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Health-based Occupational Exposure Limits for High Molecular Weight Sensitizers: How Long is the Road We Must Travel?

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In this paper pitfalls in risk assessment for high molecular weight allergens, which can cause typical Type I/IgE-mediated respiratory allergy, are discussed. The major pitfalls seem to be that no agreement exists on the preferential end point that should be used in risk assessment. As a result, it is unclear which exposure–response relationship should be considered. In addition, there is a lack of data on health risks for non-occupationally exposed reference populations, so the baseline risk is often not known and little is known about the shape of exposure–response relationships and the existence of exposure thresholds. The good news is that more and more groups have published exposure–response relationships for several allergens. The possibilities for risk assessment approaches that should lead to occupational exposure standards are explored. Specific consideration is given to situations in which data on exposure–response relationships for humans are available. Considerable progress has been made in this area by use of advanced statistical techniques for exposure–response modelling. The major practical constraint at this moment seems to be the absence of well-standardized measurement techniques (immunoassays) for the evaluation of allergen exposure in the field.

Keywords: sensitizing agents; risk assessment; allergy; allergic asthma; allergic rhinitis

INTRODUCTION

High molecular weight (HMW) molecules of animal, plant and microbial origin have long been recognized as potent respiratory sensitizers. Most of these sensitizers are naturally occurring water-soluble proteins in the 10–60 kDa molecular weight range, that in a hydrophilic environment like the respiratory mucosa are readily released from, for example skin scales, plant fibres, pollen grains and other tissue matrices. HMW sensitizers can be extracted *in vitro* from dust particles with aqueous media like buffered saline. Exposure has been associated with major outbreaks of Type I/IgE-mediated allergies, like those described for occupational exposures in the detergent industry in the 1970s (Flindt, 1996) and, more recently, environmental soy exposure in several international harbours like Barcelona (Anto *et al.*, 1993). The increased use of latex products, particularly in the health care professions, has also resulted in an epidemic of latex-associated respiratory and dermal allergies (Toraasen *et al.*, 2000). These allergies are caused by proteins in the sap of the *Hevea brasiliensis* tree, which is used to produce latex. Some of the allergens with a major public health relevance, with estimated population at risk (exposed to occupational allergen) per 1 000 000 individuals of the general population, are presented in Table 1. Latex and allergens in bakeries are associated with the largest populations at risk. These estimates have been based on a recent review conducted in The Netherlands and the most likely approximate figures for other industrialized countries (Heederik *et al.*, 1999a,b,c). Many other allergens have been reported in the literature and although the risk for developing an allergy may be high, the population at risk is usually small and involves workers in only a few occupations. The incidence of work-related asthma typically varies between 2 and 20 cases per 100 000 individuals in the general population per year (Heederik, 2000). Prevalence rates of work-related sensitization are usually

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Table 1. Estimation of the population at risk with exposure to certain high molecular weight sensitizers based on figures from The Netherlands and information on exposure–response relationships

Allergen	Population at risk per million of the general population[a]	Exposure–response relationship described in the literature
Latex	12	
Wheat	2	Houba *et al.* (1996a,b)
Enzymes (fungal amylase)	2	Houba *et al.* (1996a,b), Nieuwenhuijsen *et al.* (1999)
Laboratory animals (rats, mice)	0.3	Cullinan *et al.* (1994), Hollander *et al.* (1996), Heederik *et al.* (1999a,b,c)

[a]From Heederik *et al.* (1999).

higher and vary between a few percent up to 10–20%, depending on the potency of the allergen, the definition of the population at risk, the survey techniques (skin prick tests or IgE measurements), etc. In the case of relatively large populations at risk the magnitude of the health risk, either defined as the number of occupational asthma cases or the number of sensitized individuals, can be considerable.

In this paper we will focus on respiratory allergies caused by Type I/IgE-mediated sensitization and will discuss some of the more recent scientific developments and their implications for the possibilities for setting a health-based standard for the concentration of HMW allergens in workplace air. Although some sensitizers also cause reactions of the skin, this paper is limited to respiratory sensitizers only. The reason is that exposure standards only exist for inhalatory exposure. The discussion of whether such standards can also be derived for sensitizing agents is therefore most pertinent for exposure through the air.

REGULATORY APPROACHES FOR HMW SENSITIZERS

Regulations for this group of sensitizers are either generic or rather basic, despite their high and wide range of potency. The most common approach involves risk communication by appropriate labelling with the well-known (R42) risk phrase: 'May cause sensitization by inhalation'. However, one should realize that the criteria for use of this phrase have been widened and mechanisms other than immunological ones can be included as well. For latex rubber a more refined form of product labelling and evaluation exists, established in collaboration with industry. This includes explicit reference to the protein, or in the future the allergen content, considered the most fruitful regulatory approach in the USA and also the European Union (Medical Devices Directive 93/42/EC). Although this approach can be considered a form of risk communication as well, it may in practice function as a form of risk management, when workers avoid working with gloves with allergen contents above a certain level. However, the relevance of this approach for minimizing the risk of developing respiratory and dermal allergies has not been sufficiently established.

The possibility of establishing exposure limits for the allergen concentration in the air as a risk management procedure has only been explored in a few cases. For subtilisin, a bacterial enzyme widely used in detergents and a well-recognized respiratory sensitizer, originally produced from *Bacillus subtilis*, an 8 h time-weighted average threshold limit value (TLV) of 0.06 $\mu g/m^3$ for workplace airborne exposure has been proposed by the American Conference of Governmental Industrial Hygienists (1980). However, there is considerable doubt about the underpinning of this TLV and the proposed value seems to be determined mainly by analytical limitations, i.e. by the detection limits of some of the earlier methods for exposure measurements. An evaluation by the Nordic Expert Group for Criteria Documentation indicated that the TLV for subtilisin probably does not protect against sensitization (Brisman, 1994). A recent study also suggested that sensitization occurs at exposure levels well below the TLV (Cullinan *et al.*, 2000), although sampling and analysis of the enzyme levels measured in this study have not been described in great detail.

This raises the fundamental question as to what an occupational exposure limit should protect from. Appearance of ill-health consequences and the ability to establish and maintain an occupational exposure limit are not necessarily mutually exclusive or contradictory issues, but depend on the definition of an exposure standard. The European Scientific Committee on Occupational Exposure Limits has the aim of establishing the maximum level of exposure and relevant averaging time at which no adverse health effects occur. The level at which no health risk exists is usually operationalized by the NOAEL/UF method, in which NOAEL stands for 'no observed adverse effect level' and UF stands for 'uncertainty factor'. The NOAEL is the highest level at which no adverse effects on the health of humans or laboratory animals is observed (Dutch Expert Committee on Occupational Standards, 1996). If such a 'no adverse effect level' does not exist, the probability of an effect should be estimated at certain exposure levels, which is considered the 'pragmatic approach' (Dutch Expert Committee on Occupational Standards, 1996; Report EUR 19253, 1999). Such a pragmatic approach may be necessary in the case of sensitizers, for which an exposure threshold above which no excess risk is observed may not exist. The pragmatic approach will have similarities to approaches applied for carcinogens. For carcinogens exposure levels are calculated at which a certain predefined excess risk (specified

response level) occurs for developing the cancer of interest.

A practical problem is that exposure measurements for this and other sensitizing enzymes often rely on functional assays based on the specific conversion of a substrate by the enzyme. Such assays are not necessarily allergen specific, since other enzymes in airborne dust samples might in some cases also contribute to conversion of the substrate and this may result in overestimation of the allergen concentrations. On the other hand, partial denaturation of the protein molecules might lead to a complete loss of enzymatic activity but no or only partial loss of allergenicity, in which case enzymatic tests would underestimate the allergen concentration. In both cases the outcomes of the assay do not necessarily correlate with the sensitizing potency of the inhaled dust.

WHAT EVIDENCE IS AVAILABLE ON EXPOSURE–RESPONSE RELATIONSHIPS?

So far, most evidence on existence of exposure–response relationships is available for specific IgE-mediated sensitization. Recent overviews of the available exposure–response studies (Baur *et al.*, 1998; Heederik *et al.*, 1999b) show that several allergens, like for example rat urinary proteins and fungal α-amylase, appear to be very potent allergens and are already associated with increased sensitization rates at exposure levels in the nanogram per cubic metre range for as little as a few hours per week (Houba *et al.*, 1996a,b; Heederik *et al.*, 1999b; Nieuwenhuijsen *et al.*, 1999). Other allergens, like wheat proteins, seem less potent and sensitization rates increase when exposure occurs in the low microgram per cubic metre range (Houba *et al.*, 1998). One of the few longitudinal exposure–response studies in bakers seems to confirm cross-sectional studies on fungal α-amylase and wheat allergen exposure (Cullinan *et al.*, 2001). Clear-cut exposure–response relationships in humans have as yet not been observed for latex proteins, since few epidemiological studies on latex sensitization have yet been conducted in which exposure was assessed with the use of latex-specific immunoassays. Similar exposure–response relationships have been observed for common allergens from the house dust mite and cats, but usually the allergen levels are measured in floor dust, the major reservoir, instead of airborne dust, because of detection issues and the fact that most particles remain airborne for a very brief period because of the large particle size (Munir *et al.*, 1997).

Respiratory sensitizers have also been extensively studied in animal bioassays. Twenty years of studies of chemical allergens, such as di-isocyanates, and proteins, such as ovalbumin, have demonstrated that the induction of sensitivity is dose dependent. Sarlo *et al.* (1997a) recently investigated immunological sensitization by detergent enzymes using the mouse intranasal test. This assay relies on intranasal instillation on days 1, 3 and 10 of an enzyme solution in a saline and detergent matrix, followed by measurement of enzyme-specific IgG_1 antibody responses on day 15. These investigators reported increasing antibody responses with increasing doses of two serine proteases, Alcalase (subtilisin) and Savinase, as well as amylase, over the dose range 0.01–10 μg enzyme/mouse in C57Bl/10 mice (Sarlo *et al.*, 1997a). This supported earlier inhalation studies in guinea pigs that demonstrated increasing enzyme-specific antibody titers over weeks of repeated exposure to enzyme and with increasing exposure concentrations (Ritz *et al.*, 1993; Sarlo *et al.*, 1997b). Interestingly, the relative differences in potency seemed associated with sensitization risk in humans, although the human data underpinning this observation are relatively weak (Sarlo *et al.*, 2000). They also observed stronger sensitization to a mixture of enzymes containing proteases (Sarlo *et al.*, 1997b). How this relates to data from epidemiological studies is yet to be established. In most field studies so far workers have been exposed to mixtures of bio-allergens (wheat and enzymes, rat, mouse, other animal allergens, etc.) or mixtures of bio-allergens and chemical sensitizers, such as animal and mite allergens and disinfectants (Preller *et al.*, 1996). Allergy to natural latex has recently been investigated in mice by subcutaneous injection, percutaneous absorption, intranasal instillation and intra-tracheal instillation with non-ammoniated latex proteins (Woolhiser *et al.*, 2000). These studies demonstrated dose-dependent induction of specific IgE by all four exposure routes. Importantly, mice sensitized by intra-tracheal instillation and later challenged with latex protein demonstrated a significant broncho-constrictive response compared to naive mice, sham-sensitized mice or mice sensitized with latex protein but challenged with saline. Such toxicological evaluations could provide useful background information to facilitate risk assessments on the basis of epidemiological data and may take the place of the evaluations now based on human data.

RISK ASSESSMENT APPROACHES TO UNDERPIN EXPOSURE THRESHOLDS

It is now well recognized that immunoassays using specific antibodies against the (epitopes of) HMW sensitizers may, in most cases, be the most suitable, sensitive and specific technique for measuring allergen exposure levels (Heederik *et al.*, 1999b). Application of this technique in various occupational environments has led to unraveling of exposure–response relationships for specific IgE-mediated sensitization and exposure-related allergic symptoms for a variety of allergens. For wheat allergens knowledge about exposure–response relationships has provided scien-

tific information to use in the first *ad hoc* quantitative risk assessments by the American Conference of Governmental Industrial Hygienists and the Dutch Expert Committee of the National Health Council, as recently referred to in an editorial in this journal (Nieuwenhuijsen and Burdorf, 2001). Despite these promising applications of epidemiological study results, risk assessment for sensitizers has some major conceptual and practical pitfalls that need to be solved in the near future (Baur *et al.*, 1998; Heederik and Doekes, 1999; Nieuwenhuijsen and Burdorf, 2001). Ideally, the risk assessment for deriving an occupational exposure limit should be based on a sufficiently large epidemiological study involving exposed and control subjects to allow calculation of the relative risk due to occupational exposure for a specific health end point. This can only be done if populations exist with substantial human exposure. Ideally, a preliminary estimated exposure limit could be obtained from rodent bioassays followed by epidemiological studies. However, there is no generally accepted, well-validated 'rodent bioassay' that would facilitate this.

The conceptual pitfalls can best be illustrated by discussing the following questions and the answers that can be given at present.

1. What is the preferential health effect in risk assessment analyses: sensitization to a specific allergen, a well-defined disease, symptom or syndrome or a combination of both? Which exposure–response relationship should be considered in risk assessment?

Baur *et al.* (1998) mentioned in their paper on TLVs for sensitizers that asthma should be the end point of relevance for risk assessment. A practical problem is that the incidence of specific work-related and clinically diagnosed asthma has been estimated on the basis of registry studies to occur in 5–20 per 100000 individuals (Heederik, 2000). Although the incidence will be higher in specific occupational groups, the use of a strict clinical definition will require the use of large-scale epidemiological studies, larger than those usually conducted. A restriction to allergic asthma will exclude other end points which could also be considered as adverse, such as occupational allergic rhinitis, and which appear in a much higher proportion of exposed workers (Siracusa *et al.*, 2000).

Most epidemiological studies have focused on sensitization (defined as a positive skin prick test, presence of specific IgE or a positive challenge), asthma or rhinitis defined on the basis of questionnaires or a combination of sensitization and respiratory symptoms, because of the above-mentioned practical limitations with regard to clinically relevant end points in epidemiological studies. Brisman *et al.* (2000) evaluated an exposure–response relationship for self-reported asthma and rhinitis in a retrospective cohort study among 2923 bakery workers. The risk of asthma seemed to be increased at inhalable dust concentrations >3 mg/m^3 (dough making or bread forming), whereas the risk of rhinitis was increased at all concentrations >1 mg/m^3. The comparison with the control group implies that after correction for potential confounding variables, the observed increased risk can be attributed to occupational exposure.

Apart from the usual issue of responder bias, an additional disadvantage of using questionnaires only is that no distinction can be made between asthmatic and rhinitis symptoms with an immunological background or those caused by other mechanisms. In the case of respiratory symptoms in bakers, especially, a considerable proportion of symptomatic bakers show no sensitization to baking allergens and other causal mechanisms for development of their symptoms have been suggested (Cullinan *et al.*, 1994). The major reservation against using sensitization as an end point for risk assessment is that it is not considered a 'disease' (Tikkainen *et al.*, 1996). On the other hand, there is widespread agreement that sensitization defined as the presence of specific IgE antibodies is the first step in a disease process that is accompanied by symptoms, such as bronchial hyper-responsiveness and airway obstruction, when exposure continues (Chan-Yeung and Malo, 1999). In addition, most studies have demonstrated a strong correlation between work-related sensitization and symptoms, suggesting that most sensitized workers are symptomatic. However, the correlation between sensitization and symptoms is not perfect and most authors believe that symptoms can also be caused by non-immune-mediated mechanisms. On the other hand, one of the few longitudinal studies available for HMW sensitized workers demonstrated that wheat and fungal α-amylase sensitized individuals have a clearly increased risk of developing symptoms during follow-up (De Zotti and Bovenzi, 2000). A compromise might be to use symptomatic sensitization as the critical end point for risk assessment. The disadvantage is that this actually means that there are several exposure–response relationships to consider, which can be described by distinguishing primary and secondary causation. Primary causation involves the exposure and sensitization process, while secondary causation describes subsequent development of symptoms and respiratory impairment. For instance, there is some evidence for the existence of an exposure–response relationship between symptoms and wheat allergen exposure in sensitized workers (Houba *et al.*, 1998). The relationship of exposure with symptoms in combination with sensitization is differently shaped than the two individual relationships. In general, this cannot always be described simply because the individual exposure–response relationships (for sensitization and symptoms individually) are modified by

different effect modifiers and different underlying processes, such as the healthy worker effect, influence each exposure–response relationship differently. This issue is clearly illustrated by Heederik and Houba (2001) in their paper on risk assessment for wheat flour. However, despite the limitations of the use of a combination of sensitization and symptoms, this approach is feasible in most epidemiological studies conducted recently, some of which are still ongoing, and is to be preferred.

2. Is an 8 h average the optimal proxy of exposure for risk assessment purposes or do short-term exposure peaks play an important role?

It has been suggested that peak exposure might play an important role and increase the risk for developing allergic respiratory disease (Nieuwenhuijsen *et al.*, 1995b). On the other hand, this issue needs to be considered in its occupational hygiene context. The few studies available have suggested that, for instance in the baking industry, workers are exposed to relatively large particles (Burdorf *et al.*, 1994; Sandiford *et al.*, 1994; Houba *et al.*, 1997). As a result, the particles will remain airborne for only a short period of time, exposure will mainly occur when workers are handling products and background exposure will be extremely low. This is supported by results from exposure measurements in bakery workers with continuous registering devices, such as the Miniram (Jongendijk *et al.*, 1995). Interestingly, results from this study also suggest that the number of peaks per day can predict 8 h exposure levels accurately. These data clearly indicate that exposure occurs as a sequence of peaks over a working day and the exposure measured over an 8 h period correlates strongly with peak exposures. As a result, it will be extremely difficult to evaluate the effect of differences in risk for certain peak exposure patterns, while at the same time, because peak and average exposures are interchangeable, the issue seems of marginal relevance is some cases.

3. Is there an exposure threshold for the association between allergen exposure, sensitization and symptoms and what is the shape of the exposure–response relationship?

Few clear-cut exposure–response relationships have been published for sensitization and even fewer for symptoms or other end points such as allergic rhinitis or asthma. Recent data for cat allergens in children suggest that the exposure–response relationship for sensitization may be bell-shaped, although the relationship was more linear for the house dust mite (Platts-Mills *et al.*, 2001a,b). The lower risk for sensitization at higher exposure levels may be explained by the development of (blocking?) IgG_4 antibodies that may have protective effects. It remains to be established if the potential protective effect of IgG_4 development also occurs in longitudinal studies, in adult working populations and at lower exposure levels and what effect it has on the shape of the exposure–response relationship, especially at lower exposure levels. The paper by Heederik and Houba (2001) supports the existence of a bell-shaped relationship for wheat allergens using advanced smoothing techniques. However, IgG_4 antibodies were not evaluated in this study and a healthy worker effect, which might be an alternative explanation for these results, cannot be ruled out. The results of these analyses also suggest that an exposure threshold for wheat allergen sensitization does not exist. If the latter is also observed for other allergens, the results imply that the so-called 'pragmatic approach' has to be applied in risk assessment. The above described statistical approach seems most promising and could be of great use in risk assessments for allergens.

4. What is the background level of the chosen health effect/end point in non-occupationally exposed populations and what excess risk do we accept when we apply the pragmatic risk assessment approach?

For specific sensitization especially there is usually a lack of available data for non-exposed populations. Few studies have included control groups that give an indication of 'background' sensitization rates in the general population for occupational allergens. The most extensive evidence is probably available for latex, because of public health concerns related to latex use during operations and clinical evaluations. For allergens to which exposure is not limited to the occupational environment, such as agricultural animals, food allergens, mice and rats, some data may be available. The more exotic the allergen, the scantier the evidence will be, but at the same time the lower the risk of 'background' sensitization in non-occupationally exposed subjects. Even if some information about naturally occurring sensitization rates is available, it cannot always be used in a straightforward manner because, first, it may come from different populations and, second, diagnostic techniques to assess sensitization often differ between studies, leading to differences in estimated sensitization rates. Although limited information is available, occurrence rates of, for instance, wheat and latex sensitization in the general non-occupationally exposed population appear to be 1–5 per 100 cases. Thus, the background risk in non-occupationally exposed populations will be relatively high. Detectable excess risk levels will be of the same order of magnitude in studies of a few hundred to a thousand workers. Increases used in risk assessment approaches for carcinogens are usually considerably lower, in the range of 1–25 per 100000, but these values should not be applied to sensitizing agents because of the high background occurrence of sensitization against work-related allergens in the general population.

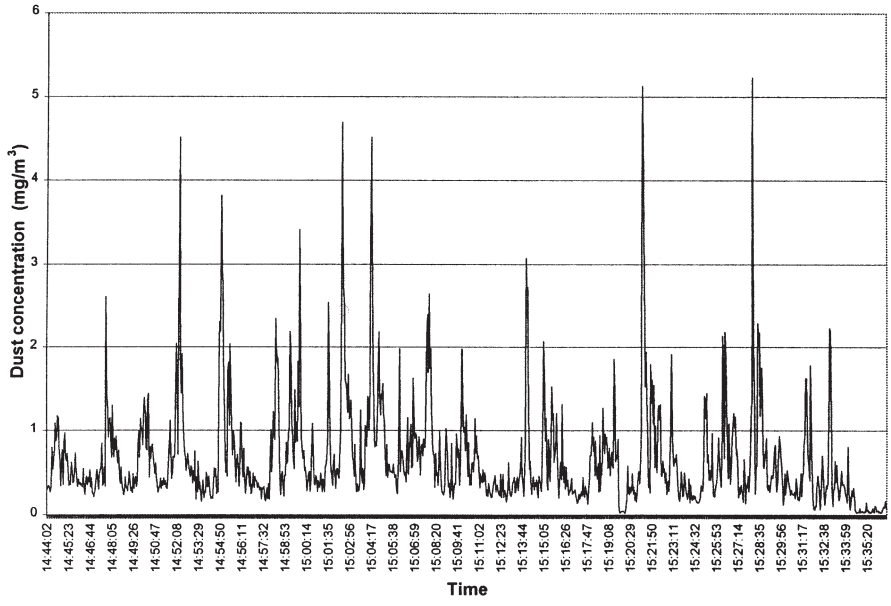

Fig. 1. Dataram results of dust measurements during dusting with flour of pastry tart bottoms (courtesy of Netty de Pater, TNO Chemistry, Zeist, The Netherlands).

Increases in risk with a factor of 1.5–2 seem practical and justifiable considering naturally occurring rates.

5. Which factors modify the risk for becoming sensitized or for developing symptoms and how should these factors be dealt with?

There is widespread agreement that atopy is an important risk modifier for sensitization. Exposure–response relationships for sensitization are steeper in atopics (Houba *et al.*, 1996a,b, 1998; Heederik *et al.*, 1999a; Nieuwenhuijsen *et al.*, 1999). Since atopy is prevalent in most Western countries, atopics cannot be considered as a small sensitive subgroup. The available evidence suggests that sensitization may also be avoided in atopics by reducing exposure. However, the costs may be high and only future intervention studies will be able to show if exposure control strategies will be sufficiently effective. Another major complication might be that sensitization to a particular allergen might be determined by exposure to other agents. Although this is a complicated and little studied area, there is evidence that simultaneous or recent exposures, occupational or non-occupational, to other agents such as endotoxins and disinfectants and possibly other chemical agents may diminish or enhance the risk of atopic immune responses to environmental allergens and exacerbate the respiratory symptoms (Preller *et al.*, 1996). In addition, animal experiment studies with enzymes suggest that enzyme mixtures containing proteases may be more potent than a single enzyme (Sarlo *et al.*, 1997b). Thus, changes in exposure to such interacting mixtures may lead to unpredictable changes in sensitization risk. Combined exposure has always been an issue in occupational health, but for allergens the indications are becoming more and more concrete and if these interactions are proved to exist this will certainly have an impact on the outcomes of risk assessments.

PRACTICAL OCCUPATIONAL HYGIENE ISSUES

Important practical problems need to be resolved before hygienists in the field can compare exposure levels with newly derived hygiene standards. For wheat allergens the risk assessments available so far have been expressed in units of inhalable dust per cubic metre, despite the fact that wheat allergens can also be measured directly by immunoassay. This can be done because wheat allergen exposure levels in the air can, in the context of one type of work environment, namely bakeries, be approximated by dust measurements, within reasonable limits (Nieuwenhuijsen *et al.*, 1994, 1995a; Houba *et al.*, 1996a). Although the correlation between dust and wheat allergen levels appeared to vary depending on the process or product (bread versus pastry baking), this variation can be accounted for by an uncertainty factor, which is reasonably small compared to uncertainty factors when a health-based exposure limit is solely based on toxicological information from animal experiments. The reasons for expressing the exposure in terms of dust levels are obvious. The assays available have not yet been rigorously standardized and thus far can only be used by research laboratories. However, for allergens that are more potent and sensitize at nanogram per cubic metre levels, expressing exposure in terms of dust levels is not appropriate, since the rela-

tionship between allergen and dust levels is usually extremely poor and significant sensitizing allergen levels may often be encountered while dust levels are below the detection limit of conventional respirable and inhalable dust sampling. Thus for most HMW allergens the exposure assessment must be based on immunoassays.

The allergen concentration measured in dust sample extracts by immunoassay may be influenced by the extraction method from the filter containing the dust, the elution buffer and the allergen standard used (Zock *et al.*, 1996; Hollander *et al.*, 1999; Renström *et al.*, 1999). A more complex issue is that the results also depend on the type of assay and the antibody source used. Different antibodies, even against the same target protein, can react to different epitopes of the protein, probably with different affinities. This probably led to the systematic differences between assays for fungal α-amylase using monoclonal antibodies observed, for instance, for Sweden and Germany (Lillienberg *et al.*, 2000). While these problems may potentially slow down progress in the epidemiological and risk assessment research fields, they may also frustrate practical hygiene studies because study results cannot be compared when different assays have been used and no comparison has been published. Although the technical issues associated with the use of immunoassays can be resolved, for instance by referring to (inter)national standards and the use of standard calibration samples, it requires mechanisms that have not been established. In Europe the ISO CEN working group (CEN TC 137 WG 5) for measurement of biological agents is active, but allergens have still to be put on the working agenda.

CONCLUDING REMARKS

The paradigm of exposure–response relationships implies that lowering allergen levels on the basis of valid health risk assessments and standard setting will lead to a change in the sensitization rate in the target population. This concept might be a simplification of reality, especially in the case of exposure to sensitizers, because of the role of sensitization in the whole disease process and modifying factors such as atopy and other exposures. This warrants careful evaluation of interventions in epidemiological studies. Such studies are now being undertaken in infants in relation to domestic allergen exposure to the house dust mite. This approach needs to be broadened to the occupational health field to substantiate whether interventions will indeed have the benefits claimed.

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