employees
		Smoke	Spray painters, polyurethane workers
		Acetic acid	
		Diisocyanates	

cated. Irrespective of the pathogenetic mechanism, pathologic changes in the airways are similar to those observed in other forms of asthma (13). Table 1 shows the more common causative agents and occupations at risk of OA.

IgE-dependent mechanism

Most high-molecular-weight occupational agents (>5 kDa) induce asthma through an IgE-mediated mechanism. High-molecular-weight agents are mainly proteins that may act as complete antigens and stimulate IgE synthesis. Some low-molecular-weight chemicals (<5 kDa), such as acid anhydrides (14), platinum salts (15), and persulfate salts (16), may act as haptens and stimulate IgE production by combining with a protein to form a hapten-protein conjugate.

Inhaled sensitizing agents bind to specific IgE on the surface of mast cells and basophils. The interaction between antigen and IgE causes the cascade of events that is responsible for the activation of inflammatory cells and for the synthesis and release of a wide variety of preformed or newly formed inflammatory mediators that trigger the inflammatory reaction in the airways.

IgE-independent mechanisms

Many low-molecular-weight compounds induce asthma, probably by IgE-independent immunologic mechanisms, although the precise pathogenesis is unclear. Cell-mediated hypersensitivity may be directly involved in mediating the inflammatory response in the airways leading to OA caused by these agents (17). In addition to their role as helper

cells for the production of antibodies by B cells, activated CD4⁺ lymphocytes may be considered inflammatory cells that secrete interleukin (IL)-5, which is specific in promoting the development and activation of eosinophils, and which is the main eosinophil-active cytokine present in bronchoalveolar fluids during allergen-induced late-phase inflammation (18). An increased number of activated T cells (expressing the IL-2R), activated eosinophils, and mast cells have been observed in patients with OA induced by some low-molecular-weight compounds (19–21). Circulating CD8⁺ lymphocytes and eosinophils have been shown to increase significantly 48–72 h after a specific inhalation challenge with toluene diisocyanate (22).

Irritant (toxic) mechanisms

Agents that induce asthma through nonimmunologic mechanisms are mostly irritant gases or vapors, solid particles, or liquid aerosols that cause a direct toxic effect on the airways (5). Solubility and particle size are the key factors in determining the site of deposition of irritant aerosols in the respiratory tract (particles of 0.5–5 µm are respirable). A high-level irritant exposure may initiate airway injury with massive epithelial damage and disruption. Possibly this is followed by direct activation of nonadrenergic, noncholinergic pathways, promulgating axon reflexes and causing neurogenic inflammation. Injured bronchial epithelial cells emit inflammatory chemotactic factors. Nonimmunologic release of mast-cell contents occurs, and microvascular exudation enhances inflammatory cell recruitment (23).

Determinants of OA

Although many factors influence the host response after exposure to workplace agents, four determinants have received particular attention (24).

Exposure

The physicochemical properties of the inhaled substance, duration and intensity of exposure, and conditions of use are important elements in the development of respiratory sensitization. The intensity of exposure necessary for initial sensitization is probably higher than that required to provoke symptoms in the sensitized subject (24). Several studies have demonstrated a relationship between indices of exposure to a sensitizing agent and work-related respiratory symptoms or bronchial hyperresponsiveness (25–27). In a study of hospital employees accidentally exposed to glacial acetic acid, the risk of irritant-induced asthma increased with the degree of exposure (28).

Cigarette smoking

Cigarette smokers run an increased risk of sensitization and of asthma caused by an IgE-mediated mechanism. An association between smoking and OA has been found in workers occupationally exposed to platinum salts (29), snow crab (30), tetrachlorophthalic anhydride (31), green coffee bean, and ispaghula (32). The direct irritant effect of cigarette smoke on the bronchial mucosa may allow inhaled allergens increased access to submucosal immunocompetent cells.

Atopy

Atopic workers, identified by positive skin prick tests to common aeroallergens, are at increased risk of asthma due to high-molecular-weight occupational agents. For instance, atopic personnel who work with laboratory animals are more likely than nonatopic personnel to develop OA (33). On the other hand, atopic personnel are not at increased risk of developing OA due to low-molecular-weight compounds that do not induce an IgE response, such as plicatic acid (34) and isocyanates (35).

Genetic predisposition

Several genetic factors are probably responsible for allergen sensitization, which is determined and restricted by HLA genotype. Allergy to laboratory animals has been associated with HLA B15 and DR4 (36), and sensitization to trimellitic anhydride with HLA DR3 (37). Individuals with HLA DQB1*0503 were found to be predisposed to isocyanate-induced asthma, whereas those with HLA DQB1*0501 were protected (38).

Clinical features

OA caused by immunologic mechanisms develops after a latency period of exposure varying from a few weeks to several years. Subsequent exposure to very low concentrations of the causative agents elicits asthma symptoms. Patients with OA with a latency period show marked clinical improvement, at least at initial stages of the disease, during weekends and holidays. Nose and ocular allergic symptoms usually precede and accompany asthma symptoms (13). Patients with irritant-induced asthma develop persistent respiratory symptoms and airway hyperresponsiveness within a few hours of exposure to an identifiable irritant, usually as a consequence of an accident or spill in the workplace (5). This type of asthma might also develop after several episodes of toxic exposure rather than a single accident (39). Patients with irritant-

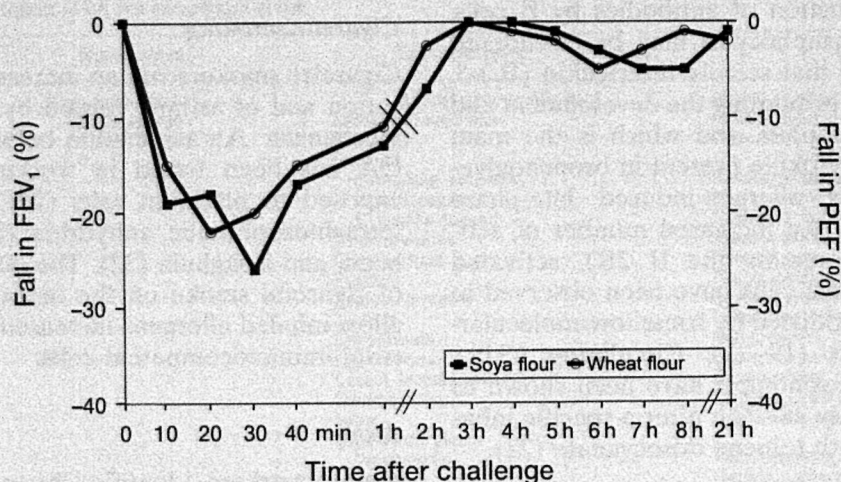


Fig. 1. Early asthmatic response in baker after bronchial challenge with wheat flour and soya flour. Wheat flour challenge was performed in chamber with monitoring of dust concentration (3 mg/m^3 for 30 s).

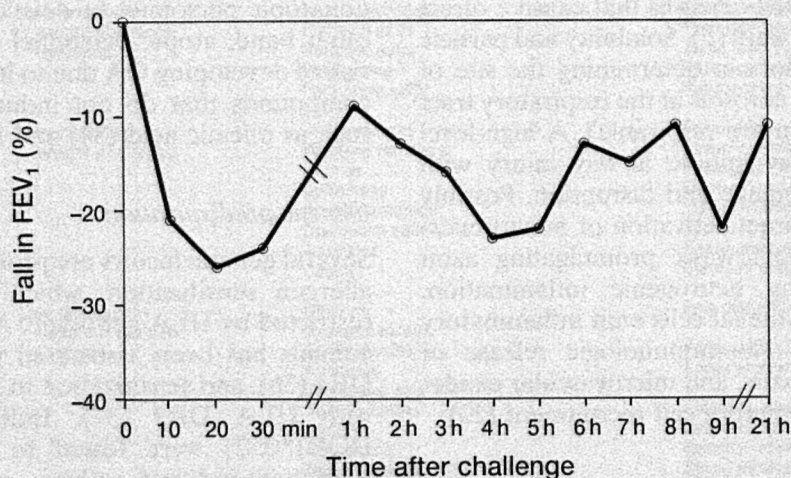


Fig. 2. Dual asthmatic response after challenge with sodium persulfate extract in hairdresser showing positive skin test to this compound.

induced asthma have less reversibility in their airflow obstruction than patients with OA with a latency period, a characteristic which is probably due to distinct pathologic changes in the airways (40).

Diagnosis

The diagnosis of OA requires both the diagnosis of asthma and the establishment of work-relatedness by objective means. Guidelines for the diagnosis of OA have been published (41, 42). The clinical history should include detailed questioning of the circumstances of the onset and severity of asthma symptoms, temporal relationships between occupational exposures and disease exacerbations, and course of the disease. However, the clinical history

is more reliable at excluding than at confirming the diagnosis of OA (43). The assessment of occupational exposure is an important step in the evaluation of the contribution of the workplace to a patient's asthma. Information from the work site can be obtained by a walk-through visit and by consulting industrial hygiene data and material safety data sheets. In special circumstances, air sampling by area or personal sampling pumps can be monitored by qualified personnel. Serial monitoring of peak expiratory flow for periods at work and off work was first used as a diagnostic tool in OA by Burge et al. (44), and it has been found to be both sensitive and specific in the diagnosis of OA (45, 46). The main pitfall of this method is the patient's noncompliance and possible malingering (47).

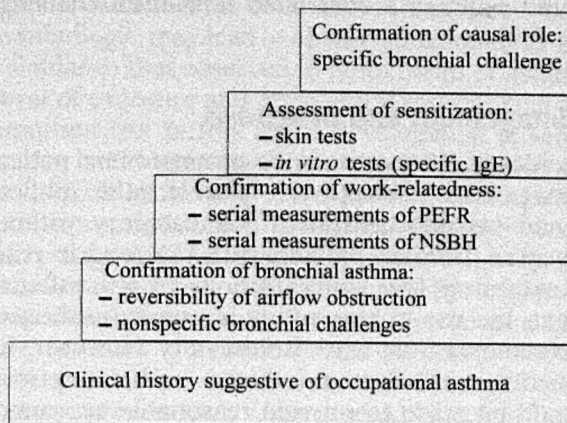


Fig. 3. Stepwise sequence for diagnosis of occupational asthma as suggested by EAACI (ref. 41). PEFR: peak expiratory flow rate; NSBH: nonspecific bronchial hyperresponsiveness.

This problem may be overcome either by using computerized peak flow meters (47) or by measuring nonspecific bronchial hyperresponsiveness when the patient is at work and away from work (45). Recently, a position statement on self-monitoring of peak expiratory flow in the investigation of OA has been published (48). For agents that act through an IgE-mediated mechanism, skin testing or serologic measurement of specific IgE antibodies can be used to assess sensitization, provided a suitable preparation of allergen is available. Unfortunately, most occupational antigens are not standardized, and information on the sensitivity and specificity of prick or intradermal tests is not available.

Specific inhalation challenge tests have been proposed as the "gold standard" in the diagnosis of OA. These tests are indicated in studying new causes of OA and in determining the precise etiologic agent, as well as for research on the mechanisms of OA. Sophisticated equipment and trained personnel are necessary to perform these challenge tests in order to ensure safety for patients and supply reliable results (49, 50). Bronchial challenge procedures have been recently reviewed in Europe (51, 52). Specific inhalation challenge tests may induce isolated early (Fig. 1), isolated late, dual (Fig. 2), or continuous asthmatic reactions (53). A stepwise procedure for the diagnosis of OA has been suggested by the Subcommittee on Occupational Allergy of the European Academy of Allergology and Clinical Immunology (EAACI) (41) (Fig. 3).

Selected causative agents

Cereal flour and dust

The prevalence of asthma among bakers has been shown to be around 10%. Most cases of OA are

elicited by IgE-mediated respiratory sensitization to both water-soluble and water-insoluble cereal proteins contained in flour (54, 55). However, flour from other sources, such as buckwheat (56), *Lathyrus sativus* (57), and soybean (58), may also cause OA. Several organic contaminants such as storage mites, fungi, and insects, as well as flour additives, particularly α -amylase, can also cause OA among bakers and cereal handlers (58–62). A relationship between the concentration of airborne flour (63) or α -amylase (64) and the development of a positive skin prick test or work-related respiratory symptoms has been reported.

Latex

Natural rubber latex is obtained from the tropical tree *Hevea brasiliensis* and contains a polymer of *cis*-1,4-polyisoprene and about 1.5% proteins. In recent years, immediate-type allergy to latex has been acknowledged as a major occupational problem among glove-wearing health-care workers, kitchen workers, housekeeping personnel, and workers in industries that manufacture latex products (65). IgE-mediated respiratory sensitization to this antigen has been recently reported (66–70). Tarlo et al. (66) surveyed a rubber-processing plant, finding 11% prevalence of immediate skin reactivity to latex and 6% prevalence of OA. Vandenplas et al. (71), using specific inhalation challenges found a 2.5% prevalence of OA among 273 hospital employees. Because of the widespread use of powdered gloves, latex is a common aeroallergen in medical centers (72). Reductions in exposure to latex proteins have been reported to be associated with decreased sensitization and symptoms (73, 74).

Wood dusts

Several wood species have been identified as etiologic agents in OA. Western red cedar-induced asthma has been studied extensively, and plicatic acid (440 Da) has been found to be the causative agent (75). The pathogenic mechanism, however, is not entirely clear. Chan-Yeung et al. (76) found a prevalence of OA of 4.1% in cedar sawmill workers. There is a good correlation between the prevalence of work-related asthma and the level of dust exposure (77). Other types of wood dust, such as African maple and ramin wood, have been shown to cause OA through an IgE-mediated mechanism (78, 79).

Acid anhydrides

Acid anhydrides (e.g., phthalic anhydride, trimellitic anhydride, tetrachlorophthalic anhydride) are used in alkyd and epoxy resins and can give rise to

hypersensitivity reactions in exposed workers. They act as haptens and combine with self-proteins to form conjugates, with IgE antibodies recognizing the hapten or conformational new antigenic determinants in the self-proteins (80). Trimellitic anhydride has been shown to cause rhinitis and asthma, late respiratory systemic syndrome, and pulmonary disease-anemia syndrome (81). The prevalence of immunologic lung disease caused by trimellitic anhydride was 6.8% among workers at a chemical plant (82).

Isocyanates

Isocyanates are a group of highly reactive, low-molecular-weight chemicals mainly used in the polyurethane industry and in the production of finish coatings. Polyisocyanates and their prepolymers are considered a leading cause of OA (83). A common feature of these compounds is the presence of an $-N=C=O$ group, making them very reactive and capable of forming plastics, adhesives, and elastomers in flexible or rigid form. The most important related compounds are 2,4- and 2,6-toluene diisocyanate (TDI), hexamethylene diisocyanate (HDI), and methylene diphenyldiisocyanate (MDI). Although the incidence of isocyanate induced-asthma varies widely depending on the form of diisocyanate and type of exposure, it is accepted that about 5–10% of exposed workers develop asthma. For those diisocyanates more volatile at room temperature (TDI, HDI), the prevalence is considered higher than for MDI or polyisocyanates. The exposure threshold limit has been set at 20 ppb (0.14 mg/m^3) as a ceiling concentration (11). Exposure to high levels in industrial accidents or spills may induce asthma similar to that induced by other agents that cause RADS (84).

The mechanism of diisocyanate-induced OA is not known. It has been attributed to specific IgE antibodies, reflex and pharmacologic stimuli, release of histamine and neuropeptides, β -adrenergic blockade, and type IV cellular hypersensitivity (85, 86). Specific IgE antibodies to a protein conjugate of monoisocyanate have been found in 10–20% of symptomatic workers (83). There is some evidence that IgE antibodies and lymphocytes may react to a neoantigen formed by a reaction of these compounds with self-proteins (87). The pathologic condition of lungs in patients with diisocyanate-induced asthma was no different from that in allergic asthma (88). Personal history of atopy and smoking are not considered risk factors for the disease. Clinical diagnosis of diisocyanate-induced OA may be difficult. In many cases, a confirmatory diagnosis with identification of the offending com-

pound requires a controlled inhalation challenge test (89).

Management and prognosis

Avoidance of exposure is the cornerstone of patient management. Whenever feasible, the patient should be relocated to a job category without exposure. Because patients with OA tend to react to extremely low concentrations of a sensitizing agent, the use of respirators is usually ineffective and removal from work is necessary. However, for patients with irritant-induced asthma, efforts should be made to provide reasonable accommodation by improving ventilation in combination with the use of respiratory protective equipment. The pharmacologic treatment of OA does not differ from the therapy of other types of asthma. A significant proportion of patients with OA continue to experience asthmatic symptoms and non-specific bronchial hyperresponsiveness after removal from occupational exposure (90). The persistence of asthma is associated with eosinophilic inflammation of the airways even after cessation of exposure (21, 91). The determinants of an unfavorable prognosis are as follows: long duration of exposure before the onset of asthma, long duration of symptoms, degree of airways obstruction at time of diagnosis, and the persistence of markers of airway inflammation in bronchoalveolar lavage fluid and bronchial biopsy (90). Treatment with inhaled corticosteroids significantly reduces bronchial hyperresponsiveness only if started immediately after diagnosis. Two years or more after removal from exposure to the offending agent, about 60% of subjects show a decrease but a persistence of specific bronchial responsiveness to high- and low-molecular-weight agents (92).

Impairment and disability evaluation should be carried out as soon as the asthma is stabilized (temporary) and 2 years later (permanent) (93), and patients should be counseled regarding compensation. There are no European guidelines for the assessment of impairment and disability and for compensation of OA; the criteria depend on national laws (94). OA results in severe socioeconomic consequences, with approximately 50% of patients suffering a reduction in income 3 years after the diagnosis was made (95).

Concluding remarks

OA has become the most common occupational lung disease in developed countries, resulting in severe socioeconomic and medicolegal consequences. More than 250 compounds have been identified as causative agents, and several patho-

genetic mechanisms, both immunologic and non-immunologic, may lead to airways inflammation that is similar to that observed in other forms of asthma. Level of exposure and often atopy and smoking are important risk factors in the development of sensitization and respiratory symptoms. Diagnosis may be difficult without a low threshold of suspicion and appropriate use of available diagnostic tests. Early diagnosis and removal from exposure are the most important factors for improving the long-term prognosis. Efforts should be made to reduce exposure (primary prevention) and to detect asthma early and minimize its duration and severity (secondary prevention). Appropriate medical care should be provided in order to prevent deterioration and complications in patients with established OA (tertiary prevention). It is recommended that European regulatory or advisory bodies with responsibility for OA release guidelines on diagnosis, assessment of impairment/disability, and compensation programs for patients with OA.

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