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The Epidemiology of Work-Related Asthma

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Work-related asthma has been used to describe all asthmatic conditions related to workplace exposures, such as:

1. Occupational asthma, which is induced by sensitizers or irritants at work
2. Work-exacerbated asthma, bronchospasm provoked by triggers and work in workers with preexisting asthma.1,2

Both conditions may coexist in the same patient and are not mutually exclusive.

Occupational asthma is defined as pulmonary disease characterized by airway hyperresponsiveness, variable airflow limitation, and inflammation attributable to an occupational environment and not to exposures encountered outside the workplace.3 There are 2 distinct subtypes of occupational asthma. The first is work-related asthma caused by either reactive chemical sensitizers or natural protein allergens after a latency period of exposure. The second is irritant-induced asthma, which has no preceding latency, no history of preexisting asthma, and occurs after single or multiple exposures to high levels of irritants at work.

Respiratory sensitizers, such as natural proteins or low-molecular-weight reactive chemicals acting as haptens, may induce occupational asthma through immunoglobulin E (IgE)–dependent mechanisms. Although immunologic mechanisms are suspected for many causative chemical sensitizers, these are not always associated with demonstrable, specific IgE responses.4

Reactive airways dysfunction syndrome is the best-defined phenotype of irritant-induced asthma. This syndrome is characterized by acute respiratory symptoms, such as cough, dyspnea, and/or wheezing, starting within 24 hours from a single, high-level exposure to a workplace irritant.5,6 If the onset of symptoms is greater than 24 hours after multiple irritant exposures, the term irritant-induced asthma is used.5

Work-exacerbated asthma, bronchospasm triggered at work, can be worsened by intermittent exposure to chemical fumes such as bleach among cleaning workers.

KEYWORDS
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and other chemical fumes such as sulfur dioxide, chlorine gas, and environmental tobacco smoke.7,8

Given the breadth of phenotypes and exposures that can be associated with work-related asthma, this article addresses the epidemiology of occupational asthma and work-exacerbated asthma by the individual environmental exposures that commonly are associated with these disorders.

ESTABLISHING AN OBJECTIVE DIAGNOSIS OF WORK-RELATED ASTHMA

An accurate estimation of the epidemiology of work-related asthma depends on the accurate characterization and diagnosis of work-related asthma phenotypes. The diagnostic methods for occupational asthma and work-exacerbated asthma have been reviewed elsewhere.9–11 The diagnosis should not be based on medical history alone without objective confirmation by measurements of lung function at work and away from work.12 Failure to establish an accurate diagnosis could allow for miscategorization of the occupational asthma phenotype and inaccurate estimates of incidence and prevalence.

There are 3 major components in the current diagnostic approach for work-related asthma. The first is obtaining a compatible occupational and medical history. The second is confirming an objective diagnosis of asthma. The third is showing decrements in lung function when exposed to conditions or substances at work, along with improvement for sufficient time away from work. A published list of agents known to cause occupational asthma can be researched as well (www.asmanet.com). Of the approximately 400 known causes of occupational asthma, most are high-molecular-weight protein sensitizers, whereas fewer than 30 are low-molecular-weight agents or reactive chemicals. If possible, skin testing or in vitro serologic testing can be used to confirm clinically relevant respiratory sensitizers from the workplace.11 As part of the evaluation, conditions that could mimic work-related asthma, such as vocal cord dysfunction, which can be triggered by workplace exposures, should be excluded.13

EPIDEMIOLOGY OF WORK-RELATED ASTHMA BY EXPOSURE

The exact incidence and prevalence of work-related asthma are not well defined. It is estimated that 10% to 25% of adult cases of asthma are aggravated by occupational factors.14–16 In a 15-year surveillance study, the annual incidence of occupational asthma was 42 (95% confidence interval [CI] 37–45) per million working population (Fig. 1).17 Of all workers identified with work-related asthma, work-exacerbated asthma cases may represent between 10% and 50%.18,19 It is likely that
work-exacerbated asthma is highly prevalent and underdiagnosed, given that an estimated 18% of the global population is affected by asthma.20

DIISOCYANATE

The diisocyanates are a family of highly reactive, low-molecular-weight chemicals, including hexamethylene diisocyanate (HDI), methylene diphenyl diisocyanate (MDI), and toluene diisocyanate (TDI). Among workers, there is extensive exposure to diisocyanates. More than 253,000 US workers in the transportation industries are employed in facilities that use isocyanates.21 Other industries with diisocyanate exposure include spray painting, particularly automobile repair (HDI), manufacture of polyurethane foam (MDI), manufacture of particle board (MDI), use in foundries (MDI), and manufacture of polyurethane foam (TDI).

The main route of occupational exposure is through inhalation. Inhalation of diisocyanate fumes is associated with various pulmonary diseases, such as occupational asthma, hypersensitivity pneumonitis and direct toxic effects.22–26 Diisocyanates are potent sensitizers, and have long been recognized as a cause of occupational disease, particularly asthma.23,27–29 The degree of exposure directly affects the prevalence and incidence of diisocyanate-induced conditions. On average, numerous studies have documented that 5% to 15% of those who work with diisocyanates develop occupational asthma, making this the most common cause of occupational asthma (Fig. 2).26

The incidence and prevalence of diisocyanate asthma can be affected by avoidance and industrial hygiene measures. Negative pressure, air-purifying, half-facepiece respirators using prefilters and organic vapor cartridges have been reported to provide effective protection for spray painters exposed to diisocyanates.30 Despite industrial hygiene measures that maintain ambient chemical exposures in a factory at less than threshold limit values, incident cases of occupational asthma still occur.31 In the case of diisocyanate chemicals, new cases of occupational asthma may develop after intermittent accidental chemical exposures during maintenance procedures or from accidental spills of MDI or TDI, when exposure may escape detection by continuous monitors.

NATURAL RUBBER LATEX

Natural rubber latex (NRL) is a complex mixture of at least 13 allergenic proteins that bind human IgE antibodies (Hev b allergens), derived from the sap of the rubber tree, Hevea brasiliensis.32 Through the use of NRL gloves, health care workers are commonly exposed to Hev b allergens in an occupational setting.

![Fig. 2. Occupational asthma from diisocyanates. Total numbers of occupational asthma cases from isocyanates per year for 15 years by job category. (From Bakerly ND, Moore VC, Vellore AD, et al. Fifteen-year trends in occupational asthma: data from the Shield surveillance scheme. Occup Med (Lond) 2008;58(3):171; with permission.)](image-url)
Among health care workers who use NRL gloves, occupational asthma as a result of exposure increased significantly during the 1990s (Fig. 3). Several studies have evaluated the long-term changes in occupational asthma with changes in NRL glove use. In a survey of 332 health care workers, 20 (6%) reported new-onset asthma in a 9-year period. Compared with controls, hospital technicians had a significant increased risk of asthma (rate ratio [RR] 4.63; 95% CI 1.87–11.5). In a 15-year occupational asthma surveillance study, 1461 cases were reported. Of these cases, 85% had a confirmatory test for asthma. Health care workers accounted for 125 cases (9%) of incident occupational asthma. Latex was implicated as the causative agent in 91 (6% of the total incident cases). With the change to latex-free or low-protein, powder-free latex gloves, there was a significant reduction in incidence in the last 2 years of the surveillance. Another estimate of the incidence of occupational asthma from NRL comes from a retrospective review of occupational claims among health care workers from 1982 to 2004. Of the 298 cases reviewed, 127 were categorized as definite NRL occupational asthma and 68 as probable NRL occupational asthma. This study also reported a significant decrease in the incidence of NRL occupational asthma among health care workers from 1999 onwards with changes away from powdered NRL gloves.

Fig. 3. Occupational asthma from NRL. (A) Annual numbers of definite and probable cases of NRL-induced occupational asthma in health care workers categorized by the year of the onset of work-related asthma symptoms. (B) Incidence rates of NRL-induced occupational asthma expressed as the number of incident cases per $10^5$ full-time equivalents of nonadministrative employees in Belgian hospitals. (C) Usage indices (expressed as percentage of total glove usage) of the different types of gloves in surveyed Belgian hospitals rectangles, powdered latex gloves; triangles, latex-free gloves; circles, powder-free latex gloves). HCWs, health care workers. (From Vandenplas O, Larbanois A, Vanassche F, et al. Latex-induced occupational asthma: time trend in incidence and relationship with hospital glove policies. Allergy 2009;64(3):418; with permission.)
**WHEAT FLOUR**

The prevalence of bakers’ asthma among bakery employees exposed to wheat flour is estimated to be 9%. In one study, 139 workers who were occupationally exposed to wheat flour were evaluated. Of these workers, 30 were found to have asthma along with either a positive skin prick test to crude wheat flour extract or an increased in vitro specific IgE to wheat flour.

Surveillance for asthma symptoms among bakery workers is an important means to detect early disease. In 1 study, the spirometric measurements of 58 bakery workers were compared with those of 45 nonbakers. There was a statistically significant difference between bakery workers and controls for baseline mean forced expiratory volume in the first second of expiration (FEV₁) percent predicted (91.6 vs 101.7) and mean forced vital capacity (FVC) percent predicted (94.5 vs 99.9). None of the controls had an obstructive defect (FEV₁/FVC ratio < lower limit of normal) compared with 12.1% of bakery workers. Another study evaluated the role of exposure to wheat in the development of occupational disease among 860 bakers. Both atopy and sensitization to wheat flour were found to be risk factors for the development of work-related asthma. The prevalence of work-related asthma was significantly higher among bakers sensitized to wheat flour (35% among sensitized vs 6% among nonsensitized) and among bakers with other atopic disease (42% among atopic sensitized vs 11% among atopic nonsensitized). A further study found a lower rate specifically of bakers’ asthma among 392 bakers. Among the bakers, 17.1% of workers complained of respiratory symptoms. Specific inhalation challenge with wheat flour extracts confirmed bakers’ asthma among 1.5% of the baker population studied.

**ANIMAL ALLERGY (MAMMALIAN PROTEINS)**

Among laboratory animal workers, allergic reactions are an important occupational health problem, with an estimated incidence of 1.32 per 100 person years and an estimated prevalence of 22% in this environment. Veterinarians are at the highest risk of developing work-related asthma of all animal workers. Early work compared the occurrence of respiratory disease between 257 veterinarians and 100 controls. The prevalence of asthma was higher among the veterinarians (16.3%) compared with controls (6%) (P<.05). Only 6 veterinarians reported asthma symptoms related to animal exposure. A larger study of 1416 veterinarians found a higher rate of work-related asthma. Among these veterinarians, 20% reported asthma symptoms in the work environment. Cats were the most commonly reported animals causing work-related symptoms in 58% of affected workers, with dogs causing symptoms in 31%. A further study investigated the risk factors for occupational asthma among 200 veterinarians working with laboratory animals. Chest symptoms were reported in 19 (9.5%) of workers. Of those veterinarians sensitized to laboratory animals by skin testing or specific IgE testing, 14 (11.4%) reported chest symptoms at work. In addition to cat sensitization (odds ratio [OR] 10.27; 95% CI 2.42–49.91), daily contact with laboratory animals (OR 4.52; 95% CI 1.53–13.73) (rat, mouse, hamster, guinea pig, rabbit), and working time of more than 10 years (OR 5.21; 95% CI 1.37–29.10) were found to be significant risk factors for the development of occupational asthma.

**SEAFOOD/SEA SQUIRT**

Employment associated with the seafood industry is common, with 43 million people worldwide reported as workers in the industry. A variety of work activities can lead to significant exposure to seafood, such as the harvesting of seafood, processing of
Seafood in factories, food preparation, and laboratory exposure. Common agents causing occupational asthma include the crustaceans (e.g., crab, lobsters, shrimp), the mollusks (e.g., clams, oysters, mussels, scallops), bony fish such as salmon and tuna, and other associated biologic agents, such as sea squirt. Seafood contains a wide variety of proteins. Of these, many seafood allergens have been identified, including tropomysin and parvalbumin. Across the seafood industry, prevalence estimates of occupational asthma range from 2% to 36%. The estimates of disease burden critically depend on the definition of disease, the type of work performed, and the allergenicity of seafood exposure. An updated review of reports of occupational asthma across the seafood industry has recently been published.

Asthma caused by exposure to sea squirt allergens primarily occurs among Japanese oyster shucking workers. The major allergens are from the body fluid of the sea squirt, *Styela plicata*, and are the acidic glycoproteins, Gi-rep, Ei-M, and DIIIa. Oyster shucking workers constantly inhale the sea squirt antigens in the mist of the body fluid of sea squirts while at work. The reported prevalence of sea squirt asthma among oyster shucking workers was 36% in 1963. This significant prevalence has dramatically decreased with industrial hygiene improvements. A more recently reported prevalence of sea squirt asthma has decreased to 8%, with an incidence of 10.1% among oyster shucking workers.

**HOUSE-DUST MITE AND DOMESTIC/NONDOMESTIC CLEANING**

House-dust mite is the most common indoor allergen. In rooms with wall-to-wall carpeting, high levels of the allergens of house-dust mite species *Dermatophagoides pteronyssinus* (Der p1) and *Dermatophagoides farinae* (Der f1) are present in the house dust. In a variety of occupations, such as domestic cleaners and janitorial staff, exposure to house-dust mite allergens (Der p1 and Der f1) is unavoidable. However, as part of the occupation, chemical and irritant exposure is also common.

To evaluate the risks of work-related asthma among domestic and nondomestic cleaners, several studies have been performed. In a cross-sectional study, 4521 women were evaluated. Among the cleaners, the prevalence of asthma and work-related respiratory symptoms was 12%. Compared with noncleaners, the cleaners had a significant increased risk of asthma (OR 1.46; 95% CI 1.10–1.92). Another study followed 43 female domestic cleaners, with data gathered through a 2-week diary. Although vacuuming and house dust mite exposure was associated with upper respiratory symptoms (OR 2.0; 95% CI 1.0–4.2), this exposure was not associated with work-related asthma. Instead, cleaning product exposure (bleach, ammonia, air freshener) was associated with work-related asthma in 30% of the cleaners. A further study evaluated 1500 cleaners, both men and women. In this study, work-related asthma symptoms were significantly associated with waxing floors, cleaning bathrooms, spot-cleaning carpet, and oiling furniture (all irritant exposures). Based on available data, it is possible that house dust mite exposure may play a role in work-related asthma, but, to date, irritant exposures seem to play a more significant role among cleaners.

**DETERGENT**

In the 1960s, alkaline-stable and heat-stable proteolytic enzymes were introduced into detergents to improve the performance of the detergent. Allergic reactions, particularly occupational asthma, to the proteolytic enzymes in detergent products were first reported in 1969. The risk of allergic antibody-mediated occupational asthma caused by enzyme use in the detergent industry was quickly recognized. In a 20-year study, the lung function in 731 workers exposed to proteolytic enzymes derived...
from *Bacillus* species in the 5 detergent factories was evaluated.\(^{50}\) During the study period, 166 cases of enzyme asthma were confirmed among workers. In a 10-year continuing surveillance study, several thousand workers were tracked for the development of occupational asthma after the continued use of industrial hygiene measures to decrease exposure to the proteolytic enzymes (Fig. 4).\(^{51}\) In the study period, only 17 cases of occupational asthma were confirmed among the workers.

**ACID ANHYDRIDE CHEMICALS**

There are rare chemical sensitizers shown to cause occupational asthma through specific IgE mechanisms. Acid anhydride chemicals (eg, trimellitic anhydride, phthalic anhydride), which represent the prototypic class of reactive chemical haptens, can form allergenic determinants by combining with autologous respiratory proteins in vivo.

A study of 27 workers with exposure to hexahydrophthalic anhydride (HHPA) from an epoxy resin molding system was performed to evaluate the nature of respiratory complaints. For each worker, estimates of exposure were made from both job description and environmental sampling. Seven workers (25.9\%) reported symptoms of asthma and rhinitis. Four workers had symptoms consistent with occupational asthma (14.8\%). None of the workers showed a significant preshift-to-postshift decrease in FEV\(_1\). The overall prevalence of work-related asthma based on these data is 40.7\%.

In another group of workers exposed to hexahydrophthalic anhydride for manufacturing an epoxy resin product, the effect of respiratory protective devices was evaluated. For the 7-year study, 66 workers were followed.\(^{52}\) With the use of respiratory protective devices, an estimated 80\% reduction in the expected incidence of occupational respiratory disease was reported. However, this preventive measure did not prevent 3 new cases of occupational asthma. During the study, the incidence per year of occupational asthma related to HHPA exposure dropped from 10\% to 2\% and the prevalence decreased from 7.5\% to less than 1\%.

![Fig. 4. Occupational asthma from detergent enzymes. Number of occupational asthma cases per year at all Latin American (filled circle) and North American (empty circle) enzyme-detergent manufacturing sites (1969–1998). (From Schweigert MK, Mackenzie DP, Sarlo K. Occupational asthma and allergy associated with the use of enzymes in the detergent industry—a review of the epidemiology, toxicology and methods of prevention. Clin Exp Allergy 2000;30(11):1512; with permission.)](image-url)
IRRITANTS

It is estimated that 25 million workers are exposed to environmental tobacco smoke (ETS) at work. The impact of various asthma triggers encountered on the job (eg, ETS, aeroallergens, exertion, and irritants) and their overall impact on the asthma disease burden is unknown. Data regarding the impact of occupational ETS exposure on work-related asthma have been provided in a prospective cohort study of 77 bar workers evaluated before and after institution of a cigarette smoking ban. The cigarette smoking ban effectively eliminated the workers' exposures to secondhand ETS. In a subset of 10 of 77 workers with preexisting asthma, there was a 10% increase in mean FEV1 and a significant improvement in quality of life measures after institution of the smoking ban. Most recently, an evaluation of the impact of a 100% smoke-free workplace legislation among hospitality workers in Argentina was reported. In 2007, a ban on cigarette smoking in public venues and workplaces was enacted. Surveys and spirometric measurements were performed before and after the smoking ban. From 101 bars and restaurants, 80 workers completed the full evaluation. There was a significant reduction in reported respiratory symptoms (cough, wheezing, dyspnea, and chest tightness) from 58% of workers before the ban to 29% or workers after the ban. However, no significant change in FEV1 was seen.

Another irritant exposure that has been studied is exposure to chlorine and halogenated disinfection by-products (DBPs) among workers at indoor pools. High rates of respiratory symptoms suggesting asthma have been reported in several epidemiologic studies. Of 334 lifeguards, 3 of 83 with the highest exposure to DBPs (3.6%) reported occupational asthma symptoms. In a case series of 3 pool workers with occupational symptoms, work-related asthma was confirmed by workplace challenge. Two of the workers reported preexisting asthma, making their diagnosis work-exacerbated asthma. In a cross-sectional survey of 624 pool workers in whom asthma symptoms were assessed by questionnaire, asthma symptoms were significantly increased compared with a population control sample (OR range 1.4–7.2). In the most recent study, the prevalence of work-related asthma was assessed with 133 pool workers in a cross-sectional study. A prevalence of asthma was reported as 7.5% across all workers (high and low exposure). However, there was a significant increase in work-related asthma among those workers with high exposure (OR 5.1; 95% CI 1.0–27.2).

PREVENTION OF WORK-RELATED ASTHMA

Primary Prevention

Incident cases of occupational asthma provide a unique opportunity to identify a high-risk work environment and to advise an employer to enact control measures that may prevent new cases among similarly exposed workers (primary prevention). Ideally, prevention of new cases could be achieved if threshold exposure limits could be defined below which the development of occupational asthma is unlikely. Interventions may include substituting a safer alternative substance for the causative agent in the industrial process. Because this is often not feasible, substantial reduction in human exposure to causative chemicals may be achieved through the introduction of new engineering controls, which may prevent new cases of occupational asthma. Understanding of the periods of risk from exposure is also important. In a recent long-term prospective cohort study, the highest incidence of bronchial hyperresponsiveness among apprentice laboratory animal workers exposed to high-molecular-weight antigens was exhibited in the first years of work. This finding might indicate a time at which increased control of exposure might modify risk.
Effective primary prevention has been shown by the successful control of occupational asthma achieved in health care workers exposed to NRL gloves. Powdered NRL gloves were substituted with powder-free NRL gloves and/or low-protein powder-free NRL gloves in 8 primary prevention programs among health care worker populations. This substitution resulted in reduced levels of ambient measurable NRL aeroallergens and decreased incident cases of occupational asthma among the previously exposed health care workers.61

Industrial hygiene programs in the detergent manufacturing industry are another example of successful primary prevention of occupational asthma. The specific measures include (1) encapsulation of detergent enzyme protein granules in inert materials; (2) frequent ambient monitoring for enzymatic proteins; (3) engineering controls to minimize ambient enzyme dust; and (4) employee training to minimize personal exposure. These approaches have been used to maintain ambient enzyme levels at less than 15 ng protein/m³ (less than the ACGIH TLV of 60 ng protein/m³). This decreased exposure had resulted in dramatic declines in detergent enzyme sensitization rates and incident cases of occupational asthma.51

As an example of substitution, diisocyanates, previously used in monomeric forms as paint hardeners or for urethane production, are now sold almost entirely as prepolymerized products (polyisocyanates), likely reducing respiratory and dermal exposure to active diisocyanate molecules. As an example of new engineering controls in most modern plants, spray painting of hard metal surfaces using hexamethylene diisocyanate, an essential paint hardener, is performed by robotic devices enclosed in independently ventilated paint booths. It is thought that, in diisocyanate-exposed workers, these measures may have reduced new cases of occupational asthma.

Secondary Prevention

Early identification of workers with occupational symptoms, such as occupational allergic rhinitis, followed by significant reduction in occupational exposure, may prevent incident cases of occupational asthma (secondary prevention). As an example, the detergent enzyme industry has instituted exemplary medical surveillance programs. Surveillance is conducted annually among exposed workers through medical questionnaires and skin testing with enzyme solutions (such as Aspergillus-derived amylase and Bacillus subtilis protease).51 If a sensitized worker develops allergic rhinitis symptoms, the worker is relocated away from potential high-exposure areas. In one detergent company, the annual incidence of newly sensitized workers was maintained at less than 3% with no incident occupational asthma cases reported in a 6-year period after the establishment of surveillance and industrial hygiene programs.51

Tertiary Prevention

Specific methods of environmental control of harmful exposures, such as removing a worker with established occupational asthma from exposure to a newly recognized occupational sensitizer, must be personalized to the specific needs of each worker with occupational asthma (tertiary prevention). In the case of a worker with preexisting occupational asthma, efforts are directed at preventing progression to more severe asthma along with the progressive loss in lung function caused by the continued exposure to offending agents at work. This approach to tertiary prevention is supported by a recent retrospective study of more than 150 consecutive cases of occupational asthma. Workers removed from occupational exposure showed a decelerated rate of decline in FEV₁ in 6 months or more after the removal of the exposure.62
SUMMARY

Much has been learned from epidemiologic studies conducted in the past 4 decades that can be directly applied to the management of workers affected with occupational asthma. The workplace is an ever-changing environment that offers unique opportunities to investigate the natural history of work-related asthma. Past investigations have provided invaluable information about host factors in workers as well as environmental exposure characteristics that may enhance disease susceptibility. Longitudinal studies have characterized those occupational agents posing the highest risks (eg, low-molecular-weight chemicals such as diisocyanates) for development of severe irreversible airway obstruction and asthma disability from occupational asthma, especially when exposure is continued after the diagnosis is established.

Identification of sentinel cases of occupational asthma have enabled investigators to develop methods for screening workers at risk and novel interventions that may prevent new cases among exposed worker populations. Primary prevention efforts including workplace exposure modification and product modifications have, in certain cases, virtually eliminated new cases of occupational asthma caused by specific sensitizers (eg, NRL). Less is known about the natural history and chronic morbidity associated with work-aggravated asthma and irritant-induced asthma syndromes; more studies are needed in at-risk worker populations.

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