

REVIEW

Exposure–response relationships of occupational inhalative allergens

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Summary

Only a few threshold limit values exist at present for allergens in the workplace known to cause bronchial asthma. This contrasts with the great number of occupational asthma cases observed in industrialized countries. Recently published studies provide clear evidence for exposure intensity response relationships of occupational allergens of plant, microbiological, animal or man-made origin. If allergen exposure levels fall short of determined limit values, they are not associated with an increased risk of occupational asthma. Corresponding data are available for wheat flour (1–2.4 mg/m³), fungal α -amylase (0.25 ng/m³), natural rubber latex (0.6 ng/m³), western red cedar (0.4 mg/m³) and rat allergens (0.7 μ g/m³). It is suggested to stipulate legally binding threshold limit values (TLV/TWA) on this basis in order to induce more effective primary preventive measures. If no reliable data on the health risk of an occupational airborne noxa exist, the lowest reasonably practicable exposure level has to be achieved. Appropriate secondary preventive measures have to be initiated in all workplaces contaminated with airborne allergens. Verified exposure–response relationships provide the basis for risk assessment and for targeted interventions to reduce the incidence of occupational asthma also in consideration of cost benefit aspects. ‘Occupational asthma is a disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes in a working environment. These causes can give rise to asthma through immunological or non-immunological mechanisms [1]. Up to 15% of all asthma cases are of occupational origin or have at least a significant causal occupational factor [1–10]. According to the New Zealand part of the European Respiratory Health Survey, an increased risk of asthma prevalence was found for several occupations such as laboratory technicians, food producers, chemical workers, plastic and rubber workers [11]. The Spain part of this study comprising 2646 Spanish subjects showed an asthma risk to be attributed to occupational exposures between 5 and 6.7% [12]. Main asthma-inducing agents in the workplace are flour, grain and feed dust, animal dander/urinary proteins and isocyanates. Further, several inhalative irritants such as chlorine, acid or alkaline aerosols play a pivotal role. Many low molecular weight chemicals have irritative as well as allergenic effects on the airways, e. g. isocyanates and acid anhydrides. In addition to chronic or repetitive exposures, also singular accidental exposure to high concentrations of irritative or toxic airborne substances can cause occupational asthma. This condition is frequently called reactive airways dysfunction [13].

Exposure–response relationships

Recent studies on exposed subjects give strong evidence for exposure intensity-response relationships between indoor or common environmental allergens on the one hand and

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Table 1. Studies on exposure-response relationships of occupational/environmental inhalant allergens

Source substance allergen	Exposure evaluation (method)	Lowest effective antigen level	Exposure-response relation of	Group	Reference
Flour dust	Dust sampling in bakery atmospheres	1–2.4 mg/m ³ 1.7 mg/m ³	Sensitization sensitization, respiratory symptoms, PD ₂₀	230 bakery employees 279 bakery employees	[18] [16]
Fungal α -amylase	Dust sampling in bakery atmospheres	0.25 ng/m ³	Sensitization	230 bakery employees	[22]
Wood dust (red cedar)	Questionnaire and dust sampling in saw mill atmospheres	0.2–0.4 mg/m ³	Decrease in FVC	243 saw mill workers	[24]
Natural rubber latex	Dust sampling in hospital atmospheres	0.6 ng/m ³	Sensitization, respiratory symptoms	145 hospital employees	[30]
Cow dander/hair Bos d 2	Analysis of room dust samples	1–29 μ g/g dust	Sensitization	40 farmers	[35]
Rat urine	Questionnaire and dust sampling in workplace atmospheres	0.1–68 μ m ³	Respiratory symptoms	323 employees with contact to laboratory rats	[38]
Dog dander/hair Can f 1	Analysis of room dust samples	10 μ g/g dust	Sensitization	Review of epidemiological studies	[63]
Cat dander/hair Fel d 1	Analysis of room dust samples	8 μ g/g dust	Sensitization	Review of epidemiological studies	[63]
<i>Chironomidae</i> Chi t 1-9	Questionnaire	> 5mg/month	Sensitization	184 Chi t 1-9 exposed subjects	[42]
Acid anhydrides	Dust sampling in workplace atmospheres	0.3–1.7 (various) 0.1–0.39 mg/m ³ (TCPA) 0.82 mg/m ³ (TMA)	Symptoms symptoms symptoms, sensitization	Overview on various studies 52 factory workers 17 factory workers	[52] [43] [69]
Isocyanates	MDA 7005	5–10 ppb	Symptoms, lung function impairment	84 industry workers	[70]

sensitization or diseases on the other hand [14,15]. As shown by an increasing number of investigations, this is also true for occupational allergens. In the following, results of several relevant studies on this issue are summarized (see also Table 1. However, in this context, it has to be differentiated between dust exposure and allergen exposure. Some of the studies mentioned below only estimated the exposure intensity related to the whole dust-concentration measured. Since the dust samples may contain different levels of allergenic and non-allergenic substances, it is particularly important to establish and employ specific assays for an accurate and precise estimates of the exposure intensity. Nevertheless, in general an increased exposure to dust is related to an increased exposure to allergen.

Bakery allergens

Flour is one of the main causes of occupational asthma. In bakeries, flour dust concentrations of 1–2.4 mg/m³ were found to be associated with a significantly elevated risk of sensitization to wheat antigens [16–19]. Using logistic or linear regression analyses, Musk *et al.* [16] found symptoms, lung function, bronchial reactivity and immediate-type skin-prick test responses to bakery allergens to be related to current or past exposure to dust. More important than the total dust measurement is the specific ascertainment of flour antigens [18–20]. The antigen proportion in total dust depends on size and type of bakeries. Wheat antigen amounts ranged from 2.4 to 6 ng per mg bakery dust.

Fungal α -amylase from *Aspergillus oryzae* (Asp o 2) is widely used as a baking additive. Some 20–30% of symptomatic bakers are sensitized to this enzyme [21,22]. Dose-dependent effects are already detectable from 0.25 ng/m³ air. A study on 178 bakers showed that in addition to the atopic state, the exposure to α -amylase in the air is an important factor of sensitization to this substance in bakeries [22].

Wood dust (western red cedar)

Total dust concentrations in the air of a red cedar sawmill were determined by Vedal *et al.* [23]. In addition, 652 employees were investigated using questionnaire and spirometry. The dust level was found to be up to 6 mg/m³ in working environment. Workplace-related eye irritations were more common at concentrations above 3 mg/m³. Workplace-related asthma was associated with an exposure of more than 10 years (found in 8% of workers). Lung function values (FEV₁ and FVC) were lower at higher wood dust concentrations.

Noertjojo *et al.* [24] investigated 243 sawmill workers in an 11-year follow-up study on the relationship between exposure to red cedar dust and lung function changes. A total of 140 office workers served as control group. Asthmatics were not included in the study. The intensity of exposure was calculated for each employee on the basis of concentration and duration of dust exposure. Three exposure groups were differentiated: low (0.2 mg/m³), medium (0.2–0.4 mg/m³) and high (>0.4 mg/m³). In the follow-up, a significant decrease of FEV₁ and FVC, inversely related to the wood dust load, was found.

Natural rubber latex

Allergy to natural rubber latex is becoming a serious occupational problem especially among health care workers. Although the direct skin contact with latex gloves is the most common way of exposure, recent studies demonstrate that latex allergens can become airborne in hospitals and doctors' surgeries with glove powder as allergen carrier [25–28]. To analyse the relationship between latex allergen load in the air and risk of sensitization, Baur *et al.* [29,30] collected dust samples in various hospital and surgical rooms and quantified the airborne latex allergen concentrations by a competitive immunoassay using pooled serum from latex-allergic patients. Specific IgE antibodies and hypersensitivity reactions of the 145 employees who worked in these rooms were measured as well.

Airborne latex allergens were detectable in all rooms in which powdered gloves were used and no ventilation systems were installed. The highest concentration of airborne latex allergens was 205 ng/m³.

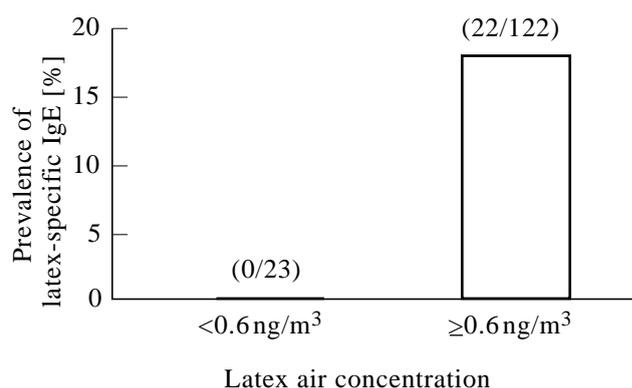


Fig. 1. Prevalence of IgE-mediated sensitization to latex of hospital employees working in rooms/units with less than 0.6 ng or \geq 0.6 ng latex allergens per m³ air.

As shown in Fig. 1, IgE-mediated sensitization was found to be significantly associated with the latex aeroallergen levels; at latex allergen concentrations of \geq 0.6 ng/m³, 18% of exposed people were found to be sensitized and 15.5% revealed hypersensitivity reactions. Lower concentrations were neither associated with IgE-mediated sensitization nor with respiratory symptoms [30].

These findings demonstrate that continuous inhalative contact with latex allergens seems to be an important risk factor for hypersensitivity reactions.

Non-occupational situations, e.g. latex allergies in spina bifida patients, also show evidence of exposure–response relations: the frequency of latex sensitization in spina bifida children was found to be strongly associated with the number of surgical procedures [31–34].

Cow dander/hair

The relationship between the levels of airborne cow dander/hair allergens and IgE-mediated sensitization in farmers was investigated by Hinze *et al.* [35]. They determined IgE antibodies to the major allergen Bos d 2 in 40 dairy farmers and analysed dust samples from living rooms. A threshold of 1–21 μ g Bos d 2 per gram dust (atopics) and of 24–50 μ g Bos d 2 per gram dust (non-atopics) was found to be significantly associated with an IgE level of >0.7 kU/L.

Rat allergens

Several investigations related to laboratory animal allergy were performed by Hollander *et al.* [36]. They developed highly specific and sensitive sandwich immunoassays for rat and mouse urinary allergens. A cross-sectional study on 540 laboratory animal workers was performed to quantify the exposure–response relationship for allergy to rats. In the

group of workers with less than 4 years of working experience with laboratory animals, the prevalence rate of sensitization to rat allergens was clearly associated with exposure levels [36]. Allergies to cat and dog seemed to be an important risk factor for laboratory animal allergy [37].

A total of 323 subjects occupationally exposed to rats was studied by Cullinan *et al.* [38]. The authors measured intensity and frequency of exposure to total dust and rat urinary allergens. In addition, workplace-related symptoms and skin-prick test results (standard and rat urinary allergens) were evaluated. There was a positive correlation between the level of rat urinary allergen exposure and the frequency of positive skin-test results. The relationship between specific sensitization and work-related symptoms was more evident for atopics than for non-atopics.

Dog and cat dander/hair

Proteins from pelt and saliva of pets are mainly environmental allergens; however, sometimes they are also of occupational relevance, e.g. for veterinarians, pet shop owners and animal dealers.

Can f 1 (dog) and Fel d 1 (cat) are well-characterized allergens. Even in rooms without animals, 1–10 µg of these allergens per gram dust can be found. Obviously, the allergens are transferred by clothes, etc. Reservoirs of Can f 1 are carpets, upholstered seats in public buildings, curtains, mattresses and soft toys [39]. The investigation of different public places by Custovic *et al.* revealed values of above 10 µg Can f 1 per gram dust in 40% of upholstered seats [39]. Such concentrations are capable of provoking asthmatic symptoms in most patients allergic to dogs. A threshold value of 8 µg Fel d 1/g dust is suggested by Gelber *et al.* [40] for cat allergens. The investigation of 114 sensitized asthmatic patients and 114 controls revealed that nearly all cat-allergic subjects showed symptoms at this concentration. In addition, it was the lowest value found in a house with a cat.

Chironomidae allergens

Red mosquito larvae of the non-biting midge (*Chironomidae*) are often used as fishfood. Their haemoglobins (Chi t 1–9) are potent allergens [41]. An association between the degree of exposure (calculated by frequency and amount of material handled) and symptoms could be found in 184 subjects exposed to this insect allergen [42]. The group consisted of fishbreeders, workers in a fish food factory and employees of zoological shops. Based on data obtained by a questionnaire, exposure levels were divided into low, medium and high. Parallel to the exposure degree, the percentage of subjects with complaints increased. In addition, a relationship between exposure and IgE-mediated

sensitization could be found. Asthmatic symptoms were associated with specific IgE antibodies to Chi t 1–9. Furthermore, asthmatic patients had the highest IgE antibody concentrations [42].

Acid anhydrides

Acid anhydrides are a class of chemical agents frequently used in the production of synthetics. Liss *et al.* [43] performed a cross-sectional study in a factory with 52 employees using tetrachlorophthalic anhydride (TCPA) as a hardener. The concentration of TCPA in the air was between 0.21 and 0.39 mg/m³. The prevalence of work-related airway complaints was high (27–39%). After ventilation installation, the TCPA concentration decreased to 0.1 mg/m³, and at the same time symptoms diminished considerably.

Eighteen workers exposed to trimellitic anhydride (TMA) were investigated by Bernstein *et al.* [44], 12 of them were observed over 3 years. Five of the workers developed IgE antibodies to TMA-HSA. Three of them suffered from late respiratory systemic syndromes, one from rhinitis. After the installation of ventilation systems, TMA concentration in the air were reduced from 0.82–2.1 mg/m³ to 0.01–0.03 mg/m³. Subsequently, the number of workers with specific IgE antibodies and symptoms decreased. At the latter concentrations, the induction of new hypersensitivity reactions seems to be improbable.

Detergent enzymes

Proteolytic enzymes derived from *Bacillus* species have been added to synthetic detergents to enhance clearing effectiveness. They have been described as asthma-causing sensitizers [45]. Even after the introduction of encapsulated enzymes, exposures at the workplaces are still sufficient to cause IgE-mediated immunological sensitization [46]. An epidemiological study covering 11 years of enzyme-detergent production and its effects on 2344 workers revealed significant differences between minimum and maximum exposure groups with regard to FEV₁ values [47].

Isocyanates

Toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), hexamethylene diisocyanate (HDI) as well as corresponding polyisocyanates are well known as causes of occupational airway diseases. Karol [48] investigated the relationship between exposure concentration and immunological response using an animal model (guinea-pigs). The animals were exposed for 3 h to TDI concentrations from 0.12 to 10 ppm on five consecutive days. Starting on day 22,

specific antibodies were detected by means of passive cutaneous anaphylaxis, and allergy skin tests as well as lung function measurements were performed. No antibodies were found in the group exposed to 0.12 ppm; 55% of animals were sensitized in the group exposed to 0.36 ppm. The exposure to higher TDI concentrations resulted in an increase in antibody level and in the percentage of sensitized animals. In addition, hypersensitivity reactions were measurable by bronchial challenge test in animals exposed to 0.36 ppm or more. More than 2 ppm were found to be pneumotoxic. No immune reaction was seen after long-term exposure to a low TDI concentration (0.02 ppm for 15 weeks).

Marek *et al.* [49] found that TDI atmospheres of 10 ppb cause bronchial hyperreactivity within 4–6 h of exposure in a rabbit model of occupational lung disease. The responses were further enhanced at 30 ppb. In guinea-pigs, 10 ppb of HDI applied over 8 weeks also induced bronchial hyperreactivity [50].

Baur [51] reported an increased frequency of sensitization and symptoms in a group of isocyanate workers exposed to 5–10 ppb when compared with a group exposed to less than 5 ppb. No influence of smoking habits was found.

In most European countries, TLVs for isocyanates have been stipulated at 5 or 10 ppb.

How can threshold limit values be defined?

Avoidance of allergen exposure in the working place is the most effective approach for the prevention of occupational asthma. With regard to appropriate measures to reduce or even eliminate occupational asthma-inducing agents, the publications of Venables [52], Corn [53] and Gordon *et al.* [54] are also referred to. Depending on the allergen source and material, different preventive procedures may be effective, e.g. the substitution of hazardous substances by harmless ones, installation of exhaust systems, use of ventilated workstations, encapsulation of machines, use of granulated or liquid products instead of powdered ones.

In contrast to many toxic and/or carcinogenic substances [55,56], only few exposure limit values for allergenic substances in the workplace exist, e.g. inhalable wood dust with a TLV/TWA¹ of 2 mg/m³ (due to carcinogenic effects) in Sweden and Germany; flour dust with a TLV/TWA of 1 mg/m³ in the Netherlands and of 4 mg/m³ in Germany and isocyanates with TLVs/TWAs mostly of 5 or 10 ppb.

To control the exposure to asthma-inducing agents in the workplace, threshold values or a maximum tolerated concentration of these agents should be established first. The question is how these legally binding threshold limit values (TLV) should be defined. Should they be based on the

significantly increased frequency of sensitization to asthma-inducing agents or on the prevalence or incidence of occupational asthma in defined workforces? And should 'time-weighted average' (TWA) concentrations¹, 'short-term exposure limit' (STEL) concentrations² and/or ceiling concentrations³ be considered? A further possibility would be to define the so-called 'no observed adverse effect level' (NOAEL) which is significantly different from the 'lowest observed adverse effect' (LOAEL) [57].

Since most allergens have no toxic or irritative effects (exceptions are several chemicals at high concentrations) it would be appropriate to stipulate legally binding TLVs/TWAs for major causes of occupational asthma based on the best available scientific work referring to the incidence (prevalence) of this disease.

If exposure to an occupational agent causes a significant increase in asthma cases in a working group when compared with the normal population, or significant increase in asthma incidence is found among the workers, the causative agent should be indicated as a hazardous substance, corresponding preventive measures should be introduced and based on the results of research works on the exposure-response relationship, a TLV/TWA for this agent should become obligatory. If this TLV/TWA is exceeded in workplaces, restrictions for work should be introduced, such as limited working duration and exposure, use of adequate personal protective devices (especially respirators) and introduction of medical surveillance programmes [30,52,58–60].

If no reliable data on asthma prevalence/incidence of a certain endangered, occupationally exposed group exist, the lowest reasonably practicable exposure level of airborne organic as well as inorganic substances has to be achieved. Furthermore, appropriate research work has to be initiated to obtain this information as soon as possible.

One major problem of defining threshold values is that methodology for quantification of different allergenic material is far from being standardized yet. This is, however, urgently needed for exact exploration of exposure-intensity relationship and it also builds the basis to establish thresholds for allergenic substances in the workplace. The recent progress on allergen analysis has been summarized by Hamilton *et al.* [61] and Esch [62]. To quantify airborne allergen concentrations in the workplace, some appropriate immunoassays, mainly based on monoclonal antibodies, already exist, e.g. for fungal α -amylase, natural rubber latex, several animal allergens and flour [22,29,38,53,54,63–68]. However, in most cases these specific assays were employed only by reporter self. Some working conditions, e.g. reference antigen or antibody are mostly not available for other investigators. In order to facilitate the comparison of exposure data obtained from different studies corroboration and standardization of these assays are necessary.

It has to be emphasized that in the context of exposure–response relationships many other issues still need to be taken into account. One of them is the exposure assessment amongst workers studied. In addition to the quantification of asthma-eliciting agents in the workplace, occupational epidemiology studies require accurate and precise estimates of the exposure intensity to explore exposure intensity response relationships [67]. With different working conditions, the level of exposure in individuals varies; and different measurement strategies may lead to different health risk estimates. A comprehensive review of the issues involved in exposure assessment for occupational epidemiology studies has been recently given by Nieuwenhuijsen [68].

Other important aspects which also have to be investigated are the detection of early disease stages and their process, a more detailed description of the underlying exposure–response relationships of single or even mixed exposures and the interference of exposure with individual predisposing/protective factors like genetic susceptibility, atopy, smoking habits, etc. The possible booting effect of peak exposures on sensitization and symptoms/dysfunctions is especially important for the study of initiation of occupational asthma. In general, this effect can be evaluated by real-time measurements and clinical examinations. So far, the information about the relationships between a single brief high-level exposure to an irritant or sensitizing agent and the initiation of new-onset asthma is only limited. Most studies available here deal with the present average exposures, i. e. did not take into consideration variations/peaks of previous and current exposure. The data presented are mostly from cross-sectional surveys of working populations where causative factors are not always identified.

Nevertheless, there is no doubt that data are enough for assessment of exposure–response relationships for several important occupational asthma causes. More detailed studies have to be performed in order to describe precisely these relationships. We are just at the beginning of understanding such underlying complex interactions and associations.

Appendix

Definitions of well-established threshold limit values of the American Conference of Governmental Industrial Hygienists [52] are given as examples, similar definitions exist in most countries

¹*Threshold Limit Value — Time-Weighted Average (TLV-TWA)*

● the time-weighted average concentration for a normal 8 h working day and a 40 h working week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

²*Threshold Limit Value – Short-Term Exposure Limit (TLV-STEL)*

● the concentration to which workers can be exposed continuously for a short period of time without suffering from [1] irritation [2], chronic or irreversible tissue damage, or [3] narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or materially reduce work efficiency, and provided that the daily TLV-TWA is not exceeded. It is not a separate independent exposure limit; rather, it supplements the time-weighted average (TWA) limit where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature. STELs are recommended only where toxic effects have been reported from high short-term exposures in either humans or animals.

In the USA, a STEL is defined as a 15 min TWA exposure which should not be exceeded at any time during a workday even if the 8 h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range. An averaging period other than 15 min may be recommended when this is warranted by observed biological effects.

³*Threshold Limit Value-Ceiling (TLV-C)*

● the concentration that should not be exceeded during any part of the working exposure.

In conventional industrial hygiene practice if instantaneous monitoring is not feasible, then the TLV-C can be assessed by sampling over a 15 min period except for those substances that may cause immediate irritation when exposures are short.

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