



Occupational asthma caused by high-molecular-weight substances

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Occupational asthma can be defined as asthma that is induced by inhaled agents encountered in the workplace. It should be distinguished from preexisting asthma, which may be exacerbated by exposure to industrial materials. The overall prevalence of occupational asthma is difficult to determine; however, surveys suggest that 2% to 15% of cases of asthma may be occupational [1,2]. The incidence of disease varies among industries and is dependent on the physiochemical properties of the agent, the level and duration of exposure, industrial hygiene, engineering practices, and host factors (Table 1).

More than 250 agents encountered in the workplace have been shown to induce asthma in susceptible individuals. Substances range from very-low-molecular-weight inorganic chemicals to complex organic macromolecules. This article discusses occupational asthma that is caused by high-molecular-weight substances.

Mechanisms

Immunoglobulin E-mediated hypersensitivity

High-molecular-weight substances, such as plant and animal proteins, enzymes, and large carbohydrate molecules, can induce an immunoglobulin E (IgE) response in susceptible individuals and cause asthma by an IgE-mediated mechanism.

In type I IgE-mediated reactions, mast cell degranulation is triggered by the bridging of IgE molecules by antigen. This bridging initiates a series of intracellular enzymatic events that culminates in the release of granule-stored medi-

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Table 1
Incidence of occupational asthma in industrial workers

Substance	Workers (%)	Reference
High molecular weight		
Various flours	10	[85]
Animal allergens	2–3	[31]
Snow-crab allergens	16	[51]
Latex	4.5	[34]
Low molecular weight		
Platinum salts	50	[86]
Acid anhydrate	20	[60]
TDI	5	[84]
Western red cedar	5	[83]

ators, including histamine, chemotactic factors for eosinophils and neutrophils, and several proteoglycans. The formation and release of leukotrienes and prostaglandins from membrane phospholipids also occur. These mediators affect smooth muscle tone, vascular permeability, airway mucus production, and cell migration and cause symptoms of asthma. IgE-mediated occupational asthma shares characteristics with asthma caused by common allergens: Only a small proportion of exposed individuals develop symptoms; there is a latent period of several weeks to years before the development of symptoms; and once occupational asthma develops, symptoms occur early after allergen exposure.

Non-immunoglobulin E-mediated immunologic mechanisms

The role of other immunologic mechanisms in occupational asthma induced by large molecules has not been established clearly. Antigen-specific IgG and IgM antibodies have been detected in sensitized workers; these antibodies are not associated commonly with asthma [3,4] but may have a role in other immunologically induced pulmonary diseases, such as hypersensitivity pneumonitis. The in vitro demonstration of activation of the alternative pathway of complement by certain occupational agents [5,6] has led investigators to propose that this antibody-independent mechanism also may have a pathogenic role in occupational asthma.

Risk factors

Factors that increase the risk for occupational asthma can be divided into two categories: host factors and industrial factors. Only a small proportion of workers develops occupational asthma, emphasizing that host factors are important in the development of the disease. Certain occupations increase the risk. Laboratory workers, spray painters, bakers, plastic workers, electronic workers (eg, welders, solderers, assemblers), farmers, and woodworkers are at higher risk for occu-

pational asthma compared with other workers in other industries. The risk for occupational asthma among healthcare workers has increased because of increased latex exposure. Industrial factors include the characteristics of the agent and the duration and intensity of exposure.

Atopy

Atopic individuals have a personal or family history of hay fever, asthma, or atopic eczema and a tendency to develop specific IgE antibodies after exposure to common environmental substances. Atopic individuals respond with immediate wheal and flare reactions after undergoing skin tests with appropriate inhalant allergens and tend to have elevated total serum IgE levels. In industries in which high-molecular-weight proteins or related organic compounds are employed, atopy is often a predisposing factor for the development of occupational asthma [7–10].

Nonspecific bronchial hyperreactivity

Increased airway responsiveness to a variety of chemical and physical stimuli is a characteristic feature of asthma. Airway hyperreactivity can be detected in up to 50% of patients with rhinitis and in some patients with chronic bronchitis and other pulmonary diseases. It also can be detected in a small percentage of normal individuals and is present in patients with occupational asthma.

The relationship between airway hyperreactivity and the development of occupational asthma is not clear. An important question is whether airway hyperreactivity predisposes a worker to the development of occupational asthma or whether airway hyperactivity develops concomitantly with exposure. In one typical study, asthma and persistent postexposure airway hyperreactivity developed in workers with no previous history of asthma who worked with western red cedar [11]. Butcher and associates demonstrated that airway hyperreactivity and toluene diisocyanate (TDI)sensitivity returned to normal after a patient with TDI sensitivity was removed from the TDI-containing area of the factory [12]. Hargreave and co-workers reported that airway hyperreactivity developed in some workers with western red cedar asthma after repeated exposure to the agent; the hyperreactivity ceased after a period without exposure [13]. Chan-Yeung and Desjardins prospectively studied four workers who developed western red cedar asthma [14]. Nonspecific airway hyperreactivity and asthma developed concomitantly, and the hyperreactivity was not present in any workers before the asthma symptoms developed. These observations suggest that airway hyperreactivity is not a prerequisite for the development of occupational asthma but that hyperreactivity develops as a result of exposure to an occupational agent.

High-molecular-weight occupational antigens

Many high-molecular-weight antigens are encountered in the workplace (Table 2) [15]. Common antigens include those from plant proteins, latex, soybean dust, and animal proteins.

Plant proteins

Bakers' asthma

Bakers' asthma is one of the most common causes of occupational asthma worldwide. It is mediated by specific IgE sensitization to wheat, rye, barley, buckwheat, or soybean flours. In a study of 405 bakers who complained of work-related symptoms, 60% of participants were sensitized to wheat flour, 57% were sensitized to rye flour, and 22% were sensitized to the enzyme α -amylase from *Aspergillus oryzae* [16]. There is significant cross-reactivity between wheat, rye, barley, and oat flours, as shown by RAST inhibition studies [17]. Exposed workers frequently develop IgE antibodies against a variety of cereal proteins.

Members of the α -amylase inhibitor family include some of the most important and best-characterized allergens in cereal flour and demonstrate significant cross-reactivity among wheat, barley, and rye [18]. The family of the α -amylase inhibitor compounds is composed of enzymes that inhibit insect and mammalian α -amylases and trypsin. These enzymes seem to have a role in defending plants against parasites and other insults.

Table 2
High-molecular-weight allergens

Substance	Industry	Source
Animal protein	Laboratory	Rat, mouse, guinea pig, insects
	Dairy	Cow, poultry
	Poultry	Northern fowl mite (<i>Ornithonyssus sylviarum</i>)
	Citrus	Citrus red mite (<i>Panonychus citri</i>)
	Seafood processing	Crab, prawn, oyster, fish
	Greenhouse	Two-spotted spider mite (<i>Tetranychus urticae</i>)
	Bait	Mealworm
	Sericulture	Silkworm
	Sewer	Sewer fly (<i>Psychoda alternata</i>)
Plant protein	Baking	Wheat, barley, rye, and soy flours; grain
	Healthcare, latex manufacturing	Latex
	Healthcare	Psyllium (ispaghula husks)
	Stevedoring	Soybean dust, green coffee dust, castor bean dust
		<i>Aspergillus</i> spp
Enzymes	Baking	<i>Bacillus subtilis</i>
	Detergent manufacturing	Pancreatin (amylase, lipase, trypsin)
	Pharmaceutical	Bromelain, papain
	Laboratory	

Bakers are exposed to other grain flours, such as soybean flour [19], and to numerous additives used to improve the properties of the flour, such as α -amylase, hemicellulase, cellulase, and glucoamylase enzymes, all of which are derived from *Aspergillus*. Bakers also may become sensitized to contaminants, such as storage mites, fungi, and insect debris.

Latex allergy

Natural rubber latex (NRL) is derived from the milky fluid of the rubber tree (*Hevea brasiliensis*) and is used in the manufacture of a variety of medical devices and everyday articles. IgE-mediated hypersensitivity reactions to latex have become an important medical problem worldwide. Although the prevalence of latex allergy in the general population is less than 1% [20], rubber-industry and healthcare workers are at risk for latex allergy in their occupational settings.

Natural rubber latex-induced occupational asthma is an IgE-mediated process that is initiated by the deposition of allergen-bearing airborne particles onto the mucosal surfaces of the respiratory tract. More than 50 peptides have been identified in NRL that bind IgE in patients with latex allergy [21]. In healthcare workers, the reported prevalence of sensitization has been between 5% and 15%, and the risk is associated with the degree of exposure. Although the available data for latex-induced respiratory disease are comprised largely from case reports and case series, it is estimated that among exposed healthcare workers with positive skin test responses to NRL, 41% to 69% have respiratory symptoms with exposure [22–24]. In workers who are sensitized to NRL and who report symptoms of rhinoconjunctivitis after using latex gloves, the concurrent prevalence or risk for asthma caused by glove exposure is approximately 18.4%, or nearly 1 in 5 [24–30]. This prevalence or risk is approximately half the concurrent risk for asthma symptoms associated with rhinoconjunctivitis in laboratory workers with sensitivity to animal dander. This lower risk for associated asthma may be explained by the fact that less than 20% of airborne NRL allergen is bound to particles that are less than 7 μm in size [31]. Most allergens from laboratory animals are bound to particles less than 7 μm , allowing deposition on the mucosal surfaces of the trachea, large airways, and more peripheral regions of the lungs [32,33]. The cumulative incidence of probable occupational asthma to latex in one study was 4.5% [34].

Individuals who are at risk for NRL occupational asthma include healthcare workers who are exposed to powdered NRL gloves and workers in industries in which latex products are manufactured, including the workers who collect and process latex from rubber trees [21,35,37]. Other risk factors for IgE sensitization to NRL include atopy and possibly race (nonwhite) and male sex [38]. Whereas the exposure–response relationship for IgE sensitization to NRL clearly is associated with the number of surgical procedures and operations in children with spina bifida [39], this relationship in healthcare workers is controversial [38,40]. Although NRL exposure occurs by numerous routes, most studies of allergen exposure in occupational asthma measure airborne exposure levels. The use of powdered latex gloves is associated with higher levels of airborne

cornstarch-associated latex allergen [41]; powdered latex gloves also are associated with increased levels of sensitization [42]. Baur and colleagues have suggested that airborne NRL allergen levels in excess of 0.6 ng/m^3 are associated with sensitization and related symptoms [43,44]. Contact exposure by way of nonrespiratory routes, such as the skin, is also likely to be important in sensitization to NRL [36].

Exposure to latex allergens can be reduced significantly in the occupational environment by a few simple measures. The use of low-allergen-containing latex gloves reduces the level of latex aeroallergen by more than 10-fold in operating rooms [45]. The use of powder-free latex gloves reduces latex aeroallergens to undetectable levels ($<0.02 \text{ ng/m}^3$) [41]. Improvement in asthma severity in sensitized individuals has been documented with these measures [46].

Asthma related to soybean dust

Exposure to soybean dust has been associated with outbreaks of asthma during the unloading of soybeans in harbors and with isolated cases of asthma in farmers and exposed workers [47]. Studies identified a 14-kD glycoprotein in the soybean hull as the main allergen in soybean dust-related asthma [48,49]. This allergen is different from the allergen responsible for causing food allergy to soy. In evaluating the possibility of soybean dust sensitization, it is important to consider that stored grains may be contaminated by other antigens, such as mites, bacteria, fungi, and insects.

Animal proteins

Seafood processing

Allergic sensitization and occupational asthma have been reported in workers who process oysters, prawns, fish, and snow crabs [50–52]. In a study of 313 workers in a snow-crab processing plant, 15.6% of the workers had occupational asthma [50]. The prevalence of occupational asthma is higher from exposure to aerosols from Crustacea than to aerosols from bony fish and mollusks. A longitudinal study of crab-processing workers demonstrated that the incidence of new cases of asthma-like symptoms occurred in 26% of all exposed workers [53]. Few studies have evaluated the dose–response relationship. In a study by Douglas and co-workers of workers in a salmon processing plant, a decrease of respirable aerosols from $237 \text{ } \mu\text{g/m}^3$ of air to less than $0.01 \text{ } \mu\text{g/m}^3$ was associated with a reduction in the incidence of occupational asthma from an initial 8% to no new cases in an 18-month period [54]. The specific allergens involved in the fishing industry-related asthma have not been identified.

Laboratory workers

Laboratory workers are at an increased risk for animal allergy from furry animals and insects. Animal sensitization occurs in approximately one third of laboratory workers, of whom 5% to 12% develop work-related asthma [55]. Urinary and salivary allergens have been identified and extracted from pelts of

guinea pigs, rabbits, dogs, and cats. Pelt allergens that are not derived from urine or saliva also have been demonstrated in these animals [56,57]. Rat allergy is a common laboratory-animal allergy. In rat urine, a major source of allergen, the allergen has been identified as a 17-kD protein of the $\alpha_{2\mu}$ -globulin class [58]. This protein is produced in a higher concentration in male rats, and its concentration in urine increases with age. Feeding and cleaning of cages increase exposure to rat allergen; exposure also is influenced by the type of cage and litter used.

Farmers

Farmers are at risk for occupational asthma from several high-molecular-weight allergen sources. Workers in the poultry industry may develop occupational asthma from exposure to airborne contaminants present in confined areas. Such contaminants include skin and feather debris, insect parts, aerosolized feed, and poultry excreta [59]. Poultry mites, such as the northern fowl mite (*Ornithonyssus sylviarum*), a common parasite of poultry, have been associated with IgE sensitization and occupational asthma [60]. Storage mites also may cause occupational asthma in farmers [61]. Cow dander is another source of asthma in farmers, particularly in Finland, where people and cattle frequently coexist [62].

Enzymes of animal origin

Porcine pancreatic extract, which is produced by drying, defatting, and milling fresh porcine pancreas, contains trypsin, amylase, lipase, and other pancreatic proteins. These enzymes are highly allergic and cause respiratory disease through IgE-mediated mechanisms and other mechanisms [63].

Enzymes of plant origin

Bromelain is a proteolytic enzyme (molecular weight, 33 kD) that is derived from pineapple (*Ananas satirus*). It is used in the pharmaceutical and brewing industries and in diagnostic laboratories. Two groups of investigators reported occupational allergy to bromelain. Gallaguiillos demonstrated occupational asthma by provocation challenge in two workers in the pharmaceutical industry [64]. Gailhofer et al studied 21 workers from a blood grouping laboratory [65]. Eleven workers had evidence of IgE sensitization to bromelain, and four workers had asthma caused by bromelain.

Papain is a proteolytic enzyme (molecular weight, 23 kD) that is derived from the papaya tree (*Carica papaya*). It is used as a meat tenderizer, to clarify beer, in pharmaceuticals, and in research laboratories. Studies have demonstrated that papain is a strong sensitizer and can induce occupational asthma [66]. There seems to be some cross-reactivity between papain and bromelain.

Enzymes of fungal and bacterial origin

Enzymes of different origin frequently are used in the food, chemical, and pharmaceutical industries, and several have been shown to be potent allergens.

Some of the most important enzymes are derived from the fungus *Aspergillus* and include α -amylase, cellulase, hemicellulase, and glucoamylase. α -Amylase is a 478-amino acid glycoprotein that is derived from the fungus *Aspergillus oryzae*. It is used in the baking industry to improve the quality of bread and enhance carbohydrate fermentation by yeast. Several studies demonstrated the importance of these enzymes in bakers' asthma [67–69]. Cellulase is a group of enzymes that is obtained mainly from *Aspergillus niger* and *Trichoderma viride* and is used frequently in the pharmaceutical and baking industries; cellulase has been associated with occupational asthma in workers in these industries [68]. Since the 1960s, proteolytic enzymes derived from *Bacillus subtilis* have been added to synthetic detergents to enhance effectiveness. Soon after their introduction, high rates of allergic sensitization to the enzymes were recognized in the detergent industry [70]. Several remedial measures were taken, including the encapsulation of the enzyme to decrease the respirable particles.

Diagnosis

History

A careful history is of utmost importance in the evaluation of patients with suspected occupational asthma. Clues that an occupational agent may be responsible for the symptoms include the onset of symptoms within months of starting a job, use of a new industrial agent or process, and improvement of symptoms during weekends and vacations. A clear-cut relationship between the length of exposure and onset of asthma may not be present. Several variables, including the duration and type of exposure, the agent's sensitizing potential, and host factors including concomitant viral infections, cigarette smoking, and atopy, may affect the development of disease.

A latent period between the initial exposure and the development of symptoms may range from several weeks to more than 20 years [71]. In general, sensitization to high-molecular-weight substances requires a longer interval between exposure and sensitization than does sensitization to low-molecular-weight substances. Although symptoms must be correlated with exposure, this correlation may not be apparent in cases with delayed onset of symptoms (several hours after exposure), repetitive patterns of response, or intermittent exposure. It is also necessary to consider whether the suspected agent acts as a specific sensitizer or as a nonspecific irritant that worsens airway obstruction in patients with preexisting asthma.

Immunologic studies

Immunologic tests are important in establishing a diagnosis of occupational asthma when an immune mechanism is operative and when appropriate antigenic material is available.

Skin testing

Immediate wheal and flare (IgE-mediated) skin tests using common environmental allergens, such as pollen, animal dander, molds, and house dust mites, can be used to determine atopic status. Skin tests with extracts prepared from suspected substances in the work environment may detect specific IgE antibodies and suggest a cause-and-effect relationship. The suspected materials are extracted into pyrogen-free water or saline solution, filtered, centrifuged to remove particulates, and frozen or lyophilized. Before testing, extracted materials are reconstituted in phosphate buffer saline solution, sterilized by filtration, cultured to confirm sterility, and tested in animals for pyrogenicity, toxicity, and mutagenicity.

Extracts should be evaluated by skin testing in a nonexposed, nonatopic control group to determine an appropriate nonirritative dose. Titration skin-prick testing can be used to distinguish between hypersensitivity and irritant responses in exposed workers. Skin tests may be important in studying the pathogenesis of certain types of occupational asthma. They can be helpful in performing large epidemiologic surveys to detect susceptible populations or to diagnose overt occupational airway disease.

RAST and similar assays

Specific IgE antibodies can be studied *in vitro* by RAST and similar immunoassays or by ELISA. Some advantages of RAST compared with skin tests are that many RASTs can be processed in a day, the patient's presence is not required, and there are fewer false-positive results. RASTs are less sensitive and more expensive than skin testing, however. Results are not immediately available, and not all antigens can be coupled to a solid phase. RASTs are most suited for protein and are less useful for polysaccharide antigens. Complex allergens that may bind nonspecifically to IgE may produce a false-positive RAST result. It is important to include appropriate controls in each assay.

An ELISA can be used to quantitate specific antibodies of all immunoglobulin classes, including IgE. When specific IgG or IgM antibodies are present, activation of the complement cascade by the occupational substance should be considered.

Inhalation challenge

In many instances, usually under conditions of diagnostic uncertainty or diagnostic dispute or for research purposes, it is important to reproduce the clinical features of the pulmonary reaction induced by an occupation-associated allergen. This step can be accomplished by inhalation challenge and careful observation of the patient. There are two methods of inhalation challenge: natural or biologic challenge and controlled provocation challenge.

Natural or biologic challenge

Natural or biologic inhalation challenge is accomplished by observing the patient in the suspected environment. The reaction is evaluated by comparing

preexposure and postexposure pulmonary function test results with those obtained on nonworking days. The patient usually is monitored at work by keeping a record of symptoms and monitoring airflow obstruction with measuring peak expiratory flow every 2 hours (a simple portable peak flowmeters can be used). Results should be compared with those obtained on control days spent outside of the work environment. Significant symptoms accompanied by changes in peak expiratory flow at work suggest that the asthma is associated with the workplace. For more accurate readings, pulmonary function tests, including spirometry (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], and forced expiratory flow in midexpiratory phase), can be performed in the workplace at different intervals throughout the work day. Testing for 24 hours may be necessary to monitor any late asthmatic and restrictive reactions that occur after leaving the workplace. This type of challenge has minimal danger, because the patient previously has experienced this degree of exposure in this setting. Work-related symptoms could result from factors that are not strictly occupational, including irritants such as smoke, dusts, pungent fumes, and natural allergens (ragweed, grass pollen). This method does not identify the specific causative agent; for this purpose, a more specialized laboratory is required.

Controlled provocation challenge

Controlled provocation challenge is carried out in a specialized laboratory. After the patient undergoes measurement of baseline pulmonary function, he or she is exposed to a pharmacologic agent by inhalation (eg, methacholine, histamine) to assess the degree of airway hyperreactivity. The patient then is exposed to the suspected environmental agents to demonstrate a possible cause-and-effect relationship. Several measurements of lung function are carried out throughout the challenge. Published guidelines for inhalation challenge techniques have been outlined [72–74].

Antigen inhalation challenge. When patients are exposed to antigens to which they have become sensitized, they may demonstrate one of four patterns of response:

1. Immediate response: the most common reaction; it consists of acute bronchospasm that occurs within minutes of exposure and is characterized by dyspnea and wheezing. Spirometry shows a rapid decrease in FEV₁ that is reversible with inhaled bronchodilators.
2. Late response: occurs 4 to 10 hours after exposure and can last for at least 36 hours. The decrease in FEV₁ is less reversible with conventional bronchodilators (eg, albuterol) and can be prevented by previous administration of steroids or cromolyn sodium. In addition to smooth muscle contraction, the mechanism involves inflammatory changes and intraluminal mucus accumulation in the bronchi.
3. Dual response: an immediate bronchospastic reaction resolves spontaneously and rapidly. Six to 8 hours later, bronchospasm and symptoms recur.

4. Restrictive response: seen more commonly in patients with acute forms of hypersensitivity pneumonitis. It occurs 4 to 6 hours after challenge and is characterized by chills, fever, dyspnea, and crepitant or subcrepitant rales on auscultation. Pulmonary function tests show a restrictive defect with a reduction in FVC and diffusion capacity. This reaction can be blocked by corticosteroids.

Laboratory challenge with dust. Workplace exposures can be simulated in the laboratory, as described by Pepys and Hutchcroft [75]. Appropriate quantities of the test dust may be added to a given amount of lactose so that the occupational exposure is simulated when the subject transfers the dust from one container to another. Lactose alone can be used for the control test; the challenge can be carried out in a single- or double-blind fashion, provided that the agent cannot be detected by its color, taste, or texture at the concentrations used in the test. This technique has been used in the investigation of occupational asthma in workers from a variety of industries. The allergenic materials can be extracted from the dust to obtain extracts for challenge with the nebulized method.

Laboratory challenge with nebulized aerosol. Laboratory challenge with nebulized aerosol is most applicable to challenge with common environmental allergens that may be present in the workplace. It may be equally suitable for soluble agents and substances that are in a natural liquid state. The advantages of this method are that control and antigen challenges are indistinguishable, provided that the antigen has no characteristic odor or taste. Its chief difficulty lies in choosing an appropriate concentration for the initial challenge and the level at which negative results exclude hypersensitivity. In general, initial doses should simulate minimum exposures that are encountered naturally, whereas maximum doses should exceed slightly the maximum that is likely to have been experienced in the workplace.

Treatment and prognosis

The ideal treatment in occupational asthma is prevention. Careful engineering and industrial hygiene controls can ensure minimal exposure to sensitizing agents [76,77]. Threshold limits not associated with increased risk for occupational asthma have been suggested for few allergens (Table 3) [78].

Once occupational asthma has been diagnosed, the individual should be removed from further exposure, because once hypersensitivity develops, asthmatic responses occur at minute exposure levels, usually at low levels that an industrial plant cannot avoid. In a study by Cote and co-workers, most of the 48 workers with western red cedar asthma who remained on the job for an average of 6 years after diagnosis deteriorated or remained stable; few workers (10%) showed improvement, and no workers recovered [79]. Stringent measures should ensure that there is no further exposure, because brief, intermittent exposure can

Table 3

Air levels of allergens associated with increased risk for occupational asthma

Substance	Air level
Rubber latex	>0.6 ng/m ³ air
Wheat flour	>1.0 – 2.4 µg/m ³ air
Fungal α-amylase	>0.5 ng/m ³ air
Rat allergen	>0.7 µg/ m ³ air

increase the severity of asthma [12]. When symptoms develop, treatment is the same as that for other types of asthma (ie, inhaled β-adrenergic drugs, cromolyn, theophylline, inhaled or systemic corticosteroids). Protective devices, including dust masks or respirators, have been used to minimize exposure. These measures are usually ineffective, however, because masks frequently do not fit well and compliance is low.

Follow-up studies of patients with occupational asthma have suggested that a significant percentage of these individuals continue to have symptoms after removal from further exposure. Individuals exposed to a wide variety of occupational agents, including TDI, trimellitic anhydride (TMA), western red cedar, formaldehyde, and antibiotics, often continue to have asthma symptoms several years after removal from exposure [11,80–82]. Some individuals, however, experience complete recovery after removal from the job area. Factors that influence prognosis have not been well defined but probably include the duration of symptoms before diagnosis, previous airway hyperreactivity, and disease severity.

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