

Respiratory Allergy to Rats: Exposure-Response Relationships in Laboratory Animal Workers

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Laboratory animal workers are at high risk of developing occupational allergy. Little is known about the relationship between levels of exposure and the risk of developing laboratory animal allergy. A cross-sectional study was performed in 540 workers at eight facilities to quantify the exposure-response relationship for allergy to rats, while controlling for determinants like atopy, gender, and smoking. All participants completed a questionnaire, underwent skin prick testing with common and occupational allergens, and total IgE as well as occupational allergen-specific IgE antibodies were serologically measured. Personal air dust samples were taken during full-shift periods to estimate the rat urinary aeroallergen exposure levels. In the whole study population no clear exposure-response relationship was observed. However, in the group of workers with less than 4 yr of working experience with laboratory animals the prevalence rate of sensitization to rat allergens was clearly associated with exposure levels. The exposure-response relationship was steepest for workers with atopy-associated risk factors, i.e., self-reported allergy or sensitization to cats or dogs, or elevated total serum IgE. The prevalence rates of sensitization to rat allergens for these workers were about 15, 9.5, and 7.3 times higher in the high, medium, and low exposure group, respectively, compared with internal reference group. **Hollander A, Heederik D, Doekes G. Respiratory allergy to rats: exposure-response relationships in laboratory animal workers.**

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Laboratory animal workers are at high risk of developing work-related allergic asthma, rhinitis, conjunctivitis, and/or urticaria. Cross-sectional epidemiologic studies have reported prevalence rates of these allergic conditions, also described as laboratory animal allergy (LAA), ranging from 11 to 44% (1-8). However, little is known about the quantitative relationship between the level of allergen exposure and the risk of developing LAA. Several studies (1-7) have addressed this issue using various measures of exposure to laboratory animal aeroallergens. Crude estimates of exposure, such as job title, duration of employment, or frequency of contact with animals per year, could not be related to the prevalence rate of LAA symptoms (1, 2, 5, 6). Four studies (2-4, 6) used more quantitative measures of exposure, i.e., hours per day or week working with animals. In only one study LAA symptoms were significantly more prevalent in workers who worked more frequently with animals (6). However, this finding has not been confirmed in the prospective part of the same study.

Quantitative exposure assessment to aeroallergens by using immunoassays has been applied in two studies (6, 7). In one of these studies three exposure categories were distinguished, based on a large number of full-shift personal air measurements (7). Allergic skin symptoms were significantly more present at me-

dium and high exposure levels of rat urinary aeroallergens (RUA) compared with the category with low exposure levels. No relationship was observed for chest, eye, and nasal symptoms. In the other study (6) the estimated task-specific rat allergen concentration was multiplied by the duration of performed tasks. This measure of exposure was positively associated with the prevalence rate of LAA symptoms. Results of both studies indicate the importance of measuring personal aeroallergen exposure in population studies on LAA.

In order to estimate the risk of LAA and identify its determinants, a follow-up study among approximately 600 laboratory animal workers is currently in progress in the Netherlands. In contrast to previous studies (1-7) on LAA, the analyses were based on sensitization to rat allergens as well as on a combination of symptoms and sensitization. Furthermore, allergen exposure is quantitatively assessed with a specifically developed immunoassay for RUA in personal airborne dust samples. This report covers the baseline part of the study and describes the relationship between the prevalence rate of respiratory allergy to rats and exposure to rat urinary aeroallergens, which is controlled for determinants like atopy, gender, and smoking.

METHODS

Study Population

Employees from laboratory animal facilities of four universities (sites A, B, C, and D), two research institutes (sites E and F), one pharmaceutical company (site G), and students of a laboratory school (site H) participated in the study. A completed questionnaire as well as skin prick test (SPT) results were available for 540 participants (9). Of these 540 participants, 458 (85%) worked with rats or had done so in the past. Eighty-two participants (15%), including 15 students from site H, had never worked with rats. These participants were used as the internal ref-

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erence group. For five of the 458 rat workers, detailed information on occupational exposure to RUA was not available and these were left out of all analyses. Furthermore, four rat workers had only been working with blood or tissues derived from rats, 51 had worked with rats in the past, and 398 had recently been working with living rats, i.e., during the preceding 12 mo. All analyses were performed with recently exposed workers, because detailed information of exposure to rat allergens was only available for this period, and the internal reference group. The four workers who had been working with blood or tissues derived from rats were included in the internal reference group ($n = 86$).

Among laboratory animal workers, five broad job titles could be distinguished: animal caretakers, animal technicians, scientists, scientific assistants, and supervisors. Over all sites a total of 20 different zones could be distinguished. A zone is an independent unit, which mostly consisted of several animal rooms and laboratories, and could be part of a building as well as a building itself (10).

Exposure Assessment

Full-shift inhalable dust was sampled using IOM sampling heads (IOM, Edinburgh, Scotland). Each sampling head contained a polytetrafluoroethylene (Teflon) filter (Millipore; pore size 1.0 μm , $\varnothing$ 2.5 cm). RUA were eluted from the filters and assayed by sandwich enzyme immunoassay. Concentrations in test samples were expressed in nanograms of rat urinary protein equivalent (ng eq) per milliliter in which 1 ng eq was defined as the amount giving the same assay result as 1 ng protein of the standard. Two-thirds of the detection limit (0.15 ng eq/ m^3) was assigned to samples in which RUA were not detectable. Details of air sampling and analysis of RUA are reported elsewhere (10).

Questionnaire

A self-administered questionnaire was distributed before the medical survey (9). Questions were asked about personal history of allergic symptoms to common allergens, history of allergic symptoms to laboratory animals, smoking history, working history, and intensity of contact with laboratory animals. Allergic symptoms due to working with rats were defined as the presence of self-reported allergic symptoms (chest tightness [asthma], runny or sneezing nose, runny or itchy eyes, and itchy or red skin) during working hours, during or after contact with rats.

Skin Prick Testing and IgE Antibodies

Five common allergens (house dust mites, grass pollen, tree pollen, cat fur, and dog fur), two occupational allergens (rat urine and rat fur), and positive (histamine 10 mg/ml, in duplicate) and negative controls (phosphate-buffered saline, PBS) were used for skin prick testing. All allergens were purchased from ALK Benelux (Houten, the Netherlands). SPTs were read after 15 min. A mean weal diameter of 3 mm or more for the common allergens and of 4 mm or more for the occupational allergens were regarded as positive, after subtraction of any response to the negative control (9).

Sera were stored at -20°C until IgE analysis. Specific IgE antibodies to RUA were measured by immunoassay (AlaSTAT; DPC, Apeldoorn, the Netherlands). Sera of class 2 or higher (≥ 0.7 Ku/L) were considered positive. Total IgE antibodies were measured with a sandwich enzyme immunoassay (11).

Sensitization to rat allergens was defined as a positive SPT response to rat urinary or rat fur allergens, and/or the presence of specific serum IgE antibodies to RUA. Workers were classified as allergic to rats if they reported allergic symptoms due to working with rats and if they were sensitized to rat allergens.

In a previous analysis of this population we identified elevated total serum IgE and type I sensitization to cat or dog allergens as important determinants of the presence of rat allergy (9). These atopy-associated risk factors were defined as either self-reported cat or dog allergy, i.e., allergic symptoms (chest tightness [asthma], runny or sneezing nose, runny or itchy eyes, or itchy or red skin) during or after contact with cats or dogs; positive SPT response to cat or dog fur; and/or elevated total serum IgE (≥ 100 Ku/L).

Statistical Analysis

All statistical analyses were performed using SAS software (version 6.09). General linear regression models (SAS procedure GLM) were used in

order to describe differences in log-transformed RUA concentrations by job title and zone. Crude prevalence rates were compared using the χ^2 (or Fisher exact) test. The relationship between level of exposure and host factors, and the prevalence rate of sensitization to rat allergens were analyzed by multiple regression techniques. Prevalence rate ratios were calculated by means of a proportional hazards model (Cox's proportional hazard regression with SAS procedure [PHREG]) (12). Statistical significance was reached at the $p < 0.05$ level (two-tailed).

RESULTS

In order to estimate the exposure to RUA in the population of rat workers, full-shift inhalable airborne dust samples were taken in a representative sample of 87 workers from all job titles and zones. Each worker was sampled for 1 wk on days when working with rats, resulting in a total of 251 personal full-shift airborne dust samples. The median RUA concentration of all samples was 0.76 ng eq/ m^3 . The exposure variability of the total samples set was large with a 175-fold difference between the 5th and 95th percentiles of the distribution. Of this variability 2%, 5%, and 18% was explained by sampling day of the week, job title, and zone, respectively. The analysis of variance revealed that the RUA concentrations were about twice as high on Mondays than on the other days of the week. Animal caretakers' exposure to RUA was about 2.5 times higher than that of the other rat workers. The most important determinant of RUA exposure was the zone in which the participant was working, with a 32-fold difference in median RUA concentration between the zone with the lowest and highest exposure. The RUA levels of the workers in the 20 zones could be divided into three groups: low (workers of site C_{zone 1,2}, D_{zone 1}, and E_{zone 1}), medium (workers of site A_{zone 1}, Ball 7 zones, C_{zones 3,4}, E_{zone 2}, and G_{zone 1}), and high (workers of site D_{zone 2}, E_{zone 3}, and F_{zones 1,2}). The median, 25th and 75th percentile and range of RUA levels of these exposure groups are presented in Figure 1. The workers of most zones had comparable RUA exposures on days working with rats and were grouped as medium exposed workers (median RUA exposure level = 0.68 ng eq/ m^3). The low exposed workers were working in zones in which the rats were housed in isolators or were only present in small numbers. In these zones RUA concentrations in 74% of the samples were below the detection limit, which resulted in a median RUA exposure level of 0.15 ng eq/ m^3 . The workers of the high exposure group had a more than average RUA exposure (median RUA exposure level = 4.2 ng eq/ m^3). These workers worked in a special unit with high numbers of rats (E_{zone 3}) or in zones in which most of the work consisted of high exposed tasks, like handling contaminated bedding or handling rats.

Among the 398 recently exposed rat workers, 78 (19.6%) reported at least one allergic symptom due to working with rats. A positive SPT response to rat allergens was present in 17.3% of the rat workers and 11.1% had specific serum IgE antibodies to rat allergens. According to our definition, 70 (17.7%) workers were sensitized to rat allergens and 53 (13.4%) had rat allergy (Table 1). In the internal reference group the prevalence rate of sensitization to rat allergens was 3.5% and only one worker reported also allergic symptoms due to rat allergens (Table 1). However, the allergic symptoms due to rat allergens could be underreported in this group, because workers had no contact with living rats. Therefore, sensitization to rat allergens was initially used as response variable in the exposure-response analyses.

In a first approach to assess exposure-response relationships, the exposure to RUA was grouped according to zone in which the participant was working. The highest prevalence rate of sensitization to rat allergens was found in medium exposed workers (18.9%) compared with low exposed workers (12.9%) and high exposed workers (13.6%, Table 2). For rat allergy a similar pattern was found (Table 2). Table 2 also shows that workers in the

high exposure group had been working for a longer period in laboratory animal facilities and this could have biased exposure-response relationships. Similar relationships between exposure and prevalence rate of sensitization to rat allergens were found when the workers were equally divided into three groups based on number of hours working with rats per week (low 16.1%, medium 19.8%, high 18.1%) or time-multiplied RUA exposure, i.e., number of hours working with rats per week multiplied by the median RUA level of the low, medium, and high zone exposure groups as an estimate of weekly cumulative exposure (low 18.1%, medium 15.3%, high 19.8%). However, if prevalence rates were observed for groups with limited years of exposure, i.e., less than 8, 6, or 4 yr, prevalence rates increased with increasing exposure. Therefore, the exposure-response relations were studied in a group of rat workers with less than 4 yr of exposure. Less than 4 yr of working experience with laboratory animals was chosen as the cutoff point, because most laboratory animal workers had a contract period of 4 yr. Characteristics of this group are also presented in Table 1.

In the restricted population an exposure-response relationship was visible. The prevalence rates of sensitization to rat allergens in the low, medium, and high exposure zone groups were about 4.1, 5.0, and 7.2 times higher, respectively, compared with the prevalence rate found in the internal reference group (Table 3). A steeper exposure-response relationship was found when grouping was based on number of hours working with rats per week (Table 3). The strongest and statistically most significant exposure-response relationship was found for the time-multiplied RUA exposure (Table 3). The prevalence rate ratio increased with the increasing time-multiplied RUA exposure and was 2.2 for low exposure (> 0 until 1 h weekly ng eq/m³), 3.3 for medium (≥ 1 until 6 h weekly ng eq/m³), and 10 for high exposure (≥ 6 h weekly ng eq/m³). The difference in prevalence rate between high and low exposed workers in an internal comparison was also statistically significant.

Relations between possible confounders or modifying factors and sensitization to rat allergens are also presented in Table 3. The atopy-associated risk factors were strongly associated with sensitization to rat allergens, prevalence rate ratio of 13 (95% confidence interval [CI] 3.9 to 45). Furthermore, sensitization was about 2.3 times more prevalent among men than among

TABLE 1
CHARACTERISTICS OF RAT WORKERS AND
WORKERS WHO HAD NEVER WORKED WITH
RATS (INTERNAL REFERENCE GROUP)

	All Rat Workers	< 4 Yr of Exposure	Never Worked with Rats
n	398	118	86
Female, %	37.4 [†]	55.9	54.7
Age, mean $\pm$ SD	35 $\pm$ 10	27 $\pm$ 6 [†]	33 $\pm$ 11
Smoking, * %	29.0 [§]	33.9 [†]	11.6
Atopy associated risk factors, † %	39.6	33.3 [§]	33.7
Allergic symptoms to rat allergens, %	19.6 [†]	23.7 [†]	1.2
Sensitized to rat allergens, %	17.7	17.1 [§]	3.5
Rat allergy, ‡ %	13.4	15.4 [§]	1.2

* When participants had quit smoking they were considered as nonsmokers.

† Allergic symptoms to cat or dog allergens, or a positive SPT response to cat or dog fur, or an elevated total serum IgE (≥ 100 Ku/L).

‡ Allergic symptoms due to working with rats and sensitized to rat allergens.

§ One observation was missing.

|| Two observations were missing.

† p < 0.01 compared with the workers who had never worked with rats.

women and about 2.4 times more prevalent among smokers (ex-smokers were considered as nonsmokers). The associations between sensitization to rat allergens and smoking were statistically significant. There was no association between age and prevalence rate of sensitization to rat allergens.

The time-multiplied RUA exposure as well as the confounders and modifying factors were studied in a multiple regression analysis (Table 4). Atopy-associated risk factors appeared to be a strong effect modifier: the effect of exposure to RUA on the prevalence rate of sensitization to rat allergens differed clearly between the workers with and without the atopy-associated risk factor. After stratification, prevalence rate ratios for the workers with an atopy-associated risk factor were 7.3, 9.5, and 15 for the low, medium, and high time-multiplied RUA exposure groups, respectively. Among workers with no atopy-associated risk factors the exposure-response relationship was much less pronounced, showing only a slight increase of the prevalence rate ratios of sensitization to rat allergens with increasing time-multiplied RUA exposure level. In the group of sensitized rat workers, 90% reported allergic symptoms due to rat allergens. When a more strict definition of allergy to rats was used, i.e., the presence of reported symptoms and sensitization to rat allergens as also used elsewhere (9), the exposure-response relationship within the group of rat workers became even steeper for those with atopy-associated risk factors (Table 4). The effect of gender and smoking on the prevalence rate of sensitization to rat allergens or rat allergy was still visible in the multiple regression analysis. However, both associations were not statistically significant.

TABLE 2
CHARACTERISTICS OF PARTICIPANTS RECENTLY
EXPOSED (PRECEDING 12 MO) TO LABORATORY
RATS, GROUPED BY ZONE

	Zone Working in		
	Low	Medium	High
n	63	313	22
Exposure time, yr, mean $\pm$ SD	10 $\pm$ 9.1*	11 $\pm$ 9.5*	15 $\pm$ 12
Median RUA level, ng eq/m ³	0.15	0.68	4.2
Allergic symptoms to rat allergens, %	14.3	21.1	13.6
Sensitized to rat allergens, %	12.9 [†]	18.9 [†]	13.6
Rat allergy, %	8.1 [†]	14.7 [†]	9.1

* p < 0.1 compared with high exposure group.

† One observation was missing.

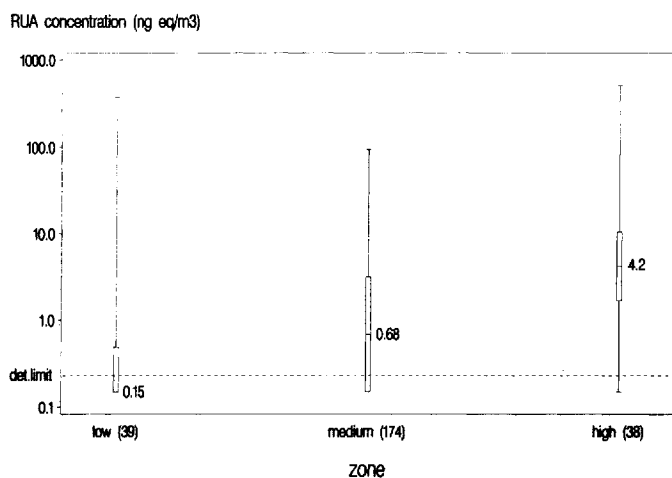


Figure 1. Median (center of box), 25th and 75th percentile (borders of box) and range (whiskers) of RUA concentrations (ng eq/m³), stratified by zone (low = site C_{zone} 1,2, D_{zone} 1, and E_{zone} 1; medium = site A_{zone} 1, B_{all} 7 zones, C_{zones} 3,4, E_{zone} 2, and G_{zone} 1; high = site D_{zone} 2, E_{zone} 3, and F_{zones} 1,2) (n = 251).

TABLE 3
SEPARATE ANALYSIS OF THE ASSOCIATION BETWEEN
VARIOUS VARIABLES MEASURING THE EXPOSURE TO RUA AND HOST
FACTORS, AND SENSITIZATION TO RAT ALLERGENS*

Exposure variable	n	Prevalence Rate (%)	Prevalence Rate Ratio	95% CI
Internal reference group (no exposure)	86	3.5	1	
Zone working in				
Low (0.15 ng eq/m ³) [†]	21	14.3	4.1	0.83–20
Medium (0.68 ng eq/m ³) [†]	92	17.4	5.0	1.5–17
High (4.2 ng eq/m ³) [†]	4	25.0	7.2	0.75–69
Hours working with rats				
0–2.5 h/wk	49 [§]	8.2	2.3	0.52–10
2.5–9 h/wk	30 [§]	13.3	3.8	0.86–17
≥ 9 h/wk	38 [§]	31.6	9.1	2.6–32
Time-multiplied RUA exposure [‡]				
> 0 until 1 h weekly ng eq/m ³ (low)	40 [§]	7.5	2.2	0.43–11
≥ 1 until 6 h weekly ng eq/m ³ (medium)	43 [§]	11.6	3.3	0.80–14
≥ 6 h weekly ng eq/m ³ (high)	34 [§]	35.3	10.1	2.9–36
Host factors				
Atopy-associated risk factors				
None	135	2.2	1	
At least one	68	29.4	13.2	3.9–45
Gender				
Male	91	16.5	1	
Female	112	7.1	0.43	0.18–1.0
Smoking				
Nonsmoker	154	8.4	1	
Smoker	49	20.4	2.4	1.1–5.5

* The group of rat workers who had been working with rats for less than 4 yr and the internal reference group were used in the analyses (n = 203).

[†] Median RUA levels for each group.

[‡] The median RUA levels for the zone groups (low, medium, and high) were multiplied by the number of hours per week spent working with rats.

[§] The exposed workers were equally divided into three groups. The number of workers in each group could differ slightly, because of workers with similar values.

DISCUSSION

Our study clearly shows that a relationship between exposure to rat urinary aeroallergens and prevalence rate of allergy to rats exists. The exposure–response relationship became visible after restriction of the analyses to the group of workers who have been working with laboratory animals for a limited period of years. The exposure–response relationship is most pronounced in workers with allergic symptoms to cat or dog allergens, or positive SPT response to cat or dog fur, or elevated total serum IgE.

In laboratory animal facilities the variability of exposure is considerable (10). In contrast to the study of Nieuwenhuijsen and coworkers (13), the zone in which the participant was working explained a larger percentage of variability in RUA levels than job title. However, in the study of Nieuwenhuijsen and coworkers (13) exposure measurements were performed in two sites, whereas we preformed our measurements in seven sites. The large variability in exposure between zones or sites may be due to differences in level of contamination of bedding in cages, varying numbers of animals of different sex and age used, way in which tasks are performed, and type and varying levels of ventilation at the sites (10). An exposure–response relationship could be demonstrated when the workers were grouped on the basis of RUA measurements, i.e., zone working in. Besides grouping based on RUA measurements, hours working with rats per week, which has been determined by questionnaire, was also associated with sensitization to rat allergens. However, this relatively crude estimate of exposure did not differentiate completely between high and low exposed workers. The combination of the actual RUA levels grouped by zone and hours working with rats per week, i.e., time-multiplied RUA exposure, resulted in the most pronounced ex-

posure–response relationship compared with the relationships found by the other grouping schemes.

A relationship between the prevalence rate of respiratory allergic symptoms to rats and exposure to rat urinary aeroallergens has also been found in two other studies (6, 7). In both studies the exposure assessment was also performed by measuring rat allergen concentrations. Kibby and colleagues (6) also found that time-multiplied exposure gave the best relationship with LAA symptoms. In contrast to our study, the number of air dust samples was limited. In the study of Cullinan and colleagues (7) a large number of full-shift personal air measurements were taken. However, they found an exposure–response relationship for allergic skin symptoms, but not for chest, eye, nasal symptoms, or sensitization.

The existence of exposure–response relationships between level of exposure and sensitization to aeroallergens has also been suggested in a limited number of studies on other aeroallergens. In occupational studies more workers were sensitized to α -amylase (14) or *Bacillus subtilis* enzymes (15) in groups with high exposure. In these populations the exposure–response relationships were also more pronounced in atopic workers.

A relationship between the prevalence rate of sensitization to rat allergens and exposure to rat urinary aeroallergens can be biased by selection, inaccurate information about the presence of an allergy to rats, and confounding. In our population, strong indicators were found that duration of exposure had an effect on the prevalence rate of sensitization and symptoms to rat allergens. Sensitization and symptoms to rat allergens were less prevalent among workers with the highest exposure. In addition these workers were exposed to rat allergens during a longer period (Table 2). Two possible explanations for this observation are a

TABLE 4
MULTIPLE REGRESSION ANALYSES OF RELATIONSHIP BETWEEN
PREVALENCE RATE RATIOS OF SENSITIZATION TO RAT ALLERGENS OR
RAT ALLERGY, AND TIME-MULTIPLIED RUA EXPOSURE*

			Sensitization to Rat Allergens		Rat Allergy	
			Prevalence Rate Ratio	95% CI	Prevalence Rate Ratio	95% CI
Time-multiplied Exposure	Atopy-associated Risk Factors					
Never worked with rats	No distinction	86	1.0		1.0	
Low	None	29	—†	—	—†	—
Medium	None	31	0.84	0.086–8.2	2.5	0.16–41
High	None	18	1.3	0.14–13	3.9	0.24–64
Low	At least one	11	7.3	1.5–37	7.5	0.46–120
Medium	At least one	12	9.5	2.1–43	29	3.2–260
High	At least one	16	15	4.0–56	42	5.2–330
Gender, female versus male			0.58	0.24–1.4	0.42	0.15–1.2
Smoking			1.6	0.69–3.9	1.8	0.71–4.6

* The analyses were controlled for atopy-associated risk factors, smoking, and gender (n = 203).

† No prevalence rate ratio could be calculated because there were no sensitized workers in this group.

healthy worker effect or so-called tolerance induction. Workers with LAA can be selected out of the workforce or be transferred to jobs with less exposure, i.e., healthy worker effect. High exposed workers can probably less easily modify their work to avoid animal contact if they develop symptoms, and might leave the site at a different rate than the lower exposed workers. The presence of a healthy worker effect was also assumed to occur in one other cross-sectional study on LAA (5). At the same time, longer duration and increased levels of exposure to an allergen by inhalation may induce tolerance to the allergen. However, to our knowledge there is no evidence in the literature of tolerance induction by inhalation. Conclusive answers about the presence of a healthy worker effect or tolerance induction can only be given after analysis of follow-up data.

In our study, we accounted for the effect of duration of exposure by restricting the population to workers with less than 4 yr of working experience with laboratory animals. Four years was chosen because most laboratory animal workers were Ph.D. students with a contract period of 4 yr. However, this cutoff point is arbitrary, but analyses with a restricted population using 3 or 5 yr as cutoff point gave similar results as shown in Tables 3 and 4. One other study on LAA (7) also restricted the population to newly exposed workers, and also used 4 yr of exposure as cutoff point.

Inaccurate information about the presence of allergy to rats could also bias the exposure–response relationship. The studies of Kibby and colleagues (6) and Cullinan and colleagues (7) as well as all other cross-sectional studies on LAA used the presence of allergic symptoms as criterion for LAA. As published elsewhere (9), allergic symptoms after contact of nonsensitized workers with rats may be the result of a nonspecific hyperresponsiveness to animal-derived or other agents, such as dust, disinfectants, or ammonia, which are present simultaneously. We therefore decided to use sensitization to rat allergens as endpoint. Of the sensitized rat workers only two workers were without symptoms and therefore a similar exposure–response relationship was found when rat allergy, i.e., the presence of reported symptoms and sensitization to rat allergens, was used as measure of response. In fact, using rat allergy as measure of response resulted in a steeper exposure–response relationship.

The relationship between the prevalence rate of sensitization to rat allergens and exposure to rat urinary aeroallergens can be modified by host factors. Host factors related to atopy are associated with LAA (1, 2, 4, 5, 7, 16–18). In a previous analysis

of this population we identified that of these factors self-reported allergy or sensitization to cats or dogs, and elevated total serum IgE were important determinants of rat allergy (9). In the present study we noticed that the effect of exposure on the prevalence rate of sensitization to rat allergens clearly varied between workers with and without an atopy-associated risk factor. The exposure–response relationship was much steeper among workers with an atopy-associated risk factor. The atopy-associated risk factor should therefore be considered as an effect modifier of exposure.

In previous studies on occupational allergy, the effect of gender received relatively little attention. Only two studies have previously studied the effect of gender on the prevalence rate of LAA (4, 8). In contrast to our study, in which sensitization to rat allergens was more prevalent in men, no differences in prevalence rates had been found between men and women. However, general population studies have found sensitization to common allergens to be more prevalent in men (19–23). In our study the atopy-associated risk factors were also more prevalent in male than female rat workers, 38.5 to 30.8%, respectively. This higher prevalence rate of atopy-associated risk factors as well as the higher time-multiplied RUA exposure levels for men, 9.0 h weekly ng eq/m³ versus 4.6 h weekly ng eq/m³ for women, could account for the higher prevalence rate of sensitization to rat allergens in men. However, after correcting for level of exposure, the atopy-associated risk factors, and smoking, sensitization to rat allergens was still about twice as prevalent in men (Table 4). This difference was not statistically significant because of the small sample size, but it suggests that gender is an independent risk factor of LAA.

In our study sensitization to rat allergens was about 1.6 times more prevalent among smokers. However, this finding was not statistically significant. There is conflicting evidence regarding the role of smoking in sensitization to occupational allergens. Some studies (7, 8, 24–27) have found sensitization to occupational allergens to be more common in smokers, whereas several other studies (2, 4, 28, 29) failed to demonstrate this relationship or even found a negative association (30). An additional explanatory factor might be the cross-sectional design of most studies. It is possible that smoking habits were influenced by the development of symptoms or that subjects allergic to common allergens would less easily pick up the habit of smoking. Whatever the role of gender and smoking is in the relation between rat allergen exposure and subsequent sensitization, gender and smok-

ing remain relatively weak effect modifiers compared with exposure to rat urinary aeroallergens and atopy-associated host factors.

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