

Original article

Frequency of allergic rhinitis to laboratory animals in university employees as confirmed by chamber challenges

Background: Occupational risk for laboratory animal allergy (LAA) is well known, but prevention is often insufficient and new cases keep appearing.

Methods: A questionnaire on work-related symptoms was sent to all laboratory animal workers in Kuopio University. Subjects with rhinitis were invited to an examination for LAA, which consisted of an otorhinolaryngological examination and skin prick testing (SPT) with 16 common environmental allergens and two to five relevant laboratory animals. In cases of occupational sensitization, a challenge test was performed.

Results: The questionnaire was completed by 156 of 245 (64%) subjects. Rhinitis was reported by 65 of the respondents (42%) of whom 47 were examined for LAA. The duration of exposure before the onset of rhinitis varied from 1 month to 18 years. Twenty-seven persons (57%) had a history of some previous atopic symptoms. Forty subjects (85%) showed positive reactions in SPT, 24 (51%) for laboratory animals. Fifteen of the 26 animal challenge tests performed were positive, confirming the diagnosis of occupational allergic rhinitis in three subjects, occupational dermatitis in five and both diseases in seven subjects. The frequency of occupational allergic rhinitis among all participants was 10 of 156 (6%).

Conclusions: Atopic constitution and work-related sensitization were common in rhinitic laboratory animal workers. Occupational allergic disease was diagnosed in nearly every third case.

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The first case of laboratory animal induced allergic rhinitis was reported in the 1950s and was attributable to exposure to mice (1). In Finland, mice and rats are the most widely used mammalian species in medical research, followed by rabbits, pigs, guinea pigs, and dogs. Hair, dander and saliva are the major sources of allergens for traditional pets (such as dogs), but for rats and mice, urine is the major source of allergenic proteins (2, 3).

There are varying estimates of the prevalence of laboratory animal allergy (LAA). At least part of the variation can be explained by differences in the diagnostic criteria and diagnostic techniques. Because of the lack of uniform criteria, it is difficult to compare the results from different studies. In many studies, the estimated prevalence is based on symptoms reported by a questionnaire. Sensitization to laboratory animals, either specific immunoglobulin (Ig)E or positive skin prick tests (SPTs), has been detected in 10–38% of laboratory animal workers (4–8). The most usual manifestations of LAA are rhinitis, conjunctivitis, contact urticaria and asthma (9). Rhinoconjunctivitis, the most

common symptom, is reported in up to 70–80% of symptomatic workers (3, 10, 11). Sensitization to an occupational agent is not sufficient to diagnose occupational rhinitis (12). In Finland, a positive challenge test result is required for the diagnosis of LAA rhinitis and for the award of any possible compensation payments.

The latency period from the beginning of the exposure to the onset of symptoms has varied in different studies from 1 month to several years, with a mean interval of 2–3 years (9). One in every three symptomatic employees has been reported to develop symptoms in the first year with up to 70% experiencing symptoms within 3 years (13). In the survey of 417 apprentices working in animal-health technology, sensitization, symptoms and work-related skin and respiratory diseases occurred maximally in the first 1–2 years of exposure to laboratory animals (14). The risk of sensitization increases with increasing concentrations of airborne allergens (9). According to the literature, other risk factors for LAA have been atopy (7, 9, 15, 16), any positive SPT (16–19), allergy to pets or domestic animals (4, 20–22), smoking (7, 15, 18, 18), and pre-employment total IgE > 100 kU/l (22, 23).

It is estimated that there are about 2000 persons in Finland occupationally exposed to laboratory animals

Abbreviations: LAA, laboratory animal allergy; MCA, minimum cross-sectional area; RAST, radioallergosorbent test; SPT, skin prick test.



Figure 1. A researcher handles rats in a chamber challenge test.

either in research units or in the pharmaceutical industry. At any given time there are about 250 individuals working with animals in the University of Kuopio. Half of them are researchers with a contract period of 2–4 years. In Finland, all diagnosed occupational diseases are recorded in the Finnish Register of Occupational Diseases. In 2000 (the year before this study), there were 56 reported cases of rhinitis because of animal allergy, but only three of them were caused by laboratory animals (24). When the national incidence data was compared with figures presented in the literature, it seemed to indicate underreporting of LAA as an occupational disease. The objective of the present study was to find out the true prevalence of laboratory animal related symptoms and LAA rhinitis in Kuopio University employees and researchers.

Material and methods

The questionnaire study

A questionnaire asking about work-related respiratory and skin symptoms, possible risk factors for LAA (atopy, smoking, domestic animals) and about other aspects of their work was sent to 254 persons who were assumed to be exposed to laboratory animals in Kuopio University. The questionnaire was completed by 164 employees (65% of the sample), from whom 156 (61% from the sample) were currently being exposed to laboratory animals and thus included into the study. The study population consisted of 99 researchers, 18 laboratory assistants and 39 animal handlers and other animal workers, whose mean age was 35 years (range 21–61 years) and mean exposure time 6 years (range 0.1–27 years). Sixty percent of the respondents were women.

The clinical study

Forty-seven of the 65 subjects who reported rhinitis could be contacted and were willing to attend an examination for LAA. They

were examined according to the clinical routine in the outpatient clinic of the department of otorhinolaryngology of Kuopio University Hospital. The patients were interviewed with a structured questionnaire about work history, exposures, history of work-related rhinitis, other respiratory, eye and skin symptoms, history of pre-existing atopic symptoms (allergic rhinitis, asthma and atopic dermatitis), smoking and domestic furry pets. One of the two otolaryngologists in the study group performed a clinical examination that consisted of an anterior and posterior rhinoscopy, mirror laryngoscopy and otoscopy. If there were signs indicative of sinusitis, paranasal sinus X-ray was taken and the subjects were treated accordingly for infection rhinitis or sinusitis before further examinations. Skin prick tests with common environmental airborne allergens and individually relevant laboratory animals (ALK-Abelló A/S, Hørsholm, Denmark) was performed and interpreted according to the recommendations of the European Academy of Allergy and Clinical Immunology (25). Histamine hydrochloride (10 mg/ml) and allergen diluent were used as positive and negative controls, respectively. A weal diameter of at least 3-mm and half of the histamine control was considered positive. The allergens used were: pollen from birch, alder, five grasses (timothy, meadow foxtail, meadow grass, meadow fescue and orchard grass), mugwort and dandelion, four animal danders (horse, cow, dog and cat), two house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), three storage mites (*Acarus siro*, *Lepidoglyphus destructor* and *Tyrophagus putrescentiae*) and one to four relevant experimental animals. In 33 patients, radioallergosorbent tests (RASTs) were made complementary to SPTs. The RAST results were graded in six classes (class 0 = 0.00–0.34, class 1 = 0.35–0.69, class 2 = 0.70–3.4, class 3 = 3.5–17.4, class 4 = 17.5–50.0 and class 5 > 50.0 IU/l). Classes 2–5 were interpreted as positive.

In this study, a challenge test was performed in an air-conditioned 7 m³ chamber with live animals (Fig. 1), because commercial test fluids for laboratory animals were not available. In order to provide also urinary antigen challenge, the test animals were brought in the chamber in a box where they had spent at least two preceding hours. The box contained bedding material and litter. The patient handled the test animals and the box contents until nasal symptoms appeared, but not for longer than 15 min. Symptoms and signs were observed during the following 60 min. The interpretation of the challenge test was based on (1) rhinoscopy findings (hypersecretion and mucosal oedema) and symptoms (obstruction and nasal itching and sneezing) and (2) minimum cross-sectional area (MCA) changes in acoustic rhinometry. The test was considered positive if hypersecretion and at least two other objective findings or symptoms were recorded (26). During the challenge test, the patient handled animals also with his/her bare hands and a dermatologist recorded the presence of skin reactions, if any.

Statistical analyses

Differences between patient groups were compared with the chi-square test for independence. When needed due to small expected counts, Fisher's exact probability test was used.

Results

The questionnaire study (156 laboratory animal workers)

Exposure and work-related symptoms. Forty percent of the 156 respondents reported handling laboratory animals almost daily, 31% weekly, 17% monthly and 12% less than monthly. Most employees were working with rats (71%) or

mice (59%). In the questionnaire, 74 of 156 (47%) subjects reported work-related respiratory symptoms and 38 of 154 (25%) work-related skin symptoms. Both respiratory and skin symptoms were reported by one-fourth of the respondents while 51% reported neither symptom. Only two of those with skin symptoms did not report any respiratory symptoms. Eye symptoms, which were always associated with respiratory complaints, were reported by 15 of 156 (10%). Rhinitis was the most common of the respiratory symptoms, and was reported by 65 individuals (42%). Other respiratory complaints were cough, reported by 27 (17%), shortness of breath by nine (6%) and wheezing by five (3%) of the respondents.

Risk factors. A history of atopic respiratory symptoms (hay fever, asthma or both) was reported by 75 (48%) and of atopic eczema by 51 (33%) of the 156 respondents, altogether some atopic symptom was reported by 92 subjects (59%). There were 33 smokers (21%), and 102 (65%) had lived with a furry pet for at least 1 year at

some point during their lives. The presence of a current pet was not asked in the questionnaire. Table 1 presents the prevalence of reported weekly work-related respiratory symptoms in different groups. Significantly more of those with a history of respiratory atopy had work-related weekly respiratory symptoms when compared with nonatopics ($P = 0.026$) whereas there was no statistical association with smoking or having had pets at home. Weekly work-related respiratory symptoms associated best with the frequency of laboratory animal contact.

The clinical study (47 rhinitic laboratory animal workers)

Work-related symptoms. The occupations and demographics of the 47 rhinitic animal workers are presented in Table 2. In all, 27 of the 30 researchers were temporary workers. Forty-five of the 47 rhinitic workers were handling either rats (42 of 47) or mice (35 of 47) or both. The other animals handled were rabbits (9), guinea pigs (6), dogs (5), foxes (4), minks (3), pigs (3), racoons (2) and hens (2). The exposure time before the occurrence of work-related nasal symptoms ranged from 1 month to 18 years. The latency period differed for occupational groups, being shortest in the research personnel and longest in animal handlers (Table 2). In 34 of 47 subjects (72%), work-related rhinitis symptoms began during the first 3 years of animal work and in 13 of them (28%), during the first month of exposure. The proportions of atopics in these groups were 17 of 34 and 10 of 13 respectively.

In the clinical interview, 25 of 47 (53%) reported in addition to rhinitis other work-related symptoms such as skin rash on hands outside the protective glove area or flushing of the face and neck (17), eye irritation (9), shortness of breath (6) and cough (2) (Table 2). Seven workers (six researchers and one animal handler) had earlier been examined for asthma, but none of them had been diagnosed with asthma.

Risk factors. A history of pre-existing atopic symptoms (hay fever, asthma, atopic eczema) was reported by 27

Table 1. Work-related respiratory symptoms according to atopy, smoking, pets, and exposure frequency reported by 156 laboratory animal workers in a questionnaire

	<i>n</i>	At least one symptom* every week or more often	%
History of hay fever or asthma	75	21	28
No history of respiratory atopy	81	11	14
Current smoker	33	5	15
Not current smoker	123	27	22
A furry pet at home†	102	24	24
Never pets at home	54	8	15
Exposure to laboratory animals			
Daily	62	19	31
Weekly	49	12	24
Less often	45	1	2
All respondents	156	32	21

* Rhinitis, cough, shortness of breath, wheezing or fever/chills.

† Sometimes during life for at least 1 year.

Table 2. Characteristics of the 47 laboratory animal workers with rhinitis (clinical study)

	Researchers (30)	Laboratory technicians (10)	Animal handlers (7)	Total (47)
Female/male	16/14	9/1	5/2	30/17
Age	24–47 years (mean 30 years, median 30 years)	25–54 years (mean 39 years, median 38 years)	36–56 years (mean 45 years, median 41 years)	24–56 years (mean 34 years, median 31 years)
Pre-existing atopic symptoms	20	4	3	27
Domestic furry pets	7	6	5	18
Currently smoking	3	3	2	8
Exposure time before rhinitis	1 month–5 years (mean 1.6 years, median 1 year)	1 month–18 years (mean 2.4 years, median 1 year)	1 month–17 years (mean 5.7 years, median 4 years)	1 month–18 years (mean 2.3, median 1 year)
Other work-related symptoms (skin rash, eye irritation, cough, dyspnea)	18	4	3	25

Table 3. Skin prick test (SPT) results in 47 laboratory animal workers with rhinitis

	Allergen group					
	Laboratory animals		Common aeroallergens		Both laboratory animals and common aeroallergens	
	Positive	Negative	Positive	Negative	Positive	Negative
Researchers (30)	18	12	19	11	12	4
Laboratory technicians (10)	3	7	8	2	2	1
Animal handlers (7)	3	4	4	3	1	1
Total (47)	24	23	31	16	15	6

of the 47 subjects with work-related rhinitis (57%) (Table 2). This figure was somewhat higher among the examined research personnel (20 of 30) than among the other animal workers (seven of 17) ($P = 0.09$). Of these 47 rhinitic subjects, the proportion of smokers was 17% and that of pet owners 38% (Table 2).

SPT and RAST results. Forty-one of the 47 workers with work-related rhinitis (85%) had at least one positive SPT or RAST, 24 of them (51%) to laboratory animals (Table 3). All positive laboratory animal RAST results were confirmed with positive SPTs to the respective allergens. Thirteen laboratory animal workers (28%) had

become sensitized to at least one of the three storage mites, which in the present study were considered as common aeroallergens.

Provocation test results. The chamber challenge test was performed in 26 subjects. Twenty-four of them had a positive SPT result to one of the laboratory animals. In the two SPT/RAST negative subjects, the association of symptoms to work was very convincing. The animal challenge provoked both nasal and skin reactions in seven cases and either a skin (5) or nasal (3) reaction in eight cases (Table 4). Rats and mice caused both nasal and skin reactions while rabbits only caused nasal reactions. Seven from the 12 persons with a positive skin challenge test reported also skin rash in connection with animal work. An occupational disease was thus diagnosed in 15 of the examined 47 workers (32%), in 13 of 30 researchers and two of 10 laboratory technicians (Table 5). The LAA was not diagnosed in any of the seven animal handlers. An occupational disease was diagnosed more frequently among the 30 researchers than among 17 other animal workers ($P = 0.048$). The duration of laboratory animal exposure preceding LAA-symptoms was <1 month in four individuals, from 1 month to 3 years in eight subjects and longer than 3 years in three workers diagnosed with an occupational disease (Table 5).

Table 4. Positive animal challenge tests in 26 subjects

Site of reaction	Occupation			Total (26)
	Researchers (19)	Laboratory technicians (3)	Animal handlers (4)	
Nose and skin	7	—	—	7
Nose only	3	—	—	3
Skin only	3	2	—	5
Total	13	2	—	15

Table 5. Sensitization to laboratory animals and laboratory animal allergy (LAA) according to the history of pre-existing atopic symptoms, pets, smoking and exposure time

	Sensitization to laboratory animals		LAA	
	Yes (24)	No (23)	Yes (15)	No (32)
Pre-existing atopic symptoms (27)	13	14	9	18
No pre-existing atopic symptoms (20)	11	9	6	14
Domestic pets (18)	7	11	3	15
No domestic pets (29)	17	12	12	17
Currently smoking (8)	5	3	3	5
Not currently smoking (39)	19	20	12	27
Exposure time before symptoms				
≤ 1 month (13)	2	11	4	9
1 month–3 years (24)	6	18	8	16
>3 years (10)	2*	8	3†	7

* 5 and 17 years.

† 4, 4 and 5 years.

Discussion

In the literature, the prevalence of LAA has been reported to be from 15 to 30% among those working with laboratory animals (17, 27–29). The present study found 15 cases of occupational diseases attributable to LAA among 156 exposed subjects. These included 10 cases of LAA rhinitis. When compared with the reports in the national register of occupational diseases, the present data indicates that this disease is under-diagnosed. Occupational health services are readily accessible for university employees in Finland. According to Finnish occupational disease legislation, the insurance company is obligated to pay for the diagnostic investigation in cases when an occupational

disease is suspected. If rhinitis is accepted as being occupational, the patient is entitled to free medication and sometimes also to other types of compensation. Thus the workers stand to gain most from the diagnosis of the disease. There are at least two possible explanations for the under-diagnosing of this condition. First, the symptoms of LAA often appear after a relatively short latency period and the symptomatic persons may change their job ('healthy worker' effect) (4, 20). Secondly, in university research units, a great many of the exposed persons, such as students and doctoral candidates, work on a temporary basis with a contract period of about 4 years. It seems that many of these young persons neglect their symptoms and do not seek the help of occupational or other health services. Researchers constituted the majority (64%) of the examined rhinitic subjects in this study and 90% of them were temporary workers.

Risk factors

Atopy (defined by positive history of atopic symptoms, positive SPT/RAST response or both) seems to be, strongly associated with the development of LAA (3, 5, 10, 16, 18, 20, 27, 30, 31). However, for occupational rhinitis, atopy has been considered as a controversial risk factor (12). In the present questionnaire study, 59% of the 156 respondents reported a history of atopic respiratory or skin symptoms. This figure was very similar (57%) in the 47 rhinitic individuals, who participated in the clinical study. Atopy was significantly more common among researchers than among other animal workers (Table 2). The 'healthy worker' effect among permanent workers probably explains this finding. Workers with a history of hay fever or asthma reported frequent work-related respiratory symptoms more often than those without previous respiratory atopy symptoms (Table 1).

Both positive (16) and negative (20) associations between pet keeping and development of LAA have been found. Fewer current or previous pet owners were found among workers with LAA (Table 5) but the present material is too small to draw any conclusions of a possible association between pets and LAA. Smoking has been found to be a risk factor for LAA (18, 32) but not in all studies (4, 15, 16). In the present questionnaire study, current smokers reported somewhat less symptoms than nonsmokers (Table 1). This may indicate that individuals with symptoms had quit smoking. However, it is not possible to draw any conclusions on the role of smoking as a risk factor because of the small size of the study.

LAA-symptoms and exposure

There is a relationship between the intensity of exposure to animal allergens and the development of respiratory disease. Although the risk increases at increasing concentrations of airborne allergen, sensitization can occur at any

level of exposure (9). In the present study, individual allergen exposure levels were not determined, but only workers in direct contact with laboratory animals were included. Especially in research work, daily animal exposure times and the allergen loads may be high at times. Temporary workers tend not to be motivated to use personal protection and thus their exposure load increases.

Nose and eye symptoms are usually the first and most commonly reported animal-related symptoms (8, 27). There may be a progression to asthma (7, 13, 17) but asthma without rhinitis is thought to be rare (4, 7, 9). In this study, eight rhinitic subjects (17%) complained of shortness of breath (6) or cough (2). Seven of them had been examined for asthma, but it had not been diagnosed. Skin symptoms in laboratory animal work are often contact urticaria, this appears soon after animal contact and disappears when contact is ceased. Therefore skin symptoms are seldom seen in clinical situations. In the present study, the chamber challenge test elicited a skin rash in most (12 of 15) of the subjects diagnosed with LAA. This has not been reported in the previous literature.

Latency

In the present material, the majority (79%) of the 47 rhinitic workers started to experience rhinitis symptoms during the first 3 years of exposure, which is in concordance with earlier reports (7, 10, 19, 21). The researchers, two-thirds of whom were atopics, had a shorter latency period than other laboratory animal workers. This agrees with the work by Kruize et al. (30) finding a shorter latency in atopics. Among the 13 subjects developing symptoms within 1 month, 10 were atopics and nine were research personnel. The 'healthy worker' effect may again explain the shorter mean latency period in researchers when compared with other laboratory animal workers (Table 2). In this study, there was no difference in the latency period between those diagnosed and those not diagnosed with occupational LAA rhinitis (Table 2). According to the results of Gautrin et al. (14) and Cullinan et al. (15) the risk of developing LAA diminishes clearly with time. In the study of Gautrin et al., after 3 years of exposure the incidence of sensitization to rat allergens was at the same order of magnitude as sensitization to common allergens. Our findings in this small material support the results of Kruize et al. (30) suggesting that the risk of sensitization and developing LAA in exposed people remains present for a prolonged period.

Diagnostic methods

In many studies, the presence of allergic symptoms has been used as criterion for LAA. Animal-derived or other agents, such as dust, disinfectants or ammonia may also cause nonspecific hyper-reactivity, especially in atopic persons (4), which may be interpreted as LAA if the

diagnosis is based only on questionnaire responses. In Finland, sensitization to laboratory animals (positive SPT/RAST) alone, even in a symptomatic person is not diagnosed as LAA. A positive challenge test result is required for the diagnosis of occupational allergic rhinitis and for possible compensation payment. There are only a few reports of studies using challenge tests for the diagnosis of LAA (33, 34). In most previous studies, the diagnosis of LAA has been made either on the basis of sensitization, or work-related symptoms or both. A high correlation between reported symptoms and sensitization has been reported (4). The chamber challenge simulates the working conditions; the patient is also exposed to proteins in urine and saliva whereas commercial laboratory animal test fluids for SPT contain only epithelial antigens. In the present study, airborne allergen concentrations in the chamber were not measured during the test, but the test resembled a high-allergen challenge situation (34) such as occurring while cleaning the cage. The exposure time in the chamber was 15 min at a maximum because in sensitized individuals nasal and eye symptoms are commonly provoked within minutes (9).

Specific sensitization to laboratory animals was detected in one of every two and an occupational allergic disease in one of every three rhinitic workers. Sensitization to environmental aeroallergens was common (66%) and the number of workers with sensitization to at least one allergen was very high (87%). Nonspecific hyper-reactivity may explain the work-related symptoms in those persons in whom no occupational allergy was diagnosed. Interestingly, 13 animal workers had a positive reaction in SPTs to at least one of the three storage mites, which in the present study were classified as common aeroallergens. Further examinations are in

progress to determine whether this sensitization in these patients could be work-related. There are no previous reports in the literature about occupational storage mite-related diseases in animal workers.

In conclusion, the development of LAA is an acknowledged occupational problem, which in the worst-case scenario can affect both an individual's health and career. It has been claimed that airway responses are strongly dependent on airborne allergen concentration. Employees with atopic diathesis and pre-existing allergic diseases are at a high risk, especially in high exposure situations, as often is the case during research projects. Most become symptomatic within 3 years, many within weeks, of exposure. On the contrary, LAA may appear after a latency of many asymptomatic years. Measurable amounts of rat urine antigen have also been detected outside of the animal facilities in a research establishment (35) indicating that employees not working with animals may also be exposed to laboratory animal allergens. Education is very important in the prevention of LAA and temporary workers should also be made aware of the risks to their health. Effective reduction of the airborne allergen concentration is crucial. Furthermore, at least all symptomatic workers should wear personal protective equipment. In general, a person with LAA should not be exposed to animals on a daily basis, but should instead be retrained or evaluated for another job or career.

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References

1. SORRELL AH, GOTTESMAN J. Mouse allergy. Case report. *Ann Allergy* 1957;**15**:662–663.
2. NEWMAN TAYLOR AJ, LONGBOTTOM JL, PEPYS J. Respiratory allergy to urine proteins of rat and mice. *Lancet* 1977;**2**:847–849.
3. BUSH RK, WOOD RA, EGGLESTON PA. Laboratory animal allergy. *J Allergy Clin Immunol* 1998;**102**:99–112.
4. HOLLANDER A, DOEKES G, HEEDERIK D. Cat and dog allergy and total IgE as risk factors of laboratory animal allergy. *J Allergy Clin Immunol* 1996;**98**: 545–554.
5. HOLLANDER A, HEEDERIK D, DOEKES G. Respiratory allergy to rats: exposure–response relationships in laboratory animal workers. *Am J Respir Crit Care Med* 1997;**155**:562–567.
6. WEISSENBACH T, WÜTHRICH B, WEIHE WH. Labortier-Allergien. Eine epidemiologische, allergologische Studie bei Labortier-exponierten Personen. *Schweiz med Wschr* 1988;**118**:930–938.
7. KRAKOWIAK A, SZULC B, GÓRSKI P. Occupational respiratory diseases in laboratory animal workers: initial results. *Int J Occup Med Environ Health* 1997;**10**:31–36.
8. VENABLES KM, TEE RD, HAWKINS ER, GORDON DJ, WALE CJ, FARRER NM et al. Laboratory animal allergy in a pharmaceutical company. *Br J Ind Med* 1988;**45**:660–666.
9. GORDON S, NEWMAN TAYLOR AJ. Animal, insect and shellfish allergy. In: BERNSTEIN IL, CHAN-YEUNG M, MALO J-L, BERNSTEIN DI, editors. *Asthma in the workplace*, 2nd edn. New York, Basel: Marcel Dekker, Inc, 1999: 399–424.
10. AOYAMA K, UEDA A, MANDA F, MATSUSHITA T, UEDA T, YAMAUCHI C. Allergy to laboratory animals: an epidemiological study. *Br J Ind Med* 1992;**49**:41–47.
11. CULLINAN P, LOWSON D, NIEUWENHUISSEN MJ, GORDON S, TEE RD, VENABLES KM et al. Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to laboratory rats. *Occup Environ Med* 1994;**51**:589–592.
12. SIRACUSA A, DESROSIERS M, MARABINI A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. *Clin Exp Allergy* 2000;**30**:1519–1534.
13. BUSH RK. Mechanism and epidemiology of laboratory animal allergy. *ILAR J* 2001;**42**:4–11.

14. GAUTRIN D, GHEZZO H, INFANTE-RIVARD C, MALO J-L. Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. *Eur Respir J* 2001;**17**:904–908.
15. CULLINAN P, COOK A, GORDON S, NIEUWENHUIJSEN MJ, TEE RD, VENABLES KM et al. Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. *Eur Respir J* 1999;**13**:1139–1143.
16. FUORTES LJ, WEIH L, JONES ML, BURMEISTER LF, THORNE PS, POLLEN S et al. Epidemiologic assessment of laboratory animal allergy among university employees. *Am J Ind Med* 1996;**29**:67–74.
17. SLOVAK AJM, HILL RN. Laboratory animal allergy: a clinical survey of an exposed population. *Br J Ind Med* 1981;**38**:38–41.
18. VENABLES KM, UPTON JL, HAWKINS ER, TEE RD, LONGBOTTOM JL, NEWMAN TAYLOR AJ. Smoking, atopy, and laboratory animal allergy. *Br J Ind Med* 1988;**45**:667–671.
19. SJÖSTEDT L, WILLERS S, ØRBÆK P. A follow-up study of laboratory animal exposed workers: the influence of atopy for the development of occupational asthma. *Am J Ind Med* 1993;**24**:459–469.
20. BLAND SM, LEVINE MS, WILSON PD, FOX NL, RIVERA JC. Occupational allergy to laboratory animals: an epidemiologic study. *J Occup Med* 1986;**28**:1151–1157.
21. GROSS NJ. Allergy to laboratory animals: epidemiologic, clinical, and physiologic aspects, and a trial of cromolyn in its management. *J Allergy Clin Immunol* 1980;**66**:158–165.
22. RENSTRÖM A, KARLSSON AS, MALMBERG P, LARSSON PH, van HAGE-HAMSTEN M. Working with male rodents may increase risk of allergy to laboratory animals. *Allergy* 2001;**56**:964–970.
23. RENSTRÖM A, MALMBERG P, LARSSON K, SUNDBLAD B-M, LARSSON PH. Prospective study of laboratory-animal allergy: factors predisposing to sensitization and development of allergic symptoms. *Allergy* 1994;**49**:548–552.
24. KARJALAINEN A, AALTO L, JOLANKI R, KESKINEN H, MÄKINEN I, SAALO A (editors). *Ammattitautidit 2000*. Helsinki: Työterveyslaitos, 2001 (The Finnish Register of Occupational Diseases 2000, English summary).
25. DREBORG S, BACKMAN A, BASOMBA A, BOUSQUET J, DIEGES P, MALLING H-J. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989;**44**:1–59.
26. PIRILÄ T, NUUTINEN J. Acoustic rhinometry, rhinomanometry and the amount of nasal secretion in the clinical monitoring of the nasal provocation test. *Clinical and Experimental Allergy* 1998;**28**:468–477.
27. BEESON MF, DEWDNEY JM, EDWARDS RG, LEE D, ORR RG. Prevalence and diagnosis of laboratory animal allergy. *Clin Allergy* 1983;**13**:433–442.
28. COCKCROFT A, EDWARDS J, MCCARTHY P, ANDERSSON N. Allergy in laboratory animal workers. *Lancet* 1981;*i*:827–830.
29. NEWMAN-TAYLOR AJ. Laboratory animal allergy. *Eur J Respir Dis Suppl* 1982;**123**:60–64.
30. KRUIZE H, POST W, HEEDERIK D, MARTENS B, HOLLANDER A, VAN DER BEEK E. Respiratory allergy in laboratory animal workers: a retrospective cohort study using pre-employment screening data. *Occup Environ Med* 1997;**54**:830–835.
31. AGRUP G, BELIN L, SJÖSTEDT L, SKERFVING S. Allergy to laboratory animals in laboratory technicians and animal keepers. *Br J Ind Med* 1986;**43**:192–198.
32. DAS R, TAGER IB, GAMSKY T, SCHENKER MB, ROYCE S, BALMES JR. Atopy and airways reactivity in animal health technicians. *J Occup Med* 1992;**34**:53–60.
33. EGGLESTON PA, ANSARI AA, ZIEMANN B, ADKINSON NF Jr, CORN M. Occupational challenge studies with laboratory workers allergic to rats. *J Allergy Clin Immunol* 1990;**86**:63–72.
34. EGGLESTON PA, ANSARI AA, ADKINSON NF Jr, WOOD RA. Environmental challenge studies in laboratory animal allergy. Effect of different airborne allergen concentrations. *Am J Respir Crit Care Med* 1995;**151**:640–646.
35. NIEUWENHUIJSEN MJ, GORDON S, TEE RD, VENABLES KM, McDONALD JC, NEWMAN TAYLOR AJ. Exposure to dust and rat urinary aeroallergens in research establishments. *Occup Environ Med* 1994;**51**:593–596.