

New Occupational and Environmental Causes of Asthma and Extrinsic Allergic Alveolitis

David Fishwick, MBChB, FRCP, MD

KEYWORDS

- Asthma • Extrinsic allergic alveolitis • Hypersensitivity pneumonitis • Antigen • Allergen
- Respiratory • Occupational • Environmental

KEY POINTS

- Asthma and extrinsic allergic alveolitis (EAA) remain prevalent respiratory diseases, and remain the cause of a significant disease burden.
- Both conditions have strong causative links to the environment.
- This article reviews the recent occupational and environmental causes described for these 2 conditions.

INTRODUCTION

Asthma remains a highly prevalent childhood and adult disease. Although research activity over recent years has contributed greatly to the understanding of this condition, and in particular asthma of childhood origin and its natural history, important causes of later-onset asthma caused by factors encountered at work, or in the wider environment, and the outcomes of this subset of disease, are less well researched. Missing the links between exposure to antigenic or irritant substances and the development of asthma is potentially disastrous for affected workers and their similarly exposed colleagues who may be at risk of further incident disease. There are parallel implications for other potentially work-related causes of immune-mediated respiratory conditions, in particular extrinsic allergic alveolitis (EAA, also known as hypersensitivity pneumonitis).

This review summarizes the recent biomedical literature relating to specific, as well as more general, aspects of selected agents that have been shown to be associated with asthma or EAA, including exposures that have been found capable of eliciting both responses. The general subject of occupational asthma has been extensively reviewed elsewhere,^{1,2} including a major textbook on this topic.³ The emphasis here is on *newly* appreciated causes of disease or emerging insights into mechanisms of initiation and progression.

By its nature, the literature on emerging hazards is largely made up of a potpourri of case reports or small case series that document interesting presentations of disease or workplace investigations, consequent upon an initial suspicion that a new exposure scenario or a novel agent may be responsible for causing respiratory illness. Consistent with the focus on new and emerging

The content of this publication, including any opinions and/or conclusions expressed, are those of the author alone and do not necessarily reflect HSE policy.

Centre for Workplace Health, Health and Safety Laboratories, The University of Sheffield, Harpur Hill, Buxton, Derbyshire SK17 3JN, UK

E-mail address: d.fishwick@sheffield.ac.uk

Clin Chest Med 33 (2012) 605–616

<http://dx.doi.org/10.1016/j.ccm.2012.07.002>

0272-5231/12/\$ – see front matter Crown Copyright © 2012 Published by Elsevier Inc. All rights reserved.

data, this review is limited primarily to citations appearing from 2007 onward. To be as broad as possible, however, and recognizing that relevant exposure conditions are frequently encountered internationally, information from abstracts in English summarizing non-English language publications has been included.

It is evident, appraising the breadth of the recent literature, that asthma and EAA remain enigmatic diseases. Articles identified for this review deal not only with new at-risk exposed populations, but also novel causes of asthma and alveolitis. Recent data also suggest that a number of allergens are being characterized and newly incorporated in clinical testing. Indeed, for associations that may appear to be well understood, the recent literature demonstrates the relative naivety of our understanding of the mechanistic role played by occupational and environmental exposures. Hamlet summarized the situation well: "There are more things in heaven and earth, Horatio, than are *dreamt of* in your philosophy!"

ASTHMA OVERVIEW

In an attempt to stratify the asthma literature into clearly definable subcategories of disease, the recent literature is categorized into 3 sections, first dealing primarily high molecular weight asthma-causing sensitizers; second, low molecular weight allergens; and third, occupational and environmental mixed low and high molecular weight potential exposures. The low molecular weight literature generally relates to chemical exposures (which can be synthetic or naturally occurring), whereas reports of high molecular weight substances generally focus on agents of biologic origin, as these are *a priori* more likely to be of high molecular weight.

ASTHMA: HIGH MOLECULAR WEIGHT AGENTS

A fascinating miscellany of evidence has emerged in relation to sensitization to high molecular weight agents, including exposures as diverse as *Ascaris lumbricoides tropomyosin* to laxative allergy and on through to risks posed by exposure in an insect-breeding facility.

The potential to develop TH2-type responses to *A. lumbricoides tropomyosin* was recently identified,⁴ given its central role in the development of immunity to parasites. This allergen was found to bind specific immunoglobulin (Ig)E, and induce mediator release from effector cells. This effect was found to be cross-reactive to mite tropomyosins. Whether this mechanism and allergen are indeed important in the pathogenesis of environmental asthma in

tropical regions remains to be seen. Similarly in terms of environmental factors, the role of an array of olive pollens has been reexamined as a major contributor to allergic diseases in Mediterranean areas.⁵ Specifically, at least 20 proteins with allergic activity have been demonstrated in olive pollen, and 10 of these have been characterized (Ole e 1 to Ole e 10). Response to Ole e 1, considered the most important of these allergens, is now identified to have a significant genetic influence. The authors postulate that exposure to high doses of olive pollen allergen in a specific genetic context can trigger different allergic conditions, including asthma.

Such "environmental" allergens can also be relevant to occupational settings. For example, allergy to *Sinapis alba* pollen (white mustard), an entomophilic species included in the Brassicaceae family, associated with allergic symptoms and in certain cases positive nasal challenge, has been recently described in a small group of olive farmers.⁶ Twelve orchard workers with a combination of rhinitis and (or) asthma were investigated with skin prick tests, alongside air monitoring to assess levels of exposure. The clinical relevance of the allergy, identified in all workers by the presence of specific IgE, was confirmed with a positive nasal challenge test, and levels of exposure to *S. alba* pollen were identified to be high in work environments, with peaks of 1801 grains/m³ detected. These levels were shown to be higher than background environmental levels.

Table grape workers also appear to be at risk of the potential for the 2-spotted spider mite to cause sensitization and allergy end points. A South African group⁶ has reported specific sensitization to the mite *Tetranychus urticae*, and present data to support the clinical relevance of this sensitization. A further novel, predominantly indoor-encountered allergen has recently been described. Nakazawa and colleagues⁷ report sensitivity to Asian ladybugs (*Harmonia axyridis*), introduced between 1916 and 1990 to the United States. Given that these beetles do not tolerate cold, they migrate indoors during winter months and are consequently a potential source of indoor allergen (of course, which can additionally include indoor occupational settings). Testing of 20 individuals with allergic symptoms living in Asian ladybug-infested accommodation confirmed positive specific IgE in a high proportion, and a lesser proportion of those with asthma. Interestingly, cross reactivity to *Blattella germanica* was found only among those with additional exposure to cockroaches.

Soybean exposure continues to interest the research community. Cummings and colleagues⁸ have recently described results of a further study of workers exposed to the products of soy bean

processing. Of interest, both soy-specific IgE and IgG were raised in exposed workers in comparison with controls, and it was specifically the IgE response that was associated with a threefold greater risk of current asthma, or asthmalike symptoms. Work from South African soybean processors⁹ produced consistent findings, and identified that the strongest predictor of work-related nasal symptoms was sensitization, as judged by specific IgE, to soybean. Recent further work in soy flake-processing workers¹⁰ has bettered the understanding of the specific immune response to soybean. Data from 135 such workers demonstrated that the prominent proteins that bound soy IgE were the high molecular weight storage proteins, β -conglycinin (Gly m 5) and Glycinin (Gly m 6). In contrast, no specific IgE reactivity could be identified to lower molecular weight allergens.

Coffee exposure, and in particular exposure to the contaminant *Neurospora sitophila*, has been described as a recent cause of occupational asthma in 2 separate case reports.^{11,12} The latter identified exposure to *Chrysonilia sitophila*, the asexual state of *N sitophila*, as the likely cause of asthma in a 43-year-old man exposed to coffee beans contaminated with a powder containing this agent. Serial peak expiratory flow (PEF) recordings identified an immediate response following a workplace challenge (a 20% fall) and specific IgE was identified to an isolate of *C sitophila*, biotinylated with a prewashed streptavidin ImmunoCAP. The exact nature of the wider range of coffee antigens capable of causing asthma has been long debated¹³ and is not yet resolved.

Various other likely high molecular weight allergens recently described as causing asthma specifically include *Plantago ovata* seed, as part of a laxative preparation, in health care workers,¹⁴ *Artemia* fish fry feed in aquaculture,¹⁵ konjac glucomannan in a food worker,¹⁶ and gum arabic.¹⁷ The latter as a cause of allergic disease, reported by a Finnish group, is supported by the identification of 4 cases (from 11 workers studied) who had developed occupational asthma as a result of exposure in the food industry. Gum arabic, a complex mix of glycoproteins and polysaccharides, is used as a food stabilizer and should be considered as a potential cause of asthma and rhinitis in exposed workers with allergic symptoms.

ASTHMA: LOW MOLECULAR WEIGHT AGENTS AND CHEMICAL IRRITANTS

Cleaning agents continue to attract the limelight and underscore that allergic sensitization with an amnestic response, irritant-induced new-onset

disease, and aggravation of preexisting asthma can all occur in association with this broad group of materials. Evidence of sensitization to chloramine T, used as a disinfectant, was recently described in a nurse working with this agent, in addition to glutaraldehyde.¹⁸ The individual reported asthma symptoms following exposure to both these agents in the endoscopy suite, but subsequent specific inhalation challenge (SIC) testing confirmed a negative challenge to glutaraldehyde but a positive dual reaction following inhalation of 0.5% solution of chloramine T. The wider issue of the role of cleaning agents as causes of asthma was also recently reviewed by Zock and colleagues,¹⁹ who concluded that recent publications have strengthened the evidence linking cleaning agent exposures and specifically the development of asthma. This link appears to hold for both asthma caused by, and aggravated by, cleaning agent exposures. The authors postulate that cleaning sprays, chlorine bleach, and other disinfectants may be the most likely candidates.¹⁹

There are no recent data to assist differentiation in relation to causative mechanisms of cleaning product-associated asthma. It is equally plausible that low molecular weight chemicals in cleaning agents may exert a primary irritant effect, rather than that mediated either via haptation, and thus IgE, mechanism, or indeed other as yet uncharacterized mechanisms (for example, adjuvant effects facilitating sensitization to other exposures).

Health care workers exposed to the antibiotic group of cephalosporins have also recently been identified²⁰ to display evidence of sensitization, as judged by specific IgE, to various cephalosporin-human serum albumin (HSA) conjugates. Using both exposed workers and a nonexposed control group, relatively high (but variable agent to agent) levels of sensitization were identified; 17.4% for any cephalosporin, 10.4% for cefotiam, 6.8% for ceftriaxone, and 3.7% for ceftizoxime. Overall, these levels were higher than those identified using skin prick testing. Of interest, a previous history of atopic dermatitis appeared to be a risk factor for the presence of IgE to the cefotiam-HSA conjugate, at least suggesting that a dermal route of sensitization may be important. This assertion is important to unravel in more detail, given the importance of developing effective simple preventive strategies for exposed workers.

A Spanish observational study²¹ has further added to the evidence base relating to the propensity for acrylates to cause both allergic skin problems and asthma. Acrylates in this context were used to sculpt artificial nails, and the investigators reported a case series of 15 female patients who

had presented over a prolonged period to their institution. Most patients were beauticians, although one client was included in the series, and exhibited a very wide range (1–15 years) of latent period of exposure during which the investigators postulated that sensitization had occurred. All had certain features of dermatitis, and 3 (including the client, interestingly) had a diagnosis of asthma. Patch testing identified that the most frequent allergens were ethylene glycol dimethacrylate (13/15, 86.7%), hydroxyethyl methacrylate (13/15, 86.7%), triethylene glycol dimethacrylate (7/15, 46.7%), 2-hydroxypropyl methacrylate (5/15, 33.3%), and methyl methacrylate (5/15, 33.3%). The investigators concluded that acrylate monomers are important, primarily skin sensitizers, although no challenge data were presented in the cases where asthma was thought to be causally related to exposures.

Metabisulphite, a low molecular weight agent previously intermittently associated with the development of allergic disease, was implicated again as the likely cause of asthma in a Dublin Bay prawns fisherman.²² The investigators describe long-term exposure to these creatures and the development of work-related respiratory symptoms. An added complication appeared to be the breakdown of ventilation systems used aboard a trawler designed to reduce these exposures. No tests of immunologic response or SIC were performed, although negative skin tests to standard allergens were reported.

Asthma related to a further low molecular weight agent was described following exposure to an electrostatic powder paint containing 2.5% to 10.0% triglycidyl isocyanurate (TGIC) in a 28-year-old worker coating aluminum frames.²³ Serial peak-flow measurements noted increased diurnal variation on work days (up to 46%) and nonspecific bronchial reactivity varied between periods of work and rest, and an isolated late reaction (20% fall in forced expiratory volume in 1 second) was observed following SIC, this response not being seen following work days. Attempts were also made to assess for evidence of immunologic response to TGIC, but no evidence of specific IgE was detected by enzyme-linked immunosorbent assay, and no IgE-binding bands were found by immunoblot analysis of patient and control serum.

ASTHMA ASSOCIATED WITH COMPLEX, MIXED EXPOSURES

Various recent studies have addressed workplaces with the potential for complex and mixed exposures, a summary of which is included here to provide the reader with a flavor of these reports.

In addition, studies relating to potential environmental causes, by definition inherently complex and mixed, will also be dealt with where appropriate.

Job tasks with wood exposure continue to attract attention. Burton and colleagues²⁴ describe a case series of occupational asthma related to medium-density fiberboard exposures (a mix of soft and hard woods bound using a resin and formaldehyde), supported variably by work-related changes in PEF and SIC testing. Schlünsen and colleagues²⁵ remind us of the limitations of immunologic testing in this group of workers, with specific reference to limitations of pine and beech sensitization testing.

Harris-Roberts and colleagues²⁶ also identified a rather unusual workplace as being associated with occupational asthma. This group identified occupational asthma as a consequence of working with multiple, presumably, high and low molecular weight allergens in an insect-breeding facility, including locust and mealworms. Work with fish has also been described recently as a cause of asthma in South African saltwater fish-processing workers²⁷ and fish-farm workers exposed to turbot.²⁸

Patiwael and colleagues²⁹ have returned to follow up their cohort of workers exposed to Bell pepper pollens. Originally fully investigated in 1999 when a high level of sensitization was found, this group of workers was reevaluated using a questionnaire and further skin prick testing. Over the follow-up period, cumulative incidences for sensitization respectively to bell pepper pollen, work-related rhinitis, and asthma symptoms were found to be 9%, 19%, and 8%. The presence of atopy and, interestingly, smoking were identified as risk factors for developing work-related symptoms.

Occupational groups commonly reported to surveillance schemes with occupational lung diseases and particularly asthma, and indeed identified in large epidemiologic studies as having levels of self-reported asthma include bakers, cleaners, and health care workers. The debate relating to the exact causative agent or agents responsible for baker's asthma continues to simmer. Rye allergens have long been assumed to play a role in the development of this disease in addition to the established role of wheat flour. Letrán and colleagues³⁰ reported 2 isolated cases of asthma where rye was thought to be central to causation. Both had evidence of asthma and rhinoconjunctivitis, and both had positive SIC to rye, but not to wheat flour alone. Immunoblotting suggested that rye flour enzymatic inhibitors might be responsible. Wheat lipid transfer protein was

also recently described as a further putative allergen responsible for baker's asthma.³¹

Two recent articles deal with allergy to lupin, a diverse and beautiful species, mostly comprising herbaceous perennial plants and shrubs with a characteristic leaf shape. The yellow legume seeds of lupins, commonly called lupin beans, are edible and popular. The first of the 2 articles explores allergic sensitization at work.³² A cross-sectional study of a food-processing company, with workers exposed to lupin, identified high levels of specific sensitization (21%), the latter clearly linked to allergic symptoms of rhinitis and asthma. Although only small numbers were challenged, one worker had a dual response following SIC.

The second article³³ provocatively, yet perhaps aptly, titled "Lupin allergy: a hidden killer at home, a menace at work," reminds us that allergy to such plants is only relatively recently appreciated, the consequences poorly understood, and that exposure at work and at home can cause the typical allergic combinations of asthma and rhinoconjunctivitis. Possible cross-reactivity to peanut allergy is also discussed, and the investigators believe that heightening awareness of this novel allergen is key to preventing future cases of allergic disease. On balance, these probably represent primarily proteinaceous high molecular weight interactions.

Environmental, as opposed to occupational, exposures are also of interest in this context. In reality, these "real life" environmental exposures are a complex, poorly characterized mix of varying antigens and irritants. As these are difficult to characterize accurately, they are dealt with in this section. The urban environment has again been placed into focus in relation to causation of asthma and allergy, with 2 recent publications relating to the contribution made by horse allergens, perhaps more typically associated with rural environments. Long understood to be allergenic to humans, the role of horse allergen has been assessed by 2 publications from the same Italian group. By assessing a large number of consecutive patients from an outpatient clinic environment, Liccardi and colleagues³⁴ identified approximately 3.5% of all those with positive skin prick tests to common allergens to be sensitized to horse dander sensitization. Interestingly, no patients were sensitized solely to horse dander, although only a minority of those sensitized reported regular horse contact. The clinical significance of these findings is less clear, given the lack of contact to horses for most of those sensitized, although most did complain of a combination of respiratory and rhinitic symptoms.

Similarly, work from the same group, published in 2011, looked further afield in Italy,³⁵ collecting

data from more than 3000 patients recruited from similar centers. Slightly higher levels of sensitization to horse dander were seen, with approximately 5.4% of those with a positive skin prick test to any tested allergen having evidence of horse sensitization. A similar mix of self-reported horse exposure was seen. It remains to be determined whether the development of such sensitization is of clinical relevance for those patients living in a predominant urban environment without regular horse contact.

Various other indoor allergens have attracted new interest in the recently published evidence base, and include further evidence relating to cockroach sensitization in children, silverfish allergen, and the role of mouse allergen. A recent Italian study,³⁶ designed primarily to assess point prevalence of sensitization to German cockroaches, identified that high levels of sensitization were seen in older children to *Blattella germanica* (BG). The number of other positive skin prick tests also increased the likelihood of BG sensitization. The investigators also estimated a high population attributable risk of approximately 20% for the effects of BG sensitization on the development of rhinoconjunctivitis.

Less familiar perhaps as a potential important indoor allergen, Barletta and colleagues³⁷ described the potential for sensitization to silverfish (*Lepisma saccharina*), one of the most primitive living insects commonly identified in the indoor environment. The investigators are currently developing an extract, so that future studies can incorporate allergen testing to this insect. *Lepisma* has been cloned and characterized as a silverfish tropomyosin and is likely to be the basis of future allergen assessments.

The role of mouse allergen is highlighted by 2 publications. The first, published in 2006,³⁸ studied US-based schoolchildren with a combination of questionnaire and assessments of indoor exposure to mouse allergen, Mus m 1. Twenty-six percent of the studied children were found to be sensitized to mouse, and interestingly there appeared to be a relationship within the sensitized group between levels of Mus m 1 exposure and reported asthma symptoms and reliever use. These effects withstood the typical corrections applied for confounding and bias. The investigators' conclusions at that time were consistent with the conclusions of a subsequent overview article published in 2009,³⁹ that exposure to mouse allergen is associated with substantial asthma morbidity, including hospitalizations, and that pest management is recommended for sensitized patients with asthma.

Recent Finnish work⁴⁰ identified certain HLA associations with the development of sensitization to cow allergens, part of a group of allergens in the

family of lipocalin proteins. The HLA-DR/DQ genotypes of 40 Bos d 2-sensitized individuals were analyzed, and compared with a larger group of unrelated Finnish participants. Various HLA class II alleles were found to be overrepresented in those sensitized.

EAA OVERVIEW

Despite its recognition for many decades, new and novel causes of EAA continue to surface in the peer-reviewed literature. Broadly speaking, causes identified in this review fall into 2 categories: first, a traditional, or, in a sense, anticipatable group of causes, largely microbiological in nature, and second, a rather more unusual or less intuitive group of possible causes. Paralleling the recent literature relating to asthma, most of the recent articles identified deal with small numbers of cases or isolated case reports. Consequently, criticism can always be leveled at the diagnostic rigor with which a diagnosis is made or how effectively differential or alternate diagnoses have been excluded. Nevertheless, the inherently fascinating nature of these observations is now detailed, dealing first with the classical, or anticipatable, causes of this condition.

EAA ATTRIBUTABLE TO CLASSICAL OR ANTICIPATABLE CAUSES

Duvet exposure has previously been associated with the development of EAA, and a Japanese case report again highlights this risk. Nishikawa and colleagues⁴¹ describe a case of shortness of breath, cough, and fever in a 44-year-old duvet manufacturer, typified by ground glass opacities on HRCT, coupled with a positive lymphocyte proliferation test to pigeon serum. Clinical improvement occurred on removal from occupational exposures.

Other various fungal or related microbiological exposures thought to be causative of EAA include *Thermoactinomyces vulgaris* exposure from a dehumidifier (Otsuka and colleagues,⁴² with supportive biopsy and precipitating antibodies), *Aspergillus niger* in a greenhouse worker working cultivating roses (Hamaguchi and colleagues,⁴³ with supportive biopsy and precipitating antibodies), and air conditioner exposures (Ishikawa and colleagues,⁴⁴ with supportive biopsy and challenge, but negative precipitating antibodies).

Thermoactinomyces were also implicated in a further cases of EAA related to sugar cane exposure in Nicaraguan workers.⁴⁵ This Italian contribution describes the consequences of bagasse exposure in a group of exposed workers, with precipitin response to *Thermoactinomyces*

sacchari and *T vulgaris* being related to the presence of reported respiratory symptoms. No further clinical characterization was undertaken, given the epidemiologic and workplace-based nature of the study.

Work in food preparation continues to carry a significant risk of EAA. Further case reports support exposure to Shiitake mushroom and dry sausage mold as causative. Kai and colleagues,⁴⁶ a Japanese group, describe a case of Shiitake mushroom chronic EAA in an elderly man with long-standing cough and breathlessness, although no biopsy evidence was given to support the assumption. An associated literature review identified a further 5 previous Japanese cases caused by the same agent. Guillot and colleagues⁴⁷ add to the gastronomic causes of EAA by describing 3 cases of EAA associated with occupational dry sausage mold exposure. Each case exhibited typical HRCT features and, although no biopsy data were included, each case was supported by positive precipitating antibodies to an extract of the sausage (containing, among presumably a complex mix of potential antigens, penicillium), and improved clinical state following cessation of exposure. Similarly, a recent Spanish⁴⁸ article described 5 cases of "Chacinero's lung," 3 with an acute form, and 2 with a subacute form. Bronchoalveolar lavage (BAL) in 3 patients showed significant lymphocytosis (17%, 40%, and 40%), with a CD4/CD8 ratio of less than 0.6. Specific IgG to *Penicillium frequentans* and *Aspergillus fumigatus* were positive in 3. No biopsy data were recorded.

The use of musical instruments play their part in the cause of EAA. Two case reports identify playing trombone (trombone player's lung⁴⁹) and saxophone⁵⁰ as being significantly bad for your health. The unfortunate saxophonist was a 48-year-old patient being investigated for interstitial lung disease, during which an open biopsy was performed, revealing a nonspecific interstitial pneumonitis appearance. A lymphocytic BAL led to further assessment of the saxophone itself, played for a hobby. Two fungi were isolated from this, *Ulocladium botrytis* and *Phoma* sp, against which the patient's serum had developed antibody responses. The investigators raise the wider and unknown issue of how commonplace colonization is in these, and related, instruments. The 35-year-old saxophonist was a professional musician who complained of a very long-standing, unabating nonproductive cough. HRCT showed evidence of a mosaic pattern on the expiratory views, and the diagnosis was suspected after improvement following a period of not playing the offending instrument, the interior of which revealed a biofilm with fungal elements, and isolation of

Mycobacterium chelonae/abscessus group, *Fusarium* sp, as well as scanty *Stenotrophomonas maltophilia* and *Escherichia coli*. The cough improved following regular cleaning.

Selected indoor water-related pursuits also appear to have adverse health consequences. Engelhart and colleagues⁵¹ describe a case of EAA in a child, highly likely to be related to exposure to fungal contaminants of indoor hydroponic cultivation. Supported by precipitins to *Aureobasidium pullulans*, a lymphocytic BAL and consistent biopsy, this case occurred in a 14-year-old girl. She improved markedly when the offending plants were removed from the home. Exposure to microbiological contaminants of poorly maintained hot tubs continues to be identified as a cause of EAA. First described more than a decade ago (for example, see Kahana and colleagues⁵²), a Canadian group⁵³ recently described a further 2 cases of this condition, one of which presented acutely, whereas the other presented as a more chronic process. Even though the exact cause probably varies among cases, nontuberculous mycobacterium have been frequently implicated.

It appears that poorly maintained hot tubs not only carry a risk of EAA, as described by Huhulescu and colleagues.⁵⁴ This Austrian group describes a fatal *Pseudomonas* pneumonia in a previously fit 49-year-old woman. This event occurred shortly after returning from a spa weekend; water samples from the hot tub revealing 37,000 colony-forming units of *Pseudomonas aeruginosa* per 100 mL. The investigators postulated that a massive biofilm had been produced in the bath circulation system as a consequence of substandard maintenance.

Other perhaps classical exposures recently associated with EAA also include steam iron exposure, previously described and accepted as a cause⁵⁵; cork exposure⁵⁶ causing the EAA called suberosis, this recent case based on BAL results and a supportive biopsy; exposure to *Trichoderma viride* from a contaminated ultrasonic humidifier,⁵⁷ confirmed by immunologic responses and improvement following removal of exposure; and work in citrus farming.⁵⁸ The latter report was of a cluster of 3 farmers with EAA confirmed by a combination of clinical features, including symptom improvement on removal from exposure and challenge testing. *Aspergillus* and *Penicillium* species were postulated by the investigators to have relevance, although testing in the patients revealed mixed results.

EAA FROM LESS ANTICIPATABLE CAUSES

Perhaps of rather more interest are a group of articles dealing with likely diagnoses of EAA caused

by agents that are less intuitively likely to be associated with this condition. Agents and exposure types in this group included zinc fume, paints, the hydrofluorocarbon 1,1,1,2-tetrafluoroethane, and the enzyme phytase. Further evidence is also included in this group relating to the previously described respiratory problems in yacht manufacturers.

Miyazaki and colleagues⁵⁹ described a respiratory problem in a 55-year-old welder after having inhaled the products of a galvanizing process on mild steel, with an array of HRCT findings that the investigators concluded were consistent with EAA, including diffuse centrilobular nodules, panlobular ground-glass opacity, and interlobular septal thickening. The patient underwent BAL, which was lymphocytic in nature, again interpreted as supportive of an EAA, as opposed to an alternate diagnosis, although lack of a definitive biopsy does leave unclear the nature of the actual pathology. Additionally, the potential for mixed exposures in welding is always present.

Other rather unusual exposures reported to cause EAA include 1,1,1,2-tetrafluoroethane⁶⁰ in the context of using this agent as a coolant for a hair-removal diode laser. The young woman exposed became unwell, complaining of shortness of breath, with an associated fever. HRCT showed diffuse centrilobular opacities, and biopsy noted eosinophil infiltration, which recurred following SIC to this agent. Although the investigators report this as EAA, the presence of an eosinophilic response suggest that a wider set of differential diagnoses should perhaps be considered.

Phytase enzyme used as an additive to cattle feed has also been highlighted in a recent publication as a potential contributor to EAA. The former case diagnosis⁶¹ was supported by restrictive lung physiology, typical radiology, lymphocytosis in bronchoalveolar lavage fluid, and a positive exposure test at work. Occupational contact dermatitis and allergic rhinoconjunctivitis has also recently been attributed to lactase exposure.⁶²

The yacht and luxury boat-manufacturing story continues with this American group reporting a further case of possible EAA associated with this type of work. Volkman and colleagues⁶³ report a 46-year-old woman with a short history of dyspnea, chest tightness, and cough with marked work effect. Her radiograph revealed pulmonary infiltrates, not responding to standard treatment for infection. Symptoms and signs improved on removal from the workplace, and the authors postulated that dimethyl phthalate and styrene were among the most likely candidate causes for this response.

ASTHMA AND EAA "CROSS-OVERS"

Various publications describe exposures that are described as causing asthma and EAA. Before reviewing these articles, it is reasonable to assume that very little is understood about the potential for single agents (or indeed single workplace exposures or work tasks) to cause the 2 separate disease manifestations in the forms of asthma and EAA. It is at least plausible that, in addition to the development of asthma or EAA attributable to exposures to different causative agents within a complex mix, that a single exposure may cause a single disease, the extremes of the clinical spectrum of which may have either asthma or EAA features. The latter will be better understood only with improved phenotyping of affected workers, better understanding of basic mechanisms, and, ultimately, developing better clinical case definitions.

Isocyanate exposure is perhaps the best example of this potential dual role. Already well-described to cause asthma, a Swiss group, Bieler and colleagues,⁶⁴ identified paint exposure as a possible cause of EAA in a worker exposed to 1,6-Hexamethylene diisocyanate (HDI) in the form of hardeners. The lung disease was characterized by rapidly progressive breathlessness, leading to respiratory failure. No biopsy was undertaken, presumably given the severity of the illness, but air sampling and urine biomarker estimates implied HDI exposure, and subsequent patch testing confirmed a delayed hypersensitivity to HDI. The investigators were keen to stress the speculative nature of these findings, but these are at least consistent with other case reports supporting the ability of isocyanates to cause EAA, including a further recent report implicating low-level exposure to diisocyanates in a secretary.⁶⁵ This latter case, from Germany, was of EAA in a secretary employed at a car-body paint facility. Although not biopsied, lung function, HRCT appearances, and the presence of IgG to diisocyanate human serum albumin conjugates were concluded as supportive evidence. The patient improved following cessation of exposure, measured to be generally below current exposure limits.

A group of other nonisocyanate exposures described as causing both conditions is now considered. A research letter by a Canadian group,⁶⁶ expert in the assessment of occupational lung disease, displayed the results for 2 challenges, 1 performed on a malt-exposed worker where the likely diagnosis was asthma owing to sensitization by an IgE mechanism, and 1 on a malt worker suspected of having developed EAA. Various outcomes differ between the challenges, the former showing a biphasic response, the latter a fall in FVC and

diffusing capacity. Body temperature did not elevate in the former, but did on the final exposure day for the latter case. Interestingly, although the latter worker, suspected of EAA, developed a peripheral blood neutrophilia, the former patient, suspected of asthma, did not show any increase in the proportion of sputum eosinophils. This latter finding aside, the investigators postulate that asthma and EAA are perhaps 2 discrete and separate outcomes that were caused by an identical exposure.

Similarly, chicory exposure is the focus of recent publications that proposed its involvement in the development of typical type I allergic-mediated sensitization causing asthma and rhinoconjunctivitis and also its involvement in causing EAA. Pirson and colleagues⁶⁷ described rhinoconjunctivitis and asthma in a worker from an insulin-producing facility, using chicory roots as a substrate. An immediate response was seen to SIC, and the worker also had evidence of type I-mediated sensitization with positive skin prick tests and specific IgE to chicory. Chicory leaf handling was also recently described⁶⁸ as a cause of presumed EAA, supported by a typical clinical features and positive specific IgG, although the actual causative agent appears not to be the chicory itself, but a fungal contaminant, *Fusarium* sp.

Similarly again, exposure to onion as part of a more general inhaled spice exposure was investigated by a South African group.⁶⁹ Detailed investigations were undertaken on 3 workers heavily exposed to spice dusts, all of whom had developed asthma. Specific IgE was measured to a range of common inhalant, food, and spice allergens. In addition, basophil stimulation was used to potentially assess non-IgE-mediated responses. Specific allergens were also identified using an immunoblotting technique. Of interest, dry powdered garlic and onion demonstrated greater IgE binding than seen from the raw plant. Onion exposure (as part of a task of onion and potato sorting) has also been recently described as a risk for developing EAA. This German paper⁷⁰ described a case report of an onion and potato sorter who developed EAA characterized by pulmonary infiltrates, a lymphocytic BAL, and specific IgG presence to *Penicillium* sp and *Fusarium solani*. Again, it was the fungal contaminant rather than any onion-derived epitope that appears to have been responsible.

Exposure to esparto grass is also worthy of discussion here. Ruiz-Hornillos and colleagues⁷¹ describe a case of occupational asthma attributed to esparto exposure. Esparto is a gramineous plant with an interesting array of potential uses, including use as a fabric and fence-building

material. This Spanish group described a 58-year-old man who developed work-related asthma symptoms and a correlated effect in serial PEF measures. Changes in PEF values appeared to relate to esparto use and there was evidence of sensitization as judged by a positive skin prick test to esparto. Potential cross-reactivity to proteins from *Aspergillus fumigatus* was also identified. Enríquez and colleagues⁷² also recently reported a further case of occupational asthma related to esparto grass usage, on this occasion in a 30-year-old man. Following 12 years of work with esparto fibers, he presented with a 3-year history of work-related cough, shortness of breath, and wheeze. There were no systemic features or fever to suggest an alternate diagnosis of EAA. Peripheral eosinophilia and a positive skin prick test to esparto were noted, and serial PEF noted a work effect. A sample of esparto cultured a *Mucor* sp. The result of subsequent skin prick testing with *Mucor* extract was positive and specific IgE against *Mucor racemosus* was detected. A SIC challenge was positive (early reaction only) when tipping esparto between trays. In contradistinction to these recent asthma data, historically, esparto exposure has also been described as causing EAA (for example, by Flandes and colleagues⁷³), although no other recent papers were identified relating to this for the purposes of this review. Flandes and colleagues⁷³ described a 25-year-old plasterer, exposed to esparto fibers as they were added to plaster to alter its consistency and strength. Supported by consistent symptoms, restrictive physiology, reduced diffusing capacity, computed tomography ground-glass changes, a lymphocytic BAL, and supportive biopsy, they concluded this case related to EAA from esparto exposure, but actually caused by exposure to *Aspergillus fumigatus*.

Excluding isocyanates, to date in this review, therefore, exposures linked to asthma and EAA appear actually to be caused by separate agents within a complex mix of exposures, rather than a body of evidence supporting a single exposure causing 2 diseases. The dual responses to malt is the exception, at least in principle, suggesting that a single exposure may lead to differing outcomes, although the exact nature of the challenge material used, and its potential contaminants, is not provided.

Finally, pertaining to the example of metal-working fluid lung diseases, the largest outbreak of this to occur in the United Kingdom was published by Robertson and colleagues⁷⁴ in 2007, and carefully reviewed recently also from the perspective of clinical features⁷⁵ and demography.⁷⁶ The article by Robertson and colleagues⁷⁴

described the clinical approach to investigating a large outbreak of respiratory illness in a group of motor vehicle manufacturing workers exposed to potentially contaminated metal-working fluids. Workers were investigated in a phased manner, to limit more detailed investigations on those least likely to have developed either EAA or asthma as a result of their exposures. Of the entire work force, 87 persons (10.4%) were diagnosed as having either asthma (n = 74) or EAA (n = 19). Seven workers were diagnosed as suffering from humidifier fever. The approach taken by the study team was to identify case definitions for each condition a priori. No discussion was entertained relating to potential overlap of these conditions, and case definitions used were based on previous work. Nevertheless, a definite cause, or group of causes, has not yet been consistently identified from outbreaks of respiratory disease related to such exposures, and it remains to be proven as to whether a single contaminant can be responsible for both asthma and EAA, whether separate individual exposures account for each separate outcome, or whether in fact a single disease entity is responsible, behaving in some workers like occupational asthma, and in others like EAA.

CONCLUDING REMARKS

The recent evidence base offers insights into a vast array of complex and difficult occupational and environmental causes of lung disease. Despite their complexity, the lungs remain vulnerable to such insults from a wide variety of sources. Hamlet may well still reign true here when he lays out such mysteries for us all to solve, but the continuing research in this field from a diverse group of interested authors is beginning to unravel some. Perhaps these Shakespearean words are more appropriate: "Their understanding begins to swell, and the approaching tide will shortly fill the reasonable shores that now lie foul and muddy?"⁷⁷

REFERENCES

1. Fishwick D, Barber CM, Bradshaw LM, et al. Standards of care for occupational asthma. *Thorax* 2012;67(3):278–80 [Epub 2011 Dec 9].
2. Malo JL, Vandenplas O. Definitions and classification of work-related asthma. *Immunol Allergy Clin North Am* 2011;31(4):645–62.
3. Bernstein IL. Asthma in the workplace. In: Bernstein DI, Chan-Yeung M, Malo JL, et al, editors. 3rd edition. Boca Raton (FL): CRC Press; 2006. ISBN 0824729773, 9780824729776.
4. Acevedo N, Erler A, Briza P, et al. Allergenicity of *Ascaris lumbricoides tropomyosin* and IgE

- sensitization among asthmatic patients in a tropical environment. *Int Arch Allergy Immunol* 2011; 154(3):195–206 [Epub 2010 Sep 21].
5. Cárđaba B, Llanes E, Chacártégui M, et al. Modulation of allergic response by gene-environment interaction: olive pollen allergy. *J Investig Allergol Clin Immunol* 2007;17(Suppl 1):31–5.
 6. Jeebhay MF, Baatjies R, Chang YS, et al. Risk factors for allergy due to the two-spotted spider mite (*Tetranychus urticae*) among table grape farm workers. *Int Arch Allergy Immunol* 2007;144(2): 143–9 [Epub 2007 May 25].
 7. Nakazawa T, Satinover SM, Naccara L, et al. Asian ladybugs (*Harmonia axyridis*): a new seasonal indoor allergen. *J Allergy Clin Immunol* 2007; 119(2):421–7.
 8. Cummings KJ, Gaughan DM, Kullman GJ, et al. Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. *Eur Respir J* 2010;36(5):1007–15 [Epub 2010 Apr 22].
 9. Harris-Roberts J, Robinson E, Fishwick D, et al. Sensitization and symptoms associated with soybean exposure in processing plants in South Africa. *Am J Ind Med* 2012;55(5):458–64.
 10. Green BJ, Cummings KJ, Rittenour WR, et al. Occupational sensitization to soy allergens in workers at a processing facility. *Clin Exp Allergy* 2011;41(7): 1022–30.
 11. Heffler E, Nebiolo F, Pizzimenti S, et al. Occupational asthma caused by *Neurospora sitophila* sensitization in a coffee dispenser service operator. *Ann Allergy Asthma Immunol* 2009;102(2):168–9.
 12. Francuz B, Yera H, Geraut L, et al. Occupational asthma induced by in a worker exposed to coffee grounds. *Clin Vaccine Immunol* 2010;17(10):1645–6 [Epub 2010 Aug 4].
 13. Osterman K, Zetterström O, Johansson SG. Coffee worker's allergy. *Allergy* 1982;37(5):313–22.
 14. Bernedo N, García M, Gastaminza G, et al. Allergy to laxative compound (*Plantago ovata* seed) among health care professionals. *J Investig Allergol Clin Immunol* 2008;18(3):181–9.
 15. Granslo JT, Van Do T, Aasen TB, et al. Occupational allergy to *Artemia* fish fry feed in aquaculture. *Occup Med (Lond)* 2009;59(4):243–8 [Epub 2009 Apr 1].
 16. Bernstein JA, Crandall MS, Floyd R. Respiratory sensitization of a food manufacturing worker to konjac glucomannan. *J Asthma* 2007;44(8):675–80.
 17. Viinanen A, Salokannel M, Lammintausta K. Gum arabic as a cause of occupational allergy. *J Allergy (Cairo)* 2011;2011:841508 [Epub 2011 May 19].
 18. Sartorelli P, Paolucci V, Rendo S, et al. Asthma induced by chloramine T in nurses: case report. *Med Lav* 2010;101(2):134–8.
 19. Zock JP, Vizcaya D, Le Moual N. Update on asthma and cleaners. *Curr Opin Allergy Clin Immunol* 2010; 10(2):114–20.
 20. Kim JE, Kim SH, Jin HJ, et al. IgE Sensitization to cephalosporins in health care workers. *Allergy Asthma Immunol Res* 2012;4(2):85–91.
 21. Roche E, de la Cuadra J, Alegre V. Sensitization to acrylates caused by artificial acrylic nails: review of 15 cases. *Actas Dermosifiliogr* 2008;99(10):788–94.
 22. Pougnet R, Loddé B, Lucas D, et al. A case of occupational asthma from metabisulphite in a fisherman. *Int Marit Health* 2010;62(3):180–4.
 23. Sastre J, Carnes J, García del Potro M, et al. Occupational asthma caused by triglycidyl isocyanurate. *Int Arch Occup Environ Health* 2011;84(5):547–9 [Epub 2010 Aug 18].
 24. Burton C, Bradshaw L, Agius R, et al. Medium-density fibreboard and occupational asthma. A case series. *Occup Med (Lond)* 2011;61(5):357–63.
 25. Schlünssen V, Kespohl S, Jacobsen G, et al. Immunoglobulin E-mediated sensitization to pine and beech dust in relation to wood dust exposure levels and respiratory symptoms in the furniture industry. *Scand J Work Environ Health* 2011;37(2):159–67.
 26. Harris-Roberts J, Fishwick D, Tate P, et al. Respiratory symptoms in insect breeders. *Occup Med (Lond)* 2011;61(5):370–3.
 27. Jeebhay MF, Robins TG, Miller ME, et al. Occupational allergy and asthma among salt water fish processing workers. *Am J Ind Med* 2008;51(12): 899–910.
 28. Pérez Carral C, Martín-Lázaro J, Ledesma A, et al. Occupational asthma caused by turbot allergy in 3 fish-farm workers. *J Investig Allergol Clin Immunol* 2010;20(4):349–51.
 29. Patiwaël JA, Jong NW, Burdorf A, et al. Occupational allergy to bell pepper pollen in greenhouses in the Netherlands, an 8-year follow-up study. *Allergy* 2010;65(11):1423–9.
 30. Letrán A, Palacin A, Barranco P, et al. Rye flour allergens: an emerging role in baker's asthma. *Am J Ind Med* 2008;51(5):324–8.
 31. Palacin A, Quirce S, Armentia A, et al. Wheat lipid transfer protein is a major allergen associated with baker's asthma. *J Allergy Clin Immunol* 2007; 120(5):1132–8 [Epub 2007 Aug 22].
 32. Campbell CP, Jackson AS, Johnson AR, et al. Occupational sensitization to lupin in the workplace: occupational asthma, rhinitis, and work-aggravated asthma. *J Allergy Clin Immunol* 2007;119(5):1133–9 [Epub 2007 Mar 26].
 33. Campbell CP, Yates DH. Lupin allergy: a hidden killer at home, a menace at work; occupational disease due to lupin allergy. *Clin Exp Allergy* 2010; 40(10):1467–72.
 34. Liccardi G, Salzillo A, Dente B, et al. Horse allergens: an underestimated risk for allergic sensitization in an urban atopic population without occupational exposure. *Respir Med* 2009;103(3): 414–20 [Epub 2008 Nov 8].

35. Liccardi G, D'Amato G, Antonicelli L, et al. Allergy Study Group of the Italian Society of Respiratory Medicine (SImeR). Sensitization to horse allergens in Italy: a multicentre study in urban atopic subjects without occupational exposure. *Int Arch Allergy Immunol* 2011;155(4):412–7 [Epub 2011 Feb 22].
36. La Grutta S, Cibella F, Passalacqua G, et al. Association of *Blattella germanica* sensitization with atopic diseases in pediatric allergic patients. *Pediatr Allergy Immunol* 2011;22(5):521–7.
37. Barletta B, Di Felice G, Pini C. Biochemical and molecular biological aspects of silverfish allergens. *Protein Pept Lett* 2007;14(10):970–4.
38. Matsui EC, Eggleston PA, Buckley TJ, et al. Household mouse allergen exposure and asthma morbidity in inner-city preschool children. *Ann Allergy Asthma Immunol* 2006;97(4):514–20.
39. Matsui EC. Role of mouse allergens in allergic disease. *Curr Allergy Asthma Rep* 2009;9(5):370–5.
40. Kauppinen A, Peräsaari J, Taivainen A, et al. Association of HLA class II alleles with sensitization to cow dander Bos d 2, an important occupational allergen. *Immunobiology* 2012;217(1):8–12 [Epub 2011 Sep 8].
41. Nishikawa E, Taooka Y, Tsubata Y, et al. A case of acute hypersensitivity pneumonia in a worker at a feather duvet factory. *Nihon Kokyuki Gakkai Zasshi* 2011;49(2):93–6.
42. Otsuka M, Akiyama T, Saikai T, et al. A case of hypersensitivity pneumonitis due to the contamination of a dehumidifier by *Thermoactinomyces vulgaris*. *Nihon Kokyuki Gakkai Zasshi* 2008;46(1):39–43.
43. Hamaguchi R, Saito H, Kegasawa K, et al. A case of hypersensitivity pneumonitis resulting from inhalation of *Aspergillus niger* in a greenhouse worker who raised roses. *Nihon Kokyuki Gakkai Zasshi* 2009;47(3):205–11.
44. Ishikawa R, Kamiya H, Ikushima S, et al. A patient with acute hypersensitivity pneumonitis with a diagnosis of air-conditioner lung, who responded to therapy. *Nihon Kokyuki Gakkai Zasshi* 2010;48(2):134–9 [in Japanese].
45. Romeo L, Dalle Molle K, Zanoni G, et al. Respiratory health effects and immunological response to *Thermoactinomyces* among sugar cane workers in Nicaragua. *Int J Occup Environ Health* 2009;15(3):249–54.
46. Kai N, Ishii H, Iwata A, et al. Chronic hypersensitivity pneumonitis induced by Shiitake mushroom cultivation: case report and review of literature. *Nihon Kokyuki Gakkai Zasshi* 2008;46(5):411–5.
47. Guillot M, Bertoletti L, Deygas N, et al. Dry sausage mould hypersensitivity pneumonitis: three cases. *Rev Mal Respir* 2008;25(5):596–600.
48. Morell F, Cruz MJ, Gómez FP, et al. Chacinero's lung—hypersensitivity pneumonitis due to dry sausage dust. *Scand J Work Environ Health* 2011;37(4):349–56.
49. Metersky ML, Bean SB, Meyer JD, et al. Trombone player's lung: a probable new cause of hypersensitivity pneumonitis. *Chest* 2010;138(3):754–6.
50. Metzger F, Haccuria A, Reboux G, et al. Hypersensitivity pneumonitis due to molds in a saxophone player. *Chest* 2010;138(3):724–6.
51. Engelhart S, Rietschel E, Exner M, et al. Childhood hypersensitivity pneumonitis associated with fungal contamination of indoor hydroponics. *Int J Hyg Environ Health* 2009;212(1):18–20 [Epub 2008 Mar 28].
52. Kahana LM, Kay JM, Yakus MA, et al. *Mycobacterium avium* complex infection in an immunocompetent young adult related to hot tub exposure. *Chest* 1997;111(1):242–5.
53. Verma G, Jamieson F, Chedore P, et al. Hot tub lung mimicking classic acute and chronic hypersensitivity pneumonitis: two case reports. *Can Respir J* 2007;14(6):354–6.
54. Huhulescu S, Simon M, Lubnow M, et al. Fatal *Pseudomonas aeruginosa* pneumonia in a previously healthy woman was most likely associated with a contaminated hot tub. *Infection* 2011;39(3):265–9 [Epub 2011 Apr 1].
55. Sogo A, Morell F, Muñoz X. Hypersensitivity pneumonitis associated with the use of a steam iron. *Arch Bronconeumol* 2009;45(5):258–9 [Epub 2009 Mar 27].
56. Villar A, Muñoz X, Cruz MJ, et al. Hypersensitivity pneumonitis caused by *Mucor* species in a cork worker. *Arch Bronconeumol* 2009;45(8):405–7 [Epub 2009 Apr 18].
57. Enríquez-Matas A, Quirce S, Cubero N, et al. Hypersensitivity pneumonitis caused by *Trichoderma viride*. *Arch Bronconeumol* 2009;45(6):304–5 [Epub 2009 May 12].
58. Yasui H, Matsui T, Yokomura K, et al. Three cases of hypersensitivity pneumonitis in citrus farmers. *Nihon Kokyuki Gakkai Zasshi* 2010;48(2):172–7 [in Japanese].
59. Miyazaki H, Hirata T, Shimane S, et al. A case of hypersensitivity pneumonitis caused by zinc fume. *Nihon Kokyuki Gakkai Zasshi* 2006;44(12):985–9 [in Japanese].
60. Ishiguro T, Yasui M, Nakade Y, et al. Extrinsic allergic alveolitis with eosinophil infiltration induced by 1,1,1,2-tetrafluoroethane (HFC-134a): a case report. *Intern Med* 2007;46(17):1455–7 [Epub 2007 Sep 3].
61. van Heemst RC, Sander I, Rooyackers J, et al. Hypersensitivity pneumonitis caused by occupational exposure to phytase. *Eur Respir J* 2009;33(6):1507–9.
62. Laukkanen A, Ruoppi P, Remes S, et al. Lactase-induced occupational protein contact dermatitis and allergic rhinoconjunctivitis. *Contact Dermatitis* 2007;57(2):89–93.
63. Volkman KK, Merrick JG, Zacharisen MC. Yacht-maker's lung: a case of hypersensitivity pneumonitis in yacht manufacturing. *WMJ* 2006;105(7):47–50.

64. Bieler G, Thorn D, Huynh CK, et al. Acute life-threatening extrinsic allergic alveolitis in a paint controller. *Occup Med (Lond)* 2011;61(6):440–2 [Epub 2011 Aug 8].
65. Schreiber J, Knolle J, Sennekamp J, et al. Sub-acute occupational hypersensitivity pneumonitis due to low-level exposure to diisocyanates in a secretary. *Eur Respir J* 2008;32(3):807–11.
66. Miedinger D, Malo JL, Cartier A, et al. Malt can cause both occupational asthma and allergic alveolitis. *Allergy* 2009;64(8):1228–9 [Epub 2009 Mar 27].
67. Pirson F, Detry B, Pilette C. Occupational rhinoconjunctivitis and asthma caused by chicory and oral allergy syndrome associated with bet v 1-related protein. *J Investig Allergol Clin Immunol* 2009;19(4):306–10.
68. Colin G, Lelong J, Tillie-Leblond I, et al. Hypersensitivity pneumonitis in a chicory worker. *Rev Mal Respir* 2007;24(9):1139–42.
69. van der Walt A, Lopata AL, Nieuwenhuizen NE, et al. Work-related allergy and asthma in spice mill workers. The impact of processing dried spices on IgE reactivity patterns. *Int Arch Allergy Immunol* 2010;152(3):271–8 [Epub 2010 Feb 12].
70. Merget R, Sander I, Rozynek P, et al. Occupational hypersensitivity pneumonitis due to molds in an onion and potato sorter. *Am J Ind Med* 2008;51(2):117–9.
71. Ruiz-Hornillos FJ, De Barrio Fernández M, Molina PT, et al. Occupational asthma due to esparto hypersensitivity in a building worker. *Allergy Asthma Proc* 2007;28(5):571–3.
72. Enríquez A, Fernández C, Jiménez A, et al. Occupational asthma induced by *Mucor* species contaminating esparto fibers. *J Investig Allergol Clin Immunol* 2011;21(3):251–2.
73. Flandes J, Heili S, Gómez Seco J, et al. Hypersensitivity pneumonitis caused by esparto dust in a young plaster worker: a case report and review of the literature. *Respiration* 2004;71(4):421–3.
74. Robertson W, Robertson AS, Burge CB, et al. Clinical investigation of an outbreak of alveolitis and asthma in a car engine manufacturing plant. *Thorax* 2007;62(11):981–90 [Epub 2007 May 15].
75. Rosenman KD. Asthma, hypersensitivity pneumonitis and other respiratory diseases caused by metalworking fluids. *Curr Opin Allergy Clin Immunol* 2009;9(2):97–102.
76. Burton CM, Crook B, Scaife H, et al. Systematic review of respiratory outbreaks associated with exposure to water-based metalworking fluids. *Ann Occup Hyg* 2012;56(4):374–88 [Epub 2012 Jan 20].
77. The Tempest. William Shakespeare. The Arden Shakespeare, Third Series. ISBN 978-1-903436-08-0.