Mechanisms of allergic occupational asthma

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Abstract

High-molecular-weight agents are a major cause of allergic occupational asthma in the workplace. High-molecular-weight agents comprise proteins from plant, microorganism or animal origin in the 10–60 kDa range. A few occupational asthma allergens are man-made chemicals such as isocyanates or acid anhydrides. Allergens with a major public health relevance are derived from flour, latex, enzymes and laboratory animals. The structures of antigenic determinants and mechanisms of many occupational allergens have been elucidated, whereas those of others, e.g. of platinum, recognized by immunocompetent cells are still obscure.

The underlying immune mechanisms of allergic occupational asthma correspond to type I allergy, i.e., antigen recognition and processing by antigen-presenting cells, induction of the Th2 immune response resulting in the production of antigen-specific IgE antibodies, and finally release and generation of bronchospastic and inflammatory mediators by mast and other cells.

The pathological mechanisms of allergic and non-allergic occupational asthma are relevant to diagnostics, management, and prevention, and are also briefly covered in this chapter. Related to this chapter is a useful listing of know occupational allergens, of high and low molecular weight, included in an Appendix.

Introduction

Asthma characterized by variable airflow obstruction due to immunological mechanisms against agents occurring in the workplace is called 'allergic occupational asthma' (allergic OA) (Fig. 1). Immunological mechanisms associated with allergen-specific IgE antibodies have been identified for most causative high-molecular weight (HMW) and for some causative low-molecular weight (LMW) occupational agents. The importance of other immunological mechanisms initiating airway inflammation without detectable IgE antibodies needs further investigations (see below).

Typically, allergic OA has a latency period, which differs from 'non-allergic OA' that is caused by exposure to irritant (non-allergenic) gases, fumes or particles (Tab. 1). Non-allergic OA or irritant OA encompasses the reactive airways dysfunction syndrome (RADS), sometimes even occurring after a single exposure but also after multiple exposure events to high concentrations of nonspecific irritants.

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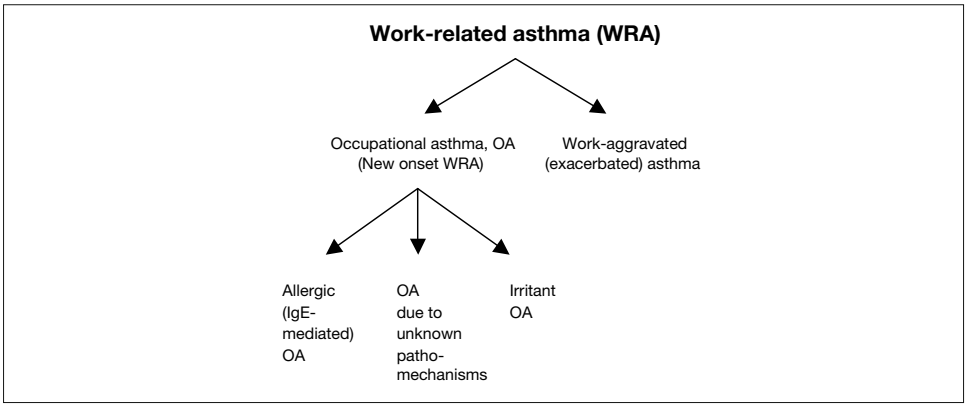

Figure 1.
Schematic representation of occupational asthma (OA) as part of work-related asthma.

Table 1. Specific aspects of allergic occupational asthma (OA) and differences in comparison with non-allergic (irritant) OA

	Allergic OA	**Non-allergic (irritant-induced) OA**
Causes	Mainly HMW and some LMW agents	Airway irritants
Mechanisms	Specific IgE antibodies	Acute or chronic irritant injury to bronchial mucosa
Essential features	Latency period of exposure and sensitization prior to onset of symptoms	Mostly sudden onset without latency period; evidence for chronic low-dose pathogenesis (rare)
Evidence of causal relationship	Specific IgE antibodies, positive skin prick test results	Temporal relationship between exposure to irritant agents and the (mostly rapid) onset of asthma symptoms
Diagnostics	Assessment of obstructive ventilation pattern, bronchial hyperresponsiveness, and eosinophilic inflammation associated with exposure Serial PEFR plus symptom diary Specific inhalation challenge	Assessment of obstructive ventilation pattern, and bronchial hyperresponsiveness associated with exposure (Serial PEFR, if possible during relevant exposure) (Specific inhalation challenge rarely of diagnostic value)
Outcome	Improvement or normalisation after removal from exposure source; airway hyperresponsiveness may persist	Improvement after removal from exposure source; frequently persistent airway hyperresponsiveness

HMW, High-molecular weight; LMW, low-molecular-weight; PEFR, peak expiratory flow recordings

Pathophysiology and immunology of allergic OA

Initial pathophysiological mechanisms of allergic OA differ fundamentally from irritant OA (Tab. 1), although similar inflammatory changes have been described for the chronic course of both disorders. Furthermore, there is no difference between asthma caused by allergens from the general environment and asthma caused by occupational allergens, as shown by various investigations including sputum cytology, bronchoalveolar lavage (BAL) analyses, bronchial biopsies and postmortem lung tissue studies.

The most relevant involved mechanisms, cells and cytokines, are shown in Figure 2.

Inhaled occupational allergens gain access to the viable airway epithelium where they engage and activate local dendritic cells, which keep mucosal surfaces under surveillance. Allergens are processed by these cells, bind to major histocompatibility complex class II (MHC-II) molecules, and their fragments (highly polymorphic

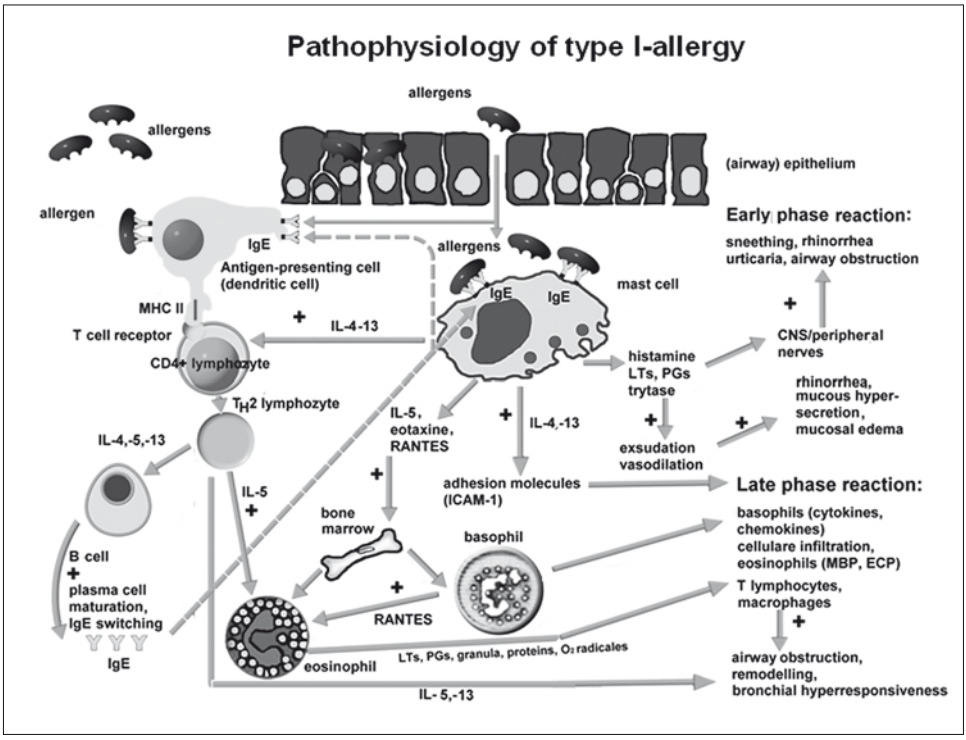

Figure 2.
Scheme on immune mechanisms, mediators and pathophysiology of type I allergy.

short peptides) are then transported by these cells to regional lymph nodes and presented to T lymphocytes, which recognize them by their T cell receptors (TCR). The cytokine milieu is critical to T cell differentiation in Th1 or Th2 responses. IL-12 production leads to Th1 phenotypes, and increased IL-4/IL-13 production leads to Th2 phenotypes. The Th2-dominant cytokine response drives the synthesis and secretion of allergen-specific IgE antibodies by B cells (plasma cells). IgE regulates the expression of its own high-affinity IgE receptors (FcεRI) and low-affinity IgE receptor (CD23) on the surface of mast cells, basophils and possibly of macrophages, dendritic cells, eosinophils and platelets. IgE-dependent up-regulation of FcεRI and CD23 receptors subsequently amplifies immunological reactions. It leads to a greater release of mast cell and basophil mediators at lower concentrations of a specific allergen. Upon new exposure, the allergen cross-links between these specific IgE antibodies on cell surfaces, gives rise to a cascade of events, and leads to an inflammatory cell activation with subsequent synthesis and/or release of a variety of preformed mediators (e.g., histamine) and newly formed inflammatory ones (e.g., prostaglandins, leukotrienes). These mediators orchestrate the inflammatory reaction in bronchial mucosa and submucosa (Fig. 2).

An interesting finding is the cleavage of the tight junction protein occludin by allergenic proteases, e.g., from house dust mites or moulds, which damage the airway epithelium barrier and subsequently increase epithelial permeability and stimulation of the release of mediators. This also orchestrates local immune responses and the inflammatory process [1, 2].

Airway remodeling, as typically found in bronchial asthma [3, 4], also takes place in OA. It can be interpreted as an exaggerated and uncontrolled injury repair process influenced by type and intensity of airway injury and modulated by host as well as genetic factors. It involves epithelial changes, increases in smooth muscle mass and subepithelial collagen deposition, proteoglycans and elastin content, angiogenesis, cartilage changes, goblet cell and glandular hyperplasia. Airway modeling may lead to persistently increased airway responsiveness and mucous production, airflow limitation, and probably to a decline in lung function [5]. Besides its detrimental effect it may protect against excessive bronchoconstriction and inflammation.

Typical morphological findings in airways of allergic OA patients include:

- epithelial desquamation or hyperplasia;
- an increased number of inflammatory cells, especially of eosinophils, in mucosal and submucosal layers (demonstrated by bronchial biopsies); they are also found in sputum and BAL;
- evidence for the activation of eosinophils and lymphocytes;
- increased airway wall thickening;
- increased thickness of the basement membrane, especially of the reticular layer due to interstitial cross-linked collagens produced by myofibroblasts;

- airway smooth muscle hyperplasia, hypertrophia, an increased secretion of cytokines as well as growth factors recruiting inflammatory cells and stimulating the production of extracellular matrix proteins; submucosal and peribronchial vessels are dilated, congested and exhibit thickening of arterial media [4];
- increased NO concentrations in exhaled air (FeNO) after exposure to causative allergens, isocyanates, ozone, swine confinements [6].

It should be noted, however, that there is no consistency with regard to the parallel changes in inflammatory cell counts and/or their activation status on the one hand and asthma severity on the other hand.

Exposure cessation does not always lead to an improvement of abnormal morphological and cellular changes and clinical findings [7]. Subepithelial collagen thickening may reverse after exposure termination and treatment with inhaled steroids.

Determinants of allergic OA

Atopy affecting approximately one third of the population, and defined as the tendency to produce specific IgE antibodies to environmental allergens like those from house dust mites, pollen, and cat or dog fur, modifies the risk of allergic OA resulting from HMW sensitizers as found in bakers (especially in those with hay fever) [8–12], laboratory animal workers (in those sensitized to pets) [13–16], subjects exposed to detergent enzymes, certain reactive dyes, latex [17], and other HMW allergens [18]. In contrast, atopy does not modify the risk for developing asthma caused by isocyanates, acid anhydrides, platinum salts or plicatic acid of red cedar wood. An increasing number of studies show convincing evidence for exposure-response relationships in allergic OA, with higher exposure levels associated with specific sensitization, symptoms, and obstructive ventilation patterns [19–30]. The exposure-response relationships show mostly a linear shape, but bell-shaped relations have also been described for some OA allergens [12]. There is a need for prospective studies with more detailed investigations on dose and timing of occupational exposures.

Recently there has been increased interest in the role of specific genes and gene-environment interactions, which are often complex and non-linear. Generally, most studies on allergic asthma are small and replication studies have seldom been published. Mostly candidate gene studies have been performed focusing on polymorphisms in genes responsible for metabolism of chemicals (like for isocyanates) or genes coding for certain steps in immunological pathways such as antigen presentation [human leukocyte antigen (HLA) genes]. Very few gene environment studies have been conducted. One of the more interesting ones refers to a promoter single nucleotide polymorphism in the CD14 gene (–159 T to C). This polymorphism and

exposure to endotoxin were found to be associated with a decreased frequency of allergic asthma in children living on farms [31–33]. One early study showed that α-1-antitrypsin alleles were associated increased hyperresponsiveness in farming students only, indicating a gene-environment interaction [34]. Recent studies provide strong evidence for a genetic basis of increased skin and mucosa permeability in atopics. This involves defects of filaggrin, facilitating terminal differentiation of the epidermis and formation of a skin barrier [35, 36]. Its mutations are linked with eczema-associated asthma and asthma severity [37]. Furthermore, overexpression of Th2 cytokines down-regulates filaggrin expression [38].

Other polymorphisms that code for genes of HLA class II or transmembrane proteins or respiratory anti-oxidant mechanisms may also explain susceptibility to a number of causative occupational agents; however, respective definitive risk factors cannot be provided yet [39–44]. Genetic studies and gene-environment studies are, at the moment, mainly of mechanistic interest. Applications for risk profiling, diagnosis or personalized treatment or prevention over the short term are not expected.

Cigarette smoking increases the risk of specific sensitization and OA due to several LMW agents [45–49]. This was shown in workers of platinum refineries [50, 51], snow-crab processing plants [52], and subjects exposed to tetrachlorophthalic anhydride [53] or *Ispaghula* dust [54].

Allergic occupational rhinitis frequently occurs as a co-morbid condition in allergic OA. Typically, allergic occupational rhinitis or rhinoconjunctivitis develop before the onset of allergic OA, indicating an increased OA risk in affected subjects [22, 26, 55–60].

Occupational allergens

List of known occupational allergens

There are about 350 OA-inducing allergens, mainly HMW compounds representing airborne (glyco)proteins from plants, microorganisms, and animals (see Tab. 2), and eliciting IgE-mediated hypersensitivity. Several LMW agents may also elicit IgE responses; some of them thus seem to be complete allergens. Other LMW agents such as acid anhydrides and isocyanates form allergenic conjugates upon reaction with autologous human proteins. Specific IgE antibody responses may be directed against the newly formed structures (especially against the binding regions of such conjugates behaving as new antigenic determinants) or against the haptenic ligand (the latter was shown for phthalic acid anhydride and himic anhydride). There is evidence that ring structures, positions of double bonds and methyl group substitutions are critical determinants of IgE-mediated sensitization [61, 62]. Many of the allergenic LMW agents also behave as irritants, i.e., OA may be due to the IgE-mediated pathway or, especially at high concentrations, due to irritative effects. This

Table 2. Allergenic agents reported to cause OA: Groups and important examples (Complete list available at: http://www.uke.uni-hamburg.de/institute/arbeitsmedizin/ →Publikationen "Allergenic agents reported to cause occupational asthma") (accessed 6 November 2009)

Group	Important examples
Microorganisms and their products	Aspergillus enzymes, e.g., fungal α-amylase, detergent enzymes
Plants	Flour, grain Latex Wood dust Flowers
Animals	Rats, mice Cows Birds Storage mites Insects Seafood
Chemicals	Isocyanates Acid anhydrides Metal dust, e.g., platinum salts Synthetic drugs Hairdressing chemicals

means that the detection of respective IgE antibodies is a specific but not necessarily a sensitive diagnostic marker of OA caused by such LMW agents.

For some occupational agents such as plicatic acid and morphine, respective IgE antibodies seem not correlated with clinical findings. This unexpected finding raises the question of the specificity of IgE tests used or the absence of IgE.

For details on OA-inducing occupations and confinements comprising some specific, heterogeneous or unidentified allergens, see the Appendix.

Clinical aspects

Exposure of a sensitized and hyperresponsive subject to a causative allergen elicits an early asthmatic reaction, which is characterized by smooth muscle contraction, mucosal edema and an inflammatory response. A late asthmatic reaction may take place several hours afterwards, which is associated with a prolific influx of inflammatory cells and followed by remarkable and long-term inflammatory reactions and an increase in bronchial hyperresponsiveness.

Diagnosis of allergic occupational asthma

The initial suspicion of OA is mostly expressed by the general practitioner, pneumologist, allergologist or occupational or factory physician due to work-related asthma symptoms. Diagnostic measures should be performed before the worker leaves her/his workplace since prolonged avoidance of contact with the causative substance(s) can reduce susceptibility and lead to false-negative diagnostic results. A basic clinical examination and environmental evaluation should be performed in any suspicious case. If there is evidence for an occupational cause of asthmatic symptoms and/or disorders a more detailed assessment should follow to establish a working hypothesis of the disorder. Evaluation tests will confirm or definitely negate the provisional diagnosis. These measures usually require considerable effort and expertise. For details, see Figure 3 and 4. One should realize that specific mechanisms involved in the different phenotypes of OA related to different causes determine to some extent the sequence and choice for specific diagnostic procedures. This makes the diagnosis a complicated process and the likelihood of making wrong

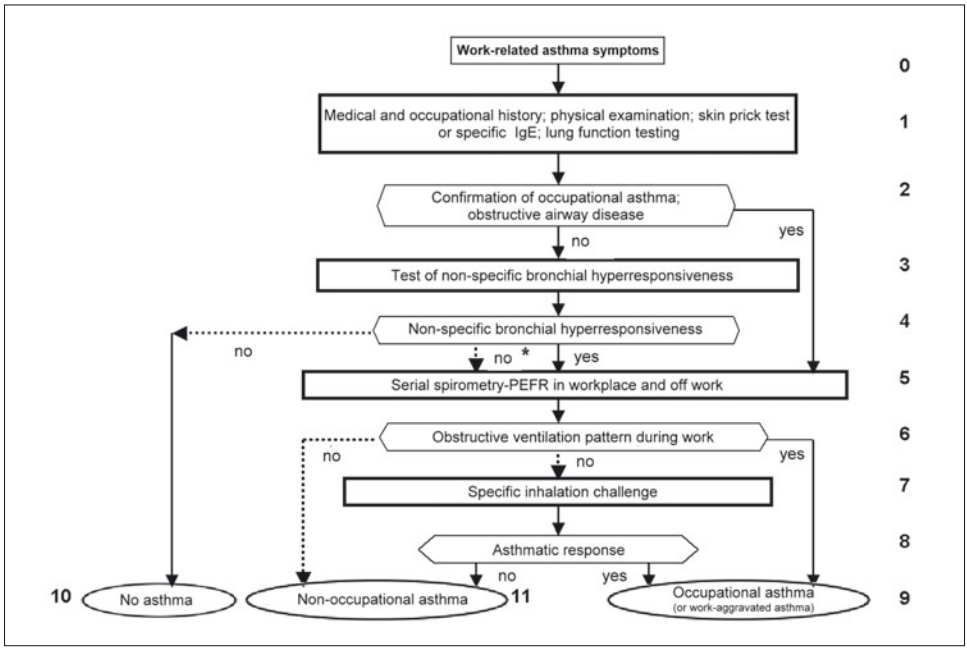

Figure 3.
*Stepwise scheme for the diagnostic procedure to confirm or exclude OA. * Consider possibility of false-negative testing of nonspecific bronchial hyperresponsiveness. In case of positive allergological test results, the diagnosis is allergic OA.*

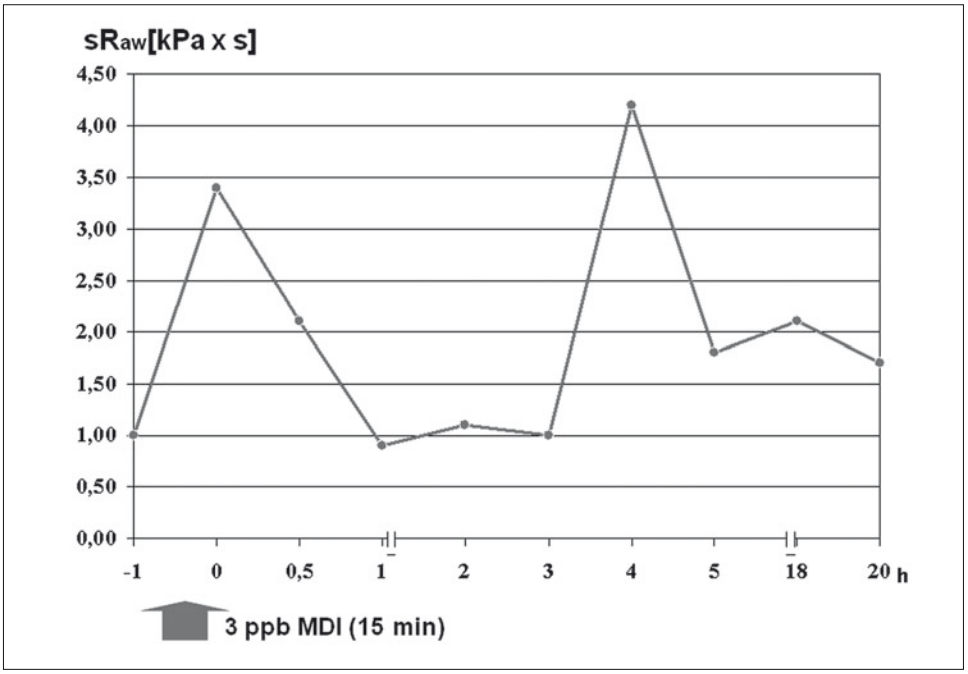

Figure 4.
Specific inhalation challenge test by the isocyanate MDI eliciting a dual asthmatic response. The 51-year-old foam worker has suffered from work-related asthma attacks for 15 months as well as from nocturnal asthmatic symptoms that could not clearly be related to a causative agent so far.

decisions is always present. In brief, the diagnostic workup consists of the following steps with some relevant details for each step related to mechanisms:

- The detailed occupational history and the detailed medical history (Tab. 1 and 3) are the central parts of the diagnostic algorithm;
- Allergic OA has to be differentiated from irritant OA (see basic toxicological information for an agent, check medical literature, interpret results of allergological tests);
- Commercially available well-standardized allergen extracts should be used for allergological testing and specific inhalative challenge tests; mostly they have to be supplemented by self-made extracts of HMW agents occurring in the workplace;
- The use of standardized and sensitive methods for the measurement of specific IgE antibodies in serum is highly recommended if the routine skin prick testing is not possible or its results are not reliable;

Table 3. Components of the medical, occupational, and environmental history

Components of the medical, occupational, and environmental history
A. History of the present illness 1. Detailed record of the circumstances resulting in the onset and worsening of disease 2. Temporal relationships between recurrent exposures and disease exacerbations 3. Course and rate of airway diseases in the particular workplace/branch 4. Asthma severity at the time of initial evaluation
B. Medical history 1. Premorbid medical history, e.g., childhood asthma, hay fever, pet allergy 2. Associated symptoms and concomitant diseases
C. Occupational and environmental history 1. Type (quality) of noxious substances in the workplace (e.g., allergens, irritants, carcinogens, etc.) 2. Intensity (concentrations) of exposure by inhalation, and skin contact 3. Cumulative dose during working life 4. Use of protective equipment

- The course of lung function parameters and symptoms before, during and after occupational exposure has to be evaluated in detail. Further, exact analyses of all medical reports before, during and after employment including medical surveillance data should be performed; Table 4 gives an overview on indications and further details of specific inhalative challenge tests.
- If the occupational exposure generated a new onset of asthma or a significant aggravation of preexisting asthma, the disorder and its deteriorating proportion have to be reported to the responsible insurance institution for occupational diseases, be recognized and compensated as an occupational disease (respective national legal definitions and regulations have to be observed).

New diagnostic tools

New additional diagnostic tools include measurements of the fraction of exhaled nitrous oxide (FeNO), and analyses of induced sputum and exhaled breath condensate during occupational exposure. These methods have been shown to provide valuable information on occupationally induced allergic airway diseases and differential diagnoses [63, 64].

Table 4. Overview of specific inhalative challenge tests: indications, methodology, advantages and limitations

Indications	- uncertain diagnosis and unclear etiology - the respective information is necessary for preventive and/or therapeutic measures or compensation.
Methodology	- generate constant, well-defined non-irritative air concentrations - start with a concentration that is expected not to cause a response and increase it in several ~15-min intervals, each with an ~3-fold increase in concentration up to the workplace atmosphere level or OEL (TLV) - monitor air concentration continuously with validated equipment, e.g., isocyanates by an MDA 7700 device.
Advantages	- Identification/exclusion of an individual occupational agent as OA cause.
Limitations	- High concentrations of an irritative agent may lead to unspecific effects, i.e., to a false-positive result - A false-negative result may occur due to: • anti-asthmatic treatment • a long latency period • use of an inappropriate substance or too low concentration of the causative agent • cumulative effects of an occupational agent over days or of several agents with additive effects present in the workplace (the latter two cannot be reproduced in the laboratory).

OEL, occupational exposure limit; TLV, threshold limit value

Appendix: Occupational asthma-inducing occupations and work environments comprising some specific, heterogeneous or unidentified allergens

Animal confinements and farm working

The prevalence of rat allergy among laboratory animal workers ranges from 12% to 31% [65]. Cross-sectional and cohort studies revealed that the exposure levels to rat urinary aeroallergens correlated positively with the frequency of positive skin test results as well as with work-related upper and lower airway responses [8, 66–68]. Atopic workers had a more than threefold increased sensitization risk at low allergen levels than non-atopics. Major allergens in rat excreta and epithelium involve α2μ-globulin (17 kDa), prealbumin (21 kDa) and a 23-kDa protein. Similar results were reported for mouse allergens/urinary proteins [65, 69]. An increase in

asthma prevalence also occurs in farm animal confinements [70–73]. Cow allergens were reported to be a major cause of respiratory allergies of farmers [74–76]. Concentrations as low as 1–20 μg (atopics), and 25–50 μg (non-atopics) of the major cow allergen Bos d 2 per gram dust were found to be significantly associated with specific IgE antibodies [77]. Furthermore, Rautiainen et al. [78] reported that the level of antibodies to bovine epithelial allergens among exposed subjects reflects the level of clinical allergies.

Working in swine confinements [79–83], poultry confinements [84, 85], poultry slaughter houses [86, 87] or contact with raw poultry [88] causes lung function declines and OA. Further, a dose-response relationship between daily working hours inside animal houses and symptoms was established for pig farmers [82]. However, recent publications indicate that endotoxins represent the predominant cause of obstructive airway diseases in poultry and swine confinement workers [81, 89]. Irritating gases such as ammonia and NO_x may also elicit OA in these environments. Thus, animal and farm working is associated with an increased prevalence of OA and also of chronic obstructive pulmonary disease [82]. In addition to specific animal allergens, causative exposures in animal confinements comprise hay and grain dusts and other animal feed as well as storage mites [90]. Allergic reactions and irritant OA have to be differentiated in these workers [91].

For flour mill workers, Peretz et al. [12] also described a positive association between exposure to up to ~10 μg EQ/m^3 and sensitization, but a decline in sensitization at higher concentrations The healthy worker effect may have contributed to these findings [92, 93]. Recently, Cullinan et al. [23] reported an annual incidence of work-related chest symptoms of 4.1%, and their association with a positive skin prick test to flour or α-amylase of 1% (sensitization to α-amylase was a little more frequent than that to flour). Interestingly, predominantly atopics became symptomatic and sensitized to α-amylase; and exclusively atopics were sensitized to flour.

Industrial enzyme production

A variety of natural and an increasing number of genetically modified recombinant enzymes produced on a large-scale behave as potent inhalative allergens [94]. These include many mould enzymes, detergent enzymes derived from *Bacillus subtilis* and other bacteria as well as plant proteins such as bromelain (a pineapple protease) or papain (derived from the papaya fruit). The latter enzyme is used as meat tenderizer and capable of sensitizing workers in industrial kitchens. Obviously all enzymes have to be regarded as inhalative allergens affecting mainly pharmaceutical factory and laboratory workers [95].

Fungal α-amylase, derived from *Aspergillus oryzae* is widely used as a baking additive; sensitizing air concentrations in bakeries are in the ng/m^3 range. In the late 1960s, the introduction of alkaline heat-stable enzymes (proteases, amylases, cel-

lulases) in the detergent industry was associated with estimated enzyme air concentrations in the workplace of ~300 ng/m^3 and higher; 40–50% of the workers were sensitized and developed asthma and/or rhinitis. Follow-up studies showed high exposures (estimates were based on the dustiness of workplace atmospheres) and atopy to be related with an increased sensitization incidence. The highest sensitization occurred within the first 2 years of observation, although follow-up was short [96]. Nevertheless, Cullinan et al. [24] found 19% of detergent workers exposed to enzymes (the geometric mean concentration was 4.25 ng/m^3) to be sensitized; 16% had work-related respiratory symptoms. In 2007, ACGIH [97] published a threshold limit value (TLV)-short-term exposure limit (STEL)-C (ceiling) of 0.06 μg/m^3 for the bacterial protease subtilisin.

More recently, it has been established that aeroallergens containing proteases may have a critical role in overcoming airway tolerogenic mechanisms that ordinarily exclude allergic responses to inhaled allergens. Proteases, e.g., from mites and moulds, probably do not only behave as typical allergens. They permit allergic responses by enhancing antigen presentation *via* the degradation of tight junction structures. Moreover, protease activation of epithelial cell protease-activated receptors (PARs) may facilitate allergic responses to aeroallergens by directly inducing the expression of chemokines required for maximal leukocytic activation and infiltration. The latter may induce a non-allergic, innate inflammatory response *via* the release of pro-inflammatory cytokines.

Floricultures, florists; greenhouses

Floriculture and greenhouse workers have an increased risk of sensitization and OA [82, 98–101]. Many fresh or dry flowers and non-flowering green plants were found to cause OA, frequently also rhinitis, and/or dermatitis including: amaryllis (*Amaryllis hippeastrum*) [102], asparagus (*Asparagus officinalis*) [103], aster (*Asteraceae*) [98, 104, 105], baby's breath (*Gypsophila paniculata*) [106–108], bells of Ireland (pollen, *Molucella laevis*) [109], canari palm pollen (*Phoenix canariensis*) [110], carnation (*Dianthus caryophillus*) [111–113], *Carthamus tinctorius* and yarrow (*Achillea millefolium*) [114], Christmas cactus (*Schlumbergia*) [115], *Chrysanthemum leucanthemum*, *Chrysanthemum* spp. and other flowers [105, 116–118], compositae such as chamomile (*Matricaria chamomilla*) [104], Easter lily (*Lilium longiflorum*) [119, 120], eggplant (*Solanum melongena*) [121], freesia (*Freesia hybrida*) [117, 122, 123], *G. paniculata* [108], German statice (*Limonium tataricum*) [124], hyacinth (*Hyacinthus orientalis*) [125], Liliaceae [102], Madagascar jasmine (*Stephanotis floribunda*) [126], mimosa pollen (*Acacia floribunda*) [104, 127], narcissus (*Narcissus pseudonarcissus*) [128], paprika (*Fructus capsici*) [122], pea, sweetpea (*Lathyrus odoratus*) [129], peach (*Prunus persica*) [130], poppy (*Papaver somniferum*) [131], rose (*Rosa* sp.) [132, 133], safflower (*Carthamus tinctorius*) [114], saffron pol-

len (*Crocus sativus*) [134], spathe flowers (*Spathiphyllum wallisii*) [135], statice (*Limonium tataricum*) [124], sunflower (*Helianthus annus*) [136–138], *Tetranychus urticae* [139], tulip (*Tulipa*) [117, 140, 141], umbrella tree (*Schefflera*) [142], various decorative flowers [98, 104, 117], weeping fig (*Ficus benjamina*) [142–144].

The predatory mites *Amblyseius cucumeris* [145], *Phytoseiulus persimilis* and *Hypoaspis* [146, 147] were also reported to cause OA among horticulturists working in greenhouses.

Further causative allergen sources are the red spider mite (*Tetranychus urticae*) [139, 148] and biopesticides containing *Bacillus thuringiensis* or *Verticillium lecanii* [149]. Furthermore, high indoor temperatures und humidity in greenhouse facilities may result in intensive mould growth, particularly of *Cladosporium herbarum*, penicillium, aspergillus and alternaria spp., which have been shown to be associated with an increased asthma prevalence [150]. For more details, see chapter "Exposure to moulds".

Exposure to other important plant allergens

A variety of plant components and plant products represent important occupational respiratory allergens, e.g., baking flour, grain and soy bean dust, natural latex. They also comprise aniseed powder [151], asparagus [103], banha [152], carrot [153], chicory [154], fenugreek [155], garlic dust [156, 157], ginseng [158], aromatic herbs [159], hobs [160], ipecacuanha [161], kapok [162], licorice roots [163], lycopodium powder [164], 'Maiko' (derived from the tuberous root of devil's tongue) [165], mushroom powder [166, 167], onion [168], peach leaves [130], pectin powder [169], potato [170], freeze-dried raspberry [171], rose hips [133], sanyak [172], sarsaparilla root [173], various spices such as coriander, mace [174], fermented tea [175–177], green tea [178, 179], herbal teas (sage, chamomile, dog, rose, mint and others). Vegetable gums derived from plant materials and containing carbohydrates produce mucilage upon reaction with water. They are frequently used in the industry and in pharmacies. Exposed workers may develop respiratory allergies inducing OA. Mostly printers exposed to acacia gum [180–183], hairdressers having contact to karaya [184], pharmaceutical workers and nurses handling psyllium seeds [185–196] and carpet manufacturers in contact with guar gum [197] are affected.

Hairdressing salons

OA-inducing hairdressing chemicals comprise persulfate salts, p-phenylenediamine, reactive dyes, henna, other dyes and natural latex and hairdressers are thus exposed to a complex mixture of HMW and LMW sensitizers and irritants [198–206].

Drug-manufacturing plants

Drug manufacturing and application may be associated with the generation of airborne dust containing particles of raw materials, intermediate or end products capable of causing OA. These materials and products include amoxicillin, amprolium (the latter also causes asthma in poultry feed mixers), ceftazidine, cephalosporins, cimetidine, hydralazine, ipecacuanha, isonicotinic acid hydrazide, methyl dopa, mitoxantrone, opiate compounds, penicillamine, penicillin and ampicillin, phenylglycine acid chloride, piperacillin, psyllium, salbutamol intermediate, spiramycin, tetracycline and tylosin tartrate. An IgE-mediated mechanism has not been proven for all of these compounds.

Isocyanate application

Isocyanates are increasingly used for the production of polyurethane foam, elastomers, adhesives, varnishes, coatings, insecticides and many other products. These highly reactive chemicals have become the number 1 of occupational airway sensitizers in several western countries. The study by Petsonk et al. [207] should be mentioned, which evaluated respiratory health in a new wood products-manufacturing plant using diphenylmethane-4,4'-diisocyanate (MDI) and its prepolymer. In the follow-up survey 15 out of 56 workers (27%) in areas with the highest potential exposures to liquid isocyanates had an onset of asthma-like symptoms. In addition, 47% of workers with MDI skin staining and 19% without skin staining developed such symptoms, which were associated with variable airflow limitation and specific IgE to MDI-HSA, while controls did not develop any OA cases. Our cross-sectional studies performed in two factories showed in comparison to the group exposed to 5–10 ppb MDI significantly fewer symptomatic subjects, lung function impairments and specific IgE antibodies in the group exposed to less than 5 ppb toluene diisocyanate (TDI) [208]. Tarlo et al. [209] found evidence for higher isocyanate exposures in facilities with OA claims. In another study [210], specific sensitization did not occur at TDI concentrations ≤ 0.02 ppm over 3 years, whereas elevated antibody levels were found in subjects who experienced accidental exposures without a clear exposure-response relationship. There is evidence that dermal exposure to isocyanates can induce OA [211, 212]. Only a minority of symptomatic isocyanate workers show IgE antibodies to diisocyanate-HSA conjugates [213–218]. Several authors observed isocyanate exposure-dependent lung function declines in the occupational exposure limit (OEL) range [219–223]. It is worth mentioning that in most western countries OELs for monomer diisocyanate exposure have been set at 10 ppb. From the clinical point of view, this value seems to be too high. According to literature, 5–2.5 ppb considering all isocyanates in a particular workplace would be health-based levels [224, 225]. OELs for isocyanates should consider gaseous as

well as aerosol forms and also the increasingly used polyisocyanates or oligomers causing similar disorders as monomeric diisocyanates. Moreover, the prevention of isocyanate skin contact is obviously also an effective measure to reduce the risk of respiratory disorders. The TLV-time weighted averages (TWAs) currently proposed by ACGIH (2007) [97] are for TDI 0.005 ppm (TLV-STEL 0.02 ppm), for MDI 0.005 ppm and for HDI 0.005 ppm based on monomer exposure.

References

1 Tai HY, Tam MF, Chou H, Peng HJ, Su SN, Perng DW, Shen HD (2006) Pen ch 13 allergen induces secretion of mediators and degradation of occludin protein of human lung epithelial cells. *Allergy* 61: 382–388

2 Wan H, Winton HL, Soeller C, Tovey ER, Gruenert DC, Thompson PJ, Stewart GA, Taylor GW, Garrod DR, Cannell MB et al (1999) Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions. *J Clin Invest* 104: 123–133

3 Bergeron C, Boulet LP (2006) Structural changes in airway diseases: Characteristics, mechanisms, consequences, and pharmacologic modulation. *Chest* 129: 1068–1087

4 James AL, Wenzel S (2007) Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 30: 134–155

5 Portengen L, Hollander A, Doekes G, de Meer G, Heederik D (2003) Lung function decline in laboratory animal workers: The role of sensitisation and exposure. *Occup Environ Med* 60: 870–875

6 Baur X, Barbinova L (2006) Isocyanate-induced increase of exhaled NO (FeNO). P3631. ERS Annual congress. *Eur Respir J* 28: 619s-620s

7 Suni Y, Foley S, Daigle S, L'Archevêque J, Olivenstein R, Letuvé S, Malo J, Hamid Q (2007) Structural changes and airway remodelling in occupational asthma at a mean interval of 14 years after cessation of exposure. *Clin Exp Allergy* 37: 1781–1787

8 Cullinan P, Lowson D, Nieuwenhuijsen MJ, Gordon S, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ (1994) Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to laboratory rats. *Occup Environ Med* 51: 589–592

9 Droste J, Vermeire P, Van Sprundel M, Bulat P, Braeckman L, Myny K, Vanhoorne M (2005) Occupational exposure among bakery workers: Impact on the occurrence of work-related symptoms as compared with allergic characteristics. *J Occup Environ Med* 47: 458–465

10 Houba R, Heederik DJ, Doekes G, van Run PE (1996) Exposure-sensitization relationship for alpha-amylase allergens in the baking industry. *Am J Respir Crit Care Med* 154: 130–136

11 Nieuwenhuijsen MJ, Heederik D, Doekes G, Venables KM, Newman Taylor AJ (1999) Exposure-response relations of alpha-amylase sensitisation in British bakeries and flour mills. *Occup Environ Med* 56: 197–201

12 Peretz C, de Pater N, de Monchy J, Oostenbrink J, Heederik D (2005) Assessment of exposure to wheat flour and the shape of its relationship with specific sensitization. *Scand J Work Environ Health* 31: 65–74
13 Cullinan P, Lowson D, Nieuwenhuijsen MJ, Sandiford C, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ (1994) Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to flour. *Occup Environ Med* 51: 579–583
14 Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL (2002) Host determinants for the development of allergy in apprentices exposed to laboratory animals. *Eur Respir J* 19: 96–103
15 Heederik D, Venables KM, Malmberg P, Hollander A, Karlsson AS, Renstrom A, Doekes G, Nieuwenhijsen M, Gordon S (1999) Exposure-response relationships for work-related sensitization in workers exposed to rat urinary allergens: Results from a pooled study. *J Allergy Clin Immunol* 103: 678–684
16 Snippe RJ, Gijsbers JHJ, van Drooge H, Preller E (2001) *Chemische allergenen in Nederland. Een onderzoek naar de blootstelling aan diisocyanaten en zuuranhydriden in Nederland*. Ministerie van Sociale Zaken en Werkgelegenheid, Directie Voorlichting, Bibliotheek en Documentatie, Den Haag
17 Archambault S, Malo JL, Infante-Rivard C, Ghezzo H, Gautrin D (2001) Incidence of sensitization, symptoms, and probable occupational rhinoconjunctivitis and asthma in apprentices starting exposure to latex. *J Allergy Clin Immunol* 107: 921–923
18 Newman Taylor AJ, Nicholson PJ (2004) *Guidelines for the prevention, identification & management of occupational asthma: Evidence review & recommendations*. British Occupational Health Research Foundation, London
19 Barbinova L, Baur X (2007) Possible influence of occupational exposure to high and low molecular-weight asthmagens on the atopic status. *Eur Respir J* 30: 4s
20 Brisman J, Jarvholm B, Lillienberg L (2000) Exposure-response relations for self reported asthma and rhinitis in bakers. *Occup Environ Med* 57: 335–340
21 Cathcart M, Nicholson P, Roberts D, Bazley M, Juniper C, Murray P, Randell M (1997) Enzyme exposure, smoking and lung function in employees in the detergent industry over 20 years. Medical Subcommittee of the UK Soap and Detergent Industry Association. *Occup Med (Lond)* 47: 473–478
22 Cullinan P, Cook A, Gordon S, Nieuwenhuijsen MJ, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ (1999) Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. *Eur Respir J* 13: 1139–1143
23 Cullinan P, Cook A, Nieuwenhuijsen MJ, Sandiford C, Tee RD, Venables KM, McDonald JC, Newman Taylor AJ (2001) Allergen and dust exposure as determinants of work-related symptoms and sensitization in a cohort of flour-exposed workers; a case-control analysis. *Ann Occup Hyg* 45: 97–103
24 Cullinan P, Harris JM, Newman Taylor AJ, Hole AM, Jones M, Barnes F, Jolliffe G (2000) An outbreak of asthma in a modern detergent factory. *Lancet* 356: 1899–1900

25 Heederik D, Houba R (2001) An exploratory quantitative risk assessment for high molecular weight sensitizers: Wheat flour. *Ann Occup Hyg* 45: 175–185
26 Houba R, Heederik D, Doekes G (1998) Wheat sensitization and work-related symptoms in the baking industry are preventable. An epidemiologic study. *Am J Respir Crit Care Med* 158: 1499–1503
27 Nieuwenhuijsen M, Baur X, Heederik D (2006) Environmental monitoring: General considerations, exposure-response relationships, and risk assessment. In: IL Bernstein, M Chan-Yeung, JL Malo, DI Bernstein (eds): *Asthma in the Workplace*. Taylor & Francis, New York, 253–274
28 Ortega HG, Daroowalla F, Petsonk EL, Lewis D, Berardinelli S Jr, Jones W, Kreiss K, Weissman DN (2001) Respiratory symptoms among crab processing workers in Alaska: Epidemiological and environmental assessment. *Am J Ind Med* 39: 598–607
29 Osterman K, Zetterstrom O, Johansson SG (1982) Coffee worker's allergy. *Allergy* 37: 313–322
30 Vanhanen M, Tuomi T, Nordman H, Tupasela O, Holmberg PC, Miettinen M, Mutanen P, Leisola M (1997) Sensitization to industrial enzymes in enzyme research and production. *Scand J Work Environ Health* 23: 385–391
31 Martinez FD (2007) CD14, endotoxin, and asthma risk: Actions and interactions. *Proc Am Thorac Soc* 4: 221–225
32 Moore WC, Peters SP (2007) Update in asthma 2006. *Am J Respir Crit Care Med* 175: 649–654
33 Schaub B, Lauener R, von Mutius E (2006) The many faces of the hygiene hypothesis. *J Allergy Clin Immunol* 117: 969–977; quiz 978
34 Sigsgaard T, Brandslund I, Omland O, Hjort C, Lund ED, Pedersen OF, Miller MR (2000) S and Z alpha1–antitrypsin alleles are risk factors for bronchial hyperresponsiveness in young farmers: An example of gene/environment interaction. *Eur Respir J* 16: 50–55
35 Candi E, Schmidt R, Melino G (2005) The cornified envelope: A model of cell death in the skin. *Nat Rev Mol Cell Biol* 6: 328–340
36 Irvine AD (2007) Fleshing out filaggrin phenotypes. *J Invest Dermatol* 127: 504–507
37 Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, Smith FJ, McLean WH, Mukhopadhyay S (2007) Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 120: 64–68
38 Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, Debenedetto A, Schneider L, Beck LA, Barnes KC, Leung DY (2007) Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 120: 150–155
39 Balboni A, Baricordi OR, Fabbri LM, Gandini E, Ciaccia A, Mapp CE (1996) Association between toluene diisocyanate-induced asthma and DQB1 markers: A possible role for aspartic acid at position 57. *Eur Respir J* 9: 207–210
40 Bignon JS, Aron Y, Ju LY, Kopferschmitt MC, Garnier R, Mapp C, Fabbri LM, Pauli G, Lockhart A, Charron D et al (1994) HLA class II alleles in isocyanate-induced asthma. *Am J Respir Crit Care Med* 149: 71–75

41 Horne C, Quintana PJ, Keown PA, Dimich-Ward H, Chan-Yeung M (2000) Distribution of DRB1 and DQB1 HLA class II alleles in occupational asthma due to western red cedar. *Eur Respir J* 15: 911–914
42 Jeal H, Draper A, Jones M, Harris J, Welsh K, Taylor AN, Cullinan P (2003) HLA associations with occupational sensitization to rat lipocalin allergens: A model for other animal allergies? *J Allergy Clin Immunol* 111: 795–799
43 Mapp CE, Beghe B, Balboni A, Zamorani G, Padoan M, Jovine L, Baricordi OR, Fabbri LM (2000) Association between HLA genes and susceptibility to toluene diisocyanate-induced asthma. *Clin Exp Allergy* 30: 651–656
44 Mapp CE, Fryer AA, De Marzo N, Pozzato V, Padoan M, Boschetto P, Strange RC, Hemmingsen A, Spiteri MA (2002) Glutathione S-transferase GSTP1 is a susceptibility gene for occupational asthma induced by isocyanates. *J Allergy Clin Immunol* 109: 867–872
45 Bernstein DI (1997) Allergic reactions to workplace allergens. *JAMA* 278: 1907–1913
46 Heederik K, Portegen L, Meijer E, Doekes G, De Meer G (1999) *Beroepsgebonden allergische luchtwegaandoeningen. Literaturstudie in opdracht van het Ministerie van Sociale Zaken en Werkgelegenheid*. Ministerie van Sociale Zaken in Werkgelegenheid, Wageningen
47 Nielsen GD, Olsen O, Larsen ST, Lovik M, Poulsen LK, Glue C, Brandorff NP, Nielsen PJ (2005) IgE-mediated sensitisation, rhinitis and asthma from occupational exposures. Smoking as a model for airborne adjuvants? *Toxicology* 216: 87–105
48 Portengen L (2004) *Risk modification and combined exposures in occupational respiratory allergy (Proefschrift)*. University of Utrecht, Institute for Risk Assessment Sciences, Utrecht
49 Siracusa A, Desrosiers M, Marabini A (2000) Epidemiology of occupational rhinitis: Prevalence, aetiology and determinants. *Clin Exp Allergy* 30: 1519–1534
50 Merget R, Kulzer R, Dierkes-Globisch A, Breitstadt R, Gebler A, Kniffka A, Artelt S, Koenig HP, Alt F, Vormberg R et al (2000) Exposure-effect relationship of platinum salt allergy in a catalyst production plant: Conclusions from a 5-year prospective cohort study. *J Allergy Clin Immunol* 105: 364–370
51 Venables KM, Dally MB, Nunn AJ, Stevens JF, Stephens R, Farrer N, Hunter JV, Stewart M, Hughes EG, Newman Taylor AJ (1989) Smoking and occupational allergy in workers in a platinum refinery. *BMJ* 299: 939–942
52 Cartier A, Malo JL, Forest F, Lafrance M, Pineau L, St-Aubin JJ, Dubois JY (1984) Occupational asthma in snow crab-processing workers. *J Allergy Clin Immunol* 74: 261–269
53 Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Taylor AJ (1985) Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *Br Med J (Clin Res Ed)* 290: 201–204
54 Zetterstrom O, Osterman K, Machado L, Johansson SG (1981) Another smoking hazard: Raised serum IgE concentration and increased risk of occupational allergy. *Br Med J (Clin Res Ed)* 283: 1215–1217

55 Cortona G, Pisati G, Dellabianca A, Moscato G (2001) [Respiratory occupational allergies: The experience of the Hospital Operative Unit of Occupational Medicine in Lombardy from 1990 to 1998]. *G Ital Med Lav Ergon* 23: 64–70
56 Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL (2001) Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. *Eur Respir J* 17: 904–908
57 Gautrin D, Infante-Rivard C, Ghezzo H, Malo JL (2001) Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. *Am J Respir Crit Care Med* 163: 899–904
58 Grammer LC, Ditto AM, Tripathi A, Harris KE (2002) Prevalence and onset of rhinitis and conjunctivitis in subjects with occupational asthma caused by trimellitic anhydride (TMA). *J Occup Environ Med* 44: 1179–1181
59 Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J (2003) Risk of asthma among Finnish patients with occupational rhinitis. *Chest* 123: 283–288
60 Malo JL, Lemiere C, Desjardins A, Cartier A (1997) Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 10: 1513–1515
61 Zhang XD, Lotvall J, Skerfving S, Welinder H (1997) Antibody specificity to the chemical structures of organic acid anhydrides studied by *in-vitro* and *in-vivo* methods. *Toxicology* 118: 223–232
62 Zhang XD, Welinder H, Jonsson BA, Skerfving S (1998) Antibody responses of rats after immunization with organic acid anhydrides as a model of predictive testing. *Scand J Work Environ Health* 24: 220–227
63 Barbinova L, Baur X (2006) Increase in exhaled nitric oxide (eNO) after work-related isocyanate exposure. *Int Arch Occup Environ Health* 79: 387–395
64 Lemiere C, Pelissier S, Tremblay C, Chaboillez S, Thivierge M, Stankova J, Rola-Pleszczynski M (2004) Leukotrienes and isocyanate-induced asthma: A pilot study. *Clin Exp Allergy* 34: 1684–1689
65 Bush RK, Wood RA, Eggleston PA (1998) Laboratory animal allergy. *J Allergy Clin Immunol* 102: 99–112
66 Nieuwenhijsen MJ, Putcha V, Gordon S, Heederik D, Cullinan P, Venables KM, Newman Taylor AJ (2001) Exposure-response relationships in laboratory animal workers. In: G-NRCfEa Health (ed): *Thirteenth conference of the International Society for Environmental Epidemiology.* Neuherberg, Garmisch-Partenkirchen, A18
67 Nieuwenhuijsen MJ, Putcha V, Gordon S, Heederik D, Venables KM, Cullinan P, Newman-Taylor AJ (2003) Exposure-response relations among laboratory animal workers exposed to rats. *Occup Environ Med* 60: 104–108
68 Hollander A, Heederik D, Doekes G (1997) Respiratory allergy to rats: Exposure-response relationships in laboratory animal workers. *Am J Respir Crit Care Med* 155: 562–567
69 Thulin H, Bjorkdahl M, Karlsson AS, Renstrom A (2002) Reduction of exposure to laboratory animal allergens in a research laboratory. *Ann Occup Hyg* 46: 61–68

70 Hoppin JA, Umbach DM, London SJ, Alavanja MC, Sandler DP (2003) Animal production and wheeze in the Agricultural Health Study: Interactions with atopy, asthma, and smoking. *Occup Environ Med* 60: e3
71 Hoppin JA, Umbach DM, London SJ, Alavanja MC, Sandler DP (2004) Diesel exhaust, solvents, and other occupational exposures as risk factors for wheeze among farmers. *Am J Respir Crit Care Med* 169: 1308–1313
72 Monso E, Riu E, Radon K, Magarolas R, Danuser B, Iversen M, Morera J, Nowak D (2004) Chronic obstructive pulmonary disease in never-smoking animal farmers working inside confinement buildings. *Am J Ind Med* 46: 357–362
73 Portengen L, Preller L, Tielen M, Doekes G, Heederik D (2005) Endotoxin exposure and atopic sensitization in adult pig farmers. *J Allergy Clin Immunol* 115: 797–802
74 Terho EO, Husman K, Vohlonen I, Rautalahti M, Tukiainen H (1985) Allergy to storage mites or cow dander as a cause of rhinitis among Finnish dairy farmers. *Allergy* 40: 23–26
75 Terho EO, Vohlonen I, Husman K, Rautalahti M, Tukiainen H, Viander M (1987) Sensitization to storage mites and other work-related and common allergens among Finnish dairy farmers. *Eur J Respir Dis* 152: 165–174
76 Virtanen T, Vilhunen P, Husman K, Mantyjarvi R (1988) Sensitization of dairy farmers to bovine antigens and effects of exposure on specific IgG and IgE titers. *Int Arch Allergy Appl Immunol* 87: 171–177
77 Hinze S, Bergmann KC, Lowenstein H, Hansen GN (1996) [Different threshold concentrations for sensitization by cattle hair allergen Bos d 2 in atopic and non-atopic farmers]. *Pneumologie* 50: 177–181
78 Rautiainen M, Virtanen T, Ruoppi P, Nuutinen J, Mantyjarvi R (1997) Humoral responses to bovine dust in dairy farmers with allergic rhinitis. *Acta Otolaryngol* (Suppl) 529: 169–172
79 Schwartz DA, Donham KJ, Olenchock SA, Popendorf WJ, Van Fossen DS, Burmeister LF, Merchant JA (1995) Determinants of longitudinal changes in spirometric function among swine confinement operators and farmers. *Am J Respir Crit Care Med* 151: 47–53
80 Cormier Y, Coll B, Laviolette M, Boulet LP (1996) Reactive airways dysfunction syndrome (RADS) following exposure to toxic gases of a swine confinement building. *Eur Respir J* 9: 1090–1091
81 Vogelzang PF, van der Gulden JW, Folgering H, Kolk JJ, Heederik D, Preller L, Tielen MJ, van Schayck CP (1998) Endotoxin exposure as a major determinant of lung function decline in pig farmers. *Am J Respir Crit Care Med* 157: 15–18
82 Radon K, Monso E, Weber C, Danuser B, Iversen M, Opravil U, Donham K, Hartung J, Pedersen S, Garz S et al (2002) Prevalence and risk factors for airway diseases in farmers – Summary of results of the European Farmers' Project. *Ann Agric Environ Med* 9: 207–213
83 Dosman JA, Lawson JA, Kirychuk SP, Cormier Y, Biem J, Koehncke N (2004) Occupa-

tional asthma in newly employed workers in intensive swine confinement facilities. *Eur Respir J* 24: 698–702
84 Danuser B, Wyss C, Hauser R, von Planta U, Folsch D (1988) [Lung function and symptoms in employees of poultry farms]. *Soz Praventivmed* 33: 286–291
85 Danuser B, Weber C, Kunzli N, Schindler C, Nowak D (2001) Respiratory symptoms in Swiss farmers: An epidemiological study of risk factors. *Am J Ind Med* 39: 410–418
86 Perfetti L, Cartier A, Malo JL (1997) Occupational asthma in poultry-slaughterhouse workers. *Allergy* 52: 594–595
87 Borghetti C, Magarolas R, Badorrey I, Radon K, Morera J, Monso E (2002) [Sensitization and occupational asthma in poultry workers]. *Med Clin (Barc)* 118: 251–255
88 Schwartz HJ (1994) Raw poultry as a cause of occupational dermatitis, rhinitis, and asthma. *J Asthma* 31: 485–486
89 Hagmar L, Schutz A, Hallberg T, Sjoholm A (1990) Health effects of exposure to endotoxins and organic dust in poultry slaughter-house workers. *Int Arch Occup Environ Health* 62: 159–164
90 Cuthbert OD, Jeffrey IG, McNeill HB, Wood J, Topping MD (1984) Barn allergy among Scottish farmers. *Clin Allergy* 14: 197–206
91 Baur X (2008) Airborne allergens and irritants in the workplace. In: AB Kay, AP Kaplan, J Bousquet, PG Holt (eds): *Allergy and allergic diseases*. Blackwell Publishing, 1017–1122
92 Heederik D, Doekes G, Nieuwenhuijsen MJ (1999) Exposure assessment of high molecular weight sensitisers: Contribution to occupational epidemiology and disease prevention. *Occup Environ Med* 56: 735–741
93 Heederik D, Thorne PS, Doekes G (2002) Health-based occupational exposure limits for high molecular weight sensitizers: How long is the road we must travel? *Ann Occup Hyg* 46: 439–446
94 Baur X (2005) Enzymes as occupational and environmental respiratory sensitisers. *Int Arch Occup Environ Health* 78: 279–286
95 Vanhanen M (2001) *Exposure, sensitization and allergy to industrial enzymes: Department of Pulmonology*. Helsinki University Central Hospital, Helsinki
96 Juniper CP, How MJ, Goodwin BF, Kinshott AK (1977) *Bacillus subtilis* enzymes: A 7–year clinical, epidemiological and immunological study of an industrial allergen. *J Soc Occup Med* 27: 3–12
97 American Conference of Governmental and Industrial Hygienists (2007) *TLVs and BEIs*. ACGIH, Cincinnati
98 Goldberg A, Confino-Cohen R, Waisel Y (1998) Allergic responses to pollen of ornamental plants: High incidence in the general atopic population and especially among flower growers. *J Allergy Clin Immunol* 102: 210–214
99 Monso E, Magarolas R, Radon K, Danuser B, Iversen M, Weber C, Opravil U, Donham KJ, Nowak D (2000) Respiratory symptoms of obstructive lung disease in European crop farmers. *Am J Respir Crit Care Med* 162: 1246–1250
100 Groenewoud GC, de Jong NW, van Oorschot-van Nes AJ, Vermeulen AM, van

Toorenenbergen AW, Mulder PG, Burdorf A, de Groot H, van Wijk RG (2002) Prevalence of occupational allergy to bell pepper pollen in greenhouses in the Netherlands. *Clin Exp Allergy* 32: 434–440

101 Monso E, Schenker M, Radon K, Riu E, Magarolas R, McCurdy S, Danuser B, Iversen M, Saiki C, Nowak D (2003) Region-related risk factors for respiratory symptoms in European and Californian farmers. *Eur Respir J* 21: 323–331

102 Jansen AP, Visser FJ, Nierop G, de Jong NW, Waanders-de Lijster de Raadt J, Vermeulen A, van Toorenenbergen AW (1996) Occupational asthma to amaryllis. *Allergy* 51: 847–849

103 Tabar AI, Alvarez-Puebla MJ, Gomez B, Sanchez-Monge R, Garcia BE, Echechipia S, Olaguibel JM, Salcedo G (2004) Diversity of asparagus allergy: Clinical and immunological features. *Clin Exp Allergy* 34: 131–136

104 de Jong NW, Vermeulen AM, Gerth van Wijk R, de Groot H (1998) Occupational allergy caused by flowers. *Allergy* 53: 204–209

105 Akpinar-Elci M, Elci OC, Odabasi A (2004) Work-related asthma-like symptoms among florists. *Chest* 125: 2336–2339

106 Antepara I, Jauregui I, Urrutia I, Gamboa PM, Gonzalez G, Barber D (1994) Occupational asthma related to fresh *Gypsophila paniculata*. *Allergy* 49: 478–480

107 Schroeckenstein DC, Meier-Davis S, Yunginger JW, Bush RK (1990) Allergens involved in occupational asthma caused by baby's breath (*Gypsophila paniculata*). *J Allergy Clin Immunol* 86: 189–193

108 Twiggs JT, Yunginger JW, Agarwal MK, Reed CE (1982) Occupational asthma in a florist caused by the dried plant, baby's breath. *J Allergy Clin Immunol* 69: 474–477

109 Miesen WM, van der Heide S, Kerstjens HA, Dubois AE, de Monchy JG (2003) Occupational asthma due to IgE mediated allergy to the flower *Molucella laevis* (Bells of Ireland). *Occup Environ Med* 60: 701–703

110 Blanco C, Carrillo T, Quiralte J, Pascual C, Martin Esteban M, Castillo R (1995) Occupational rhinoconjunctivitis and bronchial asthma due to *Phoenix canariensis* pollen allergy. Allergy 50: 277–280

111 Sanchez-Guerrero IM, Escudero AI, Bartolom B, Palacios R (1999) Occupational allergy caused by carnation (*Dianthus caryophyllus*). *J Allergy Clin Immunol* 104: 181–185

112 Cistero-Bahima A, Enrique E, Alonso R, del Mar San Miguel M, Bartolome B (2000) Simultaneous occupational allergy to a carnation and its parasite in a greenhouse worker. *J Allergy Clin Immunol* 106: 780

113 Sanchez-Fernandez C, Gonzalez-Gutierrez ML, Esteban-Lopez MI, Martinez A, Lombardero M (2004) Occupational asthma caused by carnation (*Dianthus caryophyllus*) with simultaneous IgE-mediated sensitization to *Tetranychus urticae*. *Allergy* 59: 114–115

114 Compes E, Bartolome B, Fernandez-Nieto M, Sastre J, Cuesta J (2006) Occupational asthma from dried flowers of *Carthamus tinctorious* (safflower) and *Achillea millefolium* (yarrow). *Allergy* 61: 1239–1240

115 Paulsen E, Skov PS, Bindslev-Jensen C, Voitenko V, Poulsen LK (1997) Occupational type I allergy to Christmas cactus (*Schlumbergera*). *Allergy* 52: 656–660
116 Groenewoud GC, de Jong NW, Burdorf A, de Groot H, van Wyk RG (2002) Prevalence of occupational allergy to Chrysanthemum pollen in greenhouses in the Netherlands. *Allergy* 57: 835–840
117 Piirila P, Keskinen H, Leino T, Tupasela O, Tuppurainen M (1994) Occupational asthma caused by decorative flowers: Review and case reports. *Int Arch Occup Environ Health* 66: 131–136
118 Ueda A, Tochigi T, Ueda T, Aoyama K, Manda F (1992) Immediate type of allergy in statis growers. *J Allergy Clin Immunol* 90: 742–748
119 Vidal C, Polo F (1998) Occupational allergy caused by *Dianthus caryophillus*, *Gypsophila paniculata*, and *Lilium longiflorum*. *Allergy* 53: 995–998
120 Piirila P, Kanerva L, Alanko K, Estlander T, Keskinen H, Pajari-Backas M, Tuppurainen M (1999) Occupational IgE-mediated asthma, rhinoconjunctivitis, and contact urticaria caused by Easter lily (*Lilium longiflorum*) and tulip. *Allergy* 54: 273–277
121 Gil M, Hogendijk S, Hauser C (2002) Allergy to eggplant flower pollen. *Allergy* 57: 652
122 van Toorenenbergen AW, Dieges PH (1984) Occupational allergy in horticulture: Demonstration of immediate-type allergic reactivity to freesia and paprika plants. *Int Arch Allergy Appl Immunol* 75: 44–47
123 van Toorenenbergen AW, Dieges PH (1985) Immunoglobulin E antibodies against coriander and other spices. *J Allergy Clin Immunol* 76: 477–481
124 Quirce S, Garcia-Figueroa B, Olaguibel JM, Muro MD, Tabar AI (1993) Occupational asthma and contact urticaria from dried flowers of *Limonium tataricum*. *Allergy* 48: 285–290
125 Piirila P, Hannu T, Keskinen H, Tuppurainen M (1998) Occupational asthma to hyacinth. *Allergy* 53: 328–329
126 van der Zee JS, de Jager KS, Kuipers BF, Stapel SO (1999) Outbreak of occupational allergic asthma in a *Stephanotis floribunda* nursery. *J Allergy Clin Immunol* 103: 950–952
127 Ariano R, Panzani RC, Amedeo J (1991) Pollen allergy to mimosa (*Acacia floribunda*) in a Mediterranean area: An occupational disease. *Ann Allergy* 66: 253–256
128 Goncalo S, Freitas JD, Sousa I (1987) Contact dermatitis and respiratory symptoms from *Narcissus pseudonarcissus*. *Contact Dermatitis* 16: 115–116
129 Jansen A, Vermeulen A, van Toorenenbergen AW, Dieges PH (1995) Occupational asthma in horticulture caused by *Lathyrus odoratus*. *Allergy Proc* 16: 135–139
130 Garcia BE, Lombardero M, Echechipia S, Olaguibel JM, Diaz-Perales A, Sanchez-Monge R, Barber D, Salcedo G, Tabar AI (2004) Respiratory allergy to peach leaves and lipid-transfer proteins. *Clin Exp Allergy* 34: 291–295
131 Moneo I, Alday E, Ramos C, Curiel G (1993) Occupational asthma caused by *Papaver somniferum*. *Allergol Immunopathol (Madr)* 21: 145–148

132 Demir AU, Karakaya G, Kalyoncu AF (2002) Allergy symptoms and IgE immune response to rose: An occupational and an environmental disease. *Allergy* 57: 936–939
133 Kwaselow A, Rowe M, Sears-Ewald D, Ownby D (1990) Rose hips: A new occupational allergen. *J Allergy Clin Immunol* 85: 704–708
134 Feo F, Martinez J, Martinez A, Galindo PA, Cruz A, Garcia R, Guerra F, Palacios R (1997) Occupational allergy in saffron workers. *Allergy* 52: 633–641
135 Kanerva L, Makinen-Kiljunen S, Kiistala R, Granlund H (1995) Occupational allergy caused by spathe flower (*Spathiphyllum wallisii*). *Allergy* 50: 174–178
136 Bousquet J, Dhivert H, Clauzel AM, Hewitt B, Michel FB (1985) Occupational allergy to sunflower pollen. *J Allergy Clin Immunol* 75: 70–74
137 Atis S, Tutluoglu B, Sahin K, Yaman M, Kucukusta AR, Oktay I (2002) Sensitization to sunflower pollen and lung functions in sunflower processing workers. *Allergy* 57: 35–39
138 Jimenez A, Moreno C, Martinez J, Martinez A, Bartolome B, Guerra F, Palacios R (1994) Sensitization to sunflower pollen: Only an occupational allergy? *Int Arch Allergy Immunol* 105: 297–307
139 Navarro AM, Delgado J, Sanchez MC, Orta JC, Martinez A, Palacios R, Martinez J, Conde J (2000) Prevalence of sensitization to *Tetranychus urticae* in greenhouse workers. *Clin Exp Allergy* 30: 863–866
140 Krüsmann W, Hausen BM (1987) Tulpenallergy vom Soforttyp mit Asthma bronchiale und Rhinokonjunktivitis. *Allergologie* 10: 549–551
141 Lahti A (1986) Contact urticaria and respiratory symptoms from tulips and lilies. *Contact Dermatitis* 14: 317–319
142 Grob M, Wuthrich B (1998) Occupational allergy to the umbrella tree (*Schefflera*). *Allergy* 53: 1008–1009
143 Axelsson G, Skedinger M, Zetterstrom O (1985) Allergy to weeping fig – A new occupational disease. *Allergy* 40: 461–464
144 Axelsson IG, Johansson SG, Zetterstrom O (1987) Occupational allergy to weeping fig in plant keepers. *Allergy* 42: 161–167
145 Groenewoud GC, de Graaf in 't Veld C, vVan Oorschot-van Nes AJ, de Jong NW, Vermeulen AM, van Toorenenbergen AW, Burdorf A, de Groot H, Gerth van Wijk R (2002) Prevalence of sensitization to the predatory mite *Amblyseius cucumeris* as a new occupational allergen in horticulture. *Allergy* 57: 614–619
146 Johansson E, Kolmodin-Hedman B, Kallstrom E, Kaiser L, van Hage-Hamsten M (2003) IgE-mediated sensitization to predatory mites in Swedish greenhouse workers. *Allergy* 58: 337–341
147 Kronqvist M, Johansson E, Kolmodin-Hedman B, Oman H, Svartengren M, van Hage-Hamsten M (2005) IgE-sensitization to predatory mites and respiratory symptoms in Swedish greenhouse workers. *Allergy* 60: 521–526
148 Delgado J, Orta JC, Navarro AM, Conde J, Martinez A, Martinez J, Palacios R (1997) Occupational allergy in greenhouse workers: Sensitization to *Tetranychus urticae*. *Clin Exp Allergy* 27: 640–645

149 Doekes G, Larsen P, Sigsgaard T, Baelum J (2004) IgE sensitization to bacterial and fungal biopesticides in a cohort of Danish greenhouse workers: The BIOGART study. *Am J Ind Med* 46: 404–407
150 Monso E (2004) Occupational asthma in greenhouse workers. *Curr Opin Pulm Med* 10: 147–150
151 Fraj J, Lezaun A, Colas C, Duce F, Dominguez MA, Alonso MD (1996) Occupational asthma induced by aniseed. *Allergy* 51: 337–339
152 Kim SH, Jeong H, Kim YK, Cho SH, Min KU, Kim YY (2001) IgE-mediated occupational asthma induced by herbal medicine, Banha (*Pinellia ternata*). *Clin Exp Allergy* 31: 779–781
153 Quirce S, Blanco R, Diez-Gomez ML, Cuevas M, Eiras P, Losada E (1997) Carrot-induced asthma: Immunodetection of allergens. *J Allergy Clin Immunol* 99: 718–719
154 Cadot P, Kochuyt AM, Deman R, Stevens EA (1996) Inhalative occupational and ingestive immediate-type allergy caused by chicory (*Cichorium intybus*). *Clin Exp Allergy* 26: 940–944
155 Dugué J, Bel J, Figueredo M (1993) Le fenugrec responsable d'un nouvel asthme professionnel. *La Presse Médicale* 22: 922
156 Lybarger JA, Gallagher JS, Pulver DW, Litwin A, Brooks S, Bernstein IL (1982) Occupational asthma induced by inhalation and ingestion of garlic. *J Allergy Clin Immunol* 69: 448–454
157 Anibarro B, Fontela JL, De La Hoz F (1997) Occupational asthma induced by garlic dust. *J Allergy Clin Immunol* 100: 734–738
158 Subiza J, Subiza JL, Escribano PM, Hinojosa M, Garcia R, Jerez M, Subiza E (1991) Occupational asthma caused by Brazil ginseng dust. *J Allergy Clin Immunol* 88: 731–736
159 Lemiere C, Cartier A, Lehrer SB, Malo JL (1996) Occupational asthma caused by aromatic herbs. *Allergy* 51: 647–649
160 Newmark FM (1978) Hops allergy and terpene sensitivity: An occupational disease. *Ann Allergy* 41: 311–312
161 Luczynska CM, Marshall PE, Scarisbrick DA, Topping MD (1984) Occupational allergy due to inhalation of ipecacuanha dust. *Clin Allergy* 14: 169–175
162 Kern DG, Kohn R (1994) Occupational asthma following kapok exposure. *J Asthma* 31: 243–250
163 Cartier A, Malo JL, Labrecque M (2002) Occupational asthma due to liquorice roots. *Allergy* 57: 863
164 Catilina P, Chamoux A, Gabrillargues D, Catilina MJ, Royfe MH, Wahl D (1988) Contribution à l'étude des asthmas d'origine professionnelle: L'asthme à la poudre de lycopode. *Arch Mal Prof* 49: 143–148
165 Kobayashi S (1980) Different aspects of occupational asthma in Japan. In: CA Frazier (ed): *Occupational asthma*. van Nostrand-Reinhold, New York, 229–244
166 Symington IS, Kerr JW, McLean DA (1981) Type I allergy in mushroom soup processors. *Clin Allergy* 11: 43–47

167 Michils A, De Vuyst P, Nolard N, Servais G, Duchateau J, Yernault JC (1991) Occupational asthma to spores of Pleurotus cornucopiae. *Eur Respir J* 4: 1143–1147
168 Valdivieso R, Subiza J, Varela-Losada S, Subiza JL, Narganes MJ, Martinez-Cocera C, Cabrera M (1994) Bronchial asthma, rhinoconjunctivitis, and contact dermatitis caused by onion. *J Allergy Clin Immunol* 94: 928–930
169 Cohen AJ, Forse MS, Tarlo SM (1993) Occupational asthma caused by pectin inhalation during the manufacture of jam. *Chest* 103: 309–311
170 Quirce S, Diez Gomez ML, Hinojosa M, Cuevas M, Urena V, Rivas MF, Puyana J, Cuesta J, Losada E (1989) Housewives with raw potato-induced bronchial asthma. *Allergy* 44: 532–536
171 Sherson D, Andersen B, Hansen I, Kjoller H (2003) Occupational asthma due to freeze-dried raspberry. *Ann Allergy Asthma Immunol* 90: 660–663
172 Park HS, Kim MJ, Moon HB (1994) Occupational asthma caused by two herb materials, *Dioscorea batatas* and *Pinellia ternata*. *Clin Exp Allergy* 24: 575–581
173 Vandenplas O, Depelchin S, Toussaint G, Delwiche JP, Weyer RV, Saint-Remy JM (1996) Occupational asthma caused by sarsaparilla root dust. *J Allergy Clin Immunol* 97: 1416–1418
174 Sastre J, Olmo M, Novalvos A, Ibanez D, Lahoz C (1996) Occupational asthma due to different spices. *Allergy* 51: 117–120
175 Uragoda CG (1970) Tea maker's asthma. *Br J Ind Med* 27: 181–182
176 Roberts JA, Thomson NC (1988) Tea-dust induced asthma. *Eur Respir J* 1: 769–770
177 Cartier A, Malo JL (1990) Occupational asthma due to tea dust. *Thorax* 45: 203–206
178 Shirai T, Reshad K, Yoshitomi A, Chida K, Nakamura H, Taniguchi M (2003) Green tea-induced asthma: Relationship between immunological reactivity, specific and non-specific bronchial responsiveness. *Clin Exp Allergy* 33: 1252–1255
179 Shirai T, Sato A, Hara Y (1994) Epigallocatechin gallate. The major causative agent of green tea-induced asthma. *Chest* 106: 1801–1805
180 Bohner CB, Sheldon JM, Trenis JW (1941) Sensitivity to gum acacia, with a report of ten cases of asthma in printers. *Allergy* 12: 290–294
181 Hinault G, Blacque-Bélair A, Buffe D (1961) L'asthme à la gomme arabique dans un grand atelier de typographie. *J Franc Méd Chir Thor* 15: 51–61
182 Gaultier M, Fournier E, Gervais P, Vignolet (1960) Un cas d'asthme à la gomme arabique. Histoire clinique, tests cutanés, épreuves fonctionnelles respiratoires. *Arch Mal Prof* 21: 55–56
183 Fowlers PBS (1952) Printer's asthma. *Lancet* 2: 755–757
184 Bullen SS (1934) Perennial hay fever from indian gum (Karaya gum). *J Allergy* 5: 484–487
185 Bardy JD, Malo JL, Seguin P, Ghezzo H, Desjardins J, Dolovich J, Cartier A (1987) Occupational asthma and IgE sensitization in a pharmaceutical company processing psyllium. *Am Rev Respir Dis* 135: 1033–1038
186 Malo JL, Cartier A, L'Archeveque J, Ghezzo H, Lagier F, Trudeau C, Dolovich J (1990)

Prevalence of occupational asthma and immunologic sensitization to psyllium among health personnel in chronic care hospitals. *Am Rev Respir Dis* 142: 1359–1366
187 Gauss WF, Alarie JP, Karol MH (1985) Workplace allergenicity of a psyllium-containing bulk laxative. *Allergy* 40: 73–76
188 Scott D (1987) Psyllium-induced asthma. Occupational exposure in a nurse. *Postgrad Med* 82: 160–161
189 Terho EO, Torkko M (1980) Occupational asthma from psyllium laxatives. *Duodecim* 96: 1213–1216
190 Schwartz HJ (1989) Effect of chronic chromolyn sodium therapy in a beautician with occupational asthma. *J Occup Med* 31: 112–114
191 Bernton HS (1970) The allergenicity of psyllium seed. Report of a case. *Med Ann Dist Columbia* 39: 313–317
192 Nelson WL (1987) Allergic events among health care workers exposed to psyllium laxatives in the workplace. *J Occup Med* 29: 497–499
193 Breton JL, Leneutre F, Esculpavit G, Abourjaili M (1989) [A new cause of occupational asthma in a pharmacist]. *Presse Med* 18: 433
194 Busse WW, Schoenwetter WF (1975) Asthma from psyllium in laxative manufacture. *Ann Intern Med* 83: 361–362
195 Freeman GL (1994) Psyllium hypersensitivity. *Ann Allergy* 73: 490–492
196 Morgan MS, Arlian LG, Vyszenski-Moher DL, Deyo J, Kawabata T, Fernandez-Caldas E (1995) English plantain and psyllium: Lack of cross-allergenicity by crossed immunoelectrophoresis. *Ann Allergy Asthma Immunol* 75: 351–359
197 Malo JL, Cartier A, L'Archeveque J, Ghezzo H, Soucy F, Somers J, Dolovich J (1990) Prevalence of occupational asthma and immunologic sensitization to guar gum among employees at a carpet-manufacturing plant. *J Allergy Clin Immunol* 86: 562–569
198 Gelfand HH (1963) Respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac, and beauty culture industries. *J Allergy Clin Immunol* 34: 374–381
199 Pepys J, Hutchcroft BJ, Breslin AB (1976) Asthma due to inhaled chemical agents – Persulphate salts and henna in hairdressers. *Clin Allergy* 6: 399–404
200 Starr JC, Yunginger J, Brahser GW (1982) Immediate type I asthmatic response to henna following occupational exposure in hairdressers. *Ann Allergy* 48: 98–99
201 Blainey AD, Ollier S, Cundell D, Smith RE, Davies RJ (1986) Occupational asthma in a hairdressing salon. *Thorax* 41: 42–50
202 Parra FM, Igea JM, Quirce S, Ferrando MC, Martin JA, Losada E (1992) Occupational asthma in a hairdresser caused by persulphate salts. *Allergy* 47: 656–660
203 Bolhaar ST, Mulder M, van Ginkel CJ (2001) IgE-mediated allergy to henna. *Allergy* 56: 248
204 Hollund BE, Moen BE, Lygre SH, Florvaag E, Omenaas E (2001) Prevalence of airway symptoms among hairdressers in Bergen, Norway. *Occup Environ Med* 58: 780–785
205 Munoz X, Cruz MJ, Orriols R, Bravo C, Espuga M, Morell F (2003) Occupational asthma due to persulfate salts: Diagnosis and follow-up. *Chest* 123: 2124–2129

206 Moscato G, Galdi E (2006) Asthma and hairdressers. *Curr Opin Allergy Clin Immunol* 6: 91–95
207 Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ (2000) Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 118: 1183–1193
208 Latza U, Baur X, Malo JL (2002) Isocyanate-induced health effects In: JV Bakke, JO Norén, S Thorud, TB Aasen (eds): *International consensus report on: Isocyanates – Risk assessment and management*. Norwegian Labour Inspection Authority Gjovik, 237–251
209 Tarlo SM, Liss GM, Dias C, Banks DE (1997) Assessment of the relationship between isocyanate exposure levels and occupational asthma. *Am J Ind Med* 32: 517–521
210 Karol MH (1981) Survey of industrial workers for antibodies to toluene diisocyanate. *J Occup Med* 23: 741–747
211 Rattray NJ, Botham PA, Hext PM, Woodcock DR, Fielding I, Dearman RJ, Kimber I (1994) Induction of respiratory hypersensitivity to diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. *Toxicology* 88: 15–30
212 Vanoirbeek JA, Tarkowski M, Ceuppens JL, Verbeken EK, Nemery B, Hoet PH (2004) Respiratory response to toluene diisocyanate depends on prior frequency and concentration of dermal sensitization in mice. *Toxicol Sci* 80: 310–321
213 Zammit-Tabona M, Sherkin M, Kijek K, Chan H, Chan-Yeung M (1983) Asthma caused by diphenylmethane diisocyanate in foundry workers. Clinical, bronchial provocation, and immunologic studies. *Am Rev Respir Dis* 128: 226–230
214 Baur X, Marek W, Ammon J, Czuppon AB, Marczynski B, Raulf-Heimsoth M, Roemmelt H, Fruhmann G (1994) Respiratory and other hazards of isocyanates. *Int Arch Occup Environ Health* 66: 141–152
215 Cartier A, Grammer L, Malo JL, Lagier F, Ghezzo H, Harris K, Patterson R (1989) Specific serum antibodies against isocyanates: Association with occupational asthma. *J Allergy Clin Immunol* 84: 507–514
216 Grammer LC, Eggum P, Silverstein M, Shaughnessy MA, Liotta JL, Patterson R (1988) Prospective immunologic and clinical study of a population exposed to hexamethylene diisocyanate. *J Allergy Clin Immunol* 82: 627–633
217 Karol MH (1983) Concentration-dependent immunologic response to toluene diisocyanate (TDI) following inhalation exposure. *Toxicol Appl Pharmacol* 68: 229–241
218 Keskinen H, Tupasela O, Tiikkainen U, Nordman H (1988) Experiences of specific IgE in asthma due to diisocyanates. *Clin Allergy* 18: 597–604
219 Peters JM (1970) Studies of isocyanate toxicity. *Proc R Soc Med* 63: 372–375
220 Wegman DH, Peters JM, Pagnotto L, Fine LJ (1977) Chronic pulmonary function loss from exposure to toluene diisocyanate. *Br J Ind Med* 34: 196–200
221 Wegman DH, Musk AW, Main DM, Pagnotto LD (1982) Accelerated loss of FEV-1 in polyurethane production workers: A four-year prospective study. *Am J Ind Med* 3: 209–215
222 Diem JE, Jones RN, Hendrick DJ, Glindmeyer HW, Dharmarajan V, Butcher BT, Sal-

vaggio JE, Weill H (1982) Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. *Am Rev Respir Dis* 126: 420–428

223 Omae K, Higashi T, Nakadate T, Tsugane S, Nakaza M, Sakurai H (1992) Four-year follow-up of effects of toluene diisocyanate exposure on the respiratory system in polyurethane foam manufacturing workers. II. Four-year changes in the effects on the respiratory system. *Int Arch Occup Environ Health* 63: 565–569

224 Baur X (1996) Occupational asthma due to isocyanates. *Lung* 174: 23–30

225 Bernstein DI, Korbee L, Stauder T, Bernstein JA, Scinto J, Herd ZL, Bernstein IL (1993) The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *J Allergy Clin Immunol* 92: 387–396