

Recent developments in airway and nose occupational sensitizers

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Purpose of review

To describe the latest developments in the field of occupational asthma and occupational rhinitis in 2001 and 2002.

Recent findings

Several surveillance programs of occupational diseases, such as Observatoire National des Asthmes Professionnels in France, Surveillance of work-related and Occupational Respiratory Diseases in South Africa (SORDSA), Surveillance of Work-related and Occupational Respiratory Diseases (SWORD) in UK, have reported on the frequency of occupational asthma. The causative agents were mainly flour, isocyanates and latex. The common methods of diagnosis – questionnaires, cutaneous tests, Peak Expiratory Flow Rate (PEFR), bronchial hyperresponsiveness – still create controversy. In addition, the specific bronchial challenge, the classical gold standard of diagnosis, has its limitations since it cannot be performed in every case. Other methods have been assessed as inflammatory markers in induced sputum. Occupational rhinitis appears to be a poorly diagnosed condition.

Summary

Further studies are expected to explore the effect of environmental control and medical surveillance. The key to successful management of occupational asthma and occupational rhinitis may be prospective surveillance of the occurrence of specific IgE antibodies before the onset of allergic symptoms.

Keywords

occupational asthma, occupational rhinitis, diagnosis of occupational asthma, epidemiology of occupational asthma, etiologic agents of occupational asthma

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Abbreviations

FEV1 forced expiratory volume in 1 s
GST glutathione S-transferase

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Introduction

Occupational asthma induced by various inhalative agents is one of the most commonly reported lung diseases in many countries. The last few decades have allowed better understanding of the basic mechanisms and identification of a large number of substances to which workers become sensitized in a variety of occupational settings.

The purpose of this review is to describe the recent developments in the field of occupational asthma and occupational rhinitis which have occurred since October 2001.

Frequency

In the past 10 years several studies have addressed in different ways the frequency of occupational asthma. Surveillance programs have proved to be effective and two recent studies give information on occupational asthma in France [1•] and South Africa [2•]. Both are based on voluntary reports from pulmonology and occupational medicine practitioners. In 1997, 559 cases were reported in France, and over a period of 3 years (from 1997 to 1999), 324 cases were reported in South Africa. In France, the agent most frequently involved was found to be flour (23.3%), followed by isocyanates and latex; in South Africa, isocyanates and latex were the most common agents (isocyanates 16.6% in France, 16.7% in South Africa; latex 7.5% in France, 16% in South Africa). In South Africa, low molecular weight causative agents predominated (68%) over the high molecular weight agents. In both countries health care was one of the most frequent occupations at risk (in France 12%, in South Africa 16.4%). After more than a decade, Surveillance of Work-related and Occupational Respiratory Diseases (SWORD) is continuing to gather data on occupational respiratory disease in the UK [3•]: over the past 8 years, asthma shows no consistent signs of a decrease (1168 cases in 1999), and there is an apparent increase in mesothelioma cases (1032 cases in 1999). Epidemiological and clinical studies concerning occupational asthma have been performed in occupations exposed to well known occupational allergens such as flour in bakers and isocyanates in painters. Two recent publications concern latex allergy [4•,5•]. However, there have been no studies concerning the frequency of occupational asthma in dental personnel until now. Piirilä *et al.* [6•] evaluated the causes of respiratory hypersensitivity diseases in dental personnel and consulted the well known Finnish register of occupational diseases (from 1975 to 1998) and the register of the

Finnish Institute of Occupational Health (1990–1998). Among a total of 64 cases, they reported seven cases of allergic alveolitis, 28 cases of occupational asthma and 28 cases of occupational rhinitis, and one case of organic dust toxic syndrome. Incidence rate increased from 0 in 1998 to 105 in 1995 and then decreased to 31.8 in 1998. The most suspected causative agents are latex, chloramine T and substances containing acrylate and colophane. However, the authors do not examine in detail all the causes of the reported cases.

Decision trees and epidemiological criteria used in occupational asthma diagnosis

Decision trees have been proposed to confirm baker's and latex occupational asthma [7•,8,9•]. The diagnosis can be established stepwise: the decisional algorithm is based first on the clinical history and subsequently on the results of immunological investigations (cutaneous tests and Radio-Allergo-Sorbent-Test (RAST)). Peak Expiratory Flow Rate (PEFR) measurements out of work and at work are not performed by Talini *et al.* [7•]. The bronchial provocation test is the ultimate investigation which confirms the diagnosis [8]. Recently, Kurtz *et al.* [10] proposed a new methodology for latex challenge, safe and reproducible, by using a face shield and a flexible hood for exposing subjects. Bronchial challenges to nitrogen chloride in a challenge chamber, at concentrations occurring in swimming pools, assessed the susceptibility of swimming pool workers to airborne chloramines [11•]. Since some participants do not agree to perform challenge tests, there is still the necessity to include PEFR measurements as a diagnosis procedure [12].

From an epidemiological point of view, controversies still exist as to the best questionnaires to ascertain occupational asthma and occupational rhinitis. The presence of immediate skin reactivity or positive specific IgE to a high molecular weight occupational allergen is a good predictor. This is confirmed by prospective studies performed in apprentices exposed to two different high molecular weight allergens (latex and allergens from laboratory animals) [13•,14•]. For occupational asthma, the validity of functional tests for the surveillance of work places at risk was studied in a platinum salt industry. It was shown that neither forced expiratory volume in 1 s (FEV1) measurements nor determination of bronchial hyperreactivity was useful in early detection of individuals reporting work-related symptoms [15]. In another study concerning health surveillance of enzyme workers in soap and detergent industry, the authors advise performing nonspecific inhalation tests only in cases in which the diagnosis of asthma is uncertain following completion of a questionnaire [16]. So, it appears, according to experienced authors, that the role of functional measurements in tracking occupational

asthma is still open to discussion [17•,18]. Recent publications point out the need to perform analysis of sputum eosinophils which can be increased when occupational respiratory symptoms occur. This has been demonstrated in cyanoacrylate occupational asthma [19] and latex induced chronic cough [20]. Changes in sputum cell counts induced by exposure to occupational agents may precede the onset of functional changes. Furthermore, studies are still performed for research purposes as well as exhaled nitric oxide measurements which seem to be less specific than cellular analysis of sputum [21•,22].

Etiological agents

The etiological agents of occupational asthma or occupational rhinitis can be classified as high molecular weight compounds or low molecular weight compounds.

High molecular weight compounds

Enzymes, a model of high molecular weight compounds, may give rise to IgE-mediated sensitization and occupational asthma. In baker's asthma, fungal enzymes other than the classical α -amylase are used as additives. The potential allergenic role of glucoamylase has been investigated by Quirce *et al.* [23•] in four individuals, and occupational asthma was proven by bronchial provocation tests. Skin tests were positive both for glucoamylase and α -amylase and moderate cross reactivity could be assessed by IgE inhibition assays. In contrast, the baking additives, xylanase and cellulase, can induce occupational asthma without concomitant sensitization to other enzymes like α -amylase [24]. In practice, immunological evaluation of bakers should not be restricted to flour and α -amylase. Other enzymes have a high sensitizing potency like phytase and β -glucanase to which research and analytical laboratory employees can be exposed [25]. α -Amylase is one of the components of porcine pancreatic extract, and nurses involved in grinding and mixing porcine pancreatic enzymes were found to develop asthma, as confirmed by bronchial provocation tests [26]. In the 1960s proteolytic enzymes from *Bacillus subtilis* were found to be the cause of occupational asthma occurring in those involved in the manufacture of detergents. Despite the use of encapsulated enzyme preparations the risk of persistent enzyme allergy was outlined in 2000. In the study of Kizkin *et al.* [27], 23% of 65 workers were still sensitized to one enzyme (lipolase, savinase). A 10-year follow-up of the respiratory function tests showed a more than expected fall in Forced Vital Capacity (FVC) and FEV1 of these workers, especially in the enzyme sensitized group even in the absence of respiratory complaints. A recent case report induced by a *Bacillus subtilis* derived detergent protease demonstrates that occupational rhinitis induced by this enzyme can be associated with urticaria [28•].

Among food industry employees a large number of workers are exposed to numerous high molecular weight allergens which can induce immunological reactions. IgE and non-IgE mediated mechanisms can be involved and the different occupational reactions, reviewed by Aresery and Lehrer [29•], are occupational asthma, occupational dermatitis and hypersensitivity pneumonitis. Such reactions may occur at every level of the industry from growing and harvesting of crops or animals, to storage and processing procedures, and cooking of food substances. Among food allergens, high molecular weight proteins from seafood have led to frequent reports of allergic reactions. An excellent review on occupational seafood allergy was published by Jeebhay *et al.* [30•]. Relevant manuscripts were identified from 1966 to 2000; more recently published and unpublished studies, as well as recent case reports, were also taken into account. All seafood-processing environments were checked according to the type of job carried out by the workers suffering from the allergy, the different constituents of seafood are listed, and physical, biochemical and immunological characteristics of seafood are given in detail. Gad C1, the main allergen in codfish and other allergens from cod and salmon, belong to a group of muscle tissue proteins, parvalbumine, a calcium binding protein, whereas crustacean allergens are tropomyosins. The reported prevalence of occupational asthma to seafood varies from 7 to 36%, and that of occupational protein contact dermatitis from 3 to 11%. Nearly 20 epidemiological studies are carefully analysed along with an identical number of case reports. A few studies have shown a dose response relation between the level of exposure to seafood allergens and the prevalence of sensitization. This highlights the importance of the study reported by Boeniger *et al.* [31•] concerning exposure to protein allergens in egg processing facilities. It appears that exposure to egg proteins is maximal in departments where eggs are broken and in the transfer section. Other departments (i.e. pasteurization, drying departments) have lower exposure. The amount of total proteins/m³ was correlated to some of the specific egg proteins (ovalbumine, ovomucoid, lysozyme). It was found that 53% of the total aerosol mass was respirable (<3.5 µm); the concentrations of airborne egg protein were 50–300 times higher than those found for protein aerosols of other occupational agents. Moreover, aerosolized egg proteins are the predominant source of all proteins found in the air (measured personal air exposure concentration, 185–604 µg/m³). Egg inhalative proteins can also be a problem in bakers and confectionery workers. Six patients involved in these occupations are reported by Leser *et al.* [32•]; they suffered from conjunctivitis, rhinitis and four of them from asthma. Subsequently, three out of six reported systemic allergic reactions after ingestion of food containing eggs; this points to a classical syndrome which associates respira-

tory and food induced allergic reactions caused by the same allergen present in the two routes of exposure. Recently it has also been shown that lupine seed flower, a classical food allergen, is an important cause of occupational asthma (as demonstrated in seven patients in an agricultural research center) [33•].

Airborne measurements

An approach to ascertain the characteristics of exposure necessary to induce sensitizations can be performed by measuring airborne allergens in occupational settings. Baur [34•] details methods for measurement of airborne latex allergens in two different types of area sampling, for 20 h. When powdered high-allergen gloves were used, high dust concentrations and measurable latex allergens were observed. The use of slightly powdered gloves (27.8 µg/g of rubber) generated dust but no measurable latex allergen (sensitivity of the method 0.2 ng per 14 m³ air). Well functioning ventilation systems and a fresh air supply resulted in much lower concentrations or no latex aeroallergens. When powdered latex gloves were replaced by nonpowdered or synthetic gloves, experiments performed in five rooms showed that after 1 day only borderline concentrations or no latex allergens were present. Baur calculated a statistical latex allergen threshold of 0.5 ng/m³, above which an increased prevalence of sensitizations and symptoms occur. In Ontario, where interventions have been performed since the early 1990s, including nonutilization of powdered gloves, a reduced number of claims were observed (one or two cases per year compared with 10–12 per year) [35•].

Heederick and Houba [36•] tried to define quantitative risk assessment for wheat dust and allergen exposure and wheat sensitization; they used advanced statistical analysis (generalized additive models and smoothed plots) in addition to classical epidemiological approaches. The exposure threshold (no observed effect level) for specific wheat sensitization was 0.5–1 mg/m³ of inhalable dust. It appears that the difference in sensitization risk is small in absolute terms at lower exposure levels. The analysis with symptoms (occupational asthma or rhinitis) and sensitization as critical endpoints showed a steeper relationship for sensitization only. The authors explain these findings by the fact that few sensitized individuals are symptomatic at lower exposure levels, while almost all sensitized individuals are symptomatic at intermediate allergen exposure levels.

Among occupational asthma induced by high molecular weight allergens from animal sources, one important cause occurring worldwide is spider mite induced asthma. Kim and Kim [37•] present a review on the subject: the phytophagous mites are important allergens for fruit cultivating farmers (citrus and apples) and seem

to have increased substantially in the fruit cultivation industry since the introduction of pesticides.

Low molecular weight compounds

Diisocyanates, highly reactive chemicals used in the production of polyurethane, are low molecular weight agents that are most frequently involved in occupational asthma. Redlich and Karol [38•] published an expert review on clinical aspects and immunopathogenesis. Apart from the respiratory tract, the skin may be a potential route of sensitization of isocyanates and a recent report documents routine diisocyanate skin exposure in autobody shop workers [39].

Biological monitoring of hydrolysed urine samples for diamine is sufficiently sensitive to detect the diisocyanate product at and below the current permissive exposure limit of 5 ppb. Detectable levels of diamine have also been found in nasal lavage fluid [40•]. An antibody that does not cross react with other diisocyanates has recently been developed to detect hexamethylene diisocyanate exposures [41]. A new insight into the pathogenesis of diisocyanate asthma comes from the knowledge of an important target for diisocyanates, which is glutathione (GSH). In-vitro studies using human bronchial epithelial cell cultures showed that an exposure to 20 ppb (the current permissible limit) reduced intracellular GSH [42]. This could lead to oxidative damage and contribute to the loss of airway epithelium. Moreover, diisocyanates may react with proteins via GSH conjugates and the formation of protein conjugates can give rise to immunological reactions. Therefore in the presence of decreased GSH conjugation, related to deficient glutathione S-transferase (GST) genes, impaired immunological responses could be suspected. Different groups have investigated the relation of GST-P1 genotypes and susceptibility to diisocyanate occupational asthma [43•,44•]. Piirilä [43•] investigated 109 workers with diisocyanate occupational asthma and 73 controls. Lack of the GST-M1 gene was associated with an increased risk of diisocyanate-induced asthma and other GST phenotypes were associated with diisocyanate specific IgE and a late reaction after bronchial provocation. The study of Mapp *et al.* [44•] concerned the determination of frequency of GST genotypes in 92 workers with Toluene Di-isocyanate (TDI) induced asthma and 39 asymptomatic workers. Their data suggest that homozygosity for the GST-P val allele confers protection against TDI induced asthma and bronchial hyperreactivity. These apparently non-concordant results can be related to the selection of study participants and should be confirmed in larger cohorts. Workplace diisocyanate exposures are difficult to quantify and control exposure can occur as a mixture of aerosol and vapor; moreover different monomeric and polymeric species can be found. The aim of the work of

Melin *et al.* [45•] was to characterize emitted aerosols from the thermal degradation of flexible polyurethane foam. At a temperature between 250 and 300°C an aerosol with a geometric mean particle diameter of 30–50 nm was produced. The polyurethane foam emitted contained between 5 and 9% TDI, and between 2 and 6% TDI monomers in the particle phase. This study underlines the necessity to monitor submicronic particles for evaluation of air pollution in environments in which polyurethanes are heated.

Two decades ago, legislation was introduced for the monitoring of isocyanate concentrations at work (an 8 h average concentration below 5 ppb and short-term exposure below 20 ppb). In a recent publication, Tarlo *et al.* [46•] examined the number of allowed claims for occupational asthma induced by diisocyanates in Ontario. They showed that a significant change occurred in the proportion of occupational asthma cases induced by isocyanate and occupational asthma cases induced by other causes between 1987 and 1993. A total of 425 claims for occupational asthma as a result of isocyanate were allowed between 1980 and 1993 (64% in 1988 and only 35% in 1993). Throughout the study period, asthma induced by diisocyanates was diagnosed earlier and was milder at the time of diagnosis than occupational asthma from other causes, possibly as a result of the surveillance program.

Occupational rhinitis

Occupational rhinitis appears to be a poorly diagnosed condition, especially by ENT specialists [47]. Its prevalence, however, is increasingly studied in those exposed to known allergens such as latex [48•]. In workers involved in heating polyurethane, a chronic rhinitis may occur and inflammation markers have been detected in lavage nasal fluids [40•]. Nasal symptoms may also occur without objective nasal inflammation in nasal lavage; this has been observed in workers exposed to soft paper dust complaining of symptoms of nasal blockage, nasal crusting and impaired sense of smell. Mucociliary clearance could be impaired by dust ranging in concentration from 0.5 to 10 mg/m³ in exposed workers [49•].

Conclusion

In occupational asthma, no consistent signs of a decrease in the condition have been shown over the past 2 years. Threshold values which induce sensitization to occupational agents need to be determined. New allergens (high molecular weight as well as low molecular weight agents) are continuously being discovered in occupational asthma and rhinitis. Consequently, standardized extracts for skin testing with these new agents should be made available. Moreover, new means have to be assessed as markers of inflammation, especially analysis of induced sputum. As there have been more studies

carried out on asthma, it remains difficult to determine the prevalence of occupational rhinitis in the working population.

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