Prevention and regulatory aspects of exposure to asthmagens in the workplace

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Abstract

The consequences of occupational asthma (OA) in terms of health, quality of life and costs incurred for the individual as well as society are considerable and make prevention worthwhile. The majority of cases are caused by comparatively few major asthmagens, such as flour dust, animal epithelium, natural rubber latex, and diisocyanates. A substantial reduction of these exposures is a realistic objective. It is important that preventive strategies are undertaken as concerted actions by all actors involved, i.e. regulatory authorities, branch organisations and worker unions. However, many asthmagens only cause occasional cases. Understandably, the prevention of these will rarely be highly prioritised. Aggravation of any asthma by non-specific exposures at work (work-exacerbated asthma, WEA) has turned out to be as important as OA. The costs incurred by WEA as well as the effects on quality of life equal or surpass those of OA. So far, our understanding of the nature of WEA as compared with OA is poor and far too meagre for scientifically based preventive strategies. Future research needs to focus on practically all aspects of WEA.

Introduction

From the preventive point of view, the full relationship between asthma and work environment exposures is of interest. It is generally recognised that some 15% of adult-onset asthma is attributable to work [1]. Population-based incidence studies indicate even higher figures [2, 3]. The high figures include all forms of work-related asthma, occupational asthma (OA) as well as work-exacerbated asthma (WEA). They are likely to reflect also the multifactorial nature of asthma, with the work environment as one of several interacting etiological genetic and environmental factors.

During the last, almost four decades, the vast majority of research efforts have focused on asthma with a latency period, specifically induced by sensitisation following inhalation of an asthmagen at work. The level of understanding achieved about occurrence and mechanisms of this "classical" OA is rather high and should be sufficient for preventive measures to be taken [4, 5]. However, the more than 250 identified specific inducers of OA, most of which having a low attack rate, explain

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why a realistic aim of prevention is currently to attain a substantial reduction of OA. The nature of OA, its resemblance to the much more prevalent non-OA, and the comparatively benign prognosis are factors explaining why prevention of OA has been disappointing. These and other factors influencing the prevention of OA have been listed by Cullinan and his colleagues [4] (Tab. 1). Fortunately, the vast majority of OA is caused by only a few major asthmagens, such as animal dander, flour dusts, diisocyanates and natural latex rubber.

It has been argued that exacerbation of pre-existing asthma, non-OA at work should be included when considering preventive strategies [6]. During the last decade it has become increasingly evident that the prevention of WEA will eventually be at least as important as the prevention of classical OA [7–9]. The high prevalence of asthma, especially among children and adolescents, makes the well-being of this sub-group of sensitive future workers a high priority issue.

The chapter gives emphasis to the primary and secondary prevention of the various types of OA. Some examples of successful preventive strategies are described. Although acute irritant-induced asthma fulfils the criteria of OA, the condition is almost exclusively caused by accidental exposure to high concentrations of a respiratory irritant. Preventive measures are, therefore, technical and hygienic, including worker education, and are not further dealt with in the chapter. [5]. The

Table 1. Factors influencing the prevention of occupational disease [4]

Influences	
Societal	Frequency of the disease Nature of the disease Perception of the disease Individual and societal costs of the disease
Technical	Strength of epidemiological or clinical evidence of cause/effect Identification of risk factors amenable to manipulation Availability of efficacious technical or organisational means of reducing important risk factors Availability of effective methods of secondary prevention
Business	Frequency of the disease Impact on consumers Public reputation Economic costs of the disease Efficiency and effectiveness of technical or organisational means of reducing important risk factors Effects on competitiveness Influence of employee or consumer organisations

need for preventive strategies for WEA is recognised but, so far, there is a paucity of scientific data on practically every aspect of the condition. Therefore, prevention of WEA can only be addressed in a state-of-the-art manner. Tertiary prevention aims at limiting impairment of OA in workers who are already ill. It is, by and large, synonymous with "management of cases", which is the topic of the chapter by S. Burge in this book [10].

The most important elements of the prevention of OA have been listed in Table 2.

Primary prevention

Primary prevention aims at the avoidance of exposure to agents causing OA and at the prevention of any such pathophysiological changes that may increase the

Table 2. Measures to prevent occupational asthma

Primary prevention
Measures of regulatory authorities - legislation - setting of occupational exposure limits - labelling of sensitising substances - making recommendations on the use of sensitisers - guidance on safe working practices - labour inspection activities
Screening of products before introduction into the market
Identification of highly susceptible individuals - vocational guidance - pre-employment health examinations
Pre-placement education of workers
Control of exposure - substitution of harmful agents with less harmful - automation or enclosure of processes - modification of process or agent to reduce risk of sensitisation - improvement of ventilation - working practices to reduce dust concentrations
Administrative measures to reduce numbers of exposed and time of exposure
Personal protective equipment
Secondary prevention
Medical surveillance of workers

risk of developing the disease. The main measures for assessing and controlling the exposure in work environments associated with sensitisers were reviewed by Corn in 1983 [11].

Although rarely practicable, elimination of a sensitiser from the work environment, or to never introduce it into a process is ideal. However, there are many typical high risk work environments, where elimination is impracticable, e.g. the baking industry, farming, and laboratory animal handling. In such work environments, the prevention aims at the reduction of the exposure to a minimum [12, 13]. Sufficient ventilation, healthy work practices and housekeeping are central measures of exposure control in all work environments. Although seemingly self-evident, these are often found inadequate and grossly neglected. The extent of ignorance and, at least partly, negligence was registered in a recent survey of bakeries; few were aware of the existence of an exposure limit for flour, nor of recommended work practices in bakeries [14]. Intensive education of workers at risk is a prerequisite for a high-level awareness of risks at the workplace. Investing in education and training programmes should be in the interest of all parties involved.

Testing of products before they are introduced into the market is commendable. It is also to some extent being done, although the impact of testing has so far been modest. Most screening is concerned with skin sensitising potency. For instance, methods such as local lymph node tests in animals probably do not predict the respiratory sensitisation potency with any greater reliability. Cytokine fingerprinting is considered a more promising method of assessing respiratory sensitising properties [4]. Elimination of a sensitiser is desirable, but it has rarely been feasible. The change of natural rubber latex gloves to non-rubber gloves or to powder-free gloves with a low allergen content is an example of a successful intervention (see below), reducing exposure as well as the number of exposed, e.g. users of sensitising gloves. The attempt to substitute a sensitiser may also fail, due in part to the lack of reliable methods for testing substances before introduction. An example of failure often quoted, is the substitution of toluene diisocyanate (TDI) with the less volatile methylene diisocyanate (MDI), which, however, turned out to be just another respiratory sensitiser [4, 5].

There are many ways to achieve a reduction of either exposure or numbers of exposed. In the prevention of OA, the modification of a process or an agent to reduce the risk of sensitisation has been successfully applied and documented in the detergent enzyme industry. It was achieved by encapsulating enzymes in powder form and, at least partly, by isolation of processes [16, 17]. It is also an example reminding us that prevention programmes cannot be "parachuting operations"; continuous surveillance of the work environment and the workers' health is needed. In this particular case, over the years new enzymes were introduced into the detergent production processes with unexpected new outbursts of OA [18, 19]. Complete isolation and enclosure are effective means of exposure control used, for instance, in the handling of complex platinum salts and in many processes involving organic acid anhydrides.

Control of exposure is also exerted by various administrative decisions. The numbers of workers exposed and the duration of exposure can be restricted by job rotation, rest periods, shift or location changes where fewer people are working with sensitisers or irritant exposures [5].

Role of regulatory authorities

In reviews on prevention of OA, the role of regulatory authorities is rarely addressed. However, regulatory authorities may have a decisive influence on both the primary and secondary prevention of OA. Preventive measures of the regulatory authorities include legislation, collecting information (e.g. by registers), the setting of occupational exposure limits (OELs), and supervision by labour inspection.

Laws and statutes define occupational diseases and the level of diagnostic probability, list compensable diseases and causes of disease and determine modes of compensation.

All these differ from country to country affecting accordingly comparisons of national statistics [20]. A liberal legislation including compensation for disability, loss of income inflicted by occupational diseases, and re-education serve as incentives for workers to come forward with complaints of work-related symptoms. The Finnish legislation on occupational disease and occupational safety and health (OSH) may serve as an example. Insurance policies for all employees are mandatory, voluntary for self-employed. Access to occupational health services is mandatory for all workplaces. Physicians are obliged to report occupational diseases. The modes and level of compensation is fairly high. As there is little reason to believe that the true incidence of OA differs from other industrialised countries, the comparatively liberal legislation is likely to explain the consistently far higher incidence of reported cases of OA in Finland than in the UK, Sweden and the USA [20].

By setting OELs, regulatory authorities may influence the prevention of occupational diseases in several ways. Most OELs are set as 8-hour time-weighted averages (TWA). If critical effects, such as irritation or sensitisation, are expected following brief exposure to high concentrations, a short-term exposure limit (STEL) can be set. STELs are normally recommended for a 15-minute reference period. OELs are meant to protect workers from detrimental health effects of exposure by inhalation over a working life. Health-based OELs are normally set for substances for which studies on dose-response relationships show either a threshold, i.e. a no-observed-effect level (NOEL), or a lowest-observed-effect level (LOEL). For respiratory sensitisers, like genotoxic and carcinogenic substances, NOELs or LOELs are rarely identified. In such cases it is assumed that any level of exposure might carry some risk. The recommended OELs for these substances are established pragmatically. Exposure-response data are used in the setting of these final statutory exposure limits, which include socio-economic as well as technical considerations of practicability [21, 22].

The setting of OELs are rarely, if ever, enough for the prevention of OA. However, OELs direct the attention of workers, employers and OSH personnel towards exposure levels and thereby increase the awareness of risks and safe exposure levels. They may, ideally, be used in the design of new plants and processes to ensure that exposures will be safe [22].

As full dose-response curves are rarely available for respiratory sensitisers, the approach may be to provide decision makers with quantitative risk data at different exposure levels. The final pragmatic recommendation will include socio-economic considerations and may vary substantially between countries. Flour dust is a good example. Although distinct exposure-response relationships between exposure to flour dust and wheat allergen and sensitisation with nasal and asthma symptoms exist [23–26], there seems to be no identifiable threshold for these effects [27]. Basically the same data on exposure-response relationships have been used for the setting of OELs, which, however, display a huge range between the health-based OEL of 0.5 mg/m^3 by the American Conference of Governmental Industrial Hygienists (ACGIH) [28] and a maximum exposure limit (MEL) of 10 mg/m^3 set by the Health and Safety Executive in the UK [29]. In this case, it demonstrates the differences between a health-based assessment and a tripartite compromise. Yet another approach was adopted by the Dutch Expert Committee on Occupational Standards [30]. Based on advanced analysis of the studies by Houba and colleagues [25, 26], the excess risk of sensitisation for workers over a working life of 40 years was calculated. An excess risk of sensitisation of 1% and 10% was calculated at exposure levels of 0.12 and 1.2 mg/m^3, respectively. The excess risk at various levels of exposure will eventually have to be weighted against feasibility issues [30].

In many countries, regulatory authorities have made health surveillance mandatory in all work environments associated with health risks. In a preventive programme launched by the Ministry of Labour in Ontario to reduce diisocyanate-induced asthma (see below), medical health surveillance was one of several elements [31]. In the evaluation of the programme, it was concluded that the decrease of asthma claims may have been due to several causes, one of which was medical surveillance. It was stated that medical surveillance may act in several ways. Apart from early identification of cases, it may improve worker education and general awareness of hazardous exposures, intensify the use of personal protection and, in general, working practices [31].

The formal appointment of safety representatives and industrial safety commissions at workplaces are likely to have a favourable preventive impact. The provision of training and knowledge of the regulations pertaining to bakeries was assessed in 55 bakeries in the UK following the setting of the statutory MEL of 10 mg/m^3 and a 15-min STEL of 30 mg/m^3. The study revealed that only a quarter of the bakeries were aware of the existence of a MEL or a STEL. A copy of a booklet on guidance on dust control and health surveillance in bakeries, produced by Health and Safety in Bakeries Liaison Committee [15], was found only in 28% of bakeries. However,

companies with an appointed safety representative were much more likely to be aware of the exposure limits and of the sensitising properties of flour dust, to have a written risk-assessment and to have provided some training on flour dust work [14].

Compensation modes and levels may act as incentives for both workers and employers, i.e. for workers to come forward with their work-related complaints without fearing to loose their income, and for employers to continuously pay attention to safety issues at work. The responsibility of authorities is to ensure that workers receive a satisfactory income replacement indemnity, indemnity for possible permanent disability and rehabilitation. The compensation systems vary between countries, the majority being administered by national or regional agencies and insurance companies. In most countries OA is compensated as an occupational disease [32, 33]. In countries were agents eligible for compensation are listed, e.g. UK and France, the continuous up-dating of lists is essential. It is also important that workers claims for disease caused by agents outside the list are compensated in alternative ways, for instance by national health insurance [4].

In most industrialised countries the employer is assumed to cover the costs of an occupational disease [33]. However, few countries have studied the actual partition of costs. Recently, the distribution of costs of OA in the UK was reported. The study revealed that as much as 49% of the total costs are borne by the diseased worker, 47% by tax payers and only 4% by the employer [34]. As the authors pointed out, on one hand it is understandable if workers under such circumstances hesitate to have their symptoms investigated. On the other, there is little incentive for employers to invest in improvements to reduce exposures.

Finally, data collecting pertaining to OA is an important source of information and affords a basis for preventive strategies. Data can be collected as sentinel events (e.g. USA), occupational disease registers (e.g. Finland) and compensation statistics. Although all these sources of information are known to grossly underestimate the true incidence of occupational disease, they generate useful information and may reveal important trends [5].

Pre-employment screening

Health examinations at the pre-employment stage are customary and also commendable as an instrument to protect the health of workers. Inevitably, applicants may be found unsuitable for a particular work on health-based grounds. This makes it all the more important that exclusion criteria are clearly defined and based on scientific evidence. Reasons for exclusion are comparatively few. Probably the only incontestable reason for exclusion is an applicant with an earlier confirmed OA caused by an agent to which exposure would occur in the new job. If the causative agent is totally unrelated to exposures occurring in the new job, there is little scientific justification

for exclusion [4]. Job applicants suffering from non-OA ("community" asthma) constitute a challenging category. As can be expected when there is a lack of solid scientific data for precisely formulated guidelines, the practise varies considerably and often to the disadvantages of the asthmatics [4, 35]. The assessments need to take into account the severity of asthma. Although scientifically ungrounded, it may seem justified not to subject persons with severe or moderately severe asthma to a risk of developing additional respiratory impairment [4].

Although host factors increase susceptibility to OA, screening for and applying such factors for pre-employment selection is a questionable issue. One reason is that screening for susceptible individuals may lead to the selection of workers that are thought to tolerate a work environment associated with harmful levels of exposures, whereas the preventive approach should be to make the work environment tolerable to workers despite such host factors [4, 5]. Another reason is the fact that no single marker of susceptibility has been identified having a predictive value that would justify its use for pre-employment screening [4]. Atopy undoubtedly increases the risk of sensitisation to high-molecular-weight allergens. However, the predictive value of atopy is generally accepted to be too low, even in workplaces associated with a high risk of IgE-mediated sensitisation, such as laboratory animal handling, to be used for screening purposes; a substantial number of those excluded from work would never become sensitised. Apart from a low predictive value, the prevalence of atopy in some 30–40% of young adults is common in industrialised countries and the exclusion of such a number of otherwise health individuals cannot be justified for socio-economic reasons [4, 5]. Although smoking is a risk factor in certain work environments such as laboratory animal work, and in association with exposure to platinum salts and some acid anhydrides, in practice, smoking has not been considered useful in pre-employment screening, Still, it is appropriate to inform smokers of the increased risk of sensitisation they may carry in some work environments due to their smoking habits [5].

Genetic polymorphism and susceptibility to, especially small-molecular-weight occupational agents has attracted some research interest. In particular, studies on the human leucocyte antigen (HLAs) have shown some interesting associations with OA. The HLA-DQB-0501 has repeatedly been shown to positively correlate with diisocyanate asthma, whereas HLA-DQB-503 has displayed an inverse correlation. HLA associations also exist with platinum salts and beryllium. The polymorphic occurrence of glutathione S-transferase (GSTs) and *N*-acetyl transferase (NAT) has been used for similar studies of associations with OA and sensitisation. Both GSTM1 null and NAT 1 and NAT 2 slow acetylator genotypes correlate with susceptibility to diisocyanate asthma. However, the predictive values of the so-far-identified polymorphic genes are not even remotely high enough for pre-employment selection purposes. Considering the multifactorial nature of OA, it is not to be expected that a single polymorphic gene would determine the disease, although it may well increase individual susceptibility or resistance to disease. Irrespective

of demonstrated associations with OA, genetic testing, let alone the application of individual genetic profiles for screening purposes, remains both ethically and legally a strongly contentious issue [36].

The widely accepted view is that pre-employment examinations are only meant to establish a base for periodic health surveillance. Due to low predictive values, they should not be used for screening of potentially susceptible individuals on such ground as atopy, smoking, or genetic disposition [4, 5, 37, 38].

Secondary prevention

The term 'secondary prevention' implies that primary prevention has, in one way or another, failed. Thus, the purpose of secondary prevention measures is either to detect occupational disease as early as possible to improve the prognosis of the disease, or, ideally, to detect predictive markers of disease to prevent the development of clinical disease. Another objective is to prevent further cases from developing in the same, or similar work environment. The principal means of secondary prevention is regular medical surveillance of employees. There is sufficient evidence showing that duration of exposure after onset of symptoms, as well as continuance of exposure after onset of asthma, are important prognostic factors, whereas cessation of exposure is associated with various degrees of recovery [39–41]. It is, therefore, generally accepted that we can improve the prognosis of OA by early detection of the disease and by avoidance of further exposure to the causative agent. A consensus statement by the American College of Chest Physicians (ACCP) recommends routine surveillance of all workers exposed to agents known to cause OA [42].

The main tool of health surveillance is the questionnaire on respiratory symptoms. Questionnaires are normally administered at regular intervals of 6–12 months in accordance with latencies of particular sensitisers [43]. Although, the first 2 years of exposure appears to be the most important period, surveillance mostly continues indefinitely as sensitisation and the onset of OA may occur at a much later time if exposure continues [4]. Questionnaires have rarely been validated and their sensitivity and specificity are mostly unknown. Workers' compliance with regularly administered questionnaires has mostly not been assessed. It has been postulated that the threshold for admitting to work-related symptoms is lower in large companies with good possibilities to relocate workers, than in small enterprises [4]. The interest in answering truthfully is likely to vary considerably with expected consequences of coming forward with complaints. Fear for loosing the job without trusting the compensation systems for being equitably compensated for possible incurred income loss and disability are poor incentives for participation.

Objective means of surveillance include occasional workplace spirometry and measurement of bronchial hyperreactivity. Regularly performed spirometry is not a sensitive tool to detect OA and probably does not add much to a questionnaire [44].

Unspecific bronchial hyperresponsiveness is a feature of asthma that develops as a consequence of sensitisation. As a mean of health surveillance, it does not predict OA [45]. It is also often absent in cases of OA [37].

A new and simple approach has been tested in the Netherlands [46]. A national surveillance scheme involving the Dutch government, branch organisations and unions designed to reduce the exposure to flour dust and related allergens was assessed in the bakery, mill and baking product manufacturing industry in the Netherlands. The central tool was a diagnostic questionnaire developed using the experience gained in a previous study on laboratory animals, to estimate the probability of sensitisation to wheat and/or α-amylase allergens. The participating 5546 workers were divided into three categories of probability of developing sensitisation (low 57.4%, intermediate 24.1%, high 18.5%). In the second phase of the programme, the intermediate-probability group will be evaluated further by occupational physicians and the high-probability group will be referred to an occupational respiratory clinic. The low-probability group will be enrolled in the next surveillance cycle. The preliminary results indicate that the simple two-page questionnaire comprising only 19 questions can capture workers with different risks of sensitisation. The approach is thought to be applicable in small and medium-size enterprises [46].

The regular testing for specific IgE antibody, as rule by skin testing, with workplace allergens has been useful in some work environments. During work with complex platinum salts, the positive skin test has a high predictive value for the development of OA [47]. In the production and use of enzyme, e.g. the detergent industry, skin testing is common. It may, in combination with questionnaires, guide decision making. It is also used as a kind of biological monitoring of the successfulness of exposure control [48, 49].

Rhinoconjunctivitis is known to precede the development of symptoms from the lower respiratory tract. It has been shown to precede development of asthma, although the predictive value was low [50]. This pertains to high-molecular-weight allergens, whereas rhinoconjunctivitis is less frequent in exposure to low-molecular-weight agents [50, 51]. Although rhinoconjunctivitis is a rather poor predictor of OA, the condition in itself is an occupational disease that ought to be prevented.

Examples of preventive approaches in specific work environments

There are only a few successful preventive programmes that have been both evaluated and published. The study designs have been rather crude, and control groups have regularly been lacking. There are a number of reasons for the low number of published studies, most of which pertain to the nature of OA and the low public profile of the condition (Tab. 1) [4]. Formal assessment of the successfulness of preventive programmes can be expected only in large industries or in certain branches, for instances bakeries. Only a handful of agents, such as flour dust, animal epithe-

lium and dander cause exposure of great numbers of workers and are, therefore, good environments for interventions [4].

Enzymes

A classical example of primary prevention by alteration of processes and working practices was carried out in the detergent industry in the early 1970s. Asthma symptoms were described in a detergent factory in the course of the first year of employment. The symptomatic workers (primarily respiratory) were sensitised to protease products [52]. Clusters of enzyme allergy in such plants were shown to be caused by *Bacillus subtilis* proteases. This resulted in primary preventions measures to control the exposure. The enzymes were encapsulated to prevent dusting, enclosure of processes was undertaken and the use of protective respiratory equipment was introduced. A major reduction of sensitisation and symptoms was consequently reported [16, 17, 53]. Thus, enzyme allergy abated and cases of enzyme-induced asthma in the detergent industry were rare during the 1990s [48, 54].

However, despite encapsulation of enzyme preparations, the risk of enzyme sensitisation and respiratory allergy still exists in the detergent industry. The use of enzymes has increased and new enzymes such as cellulase, amylase and lipase have been introduced into the washing powder production. Some 25 years after the outbreaks described above, an epidemic of asthma was revealed in a detergent producing plant in the UK with a prevalence of enzyme sensitisation of 26% and work-related lower-respiratory symptoms in 16% of exposed workers [18]. In a Finnish detergent plant having no recognised health problem, a survey disclosed a prevalence of sensitisation among exposed workers of 22%, either to protease, lipase or cellulase compared with unexposed office workers (0%). When interviewed, all sensitised workers reported work-related respiratory symptoms [19]. These incidences emphasise the continuous need of monitoring of exposure, and education of workers, combined with secondary preventive measures such as health surveillance.

The enzyme using industry is aware of the minute amounts (nanogram levels) of enzyme needed to sensitise and have adopted guidelines as low as 15 ng/m^3 for proteases [48]. Health surveillance schemes have been suggested. They include the periodic skin testing of workers as a secondary preventive measure [49].

Natural rubber latex

Primary prevention by substitution of an allergen is ideal, although not very often practicable. The interventions applied to decrease latex allergies, including OA, serves as a rare example of this strategy. In the late 1980s and 1990s, powdered

gloves with a high protein content was recognised as the cause of high prevalences of sensitisation to latex and latex-induced allergies including OA among hospital personnel [55–57]. Interventions at an institution level including replacement of powdered gloves having a high protein content with non-powdered, low-protein gloves have been reported to be successful, leading to cessation or significant decrease in sensitisation rate. Moreover, already sensitised and even asthmatic workers have been able to continue working avoiding the use of latex products [58–60].

In 1996, the Ontario Workplace Safety and Insurance Board recommended the reduction of aerosols of latex proteins and encouraged hospitals to use powder-free, low-protein or non-latex gloves. At various points of time, hospitals introduced latex policies including education and medical surveillance. The latex strategies were temporally associated with a decline in claims for latex-induced asthma [61]. In Germany, a nationwide interdisciplinary information campaign was carried out in 1997–1998. The campaign was accompanied by a revision of the technical regulations for dangerous substances, demanding only powder-free, low-allergen latex gloves to be used in institutions providing health-care services. An insurance company covering 60% of hospitals in Germany made financial resources available for the information campaign. The preventive programme was evaluated by monitoring compensation claims before and after the campaign, as well as by assessing changes in glove-wearing behaviour. A temporal association, with a 2-year delay, was registered between the amount of purchased powdered gloves by acute care hospitals and the fall in reported cases of OA (Fig. 1). The use of powdered gloves decreased by 50% and the use of non-powered gloves doubled [58, 62]. After recognising that latex allergy is caused by the inhalation of latex allergen that, adhered to the starch powder, becomes airborne, the preventive strategies have proven successful in reducing latex allergy. Unfortunately, the possibility of removal of a sensitising agent or substitution of it with a non-sensitising is a rare occasion.

Laboratory animal allergy

Due to the nature of some working environments, total avoidance of exposure cannot be achieved.

Typical for such environments are animal laboratory work, farming, veterinary work, bakeries and mills. Laboratory animal handling is associated with a well-recognised risk of sensitisation and respiratory allergies. In a prospective study of a cohort of laboratory animal workers, the incidence of allergic symptoms was as high as 37% in 1979–1980. In 1982–1983 there was a decrease to 10–12%. The drop in incidence coincided with the introduction of a site order and code of working practice together with an education programme to increase awareness of the problem. For instance, the use of personal protective equipment became mandatory [63]. A further follow-up of employees recruited in 1987–1990 revealed that

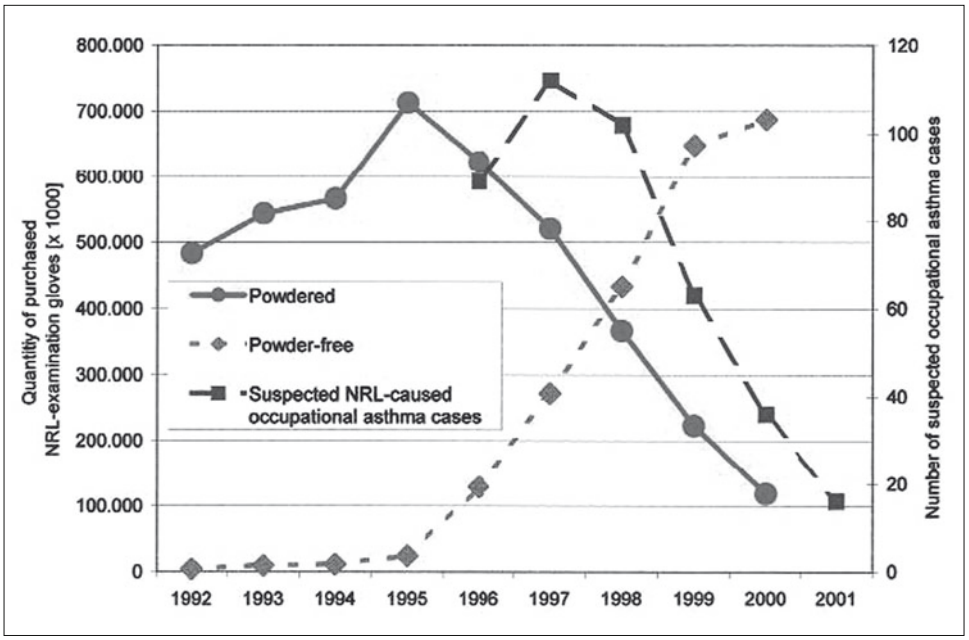

Figure 1.
Reported cases of latex-induced occupational asthma (OA) in relation to purchases of gloves 1992–2001 [58].

the incidence of laboratory animal allergy had remained at the same level of about 10%. The predictive value of atopy and sensitisation to laboratory animal during this 2-year follow-up was 66% and 87%, respectively [64]. The studies by Botham and colleagues show that primary preventive measures aiming at the reduction of exposure do reduce the incidence of animal-induced allergic symptoms, and may make it possible for already sensitised individuals to continue working with laboratory animals.

Flour dust

Considering the size of the exposed population and the high prevalence of sensitisation, the prevention of baker's asthma appears highly meaningful. Sensitisation to flour dust may occur in more than 20% of those exposed, and asthma may be prevalent in 10% [25]. The exposure levels have remained high in the baking industry in general and, contrary to expectations, levels have been even higher in modern medium and large size bakeries than in small enterprises [14]. Primary prevention

is difficult due to several circumstances, e.g. the great number of sensitisers including a number of antigens such as various flours, storage mites, enzymes and other so-called dough improvers present in the baking industry. The background sensitisation to wheat of 2–4% of the unexposed population makes a total avoidance of sensitisation impossible. As prevention cannot aim at a total avoidance of exposure, exposure has to be controlled in other ways.

Setting OELs is a way of directing focus on exposure levels. Despite access to solid data, most countries have set pragmatic exposure limits far too high for protection. Regulatory authorities have access to better exposure-response data on wheat flour and α-amylase than for any other occupational sensitisers [23, 24, 27, 65]. It appears that the risk of asthma in a previously un-sensitised population starts at about 3 mg/m^3 and rhinitis at about 1 mg/m^3 [23]. Reviews of the scientific evidence agree that, although no distinct threshold for symptoms or sensitisation can be identified, the risk of both end-points below 1 mg/m^3 would be small and symptoms would most likely be mild [30].

From the point of view of sensitisation, frequent peak exposures in the baking process are recognised as an important problem. The scientific basis for recommending a 15-min STEL is, however, lacking. On the other hand, peaks are related to some specific tasks such as weighing/sieving, mixing, and cleaning. Exposure levels can be significantly reduced by ensuring sufficient exhaust ventilation and by applying good working practices such as the use of dredgers instead of hand throwing and vacuum cleaning instead of brushing. A study on 55 UK bakeries revealed a poor knowledge of elementary working practices for reducing dust levels; only 27% of bakeries were aware of the existence of an OEL, the MEL or a STEL. Less than one third possessed a copy of a booklet on guidance to reduce exposures released by the Health and Safety in Bakeries Liaison Committee [14, 15].

Secondary prevention measures to reduce morbidity by early detection of OA or sensitisation are common in the baking industry [4]. They comprise pre-placement evaluations followed by periodic questionnaires on respiratory symptoms and frequent periodic spirometry, sometimes combined with skin testing. Preventive programmes have rarely been evaluated. The rationale for carrying out medical surveillance has been questioned [44]. The accuracy of such a surveillance programme was tested by Brant and colleagues [66]. They carried out a study on 324 supermarket in-store bakeries using a health surveillance programme focusing on work-related chest symptoms together with specific IgE either to wheat flour or fungal α-amylase as a surrogate for OA [66]. The surveillance included three stages starting with a short questionnaire on respiratory symptoms (stage 1), a further questionnaire on work-relatedness of symptoms, if any, (stage 2) and, finally an IgE-analysis of a serum samples (stage 3). To assess the accuracy, a cross-sectional survey was undertaken in 20 bakeries. The surveillance system resulted in a quarter of those with symptoms reporting that symptoms were work-related; 61% of those

with work-related chest symptoms had specific IgE antibodies to wheat or fungal α-amylase, which corresponded to 1% of the bakers. However, the cross-sectional survey arrived at a prevalence of 4%. Thus, the surveillance system underestimated the presence of disease and the conclusion was that a more efficient method of surveillance in bakeries is needed [66].

Much remains to be done to prevent asthma and other allergies in the baking industry. The setting of health-based OELs will necessarily include socio-economic consideration of practicability and will not protect the entire workforce. It is obvious that a successful reduction of OA in the baking industry needs a closer co-operation between regulatory authorities, branch organisations, unions and OSH personnel. It should be in the interest of all parties involved to ensure that recommendations and guidance reaches the workplaces and are actively implemented.

Diisocyanates

An example showing how regulatory authorities can exert preventive strategies is afforded by a Canadian legislation initiative for the prevention of diisocyanate-induced asthma. In 1983 the Ontario Ministry of Labour introduced a preventive programme consisting of two components.

As a primary prevention measure, employers had to ensure that the time-weighted average of diisocyanate exposure did not exceed 0.005 ppm. The second component was a mandatory medical surveillance including pre-employment respiratory questionnaires and spirometry. The questionnaires were repeated every 6 months and spirometry at least every second year. Respiratory symptoms and/or changes in spirometry were followed by an assessment by a physician as to the safety of continuing work [31].

The programme was retrospectively assessed from workers' compensation statistics. Following the introduction of the programme, there was an increase in annual compensation claims, which reflected a more efficient case finding. Starting in 1991, the claims decreased, whereas claims of OA of other causes remained at an earlier level. The time from onset of symptoms to diagnosis decreased from 2.7 to 1.7 years and cases had milder asthma. Companies with claims were more likely to have exceeded the exposure level of ≥0.5 ppb. The conclusion was that one or more component of the programme had a beneficial effect. There was a comparatively long time lag before the decrease of claims became discernible (Fig. 2). It is possible that the programme *per se* has initiated a series of favourable measures undertaken by separate companies following the introduction of the mandatory programme. These may have included technical improvements to reduce exposures, more active education of workers, supervision of working practices including the use of protective equipment, etc. [31].

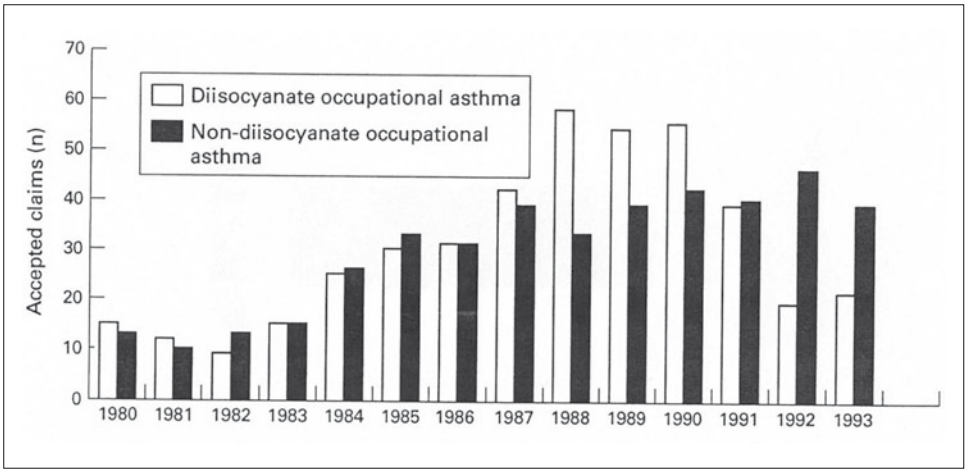

Figure 2.
Accepted workers claims of diisocyanate-induced OA and OA induced by other causes in Ontario [71].

Work-exacerbated asthma

Non-OA, being an increasingly common disease and getting worse because of the vast number of various irritant exposures in the workplace, has attracted more and more attention over the last few years. A definition of WEA was suggested in 1995 by the American College of Chest Physicians (ACCP) as concurrent asthma worsened by non-toxic irritants or physical stimuli in the workplace. The suggested medical case definition requires a diagnosis of asthma and an association between symptoms of asthma and work, provided that the subject has had symptoms or medication before, and experiences an increase of symptoms or needs more medication after entering a new occupational setting [43]. Because of the obvious need for preventive strategies concerning work-related aggravation of non-OA, Wagner and Wegman [6] in an editorial suggested that work-aggravated asthma should be included into the definition of OA. The proposal, although not uniformly accepted as such by the scientific society [67], led to the now generally adopted, broader concept of 'work-related asthma' covering both OA and WEA [68]. WEA indicates 'aggravation of pre-existing or coincident adult new-onset asthma because of workplace environmental exposure' [68, 69].

The need to prevent work-related worsening of any asthma is becoming widely recognised, but the scientific knowledge about the condition is still scanty. From the point of view of prevention, it is interesting to note that WEA is associated with a similar impact on work productivity and loss of income as OA. Some studies indi-

cate that WEA may be associated with higher rates of symptoms and exacerbations than asthma unrelated to work exposures [9].

Preventive strategies including guidelines as to the health surveillance of WEA require that the condition can be separated from OA. However, the differentiation between WEA and OA is still a diagnostic challenge and not always possible. Negative specific inhalation challenge tests, when available, often exclude OA. In cases where inhalation challenges are not practicable, serial peak-flow (PEF) recordings are normally used; however, they do not necessarily discriminate between WEA and OA [70].

Regrettably little is so far known about the frequency of WEA and, especially, what aggravation of symptoms means in terms of health. In the few reports available, the frequency of WEA varies depending on differences in information collection and definition. Focusing on studies including employed adults with asthma, the prevalence estimates have been in the range of 8–25% [71, 72]. A prevalence as high as 52% has been reported [8]. The frequency of symptom aggravation was included in an interview study with 969 asthmatics, where 21% reported work-related aggravation for symptoms at least once a week [73]. These studies comprise self-reported symptoms. Objectively assessed work-related functional changes, e.g. by serial PEF recordings or the monitoring of inflammatory responses, are necessary to assess the health risk involved. Similarly, studies with optimal medication are needed to evaluate how the increased frequency and aggravation of symptoms should be managed without risking permanent health implications, but also to avoid unnecessary discrimination of workers with asthma or bronchial hyperreactivity.

Asthma symptoms may be aggravated by a number of factors such as irritant agents, dusts, fumes, physical exercise, changes in temperature and strong odours. When such exposures occur in the workplace, the prevention of choice is to reduce exposures. However, it is rarely known to what extent the exposure ought to be reduced to protect asthmatics from aggravation of symptoms. For most substances exposure-response data are lacking. Solid data on nitrogen dioxide (NO_2), a typical respiratory irritant, show that asthmatics and hyperreactive individuals are far more sensitive to the irritant effects of NO_2 than healthy individuals [74]. Safe exposure levels for asthmatics appear to be as low as 0.2–0.4 ppm, which may make asthmatics unsuitable for tunnelling and under-ground mining work, where such low exposure limits may be impracticable. A risk assessment on similar dose-response data for another irritant, sulphur dioxide (SO_2), likewise found a higher vulnerability of asthmatics to SO_2 at or even below current OELs [75]. However, the assumption that asthmatics are invariably more sensitive to all irritants may lead to discrimination of asthmatics, similarly to the ungrounded weeding out of atopics in the 1980s. Exposure-response data are needed for preventive strategies. A more active use of exposure assessments have been suggested as a routine means of prevention [76].

The implementation of scientific-based preventive strategies requires more information on all aspects of WEA. There is a need for clinical assessments of WEA to obtain objective data, in addition to the self-reported data, on inflammatory responses and on the effect of continuing exposure on the underlying condition with or without treatment. It is also important to have exposure assessments to better understand what levels of exposures are hazardous to asthmatics. Such data are needed for the production of guidelines to primary health care, and occupational health personnel. The awareness of WEA should be improved among physicians working in respiratory clinics.

Asthma attributable to work

A significant proportion of asthma is attributable to work. In a review of available literature, the authors arrived at a median of 9% for the attributable risk, whereas inclusion of the 12 studies of the highest quality resulted in a median of 15% [1]. Similar estimates have subsequently been reported in a study on physician-diagnosed asthma in Beijing residents [77] and are even higher for asthma including wheezing [78].

Only a few population-based incidence studies have been conducted. In one such study a cohort of 79 204 health maintenance organisation members was followed for 3 months registering new-onset asthma, re-activation of previous asthma and exacerbation of asthma. Criteria for onset of asthma attributable to work exposures were met by 21% [2]. In another large study covering the entire employed Finnish population aged 25–59 years, the cohort was followed from 1986 to 1998. Combining a register on asthmatics entitled to reimbursement of medication costs and the census data of 1985, 1990 and 1995 classified according to occupation, relative risks of the 49 575 incident cases of asthma were estimated. The attributable fraction of occupation for men was 29% and for women 17% [3].

From the preventive point of view, it is interesting that studies, despite different designs, report increased risks of asthma in work environments associated with irritant chemical agents and dusts [2, 3, 77–80]. An increased risk of OA among cleaners has been reported repeatedly [79, 81, 82]. In a study on identical twins discordant for asthma, solvent were found to significantly increase the risk of contracting asthma [83]. Similar exposures may explain an increased risk among shoemakers [79]. Moulds in water-damaged buildings have been suggested as a possible explanation for an increased risk of asthma among educators [84]. This receives some support by a meta-analysis on the associations between water-damaged buildings and respiratory outcomes [85].

Population-based studies on attributable risk consistently show risks that are several times higher than can be estimated from reporting programmes, surveillance schemes and disease registers [5]. The risk of asthma is frequently associated with

exposures not previously recognised as being sensitising. Several possibilities are conceivable. To some extent the differences may reflect a failure in finding, or at least reporting, cases of OA. This is supported by the subsequent analysis by Karjalainen and co-workers [79] of their population cohort. When all registered cases of OA were deleted from the analysis, an increased relative risk of asthma remained in the typical high-risk occupations baking 2.13 (95% CI 1.74–2.83) and farming 1.76 (95% CI 1.64–1.89). Both environments are known to cause IgE-mediated OA without posing diagnostic difficulties.

However, the excess risk of asthma in workers exposed to dusts, gas, and chemical fumes, i.e. irritants, may be due to other reasons. For one thing, diagnostics of OA has focused on specific sensitisers previously recognised as inducers of OA. Other unknown and less frequent inducers may have been overlooked. A probably more important explanation is the complex aetiology of asthma. Various host factors are likely to interact with environmental exposures including occupational sensitisers, irritant chemicals, dusts, viruses and other microbes. The occupational exposures are not necessarily the main inducers of disease. However, the attributable factor by definition signifies the fraction of disease in the population that would not have occurred if exposure to the risk factor had not taken place. Thus, learning more about the associations between asthma and the work environment will eventually afford strategies for the prevention of the induction of adult-onset asthma [5, 6, 61].

Is prevention feasible and worthwhile?

Feasibility issues

OA should to a large extent be preventable. What makes prevention difficult are the manifold causative agents and the low attack rate in single workplaces together with a comparatively low public profile [4] (Tab. 1). An evidence-based assessment of preventive measures concluded that a reduction of exposure leads to a decrease in the number of workers who become sensitised and who develop asthma [37]. Health surveillance is generally considered an effective way of detecting OA at an early stage and the prognosis of disease is better in workers who have participated in health surveillance programmes [4, 5, 37]. Still, few studies have evaluated the efficacy in terms of reduced morbidity [4, 37].

Some preventive programmes conducted in specific working environments have included evaluations of the impact. The preventive programmes on natural rubber latex [58, 59], diiscoyanates [31] and flour dust [46] represent strategies in which authorities, the industry and unions have joined forces. The programme directed against diisocyanate exposure was successful in reducing the number of claims, although the design of the programme did not allow the assessment of the effec-

tiveness of separate components of the programme [31]. The successful preventive programmes on natural rubber latex [31, 58, 59] also represent before and after comparisons.

The prevention of WEA is a fairly new domain. The knowledge about associations between adult-onset asthma and occupational exposures are still too fragmented for science-based preventive initiatives. Asthma-outcomes have mostly been based on self-reported symptoms without objective assessments of functional disturbances as a consequence of exposures, and exposure-response relationships have not been studied. Thus, strategies for prevention of work exacerbation of asthma are confined to vocational guidance and education of OSH personnel as to health surveillance of asthmatics in work environments associated with dusts and irritants.

Is prevention worthwhile?

Many countries report OA as the most common cause of occupational respiratory occupational disease [20]. Ethically, occupational disease is unacceptable, and all reasonable means available should be used to prevent it. However, only a few attempts have been made to assess the costs of OA and possible saved costs as a result of successful interventions. In one recent study commissioned by the Health and Safety Executive in the United Kingdom, the true costs of OA were calculated [34]. The total lifetime costs were derived from both direct costs (e.g. use of health care resources, treat and rehabilitation costs), and indirect costs (e.g. costs from sickness absence, labour turnover, compensation and insurance). OA caused on an average 3.5–4.5 days of absence from work per year. The total lifetime cost incurred by reported new cases (631 cases) of OA in 2003 was estimated at £ 36–78 millions. Taking into account that OA is probably under-reported by up to one third, the costs increase substantially [34].

The cost effectiveness of specific preventive programmes has rarely been calculated. In the successful German preventive programme directed against natural rubber latex (see above), the number of claims decreased drastically with a time lag of a few years, the use of latex gloves was halved and that of latex-free gloves doubled. The saved costs of professional training were calculated to exceed those invested by some ten times [62].

Recent assessments of the socio-economic implications of WEA have arrived at the conclusion that WEA inflicts considerable costs to employers and the community. Assuming that 15% of asthma can be attributed to work exposures, the annual costs of WEA in the United states could be as high as US$ 1.6 billion [9]. WEA may be associated with higher rates of symptoms and exacerbations as asthma unrelated to work. The effect of WEA on the work productivity and earning capacity is similar to those of specifically induced OA [9]. It is obvious that more attention has to be paid to the prevention of WEA in the coming years.

Future developments

A shift in priorities of research related to the complex associations between asthma and the work environment is discernible. With respect to "classical" OA with a latency period, the level of understanding of causation of OA is already sufficient for the implementation of preventive strategies. Preventive programmes should focus primarily on exposure control and worker education. In the design of such programmes, there is a need for a more scientific approach; for instance, the design should include measurable parameters allowing a quantitative evaluation of programmes. It is important that evaluations of interventions, also smaller ones conducted in single enterprises and institutions, are reported. Also secondary preventive measures need to be refined. Considering the present extensive routine use of secondary preventive measures, it should be easy to plan, evaluate and report the impact of such activities. Further research on markers predictive of OA seems necessary for secondary preventive purposes as well as for the discrimination between OA and WEA.

WEA has become increasingly important. Epidemiological studies indicate that WEA is a common problem. It seems to have a similar socio-economic impact as OA. When allocating resources, it seems advisable to invest in the research of WEA. The current level of knowledge and understanding of WEA is modest. Although work-related aggravation of asthma is encountered by occupational physicians at least as often as OA, the exposures, mechanisms, extent and consequences in term of the worker's health are largely unknown. From a preventive point of view, WEA will be an important issue owing to the still increasing prevalence of asthma and asthma-like conditions among children and adolescents. There is a need for science-based information already at the stage of vocational guidance.

Recognising that some 10–30% of adult-onset asthma is attributable to work, there is a need for a more profound understanding of the full phenotype of asthma and, especially, the associations with different work environments. Well-conducted epidemiological studies frequently show an increased risk of asthma in work environments and occupations not formerly known to be associated with specific inducers of OA. In particular, long-term exposure to a broad range of irritants seems to be important. A full understanding of the role of work exposures in the development of asthma may eventually lead to new preventive insights.

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