

Cat and dog allergy and total IgE as risk factors of laboratory animal allergy

Albert Hollander, MSc, Gert Doekes, PhD, and
Dick Heederik, PhD Wageningen, The Netherlands

Background: Laboratory animal workers are at high risk of developing occupational allergy. In many cases the severity of allergy symptoms makes further work with laboratory animals impossible.

Objective: This study was designed to estimate prevalence rates of sensitization and symptoms of allergy in a population of laboratory animal workers and to determine the association between various host factors and these prevalence rates.

Methods: A cross-sectional survey was undertaken in 540 workers at eight facilities in the Netherlands. All participants completed a questionnaire and underwent skin prick testing with common and occupational allergens. In addition, total and specific IgE measurements were obtained.

Results: Prevalence rates of allergy symptoms caused by working with rats and mice were 19% and 10%, respectively. Symptoms, especially chest tightness, were strongly related to sensitization. Rat and mouse allergy, defined as symptoms of allergy accompanied by specific atopic sensitization, were highly associated with elevated total IgE, reported adverse reactions, and positive skin prick test responses to common allergens. This relationship could be explained by a response to cat or dog allergens.

Conclusions: Allergy to cats or dogs seemed to be an important risk factor for laboratory animal allergy, whereas allergy to pollen or house dust mite, in the absence of cat and dog allergy, appeared to be insignificant. More conclusive evidence about cat and dog allergy preceding laboratory animal allergy can only be provided after analysis of follow-up data. (*J Allergy Clin Immunol* 1996;98:545-54.)

Key words: Laboratory animal allergy, cross-sectional, atopy, gender, smoking

Laboratory animal workers are at 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%.¹⁻¹⁵ The most commonly reported symptoms are rhinitis and conjunctivitis. Asthmatic symptoms, with prevalence rates ranging from 4% to 12%, are mostly accompanied by other respiratory

Abbreviations used

CI:	Confidence interval
LAA:	Laboratory animal allergy
MUAs:	Mouse urinary allergens
OR:	Odds ratio
PRR:	Prevalence rate ratio
RUAs:	Rat urinary allergens
SPT:	Skin prick test

From the Department of Epidemiology and Public Health, Agricultural University Wageningen, The Netherlands.

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Reprint requests: Dick Heederik, Department of Epidemiology and Public Health, Agricultural University Wageningen, P.O. Box 238, 6700 AE Wageningen, The Netherlands.

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symptoms and are considered end-stage LAA.^{5, 10, 13, 15} In many cases these symptoms are severe and make direct or even indirect contact with laboratory animals impossible.^{2, 7}

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. This article covers three study objectives of the baseline part of this study. First, the prevalence rates of the various

different symptoms of allergy attributable to rats and mice were assessed and compared with prevalence rates found in studies in other countries. The majority of studies on LAA did not distinguish between species of animals causing the symptoms, despite possible differences in exposure and potency of allergens of different species. Therefore the prevalence rates of symptoms of allergy to rats and mice, the species most often used, have been analyzed separately in this study.

Second, we studied the associations of reported allergic respiratory symptoms with allergen-specific atopic sensitization, measured by skin prick or specific IgE test. High correlations between symptoms and sensitization have been reported previously, suggesting that LAA is a "classical" example of symptomatic type I allergy. However, not all symptoms seemed to be IgE-mediated¹⁶ because some workers reported symptoms without detectable specific IgE or a positive skin prick test (SPT) response, which can be of importance in epidemiologic studies on LAA.

Finally, the association with host factors such as gender, smoking, and atopy was quantified. Little is known about gender and smoking as risk factors for LAA. Some studies^{15, 17} have demonstrated sensitization to laboratory animals to be more common in smokers. Other studies^{3, 5, 8} have demonstrated no association between smoking and LAA. The effect of gender on the presence of LAA has only been studied once,⁷ and no association could be found. Unlike gender and smoking, atopy has been found to be a strong determinant of LAA. However, in these studies different definitions of atopy were used. The strength of the association between atopy and LAA seemed dependent on the definition used.^{12, 14, 18, 20, 21} We have therefore distinguished various definitions of atopy on the basis of total serum IgE level, a self-reported history of symptoms of allergy to common allergens, or a positive SPT response to common allergens and quantified the associations of these various definitions of atopy with the prevalence rate of LAA.

METHODS

Study population

Employees from laboratory animal facilities of four universities, two research institutes, and a pharmaceutical company and students of a laboratory school participated in the study. All subjects working with small laboratory animals or having contact with material from these animals were invited to participate. Of approximately 750 eligible subjects, 579 (77%) participated. Questionnaires were completed by 577 subjects (99.6%),

577 subjects (99.6%) provided blood samples, and 542 subjects (94%) were skin prick tested. A completed questionnaire and SPT results were available for 540 participants, and this group was used for the analyses presented in this article. The baseline survey was carried out between June 1992 and December 1993.

Questionnaire

A self-administered questionnaire was distributed before the health survey. It was based on a Dutch version of an internationally accepted respiratory questionnaire,²² which has been used previously in other studies on occupational asthma in the Netherlands.^{23, 24} In addition, questions were asked about personal history of symptoms of allergy to common allergens, history of symptoms of allergy to laboratory animals, and hyperresponsiveness. In this study the responses to the following questions were used.

Personal history of symptoms of allergy to common allergens. "Are you (or have you been) allergic to one or more agents?" If response was positive, questions were asked on type of symptoms (chest tightness [asthma], runny nose or sneezing, runny or itchy eyes, and itchy or red skin) and putative agents causing the symptoms (house dust, pollen, and/or domestic animals).

History of symptoms of allergy to rats or mice. "Do you have symptoms of allergy during working hours, after contact with certain agents at work?" If response was positive, questions were asked on type of symptoms (chest tightness [asthma], runny nose or sneezing, runny or itchy eyes, and itchy or red skin) and animal species causing the symptoms.

Reported hyperresponsiveness. "Did you ever have problems with breathing in one of the following situations: when going from warm to cold surroundings, from cold to warm surroundings, during foggy weather or during cold weather?"

Other questions included in the questionnaire regarded smoking history and intensity of contact with laboratory and domestic animals.

Skin prick testing

Five common allergens (mixture of two house dust mites *Dermatophagoides pteronyssinus* and *D. farinae*; mixture of timothy, rye, foxtail, orchard, and meadow grass pollen; mixture of birch, hazel, and alder pollen; cat fur; dog fur [all from ALK Benelux, Houten, The Netherlands]), four occupational allergens (rat urine, rat fur, mouse urine, mouse fur, [all from ALK Benelux]), and positive (histamine, 10 mg/ml in duplicate) and negative controls (phosphate-buffered saline) were used for the SPT. The concentrations of the common and occupational allergens were 10,000 BU/ml and 5 mg/ml, respectively.

For this study, rat and mouse urine allergen preparations were produced by ALK Benelux. Urine from Wistar rats and BALB/c mice was collected by use of metabolic cages. Male and female (3:1) pubertal and

adult animals (1:1) were used to control for sex and puberty effects on protein content and composition of urine.²⁵ Proteins in the pooled rat urine and pooled mouse urine were isolated through extensive dialysis against phosphate-buffered saline and distilled water and concentrated by lyophilization. The two freeze-dried urinary allergen preparations (rat 15.79, mouse 15.78) were also used in the immunoblotting experiments and in studies on aeroallergen exposure.

SPTs were performed by using uncoated Phazet needles with 1 mm tips (ALK Benelux). The Phazet needle was pressed at 90 degrees to the skin surface through a drop of the test solution.²⁶ All SPTs were performed by two skilled technicians. The tests were performed on the volar aspect of the forearm and read after 15 minutes. Wheals were traced and transferred to a registration sheet by transparent tape. The mean of the longest and midpoint orthogonal diameters was determined by using a drawing board connected to a computer. A wheal diameter of 3 mm or more for the common allergens, after subtraction of any response to the negative control, was regarded as a positive response. Similar testing with the five common allergens and rat fur allergens was performed in a control group of 169 bakery workers.²⁴ In this control group all SPT responses to rat fur were smaller than 4 mm. Therefore a wheal diameter of 4 mm or more for the occupational allergens was regarded as a positive response, after subtraction of any response to the negative control.

The mean wheal diameter of the positive controls was 6.6 mm (standard deviation, 1.5). The coefficient of variation, based on the diameters of both positive controls, was 10.6%.

IgE antibodies

Sera were stored at -20°C until IgE analysis was performed. Blood samples of two workers were missing ($n = 538$). Specific IgE antibodies to rat urinary allergens (RUAs) and mouse urinary allergens (MUAs) were measured by immunoassay (AlaSTAT; DPC, Apeldoorn, The Netherlands).²⁷ Sera of class 2 or higher (≥ 0.7 kU/L) were considered positive. Total IgE antibodies were measured with a sandwich enzyme immunoassay.²⁸ Briefly, mouse monoclonal anti-IgE was coated in microwells. Sera were added in four dilutions and incubated for 2 hours at 37°C . Bound IgE was measured after incubation with peroxidase-labeled mouse monoclonal anti-IgE for 1 hour at 37°C , followed by a 30-minute incubation with o-phenylenediamine at 20°C in the dark. The reaction was terminated by the addition of HCl, and the optical density was read at 492 nm. Each microtiter plate included a serially diluted reference sample (10-9123-01; Kabi-Pharmacia, Uppsala, Sweden). Elevated total serum IgE was defined as a level above 100 kU/L.

Host factors related to atopy

Atopy was defined in various ways on the basis of the following parameters: (1) history of symptoms of allergy

to common allergens reported in the questionnaire, (2) SPT response to the five common allergens (grass pollen, tree pollen, house dust mite, cat, and dog), and (3) total serum IgE.

Statistical analysis

All statistical analyses were performed with SAS software (version 6.09; SAS Institute, Cary, N.C.). Crude prevalence rates were compared by using the chi square test (or Fisher's exact test). For testing differences between means, Student's *t* test was used. The effect of host factors on the prevalence rate of LAA was analyzed by multiple regression techniques. Prevalence rate ratios (PRRs) were calculated by means of a proportional hazards model (Cox's regression with SAS procedure "PHREG").^{29, 30} Statistical significance was defined as a *p* value of less than 0.05 (two-tailed).

RESULTS

Prevalence rate of symptoms of allergy

Allergy symptoms (chest tightness [asthma], eye, nose, or skin symptoms) attributed to working with laboratory animals were highly prevalent among the laboratory animal workers. Most symptoms of allergy were reported by individuals working with rats. Among the 458 workers who had ever worked with rats, 86 (18.8%) reported at least one rat-related allergic symptom. Among individuals who had ever worked with mice ($n = 377$), at least one mouse-related allergic symptom was reported by 10.1% of the workers. Nose or eye symptoms were reported most frequently (Fig. 1: rats, 16.8%; mice, 9.0%), followed by skin symptoms (rats, 10.7%; mice, 4.2%) and chest tightness (asthma) (rats, 6.1%; mice, 3.2%). Of all persons with symptoms of allergy caused by working with rats, 52 (60.5%) had more than one symptom. For persons working with mice, this figure was 44.7%. As shown in Fig. 1, chest tightness (asthma) was rarely present in the absence of nose or eye symptoms.

Three hundred forty-two individuals worked with both mice and rats. Of these workers, 26 (7.6%) reported symptoms caused by working with rats, 10 (2.9%) reported symptoms caused by working with mice, and 23 (6.7%) reported symptoms of allergy in response to both species.

Symptoms versus sensitization

The prevalence rates of symptoms of allergy and specific sensitization were nearly identical. Eighty-two subjects working with rats (17.9%) and 37 subjects working with mice (9.8%) had a positive SPT response to urinary or fur allergens, respectively. When sensitization was measured by specific serum IgE to RUAs or MUAs, the prevalence

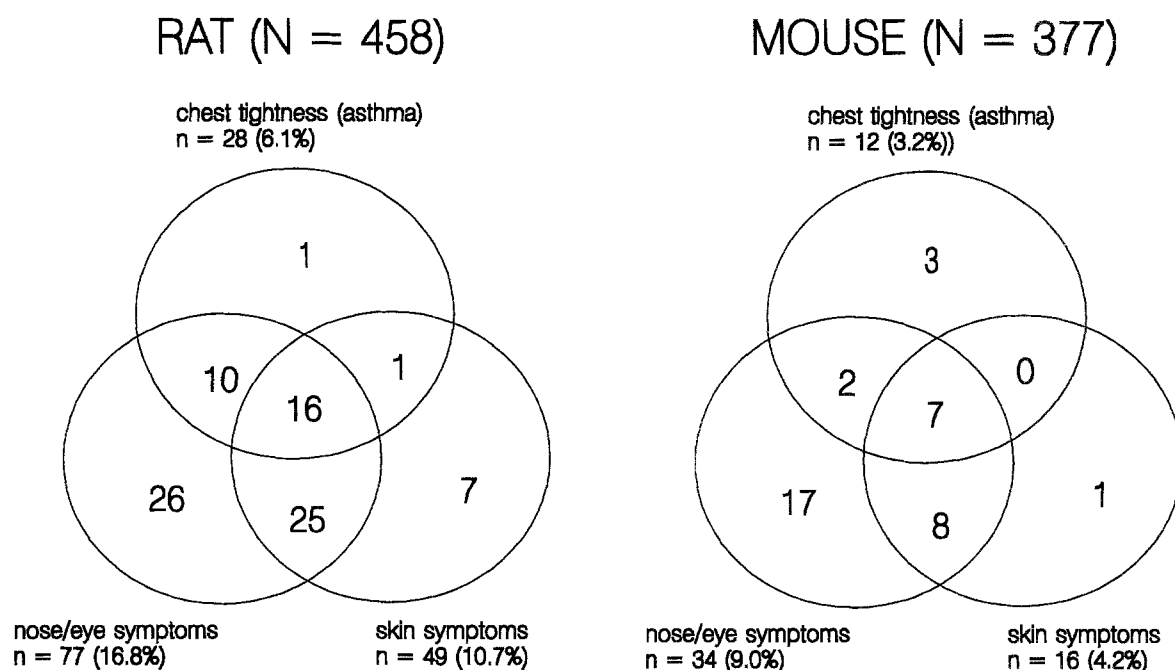


FIG. 1. Prevalence rates of reported allergy symptoms caused by working with rats and mice.

rates were lower, 11.0% and 6.1%, respectively. Almost all workers with specific serum IgE to RUAs or MUAs had a positive SPT response. When a positive SPT response and/or the presence of specific serum IgE were used as measures of sensitization to RUAs or MUAs, the prevalence rates increased only slightly to 18.2% and 10.7%, respectively. Symptoms and sensitization were highly correlated. Of all workers with symptoms of allergy caused by working with rats, 59 (69%) were sensitized to rat allergens (SPT and/or serum IgE positive). The correlation between symptoms and sensitization was more evident when chest tightness (asthma) was present (Table I). Sensitization was rare among workers without symptoms of allergy caused by working with rats, 6.5%. Symptoms caused by working with mice and sensitization to mouse allergens were also significantly correlated (Table I). However, this correlation was less pronounced.

Selection out of the work force is often assumed to occur in populations at risk of LAA.¹⁰ Persons with symptoms had worked for shorter periods in laboratory animal facilities than workers without symptoms (Table I), suggesting the presence of the so-called "healthy worker effect" in these groups.

The population was divided into four groups on the basis of the presence or absence of symptoms of allergy caused by working with rats or mice and sensitization to the respective animal, defined as

positive SPT responses to urinary or fur allergens and/or serum IgE positive to urinary allergens (Table II). Among those who worked with rats, subjects in the symptomatic/sensitized group reported hyperresponsiveness significantly more often and had significantly more positive SPT responses to common allergens than subjects in the nonsymptomatic/nonsensitized group. The symptomatic/sensitized group also included significantly more men.

The nonsymptomatic/sensitized group was comparable with the symptomatic/sensitized group but included fewer individuals who reported hyperresponsiveness (30.5% vs 12.5%). The mean wheal diameter of the SPT response to RUAs in the nonsymptomatic group was significantly smaller than that in the symptomatic group, 7.6 mm (95% confidence interval [CI], 5.9-9.3) versus 10.4 mm (95% CI, 9.4-11.4), respectively.

Despite the high correlation between reported symptoms and sensitization, not all symptoms seemed to be IgE-mediated. Of all subjects who worked with rats, 5.9% reported symptoms in the absence of a positive SPT response to RUAs. This symptomatic/nonsensitized group was largely similar to the nonsymptomatic/nonsensitized group but differed in having significantly higher prevalence rates of self-reported hyperresponsiveness (37.0% vs 11.6%) and positive SPT responses to house dust mite allergens (40.7% vs 18.8%).

TABLE I. Sensitization rates and characteristics of laboratory animal workers with and without allergy symptoms caused by rats or mice

	Rat			Mouse		
	No symptoms	Chest tightness (asthma)	Other symptoms	No symptoms	Chest tightness (asthma)	Other symptoms
<i>n</i>	372	28	58	339	12	26
Female (%)	39.0	35.7	25.9	38.9	41.7	30.8
Smoking (%)	29.1*	25.0	27.6	30.2*	16.7	19.2
Years working with animals†	11.4 (9.9)	8.4 (7.4)	8.3 (7.3)‡	10.3 (9.9)	9.3 (8.7)	10.3 (7.6)
Reported hyperresponsiveness§ (%)	11.9*	42.9	27.6	12.8*	50.0	19.2
Positive SPT response to urinary or fur allergens (%)	6.5	82.1	60.3 ¶	6.8	58.3	26.9
Positive IgE to urinary allergens (%)	2.4*	67.9	37.9 #	3.9*	33.3	23.1
Sensitization (SPT and/or IgE positive) (%)	6.5*	82.1	62.1	7.4*	58.3	30.8

*Denominators were 371 and 338 for smoking and 370 and 337 for hyperresponsiveness symptoms and specific IgE.

†Mean (standard deviation).

‡*p* < 0.05 compared with group with no symptoms.

§Respiratory symptoms when going from warm to cold or cold to warm surroundings or during foggy or cold weather.

||*p* < 0.01 compared with group with no symptoms.

¶*p* < 0.05 compared with group with chest tightness (asthma).

#*p* 0.01 compared with group with chest tightness (asthma).

TABLE II. Characteristics of workers grouped by presence of allergy symptoms caused by rat or mouse and atopic sensitization to the respective animal

Allergy symptoms* Sensitization*	Rat				Mouse			
	-	-	+	+	-	-	+	+
	-	+	-	+	-	+	-	+
<i>n</i>	346	24	27	59	312	25	23	15
Female (%)	39.6	25.0	37.0	25.4†	39.4	28.0	34.8	33.3
Smoking (%)	29.9‡	16.7	26.0	27.1	30.6‡	24.0	21.7	13.3
Reported hyperresponsiveness (%)	11.6‡	12.5	37.0§	30.5§	11.3‡	28.0†	39.1§	13.3
Positive SPT response (%) to								
Grass pollen	13.9	25.0	22.2	40.7§	16.7	28.0	17.4	33.3
Tree pollen	9.5	41.7§	14.8	22.0§	11.2	24.0	17.4	26.7
House dust mite	18.8	37.5†	40.7§	40.7§	20.5	36.0	56.5§	46.7†
Cat fur	10.7	41.7§	14.8	44.1§	12.2	36.0§	17.4	33.3†
Dog fur	8.7	54.2§	7.4	52.5§	10.3	52.0§	21.7	73.3§

*Allergy symptoms when working with rats or mice; SPT positive to fur or urinary allergens, or IgE positive to urinary allergens.

†*p* < 0.05 compared to nonsymptomatic/nonsensitized group.

‡Denominators were 345 and 311 for smoking and 344 and 310 for hyperresponsiveness symptoms.

§*p* < 0.01 compared with nonsymptomatic/nonsensitized group.

||*p* < 0.01 compared with symptomatic/sensitized group.

Similar analyses were performed for subjects who worked with mice, but less pronounced results were found (Table II).

Host factors

In all further analyses, "rat allergy" and "mouse allergy" were defined as the presence of symptoms caused by working with rats or mice and atopic

sensitization to the respective animal (symptomatic/sensitized group). The analyses were performed by comparing workers who were allergic according to this definition with all other subjects working with the same animal species.

The relationships between host factors and rat and mouse allergy are presented in Table III. Rat and mouse allergy were more prevalent among

TABLE III. Separate analyses of association between gender, smoking, and host factors related to atopy and prevalence rates of rat and mouse allergy

	Rat				Mouse			
	<i>n</i>	Prevalence rate (%)	PRR	95% CI	<i>n</i>	Prevalence rate (%)	PRR	95% CI
Gender								
Male	288	15.3	1		232	4.3	1	
Female	168	8.9	0.58	0.33-1.1	143	3.5	0.81	0.28-2.4
Smoking*								
Nonsmoker	210	13.3	1		164	4.9	1	
Former	115	13.0	0.98	0.52-1.8	102	4.9	1.0	0.33-3.1
Current	130	12.3	0.92	0.50-1.7	108	1.9	0.38	0.08-1.8
History of allergy symptoms								
No symptoms	326	8.0	1		275	2.2	1	
Symptoms to common allergens	130	25.4	3.2	1.9-5.3	100	9.0	4.1	1.5-12
Symptoms to house dust/pollen but not to pets	70	15.7	2.0	0.97-4.0	56	5.4	2.5	0.61-9.8
Symptoms to pets	60	36.7	4.6	2.6-8.1	44	13.6	6.3	2.0-19
Positive SPT response to								
None of the five common allergens	257	5.4	1		214	0.9	1	
At least one allergen	199	22.6	4.2	2.3-7.6	161	8.1	8.6	2.0-38
Grass, tree, or mite; negative to cat and dog	84	6.0	1.1	0.40-3.0	71	1.4	1.5	0.14-17
Cat and/or dog fur	115	34.8	6.4	3.5-12	90	13.3	14.3	3.2-64
Total IgE (kU/L)								
<100	363	7.7	1		305	2.6	1	
≥100	93	33.3	4.3	2.6-7.2	70	10.0	3.8	1.4-11

Rat and mouse allergy are defined as symptoms caused by working with rats or mice *and* sensitization to the respective animal.

*Smoking habit of one worker was not known.

men than among women, but the difference was not statistically significant. No association was found with smoking (nonsmoker, former, or current).

All host factors related to atopy were significantly associated with rat and mouse allergy (Table III). For elevated total serum IgE (≥ 100 kU/L) the PRRs of rat and mouse allergy were 4.3 and 3.8, respectively. The prevalence rates of rat and mouse allergy were, respectively, 4.2 and 8.6 times higher when a positive SPT response to at least one of the five common allergens was present. However, the association became stronger when only the SPT responses to cat and dog fur were taken into account (rat allergy PRR, 6.4; mouse allergy PRR, 14.3). Among workers with positive SPT responses to grass pollen, tree pollen, or house dust mite allergens but negative responses to cat and dog fur, the prevalence rates of rat and mouse allergy were not increased compared with workers with no response to any common allergen (PRRs of 1.1 and 1.5, respectively). Similar results were found for personal history of symptoms of allergy

to common allergens as reported in the questionnaire.

Cat and dog allergy and elevated total IgE seemed to be important risk factors of rat and mouse allergy. However, in a cross-sectional analysis it is not possible to verify whether a positive SPT response to cat or dog fur or elevated total serum IgE precede LAA. Therefore the SPT response to common allergens and the presence of elevated total IgE have been compared with those of the control group (Table IV). SPT responses to all common allergens and the presence of elevated total IgE were similar for control subjects and rat-exposed workers.

Three risk factors for rat and mouse allergy (history of symptoms of allergy to pets, positive SPT response to cat or dog fur, and elevated total IgE) were analyzed simultaneously (Table V). When none of the three risk factors was present, the prevalence rates of rat and mouse allergy were very low, 1.8% and 0.43%, respectively. Therefore the PRRs of rat and mouse allergy became, respectively, 16.0 and 22.2 for workers with at least one

risk factor present, controlled for gender and smoking. These PRRs were roughly similar, despite the different prevalence rates of rat and mouse allergy. The PRRs of rat and mouse allergy increased with increasing number of risk factors present, from 11.2 and 13.9, respectively, when one risk factor was present to 24.8 and 39.9, respectively, when at least two risk factors were present.

DISCUSSION

This study is one of the largest on LAA in which symptoms and sensitization to rats and mice, measured by SPTs and specific IgE, have been studied. The overall prevalence rate of symptoms of allergy to rats in our study was 19%, which is roughly similar to prevalence rates found in other studies on rat allergy in the United States (12%⁷), United Kingdom (18%¹⁰ and 31%¹⁵), and Japan (25%¹³). The prevalence rate of mouse-related symptoms was 10% and tended to be lower than described in most other studies (United Kingdom, 11%¹⁰; Japan, 26%¹³; Australia, 32%⁴). A comparison with other studies should, however, be made with care because of differences in definitions of allergy to rats and mice and differences in population characteristics and work environment. The 540 workers in our study are a representative selection of approximately 10%³¹ of the Dutch laboratory animal worker population. In our study the response rate was 77%. Two important reasons for not participating were a lack of interest in the study and fear of disclosure of animal-related symptoms to the employer. Therefore the presented prevalence rates could have been slightly higher or lower. Selection out of the work force (healthy worker effect), as suggested in Table I, could also have an effect on the presented prevalence rates. When the population was restricted to workers with less than 4 years of exposure to laboratory animals, the prevalence rate for symptoms of allergy caused by working with rats or mice would only be slightly different, 23.7% and 8.3%, respectively. Four years of exposure to laboratory animals was chosen because most laboratory animal workers were doctoral candidates with a contract period of 4 years. In this period, selection will be minimal but will still have occurred.^{15, 32}

In exposure-response studies on occupational allergy it is important to make sure that reported symptoms of allergy are indeed provoked by the aeroallergen under study. We therefore assumed that rat allergy and mouse allergy were most likely present if subjects reported symptoms of allergy caused by working with rats or mice and were also

TABLE IV. SPT responses to common and rat fur allergens of subjects working with rats compared with the control group of bakery workers²⁴

	Workers exposed to rats	Bakery workers
<i>n</i>	458	169
Female (%)	37.1*	11.8
Current smoker (%)	28.7*†	55.0
Former smoker (%)	25.2†‡	19.5
Positive SPT response (%) to		
One or more common allergens	43.4	38.5
Grasses	18.3	20.7
Trees	13.1	8.9
House dust mite	23.8	24.3
Cat	16.8	16.6
Dog	16.6	16.6
Rat fur	14.5*	0.0
Total IgE ≥ 100 kU/L (%)	20.4†	21.3

**p* < 0.01 compared with the bakery workers.

†Denominators were 457 for smoking and 456 for total IgE.

‡*p* < 0.05 compared with the bakery workers.

sensitized to the corresponding animal (symptomatic/sensitized group, Table II). Workers with symptoms of allergy (chest tightness [asthma], runny nose or sneezing, runny or itchy eyes, and itchy or red skin) during work after contact with rats or mice, but without being sensitized to rat or mouse allergens (symptomatic/nonsensitized group, Table II), had an elevated prevalence rate of positive SPT responses to house dust mites and self-reported hyperresponsiveness compared with workers in the nonsymptomatic/nonsensitized group. In a study among pig farmers, the self-reported hyperresponsiveness was compared with bronchial responsiveness to histamine (Unpublished data. Preller et al.). A mild bronchial responsiveness (i.e., a decrease in FEV₁ of at least 10% at a histamine concentration ≤ 16 mg/ml) was correlated the presence of self-reported hyperresponsiveness (odds ratio [OR] = 2.3, chi square = 4.0, *p* = 0.046). Thus the symptoms after contact with rats or mice of workers in the symptomatic/nonsensitized group seemed to be non-IgE-mediated but may be the result of a nonspecific hyperresponsiveness to animal-derived or other agents such as dust, disinfectants, or ammonia, which are present simultaneously. It is also possible that our cutoff level of 4 mm is too stringent. The occupational allergens used for the SPTs were not standardized and seemed more potent than the stan-

TABLE V. Multiple regression of associations between personal history of allergy symptoms to pets, positive SPT response to cat or dog fur, and elevated total IgE (≥ 100 kU/L) and prevalence rate of rat and mouse allergy

Allergy symptoms to pets SPT response to cat and/or dog total IgE level (≥ 100 kU/L)	Rat				Mouse			
	<i>n</i> *	Prevalence rate (%)	PRR	95% CI	<i>n</i>	Prevalence rate (%)	PRR	95% CI
None present	273	1.8	1.0		233	0.43	1.0	
At least one present	182	29.7	16.0	6.4-40	141	9.9	22.2	2.9-169
One present	119	21.0	11.2	4.3-29	95	6.3	13.9	1.7-116
At least two present	63	46.0	24.8	9.6-64	46	17.4	39.9	5.0-320

Rat and mouse allergy are defined as reported symptoms caused by working with rats or mice *and* sensitization to the respective animal. The associations were controlled for gender and smoking.

*Smoking habit of one worker was not known.

dardized common allergens, for which 3 mm was used. However, when 3 mm was used as a cutoff level for the rat and mouse allergens, only one additional worker with symptoms would be sensitized, but 12 rat and nine mouse workers without symptoms would be sensitized. Using 3 mm instead of 4 mm will probably lead to more false-positive SPT responses, and 4 mm is therefore the cutoff level to be used in this study.

We also found a substantial number of sensitized workers without symptoms of allergy (non-symptomatic/sensitized group, Table II). This group should not simply be dismissed as having false-positive results. A recent prospective study¹⁹ showed that among laboratory animal workers without symptoms of LAA, those with sensitization were much more likely to become symptomatic than those with a negative SPT for rat sensitization (relative risk of 7.6 after 2 years of follow-up). Therefore these workers may be an important group that should be included in a follow-up study.

Of the host factors that were studied, smoking was not associated with allergy to rats and mice. Some studies^{15, 17, 33-35} have demonstrated sensitization to occupational allergens to be more common in smokers. Several other studies^{3, 5, 8, 36} have, however, failed to demonstrate a relationship between allergy and smoking. The discrepancy of these results may be partly caused by the cross-sectional design of the studies. It is possible that smoking habits were influenced by the development of symptoms. Therefore the possible association of smoking with LAA requires further study, and smoking habits at the time of first exposure should be known.

LAA was more prevalent in men, but this finding was not statistically significant. Only in one other study on LAA⁷ was the effect of gender on the

presence of allergy analyzed. No significant differences in prevalence rates of LAA between men and women were found. In our study men performed tasks with high levels of aeroallergen exposure more often. The differences in exposure between men and women could account for the higher prevalence rates for men and should be studied in more detail.

The host factors related to atopy were all associated with allergy to rats and mice, which is consistent with findings in other studies.* Interestingly, we found that allergy to cats and dogs was highly associated with rat and mouse allergy. This was also found in two other studies on LAA. In a study among 56 laboratory animal workers¹⁴ a positive SPT response to common allergens was associated with LAA (OR = 9.3; 95% CI, 2.4-37), but when the responses to dog and horse were excluded, the association was much weaker (OR = 3.3; 95% CI, 0.7-16). In another study²¹ five of 10 workers with LAA had positive SPT responses to dog and/or horse, and all workers who were free of symptoms had negative SPT responses to these animals. In our study the prevalence rates of rat and mouse allergy in workers without SPT responses to cat and dog fur but a positive response to at least one of the other common allergens (grass pollen, tree pollen, and house dust mite) were comparable with those among workers with no SPT response to any common allergens. Therefore atopic sensitization to allergens other than those of pets as a risk factor for LAA will be of no additional value and will even have a negative effect because of its high prevalence rate (16%). When a positive SPT response to cat or dog fur was used as a risk factor for rat or mouse allergy

*References 1, 3-5, 7, 10, 12, 14, 15, and 19.

instead of a positive SPT response to any of the common allergens (Table III), the PRRs increased from 4.2 (95% CI, 2.3-7.6) to 6.2 (95% CI, 3.6-11) and from 8.1 (95% CI, 2.0-38) to 12.7 (95% CI, 3.6-45), respectively.

Elevated total IgE (≥ 100 kU/L) was also strongly associated with rat and mouse allergy, which is in agreement with other studies.^{12, 20, 21} When three risk factors (history of symptoms of allergy to pets, positive SPT response to cat or dog fur, and elevated total IgE) were combined in one model, a very strong association with rat and mouse allergy was found (Table V). The high PRRs were partly due to the low prevalence rates among workers with all three risk factors absent. Therefore cat or dog allergy and elevated total IgE seem to be suitable risk factors for use in epidemiologic studies on LAA.

Because of the cross-sectional nature of our study, it was not possible to verify whether the SPT response to pets and an elevated total IgE precede LAA. However, similar prevalence rates of positive SPT responses to cat and dog fur and total IgE were found among bakers (control group, Table IV), which makes it more likely that allergy to pets and an elevated total IgE precede LAA. However, more conclusive answers can only be given after analysis of follow-up data.

Despite the higher prevalence rate of symptoms of allergy to rats compared with mice, the PRRs of the host factors (Tables III and V) were roughly similar. The host factors seem to have a similar effect on the prevalence rate of both rat and mouse allergy. The difference in prevalence rate of rat and mouse allergy can possibly be explained by other factors such as level and intensity of exposure and allergenic potency of both species.

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