Are we closer to developing threshold limit values for allergens in the workplace?

Xaver Baur, MD

Objective: To define threshold limit values and legally binding occupational exposure limits.

Data Sources: Review of suitable literature.

Study Selection: Studies based on detailed descriptions and/or measurements of airborne allergenic dust, total allergens, or even key allergens were selected.

Results: Prevalences of IgE-mediated sensitization and occupational asthma are related to the aeroallergen load in workplaces. Data to set threshold limit values for flour, latex, α-amylase, and isocyanates are already sufficiently available.

Conclusions: To optimize primary prevention in workplaces, health-based occupational exposure limits should be set for major occupational allergens.

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INTRODUCTION

Health-endangering irritative, toxic, or carcinogenic substances found in the workplace and/or in the general environment are usually subjected to regulatory measures, such as the approval of threshold limit values (TLVs), administrative standards (occupational exposure limits [OELs]), biological exposure indices, exposure equivalents to carcinogenic substances, or even application bans. These restrictions do not yet apply to occupational allergens, which cause a great number of diseases worldwide.

Due to the interindividual varying susceptibility (eg, atopic vs nonatopic patients, smokers vs nonsmokers), age dependencies, heterogeneity of immunogenic properties of allergens, and differences between doses that induce sensitization and those that elicit symptoms, it may be more difficult to define corresponding thresholds for allergens. At present, it is also difficult to define appropriate regulations for occupational allergens, since only a few comprehensive studies exist, most of which are small and/or cross-sectional. Furthermore, allergen exposures are mostly not quantified; substitutes used are dust concentrations, room dust content, amount of material used, and duration of exposure. In addition, several studies focus only on sensitization but not on diseases.

Nevertheless, useful data on more than a dozen occupational allergens are available. Among these allergens are those that top the "hit list" of substances that cause obstructive airway diseases in the workplace, such as flour, latex, isocyanates, and animal dander dust (Fig 1).

We reviewed the respective literature to summarize data suitable for defining TLVs, legally binding OELs, and respective recommendations that may prevent disorders caused by allergens in the workplace (eg, asthma, rhinitis, conjunctivitis, and dermatitis). Studies based on detailed descriptions and/or measurements of airborne allergenic dust, total allergens, or even key allergens are considered.

EXPOSURE-RESPONSE RELATIONSHIPS OF SPECIFIC OCCUPATIONAL INHALANT ALLERGENS

Flour

Measurements of inhalable dust concentrations in bakeries were taken by several groups using personal or area dust samplers (Table 1).[1–4] Concentrations varied considerably and were partly above 30 mg/m^3. Flour dust concentrations as low as 1 to 2.5 mg/m^3 are associated with a significantly elevated risk of sensitization to wheat allergens.[3–6] Using logistic or linear regression, Musk et al[3] studied 279 workers of a modern bakery and found immediate-type skin prick test responses to wheat and symptoms, lung function decrease, and bronchial reactivity related to current or past exposure. Similarly, Heederik and Houba[6] clearly demonstrated dose-response relationships between cumulative wheat allergen load on the one hand and sensitization and asthma on the other. More important than total dust is the concentration of flour antigens, which only shows an approximate relationship to total dust (1 mg of bakery dust referred to 2.4 to 6 μg of wheat allergens).[2]

Enzymes

Another important bakery allergen is fungal α-amylase, derived from *Aspergillus oryzae*. It is widely used as a baking additive. Air concentrations in bakeries are in the nanogram per cubic meter range. Approximately 20% of symptomatic bakers are sensitized to this enzyme.[7]

A study of 178 Dutch bakers performed by Houba et al[1] revealed dose-response relations with an increased frequency of sensitization at 0.25 ng/m^3 or more. This effect is much more pronounced in atopic than in nonatopic patients.

Institute of Occupational Medicine, University of Hamburg, Hamburg, Germany.

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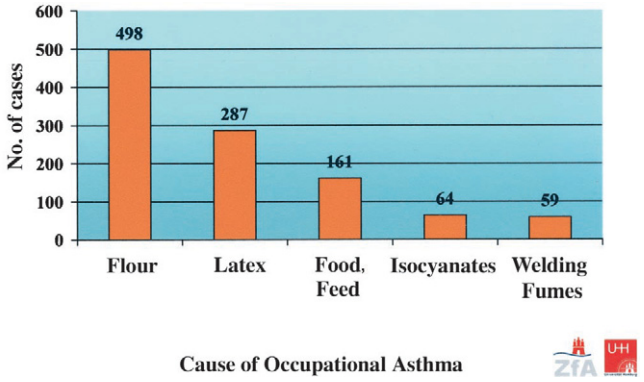

Figure 1. Major causes of accepted occupational asthma cases in Germany in 1999, including approximately 25% rhinitis cases in 1999. The total number was 1218; 525 cases were compensated. The number of new claims for compensation of occupational asthma and/or rhinitis in 1999 was 6795. Because of differences in the industry, hygiene standards, legal aspects, and other factors, this "hit list" differs from country to country (eg, latex was reported to be the predominant cause in South Africa[64] and isocyanates seem to be the predominant cause in several Western countries[65]).

In the late 1960s, the introduction of alkaline heat-stable enzymes (proteases, amylase, cellulase) in the detergent industry was associated with estimated enzyme air concentrations in the workplace of approximately 300 ng/m^3 and higher. A total of 40 to 50% of the workers were sensitized and developed asthma and/or rhinitis. In the meantime, mainly due to enzyme encapsulation, exposures have been reduced to less than 15 ng/m^3. This decrease is reported to be associated with less than a 20% sensitization of the plant population during a period of 10 years and an annual incidence of less than 3%.[8,9]

Cullinan et al,[10] however, found 19% of detergent workers exposed to enzymes (geometric mean, 4.25 ng/m^3) to be sensitized; 16% had work-related respiratory symptoms. In this study, 7 of a subgroup of 74 subjects who starting work 3 years ago were sensitized (5 to protease and/or amylase and 4 to cellulase) and 7 noticed work-related symptoms of the upper respiratory tract or chest. Due to these rather high prevalences, the authors concluded that enzyme encapsulation alone is not sufficient to prevent enzyme-induced allergy and asthma.

Wood Dust

Vedal et al[11] and Noertjojo et al[12] investigated sawmill workers exposed to western red cedar dust. In the longitudinal study of Noertjojo et al,[12] three exposure groups were differentiated: low (0.2 mg/m^3), medium (0.2 to 0.4 mg/m^3), and high (>0.4 mg/m^3). An exposure-related significant annual decline in forced vital capacity (FVC) was found. Similarly, Vedal et al[11] observed that forced expiratory volume in 1 second (FEV_1) and FVC deteriorations were inversely related to the wood dust load.

Natural Rubber Latex

Natural rubber latex has become a major cause of skin diseases, asthma, and rhinitis among health care workers. Latex

Table 1. Studies of Exposure-Response Relationships of Occupational and Environmental Inhalant Allergens

Allergen	Source	Exposure evaluation	No. of patients	Lowest observed effective allergen level	Exposure-response relation
Flour dust	Houba et al[5]	Air concentration	230	1–2.4 mg/m^3	Sensitization
	Musk et al[3]	Air concentration	279	1.7 mg/m^3	Sensitization symptoms, PD_{20}
α-Amylase	Houba et al[1]	Air concentration	230	0.25 ng/m^3	Sensitization
Alkalase	Cullinan et al[10]	Air concentration		<5 ng/m^3	Sensitization, asthma
Red cedar	Noertjojo et al[12]	Air concentration	243	0.2–0.4 mg/m^3	Lung function
Natural rubber latex	Baur[18]	Air concentration	145	0.6 ng/m^3	Sensitization, symptoms
Cow, Bos d 2	Hinze et al[27]	Room dust	40	1–29 μg/g	Sensitization
Rat urinary proteins	Cullinan et al[31]	Questionnaire, air concentration	323	0.1–68 μg/m^3	Symptoms
Dog, can f 1	Chapman et al*	Room dust	Review	10 μg/g	Sensitization
Cat, Fel d 1	Chapman et al*	Room dust	Review	8 μg/g	Sensitization
Midge, Chi t 1–9	Liebers et al[38]	Questionnaire	184	>5 mg/mo	Sensitization
Acid anhydrides	Venables[39]	Air concentration	Review	0.3–1.7 mg/m^3	Symptoms
TCPA	Liss et al[42]	Air concentration	52	0.1–0.39 mg/m^3	Symptoms
TMA	Boxer et al[40]	Air concentration	17	0.82 mg/m^3	Symptoms, sensitization
TMA	Barker et al[41]	Air concentration	49	<0.04 mg/m^3	Symptoms, sensitization
Isocyanates	Baur et al[46]	Air concentration	84	5–10 ppb	Symptoms, lung function
Colophony	Burge et al[59]	Air concentration	88	<0.01 mg/m^3	Asthma, lung function
Platinum salts	Calverley et al[60]	Air concentration	78	≤2 μg/m^3	Sensitization, asthma

Abbreviations: PD_{20}, provocative dose of methacholine producing a 20% decrease in forced expiratory volume in 1 second; TCPA, tetrachlorophthalic anhydride; TMA, trimellitic anhydride.

* Chapman MD, Heymann PW, Sporik RB, et al. Monitoring allergen exposure in asthma: new treatment strategies. *Allergy*. 1995;50(Suppl):29–33.

protein allergens are adsorbed to glove powder, which functions as an airborne allergen carrier. In a recent prospective study by Gautrin et al,[13] apprentices were tested for latex allergy before and 1 to 3 years after workplace exposure. Latex sensitization and allergic symptoms developed only in latex-exposed dental hygiene apprentices but not in other employees.

As a surrogate for latex exposure, Tarlo et al,[14] Heese et al,[15] and Levy et al[16] used the duration of training of dental students. All three studies showed an increase in latex sensitization parallel with exposure. In children with spina bifida, the number of operations that indicate a cumulative latex allergen dose also correlates with the frequency of latex sensitization.[17]

We quantified latex allergen concentrations in different hospital rooms and analyzed the relationship between the inhalable allergen load and the frequency of sensitization and symptoms. The allergen content in air dust samples was measured by a competitive immunoassay using pooled serum from latex-allergic patients. As shown in Figure 2, all hospital rooms without ventilation systems and filters contained measurable latex allergens. Approximately 30% of the rooms with such ventilation systems and filters also contained latex allergens in the air.[18]

A total of 22 of 145 health care workers engaged in these hospital rooms and participating in our cross-sectional study were found to be sensitized to latex. All of them worked in rooms with more than 0.5 ng/m^3 of latex allergen. A total of 19 of the 22 sensitized employees reported work-related rhinitis (n = 19), conjunctivitis (n = 15), and/or dyspnea (n = 5), but none of the workers in rooms without detectable latex allergens reported such symptoms or was sensitized. Based on these data, we suggested a theoretical threshold limit value of 0.5 ng/m^3. According to our clinical findings and allergen analyses of gloves,[19,20] a health-based allergen threshold of 2 μg/g of rubber for latex gloves was proposed, which would prevent nearly all hypersensitivity reactions.

An intervention was performed in five hospital rooms with significant levels of latex aeroallergens. Powdered latex gloves were replaced by nonpowdered latex gloves or synthetic ones. After several days, no latex allergens were measurable in the air. After 1 year, a follow-up study of six latex-sensitized workers showed a persistent absence of work-related symptoms and a small decline in IgE antibodies.[21]

Similarly, Tarlo et al[22] reported that in an Ontario teaching hospital with approximately 8,000 employees, hospital conversion from powdered to nonpowdered low-protein gloves with an estimated reduction of the latex allergen load from 300 to less than 5 ng/m^3 was associated with a decrease in incidence reports, allergy clinic visits, diagnoses of latex allergy, and workers' compensation claims for latex allergy. This intervention strategy was accompanied by workers' training and voluntary medical surveillance.

NATIONWIDE INTERDISCIPLINARY CAMPAIGN AND REGULATIONS OF LATEX ALLERGY PREVENTION IN GERMANY

The effectiveness of a change from powdered latex gloves to nonpowdered low-allergen latex gloves (<30 mg of protein per gram of rubber) or synthetic ones could be demonstrated after establishing a regulatory measure prescribing "powdered latex gloves have to be replaced by nonpowdered low-allergen or allergen-free gloves" and a nationwide interdisciplinary campaign for the prevention of latex allergy. A recent survey demonstrated a decrease of 40% in the use of powdered latex gloves in hospitals and of 15% in dental practices in 2 years (Haamann F, Latza U, Baur X, unpublished data, 2002). One year after the campaign, the number of compensation claims due to work-related latex allergies was significantly lower than before (278 vs 378 cases of rhinitis and/or asthma and 567 vs 884 cases of allergic skin diseases).

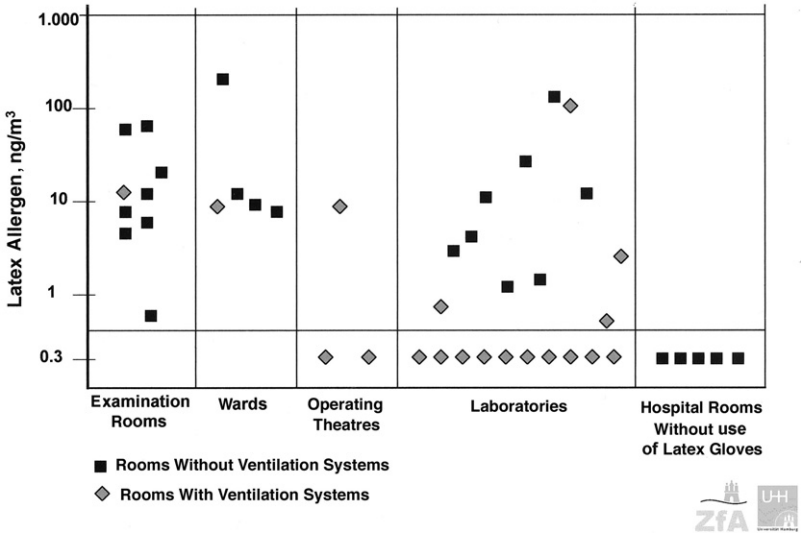

Figure 2. Air concentrations of latex allergens in 45 hospital rooms. See the text for details.

Cow Allergen

Cow allergens are a major cause of respiratory allergies of farmers.[23–25] Hinze et al[26] investigated 40 dairy farmers and analyzed dust samples from their living rooms. Thresholds of 1 to 20 μg (atopic patients) and 25 to 50 μg (nonatopic patients) of the major cow allergen Bos d 2 per gram of dust were found to be significantly associated with IgE levels of more than 0.7 kU/L in atopic and nonatopic patients. Rautiainen et al[27] reported that the level of antibodies to bovine epithelial allergens among exposed patients reflects the level of clinical allergies.

Rat Urinary Proteins

Prevalence of rat allergy among laboratory animal workers ranges from 12 to 31%.[28] Already in 1981, Schumacher et al,[29] comparing areas with low rat allergen levels (mean, 9.6 ng/m^3) with those of high levels, described clear dose-response relationships for rhinitis and bronchial asthma. Cullinan et al,[30] Nieuwenhuijsen et al,[31] and Hollander et al[32] used highly specific immunoassays for the quantification of rodents' urinary allergens in workplace atmospheres. Cross-sectional studies revealed that the exposure levels to urinary allergens of rats (range, 0 to $>$1.25 ng EQ/m^3) correlated with the frequency of positive skin test results and with upper and lower respiratory tract responses. Atopic workers had a more than threefold increased sensitization risk at low allergen levels than nonatopic patients. Data were consistent in all three previously mentioned studies.[33] Similar results have been reported for mouse fur allergens and urinary proteins.[28,34]

Chironomid Hemoglobins

Dried red mosquito larvae of nonbiting midges (Chironomidae) frequently used by fish hobbyists contain hemoglobins (Chi t 1 to 9) that are highly allergenic. They were identified as the first structurally defined allergens.[35] We could demonstrate an association between the degree of exposure as calculated by frequency and amount of material handled and symptoms and IgE-mediated sensitization. Asthma was significantly more often observed in heavily exposed workers of fish food factories (16 of 85) than in moderately exposed fish hobbyists (25 of 205).[36] Furthermore, asthmatic symptoms were associated with high levels of specific IgE antibodies to Chi t 1 to 9.[37]

Acid Anhydrides

Acid anhydrides, a class of chemical agents frequently used in the production of resins and plastics, were found to cause respiratory symptoms in the milligram per cubic meter range [38–40] Barker et al,[40] who investigated 506 acid anhydride workers, described work-related respiratory symptoms and elevated prevalence of sensitization related to increasing full-shift exposures; exposure-response relations were consistent with trimellitic anhydride at concentrations of less than 0.01 to more than 0.04 mg/m^3 and were not modified by smoking and atopy.

Liss et al[41] also found a high prevalence of work-related airway complaints (27 to 39%) in workers who had contact with tetrachlorophthalic anhydride; the prevalence decreased significantly when tetrachlorophthalic anhydride was reduced from 0.21 mg/m^3 to 0.30 to 0.1 mg/m^3. A corresponding effect was observed by Bernstein et al[42] for trimellitic anhydride, which was reduced from 0.82 to 2.1 mg/m^3 to 0.01 to 0.03 mg/m^3. The latter study showed also a decrease in the number of workers with specific IgE antibodies.

Isocyanates

Isocyanates have been increasingly used for production of polyurethane foam, elastomers, adhesives, varnishes, coatings, insecticides, and many other products. These highly reactive chemicals have become the No. 1 occupational airway sensitizer in several western countries.

An example of a recent study is the work of Petsonk et al.[43] Their study evaluated respiratory health in a new wood products manufacturing plant using 4,4′-methylene diphenyl isocyanate (MDI) and its prepolymer. In the follow-up survey, which included 178 employees, 15 (27%) of 56 workers in areas with the highest potential exposures to liquid isocyanates (vs 0 of 43 workers in the lowest potential exposures) had an onset of asthma-like symptoms. A total of 47% of workers with MDI skin staining vs 19% without skin staining developed such symptoms, which were associated with variable airflow limitation and specific IgE to MDI-human serum albumin. Our cross-sectional studies performed in two factories showed, in comparison to the group exposed to 5 to 10 ppb of MDI, significantly fewer symptomatic patients, lung function impairments, and specific IgE antibodies in the group exposed to less than 5 ppb of MDI (Table 2).[44]

As previously shown by several other authors, only a minority of symptomatic isocyanate workers showed IgE antibodies to diisocyanate–human serum albumin conjugates.[45–50] Several authors observed isocyanate exposure–dependent declines in lung function in the OEL range.[51–55] In most Western countries, OELs for diisocyanates have been stipulated at 10 ppb. This value seems to be too high. According to the literature, 5 or 2.5 ppb would be a health-based level.[56,57] The OELs for isocyanates should consider gaseous and aerosol forms and also the increasingly used polyisocyanates, which cause the same disorders as diisocyanates. Furthermore, the prevention of isocyanate skin contact is obviously also an effective measure to reduce the risk of respiratory disorders.

Colophony

Burge et al[58] studied 88 factory employees who manufactured flux-cored solder and were exposed to colophony fumes generated at 140° C. Airborne colophony levels in the workplace were measured spectrophotometrically at 455 nm, and three grades of exposure could be defined with medium levels of 1.92 mg/m^3 (6 workers), 0.02 mg/m^3 (14 workers), and less than 0.01 mg/m^3 (68 workers). Occupational asthma was present in 21% of the two groups with higher exposure and in

Table 2. Mandatory Medical Surveillance Programs as an Instrument of Health-Based Institutional Policies in Germany

Airway sensitizer	NOAEL	OEL	Criterion of mandatory medical surveillance	
			Concentration	Listed exposures
Flour*	0.5–1 mg/m^3	4 mg/m^3	>4 mg/m^3	
Cereals/feed*			>4 mg/m^3	
Hard wood dust	<0.2 mg/m^3	2 mg/m^3	>2 mg/mg	
Latex*	0.5 ng/m^3		>30 μg of protein per gram of rubber	
Laboratory animals*	<0.1 ng EQ/m^3			Yes
Isocyanates	0.05 mg/m^3	0.02–0.07 mg/m^3	>0.05 mg/m^3	Yes†
Epoxy resins*	<0.1 mg/m^3	0.04-1 mg/m^3		Yes†‡
Welding fumes			>3 mg/m^3 (inhalable dust)	

Abbreviations: NOAEL, no observed adverse effect levels; OEL, occupational exposure limit.
* Bill.
† Hand contact.
‡ Inhalative exposure.

4% of the lowest-exposure group. Furthermore, mean values of FEV_1 and FVC decreased with increasing exposure. The authors conclude that sensitization to colophony will not be prevented unless exposure is kept well below the present threshold limit value and that the whole resin acid rather than decomposition products (aldehydes) causes asthma. Therefore, the authors suggest that the threshold limit value at the temperature of 140° C should be based on the resin acid content of colophony fume and not on the aldehyde content.

Platinum Salts

Calverley et al[59] performed a prospective cohort study of 78 new recruits to a platinum refinery. Thirty-four of them worked in high-exposure production areas (27% of samples >2 μg/m^3; TLV) and 44 in low-exposure nonproduction services (all samples <2 μg/m^3). After 2 years, 32% of the patients were found to be platinum salt sensitive, 28% had positive skin prick test results to platinum salt and work-related symptoms, and 13% had work-related symptoms only. Multivariate analyses showed that the risk of sensitization was 6 times greater at high exposures than at low-intensity exposures (after adjustment for smoking). Furthermore, the risk of sensitization was approximately eight times higher for smokers than for nonsmokers. Bolm-Audorff et al[60] identified sensitization and respiratory symptoms even at concentrations lower than 0.1 μg/m^3, whereas Merget and Schulze-Werninghaus[61] observed no symptoms at 0.01 μg/m^3.

DISCUSSION

Although there are still many unanswered questions, increasing data prove the hypothesis of a dependency of IgE-mediated sensitization and occupational asthma on the aeroallergen load in the workplace. This has been shown for all previously investigated occupational allergens. For some allergens (eg, flour, latex, and α-amylase), TLVs that prevent sensitization and allergic diseases are available. The same is obviously true of some low-molecular-weight chemicals, such as isocyanates, although they can induce allergic pathomechanisms and imitative and toxic effects.

If we summarize current clinical epidemiologic and exposure evaluation findings, theoretical relationships between doses or concentrations of respiratory allergens or noxae in workplaces and prevalence of sensitized workers, lung function impairment, symptoms, and/or frequency of occupational asthma can be demonstrated. Corresponding slopes can be placed in the nanogram per cubic meter range for latex, purified enzymes, and rat urinary proteins; in the microgram per cubic meter range for wheat flour allergens, isocyanates, and platinum salts; and in the milligram per cubic meter range for acid anhydrides, wood dust, and the rather heterogeneous bakery flour dust (ie, differences by 10^3, partly depending on the purity of the allergen, exist). This means that specific, currently unknown (intrinsic) properties of allergens obviously play an important role.

Figure 3 shows a theoretical exposure-response curve of asthma-inducing occupational sensitizers with a range of no observed adverse effect levels and a lowest observed adverse effect level. Regarding such relationships, we have to consider different susceptibility factors in subgroups, such as atopy, bronchial hyperreactivity, other genetic influences, smoking, and age. For some allergens, increased risks of presensitized patients due to cross-reactivity of nonoccupational and occupational allergens have to be considered (eg, in animal allergy, latex fruit, and latex pollen syndromes). Concomitant exposure to other allergens and airway irritants may also increase the susceptibility to occupational asthma. Proteases for instance have been shown to have adjuvant properties for other allergens.

CONCLUSIONS AND RECOMMENDATIONS

Data to approve TLVs for some major occupational allergens are available. The ultimate goal, of course, is to establish workplace concentrations without health risk (ie, health-based legally binding OELs corresponding to TLVs). Until then, a suitable institutional policy should include mandatory medical surveillance programs for workers with well-defined endangering activities. As already mentioned by Bernstein et al[57] and demonstrated by Merget et al,[62] this strategy can be

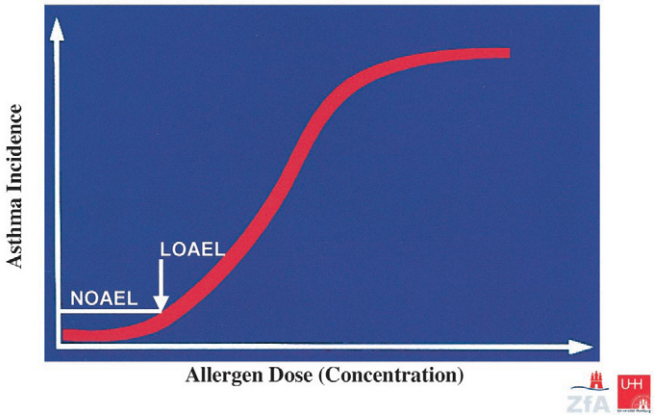

Figure 3. Theoretical exposure-response curve for asthma-inducing occupational sensitizers. NOAEL indicates no observed adverse effect levels; LOAEL, lowest observed adverse effect level.

successfully applied (Table 2). It is also necessary to obtain more and better data on dose-response relations. This requires the development of routine methods for a standardized quantification of mentioned and further occupational sensitizers.[63]

These methods have to be included in epidemiologic studies for detailed risk assessments and the description of dose-response relationships. These new data will enable us to optimize primary prevention by enforcing appropriate institutional policies and stipulating additional legally binding health-based OELs while also taking into consideration other aspects such as cost-effectiveness.

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Requests for reprints should be addressed to:
Xaver Baur, MD
Ordinariat und Zentralinstitut für Arbeitsmedizin Hamburg
Institute of Occupational Medicine
University of Hamburg
Adolph-Schoenfelder-Str. 5
D-22083 Hamburg, Germany
E-mail: baur@uke.uni-hamburg.de