

Work-Related Asthma and Implications for the General Public

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Asthma has been increasing over the last two decades in the United States. The onset of asthma has also been increasingly reported as a result of occupational exposures to over 350 different agents. Work-related asthma (WRA) has become the most frequently diagnosed occupational respiratory illness. Epidemiologic studies from the United States reported WRA incidence rates of 29–710 cases per million workers per year and suggest that 10–25% of adult asthma is work related. Much can be learned about asthma in the general population from investigations of asthma in the workplace. Surveillance of WRA continues to highlight an important role for low molecular weight chemical sensitizers, as well as high molecular weight antigens. Additionally, recent reports implicate mixed exposures, including commercial cleaning solutions, solvents, and other respiratory irritants, as well as contamination in nonindustrial environments, including schools and offices. Investigations of WRA have demonstrated a clear dose-related increase in sensitization and symptoms for exposures to both chemical and protein sensitizers. High proportions of exposed working groups can be affected. Skin exposures may affect the likelihood of individuals developing respiratory symptoms. Atopy increases the risk of sensitization and illness from workplace exposure to antigens but not to chemical sensitizers. Irritant exposures can act as adjuvants among individuals exposed to sensitizing substances, increasing the proportion who become sensitized. Atopy might also be a result of irritant exposures in some persons. Occupational asthma often has important long-term adverse health and economic consequences but can resolve completely with timely control of exposures. Detailed study of such asthma “cures” may prove useful in understanding factors that influence asthmatic airway inflammation in the general population.

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During the last decade, a remarkable increase has occurred in the prevalence of asthma in the United States as well as in a number of other countries. This increase has occurred among both children and adults (1). Studies have associated asthma symptoms with a number of factors, including familial (2), nutritional (3), socioeconomic and psychosocial (4), and environmental (5) factors. Widely accepted definitions of asthma describe a chronic inflammatory disorder of the airways with characteristic pathologic features that can be attributed to a variety of recognized and undefined factors (6). The specific cause or causes of the rise in asthma morbidity and mortality remain incompletely understood. Although knowledge of the genetic determinants of asthma is expanding, it is generally acknowledged that the explanations for the recent increase in asthma must be found among the many changes in our living environments, including lifestyles as well as exposures at work, school, and home (7–10).

Work-Related Asthma Is Increasingly Recognized

During the same period as the overall rise in asthma prevalence, work-related asthma (WRA)—asthma caused or significantly exacerbated by work exposures (11)—has emerged as the most commonly reported

occupational lung condition (12,13). Over 350 chemicals, mixtures, and processes found in the workplace have been associated with the onset or exacerbation of asthma, with over 250 documented as airway sensitizers (14,15). Recent studies implicate workplace exposures in an important proportion of cases of new-onset asthma among adults, and exposures to agents in the workplace that result in the onset of asthma continue to be described (16,17). In addition to the new onset of asthma from occupational exposures, individuals with preexisting asthma can experience work-aggravated asthma caused by a variety of exposures during work. Work-aggravated asthma results in increasing medication requirements and/or clinical deterioration among affected persons and contributes to the importance of occupational factors in asthma morbidity. Overall, the findings from research, surveillance, and clinical experience among individuals with WRA have yielded a wealth of information that can enlighten understanding of the initiation, exacerbation, management, and even cure of asthma in the general population.

Work-Related Asthma Surveillance

Reports from Canada and the United Kingdom as well as the United States indicate

that occupational asthma has surpassed the traditional occupational dust disorders to become the most commonly reported occupational lung disease (18–20). These surveillance systems highlight the contemporary importance of WRA but do not document trends over time. However, time trends have been documented in Finland, where a 70% increase in confirmed cases of occupational asthma was noted from 1986 to 1993, on the basis of data from the comprehensive Finnish national registry of occupational illnesses (21). In the United States, four states are currently submitting reports of WRA as part of the Sentinel Event Notification System for Occupational Risks (SENSOR) surveillance system, which is sponsored by the National Institute for Occupational Safety and Health (NIOSH) (22). In this program a number of core variables are collected from cases meeting defined criteria for WRA. The pattern of agents implicated in these reports is of interest (Table 1). The diisocyanate group of chemicals, which are used in the production of a wide variety of consumer and commercial products, represented the largest single group of agents—a finding similar to that reported from several other countries (18,19,23). Contamination in nonindustrial workplaces such as offices and schools represented the second largest group of agents reported in association with asthma onset. To better understand the role in asthma of exposure to molds, bacteria, volatile organic compounds, and other contaminants found in buildings, NIOSH has initiated a major research effort. Surveillance reports have identified several additional agents increasingly associated with asthma, including commercial and industrial cleaning products, and metal-working fluids, which are used in foundries, mills, and machine shops. Overall, surveillance of WRA underscores the importance of exposures to highly reactive low molecular weight (<5 kDa) chemical sensitizers, mixed contaminant exposures in nonindustrial settings, and respiratory tract irritants such as cleaning solutions and solvents.

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Table 1. Work-related asthma: agents associated with reported cases.^a

	Total cases	New-onset asthma	Work-aggravated asthma
Isocyanates	103	99	4
Indoor air	86	67	19
Dusts	79	45	34
Chemicals	73	56	17
Metal-working fluids/lubricants	57	55	2
Cleaners	51	42	9
Smoke	50	40	10
Solvents	43	36	7
Stainless welding	37	31	6
Formaldehyde	35	32	3
Paint	35	22	13
Pesticides	29	21	8
Latex	26	24	2

^aData from NIOSH SENSOR surveillance system, 1993–1995; *n* = 1,101 (22).

Work-Related Asthma: Population-Based Studies

Population-based epidemiologic research of asthma in the workplace has evaluated the incidence of WRA and the proportion of asthma in adults that can be attributed to occupation. Studies from Europe, Asia, and the United States have varied widely in the proportion of asthma morbidity among adults that can be attributed to workplace exposures (24). The variability in these estimates is likely due to differences in study methodology as well as the differing profiles of occupational exposures found in the study locations. Several recent studies have suggested that between 10 and 25% of adult asthma is likely to be related to occupational exposures (25,26). Estimates of the overall yearly incidence of occupational asthma in the U.S. working population have ranged in different studies from 29 to 710 cases per million workers. The corresponding rate was reported to be 174 in Finland but varies greatly by industry and occupational categories (27–29). The relatively broad range of estimates emphasizes the importance of design factors in results of these studies. Additional studies are under way to define further the overall impact of occupation on asthma, including both the new onset of asthma and the exacerbation of existing asthma due to job exposures.

Work-Related Asthma: Workforce-Based Studies

Workforce-based studies of asthma have demonstrated that people who work with asthma-causing agents, such as bakers, animal handlers, and isocyanate workers, often have an elevated prevalence of asthma symptoms (12,13). Recently, several detailed studies, including those with quantitative

measurements of exposure to sensitizers, have been completed in various work environments. For example, among bakers, the proportion of workers sensitized (as evidenced by responses to skin prick tests) to alpha amylase, a flour additive, increased with increasing measured airborne exposure to the amylase (30). Similarly, exposure-related increases in sensitization have been observed among laboratory animal workers (31,32). In these studies, tobacco smoking, which may be a risk factor for development of asthma (33), was associated with increased sensitization in the animal handlers; a smoking effect was not observed among the bakery workers. Smoking has also been associated with increased rates of sensitization among workers exposed to platinum salts and certain acid anhydrides but not to diisocyanates or plicatic acid (34).

Study designs of WRA have important consequences for the results. Emphasis on rigorous case finding or a more extensive case confirmation process may result in greater or lesser numbers of individuals with asthma who are eventually available for analysis in a study. Individuals who develop asthma symptoms from workplace exposures may transfer out of the exposed job or leave the workplace altogether (35). Workers with airway hyper-responsiveness, a cardinal finding in asthma, appear to choose jobs that minimize dust exposures (36). Because of these selection factors (manifestations of the healthy worker effect), cross-sectional prevalence studies are likely to underestimate the risk of asthma related to occupational exposures compared with more resource-intensive longitudinal study designs. Similarly, when susceptible or symptomatic workers avoid or leave jobs with potential exposures, the relationships among job exposures, work tenure, and asthma-related outcomes can be obscured (32).

A number of studies have found that persons with atopy (IgE-mediated sensitization to common environmental allergens) have an increased risk of sensitization in relation to workplace exposures to a number of high molecular weight (generally protein) antigens. In contrast, atopy does not consistently affect the risk of sensitization among workers exposed to low molecular weight reactive chemicals such as diisocyanates (12,13). An intriguing finding was reported from a study of Dutch pig farmers (37). The authors found that atopy was significantly more common among farmers who reported using certain disinfectants in their work, particularly quaternary ammonium compounds. This finding, which calls for further study and confirmation, suggests that an individual's tendency to produce IgE antibody on exposure to an aeroallergen, in addition to reflecting his or her genotype, is influenced by certain environmental chemical exposures.

Similar accentuated specific antibody responses in human volunteers have been observed after nasal mucosal exposure to diesel exhaust particulate (10). Animal studies have also indicated that respiratory mucosal exposures to chemical agents can result in augmentation of immunologic responses to airway antigen exposure (38). This augmentation effect can depend on the timing and site of the chemical exposure: for example, rats showed a 6-fold increase in peak specific IgE levels after ovalbumin aerosol when exposed to lower airway irritant (1 hr of NO₂ at 100 ppm) 24 hr before antigen but not when the irritant exposure occurred 7 days before antigen. Upper airway irritation (NH₃) did not augment levels of ovalbumin specific IgE.

Another interesting observation was reported from a study of workers in a wood products plant that uses methylene diphenyl diisocyanate (MDI), a low molecular weight sensitizer (39). Workers in this study were at increased risk of developing asthmalike symptoms if they had noted skin stains due to the MDI. This association was significant even after accounting for potential exposure to airborne MDI. This finding suggests that immunologic sensitization from diisocyanates may initially result from skin exposure and subsequently be manifest by respiratory symptoms, consistent with reports of some previous human and animal studies (40,41).

In light of the recognized familial aggregation of asthma, several studies have investigated genetic markers among individuals with WRA. Although results are still preliminary, several human leukocyte antigen (HLA) markers have been identified that appear to be protective, whereas other markers appear to confer increased risk of WRA (42,43).

Work-Related Asthma: Preventive Interventions

For certain agents associated with occupational asthma, the ability of investigators to identify and quantify allergen exposures has facilitated the assessment of interventions designed to prevent or reduce asthma symptoms among workers. For example, a number of interventions have been recommended to reduce asthma symptoms caused by exposure to protein allergens found in natural latex gloves (44). Use of reduced-protein gloves during surgery has been documented to reduce airborne allergen levels (45). Latex-specific IgE levels in the serum of sensitized healthcare workers decline with time after the adoption of a policy regarding low-allergen gloves (46). Levy et al. (47) reported that among dental students, the adoption of a policy of using only reduced-allergen powder-free gloves diminished the onset of sensitization during training

from 11 to 0%. Thus, occupational intervention studies have indicated that control of antigen exposure can both reduce symptoms and specific IgE among sensitized individuals as well as prevent the onset of sensitization among newly exposed individuals. Clinical follow-up among persons with occupational asthma caused by a variety of agents has indicated that prompt control of exposures is associated with a better chance of improvement or resolution of symptoms and findings, whereas workers who have continued exposures have a poorer prognosis (23,48).

Irritant-Induced Asthma

Occupational exposures to irritants can result in airway hyperresponsiveness, bronchospasm, and persistent respiratory symptoms. This represents a third mechanism for WRA onset, in addition to exposures to high molecular weight allergens and low molecular weight chemical sensitizers. Symptoms and hyperresponsiveness, often called the reactive airways dysfunction syndrome (RADS), may develop after a single intense inhalational exposure to a respiratory irritant such as an acid or alkali (49). Although the clinical symptoms mimic asthma, the airway pathology associated with RADS may be distinguishable from the airway inflammation typically associated with asthma (50). A similar syndrome of persistent asthmalike symptoms has been observed among pulp mill workers who experienced repeated but less intense exposures to chlorine gas (51,52). Consistent with these workplace observations, a recent report has associated incident asthma among children with exercise in environments with high ozone exposure (53). Preexisting allergies may play a role in the development of asthma symptoms after repeated inhalation exposures to irritants (54).

Summary: Lessons from the Study of Work-Related Asthma

Studies of asthma in the workplace have demonstrated that with increasing levels of airborne exposure, an increasing proportion

of the exposed population is sensitized. These exposure–response relationships have been observed for high molecular weight allergens as well as low molecular weight chemical sensitizers. The susceptibility to sensitization varies among working populations (Figure 1). Workers who are susceptible may select out of exposed working populations, particularly if sensitization and symptoms develop, whereas studies in some settings find that a high proportion of workers are sensitized. Skin exposures may play a role in initial immunologic sensitization. For a given measured airborne exposure, atopic workers appear have an increased likelihood of becoming sensitized to high molecular weight allergens but not to low molecular weight occupational sensitizers such as diisocyanates. Concurrent exposure to airborne antigens with nonsensitizing chemical irritants (such as diesel exhaust particulate, nitrogen oxides, or tobacco smoke) may increase the likelihood of immunologic sensitization. Thus, the expression of atopy may at least in part be a result of nonsensitizing environmental irritant exposures. Even in the absence of specific sensitizing exposures, inhalational exposure to irritants can at times result in the development of persistent asthmalike symptoms (e.g., RADS). After sensitization has occurred, continuing exposure to an occupational sensitizer is often associated with persistent symptoms and airway hyperresponsiveness. Conversely, timely control of workplace exposure to sensitizers may result in improvement in both symptoms and immunologic sensitization, or even complete resolution of all symptoms and signs of asthma. Detailed study of such asthma cures may prove useful in understanding risk factors and mechanisms that control asthmatic airway inflammation in the general population.

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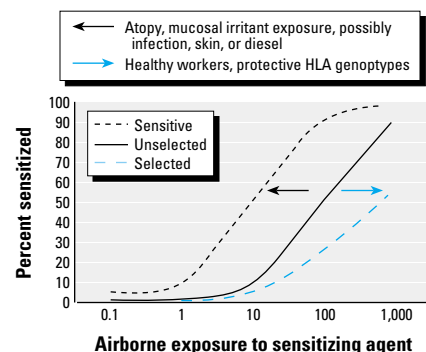


Figure 1. Factors influencing population susceptibility to sensitizing exposures.

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