

Epidemiologic Assessment of Laboratory Animal Allergy Among University Employees

Laurence J. Fuortes, MD, MS, LeAnn Weih, MS, Martin L. Jones, MS, Leon F. Burmeister, PhD, Peter S. Thorne, MS, PhD, Sue Pollen, RN, and James A. Merchant, MD, DrPH

The prevalence of, and risk factors for, laboratory animal allergy (LAA) among university employees were evaluated in a cross-sectional university-based study. A stratified random sample was drawn based on current or no laboratory animal exposure and smoking status. Participants received a modified ATS questionnaire; spirometry; methacholine challenge; and intradermal allergen skin tests. One hundred three currently animal-exposed and 113 never-occupationally-exposed employees participated. Controlling for smoking, currently exposed workers were significantly more likely than controls to describe work-related cough, odds ratio (O.R.) = 6.87; wheeze, O.R. = 12.96; and chest tightness, O.R. = 2.89. Skin test reactivity to non-animal antigens was associated in a dose-response fashion with both upper and lower respiratory symptoms, O.R. = 1.45 and 1.65, respectively, for each additional positive skin test. Exposed workers were significantly more likely than controls to react to methacholine at either 10 or 25 mg/ml, while controlling for smoking status, prior allergy, or asthma. Multiple logistic regression analysis revealed history of hay fever, family history of allergy, non-animal skin test positivity, animal bites, age, and smoking status to each be associated with work-related respiratory symptoms. These data suggest that atopy and smoking status are risk factors for LAA symptoms. Smoking was associated with work-related respiratory symptoms among animal-exposed workers, but not with skin test positivity. It is therefore recommended that periodic screening evaluations be performed on laboratory animal workers and that workers who are atopic, are smokers, or are symptomatic be placed in low exposure settings. These data further support the need for efficient exhaust ventilation, personal protective clothing and, among high risk workers, the use of efficient respiratory protection. © 1996 Wiley-Liss, Inc.

KEY WORDS: laboratory animal allergy, asthma, atopy, skin prick tests, occupational exposure

INTRODUCTION

Allergy to laboratory animals is an increasingly recognized occupational problem. Manifestations of laboratory animal allergy (LAA) include conjunctivitis, rhinitis, urticaria, and asthma. It has been estimated that there are over

90,000 workers in the United States handling animals in research or industrial settings and many others are exposed to those same animal species as pets [U.S. Department of Agriculture (USDA), 1990; Newill et al., 1986]. Multiple studies have described prevalence rates of LAA of 15–30% and prevalence rates of laboratory animal asthma of 2–13% [FauskerBler and Tritschler, 1992].

Several studies have examined the association of atopy with subsequent development of LAA, but these cross-sectional studies have not consistently found atopy to be a risk factor for LAA. Initial studies in Great Britain found no association between family history of atopy and LAA symp-

Department of Preventive Medicine and Environmental Health, University of Iowa, Iowa City.

Address reprint requests to Laurence J. Fuortes, M.D., University Occupational Health Service, 228 Westlawn Building South, Iowa City, IA 52242-1100.

Accepted for publication February 9, 1995.

toms among 474 laboratory animal handlers [Taylor et al., 1976]. Similarly, Davies and McArdle [1981], in two separate surveys, did not find any difference in the prevalence of LAA symptoms in atopic individuals (defined by personal history) as compared to nonatopic individuals. In a study by Slovak and Hill [1981], atopy as defined by family history was not a risk factor for LAA, whereas atopy as defined by intradermal skin test reactivity to environmental antigens was found to be a significant risk factor. Conversely, several studies have demonstrated an association between LAA and atopy [Agrup et al., 1986; Aoyama et al., 1992; Bland et al., 1986; Gross, 1980; Kibby et al., 1989; Lincoln et al., 1974]. Several of these studies also indicate that atopy is more strongly associated with more severe manifestations of LAA such as asthma [Slovak and Hill, 1981; Cockcroft et al., 1981]. In addition, an association of LAA symptoms with smoking has been reported in two studies [Venables et al., 1988; Das et al., 1992] but this association was not found in studies by others [Agrup et al., 1986; Cockcroft et al., 1981; Lutsky and Neuman, 1975].

Upon this background, a comprehensive epidemiologic and environmental study was designed. The specific aims of the cross-sectional study were to:

1. Determine the prevalence of LAA among a population of university animal handlers and researchers.
2. Evaluate relevant risk factors for LAA and measures of airway reactivity using multivariate analyses.
3. Recommend prevention measures based on the study results.

SUBJECTS AND METHODS

A 1986 University Occupational Health Service survey was conducted of every department of the university to determine in which laboratories animals were used or housed. Based on this survey, 2,031 employees were identified as working in departments in which animals might be present. These employees were sent brief questionnaires for occupational history and work-related symptoms. A total of 1,757 questionnaires were returned, for a response rate of 87%. Of these, 249 people responded that they were not currently employed in laboratory settings and were thus excluded from the cross-sectional study. Of the 1,508 remaining employees, 818 responded that they were currently exposed to animals in laboratories, 224 responded they had only previous exposure, and 466 stated they never had occupational exposure to animals. The target population for this study was 100 currently animal-exposed and 100 never-occupationally animal-exposed laboratory workers. The 818 current and 466 never-exposed workers were entered into a database. Forty-five of the currently exposed workers comprised the entire Animal Care Unit staff. Attempts were made to recruit each of the Animal Care Unit staff and a

random sample of other currently exposed workers to total a sample of 100. These individuals were contacted by mail and subsequently by phone and invited to participate in a clinical study of "laboratory-associated health hazards." The sample for this study comprised 34 animal care workers and 69 randomly selected animal-exposed laboratory workers and 113 never-exposed control subjects, also randomly selected from the above population.

One interviewer administered an ATS questionnaire modified with additional questions including work history and work-related symptoms to each subject [Ferris, 1978]. Animal-exposed subjects completed additional questions concerning species-specific work history and symptoms associated with particular species from the population identified in the 1986 survey. Subjects were considered atopic if they responded positively to having a physician-confirmed diagnosis of allergic rhinitis, conjunctivitis, or asthma (defined by medical treatment for that condition) or had two or more positive intradermal skin tests to non-animal, environmental aeroallergens. A positive intradermal skin test was defined as the presence of both a wheal and flare, the wheal being more than 5×5 mm greater than the negative control skin test. A case of LAA was defined by responses on the questionnaire indicating two or more work-related mucosal or respiratory symptoms, consistent with allergy, attributed by the subject to specific animal exposure (conjunctivitis, rhinitis, sneezing, wheezing, shortness of breath, coughing, or chest tightness). Symptoms thought to be consistent with laboratory animal asthma were work-related lower respiratory symptoms (wheezing, shortness of breath, coughing, or chest tightness).

Spirometry was assessed using a Spirotech S-500, dry rolling seal spirometer. A minimum of three acceptable tracings were collected using Spirotech software and ATS spirometry standards. Predicted spirometric values were based on the Knudson model [Knudson et al., 1976]. Intradermal skin testing was performed utilizing 0.02 cc of six common aeroallergens and nine laboratory animal antigens (Greer Labs). Methacholine challenge was performed utilizing a Johns Hopkins-Rosenthal-French dosimeter connected to a 346 DeVilbiss nebulizer as per previously described protocol [Chai, 1975; Muller et al., 1993]. Five breaths through the nebulizer were administered with incremental doses of methacholine from 0.075 to 25 mg/ μ l and FEV₁ was assessed after five inhalations at each dose within 5 min from the last dose. Individuals were excluded if they had had recent respiratory infection or had an FEV₁ of less than 80% of predicted.

Those who declined to participate in this study were contacted by phone in order to measure potential response biases. An abbreviated questionnaire covering allergic history was administered. We were able to contact approximately 40% of those who declined to participate in the study. The remaining persons were either no longer em-

TABLE I. Comparison of Symptoms: Animal-Exposed vs. Control Subjects (Controlling for Smoking)

Symptom	Prevalence in exposed (%)	Odds ratio	95% C.I.	p Value
Cough >3 months	11.8	2.08	0.74–5.84	0.164
Non-smokers	6.4	1.02	0.29–3.45	0.981
Smokers	36.8	Inexact ^a	Inexact ^a	0.017 ^b
Work-related cough	6.9	6.87	0.95–47.85	0.052
Wheeze without cold	26.5	2.41	1.18–4.91	0.015 ^b
Work-related wheeze	10.8	12.96	2.39–70.12	0.003 ^b
Dyspnea	31.1	3.45	1.67–9.54	0.001 ^b
Medication for dyspnea	20.6	3.97	1.65–9.54	0.002 ^b
Chest tightness	51.3	0.87	0.51–1.49	0.622
Work-related chest tightness	42.1	2.89	1.08–7.69	0.034 ^b

^aInexact odds ratios reflect a denominator of zero.^bSignificant at the 0.05 level, Mantel-Hantzel chi square controlling for smoking status.

ployed at the university or repeatedly inaccessible. Environmental assessments including area and personal gravimetric analyses of dust, aeroallergen concentrations (determined by radioallergosorbent test [RAST] inhibition to quantify specific animal (antigens), and other air quality measures were performed for a sample of 44 workers and will be reported separately.

Statistical analyses were performed using PC SAS software [SAS Institute, 1990]. Chi square and logistic regression analyses were used to test associations and to determine odds ratios. *p* values less than 0.05 were considered statistically significant. This study was approved by the University's Human Subjects Review Board and informed consent was obtained from all subjects.

RESULTS

There were no statistically significant differences between the animal-exposed and never-exposed university employees in proportions of gender, smoking status, and age. There were no statistically significant differences between the exposed and control workers' mean baseline pulmonary function levels. The response rate among animal-exposed workers was 64% (103 of 162 randomly selected subjects); among controls, the rate was 47% (113 of 263).

After controlling for smoking status, animal-exposed workers were statistically significantly more likely than controls to report work-related cough, wheezing without colds, work-related wheeze, dyspnea, medications for dyspnea, and work-related chest tightness. The prevalence of work-related cough, wheeze, and chest tightness among animal-exposed workers were 6.9%, 10.8%, and 42.1% respectively (Table I). There was a positive interaction between smoking and usual cough. Among smokers, 36.8% of the animal-exposed workers as compared to 0% of nonex-

posed workers described usual cough lasting 3 months or longer. The Breslow-Day test for homogeneity between the smoking status strata for the Mantel Hantzel chi-square test of association between usual cough and animal exposure was significant at *p* = 0.036, indicating that the association between animal exposure and usual cough was strongest among smokers.

There were no statistically significant differences between the animal-exposed workers and controls in the mean spirometric values FVC, FEV₁, PEF_R, or FEF_{25–75%} expressed as measured values or as percent of predicted. However, animal-exposed workers were more likely than controls to experience a 20% or greater decline in FEV₁ with methacholine challenge. Approximately 27% of the exposed workers reacted positively at a dose of 25 mg/ml or less, and 17% reacted at 10 mg/ml or less compared to 13% and 7%, respectively, among controls. The association between animal exposure and methacholine reactivity remained significant controlling for history of asthma, smoking status, atopy, and worker age.

The prevalence of seasonal rhinitis or allergy confirmed by a physician was comparable between animal-exposed participants and controls. History of asthma was 1.4 times as common among exposed participants as controls; however, animal-exposed workers were more likely to participate if they had a history of asthma (Table II). There were no significant differences in intradermal skin test reactivity to non-animal environmental antigens between exposed and control subjects. However, animal-exposed workers were more likely than controls to react to each of the five rodent species antigens to which they were tested (Table III).

Figure 1 shows the prevalence and combinations of work-related symptoms attributed by employees to laboratory animals. Among animal-exposed workers, 34% reported at least one symptom which they attributed to labo-

TABLE II. History of Allergy Comparisons Between Animal-Exposed Participants and Sampled Non-Participants and Between Control Participants and Sampled Non-Participants

	Targeted animal-exposed (N = 162)		Targeted controls (N = 243)	
	Participants	Sampled non-participants	Participants	Sampled non-participants
No.	103	25	113	54
Hay fever	20.4%	20.0%	15.9%	20.4%
Allergy	40.8%	40.0%	34.5%	33.3%
Asthma	13.6% ^a	0.0%	9.7%	9.3%
Family history of allergy	49.5%	NA ^b	42.5%	NA

^aSignificant difference at a chi-square $p = 0.05$ between participating and non-participating exposed workers.

^bNA = not assessed.

ratory animals. The most common symptomatology was upper respiratory irritation, reported by 85% of symptomatic workers. Approximately 42% of symptomatic workers described lower respiratory symptoms, 30% described dermal symptoms, and 21% reported all three classes of symptoms.

A variety of worker-specific and workplace-specific independent variables were tested for association with symptoms of LAA and methacholine reactivity among animal-exposed workers using logistic regression (Table IV). Independent variables tested included age, number of positive skin tests, smoking status, gender, years worked with laboratory animals, and number of animal bites. Skin test reactivity to non-animal antigens was associated with upper respiratory irritation attributed to animal exposure with an odds ratio of 1.45 for upper respiratory symptoms with each additional positive skin test. Lower respiratory LAA symptoms were significantly associated with age of worker (odds ratio of 1.09 with each 1 year increase in age), number of positive non-animal skin tests (odds ratio of 1.65 for each additional positive skin test), smoking status (odds ratio of 3.03 for current smokers compared to never or ex-smokers), and number of animal bites (odds ratio of 1.91 for each additional bite) while controlling for each of the other variables. The number of years worked with animals was not associated with symptoms. Methacholine reactivity was associated with number of positive skin tests at both 10 and 25 mg/ml cutoffs, odds ratios of 1.62 and 1.56, respectively, and with smoking status at both doses, odds ratios of 1.93 and 1.97, respectively (Table V).

Of the various indicators of atopy, history of hay fever, family history of allergy, and two or more positive non-

animal skin tests were the most consistently associated with LAA symptoms. The estimated odds ratios and 95% confidence intervals for those significant associations are displayed in Table VI. A scale of atopic indicators was created (summation of the positive atopic indicators) ranging from 0 to 5 and found to be significantly associated with LAA symptoms in a dose-response fashion (Table VII).

The association of two or more positive non-animal skin tests with work-related lower respiratory symptoms was 57% sensitive and 69% specific with a predictive value positive of 46%. The association of one or more positive skin test to animals worked with and work-related lower respiratory symptoms was 59% sensitive and 87% specific with a predictive value positive of 68%. The association of one or more animal skin test and upper respiratory symptoms (rhinitis, sneezing, watery or itching eyes) was 77% sensitive and 86% specific with a predictive value positive of 45%.

DISCUSSION

Reduced participation rates make calculations of prevalence of LAA and asthma uncertain in previously published studies. In this study there was evidence for bias which could affect the data in both directions. On the one hand, the telephone follow-up of non-participants revealed that animal-exposed workers were more likely to participate if they had a history of asthma (response bias). On the other hand, several of the most severely affected workers refused to participate because of expressed concern regarding employment (selection bias). The prevalence figures reported herein (Tables I and III) may be affected by both response or selection bias.

Another methodological problem in comparing prevalence of LAA between studies is the lack of uniformity in case definitions. For this study, we used standard ATS questions, but added questions specifying temporal work-relatedness of laboratory animal exposure with a given symptom. For epidemiologic purposes, we believe such a case definition to be relatively sensitive. There are most likely both allergic, and non-allergic, causes of the LAA syndrome. In general, the presence of skin test reactivity or serum RAST positivity are supportive evidence for sensitization to specific aeroallergens. In this study, the specificity of animal skin test positivity in association with LAA symptoms was quite high, 89%; however 41% of those with LAA symptoms did not have positive skin tests to animals with which they worked. This suggests that sensitization to antigens of animals one works with is strongly associated with work-related symptoms of allergy. However, in the 41% of those with symptoms who did not have positive skin tests to the animal(s) with which they worked, symptoms may reflect airways irritation from a variety of non-specific agents or lack of the appropriate antigen in the skin test reagent.

TABLE III. Intradermal Skin Test Reactivity to Non-Animal and Animal Allergens

Antigen	Animal-exposed (N = 103)	No. positive (%)	Control (N = 113)	No. positive (%)
Nonreactive to any non-animal allergen	28	46.6	23	53.9
Alternaria	19	18.5	19	16.8
Aspergillus	19	18.5	13	11.5
Hormodendrum	9	8.7	8	7.8
Ragweed	18	17.5	15	13.3
KDT grass	27	26.2	22	19.5
Tree mix	24	11.1	26	23.0
Cockroach	7	6.8	9	8.0
Cat	24	23.3	19	16.8
Rat	20	19.4 ^a	5	4.4
Mouse	11	10.7 ^b	2	1.2
Dog	11	10.7	7	6.2
Rabbit	13	12.6	8	7.1
Guinea pig	9	8.7 ^c	2	1.8
Hamster	8	7.8 ^d	3	2.7
Gerbil	7	6.8 ^e	2	1.8
≥2 Non-animal antigens	31	30.1	29	25.7

^aOdds ratio = 5.21, p value = 0.001.^bOdds ratio = 6.64, p value = 0.006.^cOdds ratio = 5.31, p value = 0.020.^dOdds ratio = 3.09, p value = 0.089.^eOdds ratio = 4.05, p value = 0.065.

These findings are consistent with several other studies reporting an association of atopic indicators, particularly history of hay fever, family history of allergy, and skin test reactivity; with symptoms of LAA. The analyses of associations of hypothesized risk factors with respiratory symptoms were performed on only the animal-exposed group, which we expect to lessen any effect of response bias. Both upper and lower work-related respiratory symptoms were associated with indices of atopy. Upper respiratory symptoms were univariately associated with skin test positivity on non-animal antigens. Lower respiratory symptoms were associated with a past history of hay fever and skin test positivity to non-animal antigens and to a lesser extent with animal bites. Dermal manifestations of LAA (urticaria and atopic dermatitis) were associated with hay fever, family history of allergy, and non-animal skin test positivity. In order to further assess the association of atopy with LAA, a scale was made ranging from 0 to 5 for the sum of the presence of the following atopic conditions: non-animal skin test positivity, past hay fever, family history of allergy, physician's diagnosis of allergy, and a physician's diagnosis of asthma. Using a chi-square test of trend, there was a dose-response relationship between the number of atopic indicators and each of the LAA symptoms, further supporting the hypothesis that LAA is more common among atopic

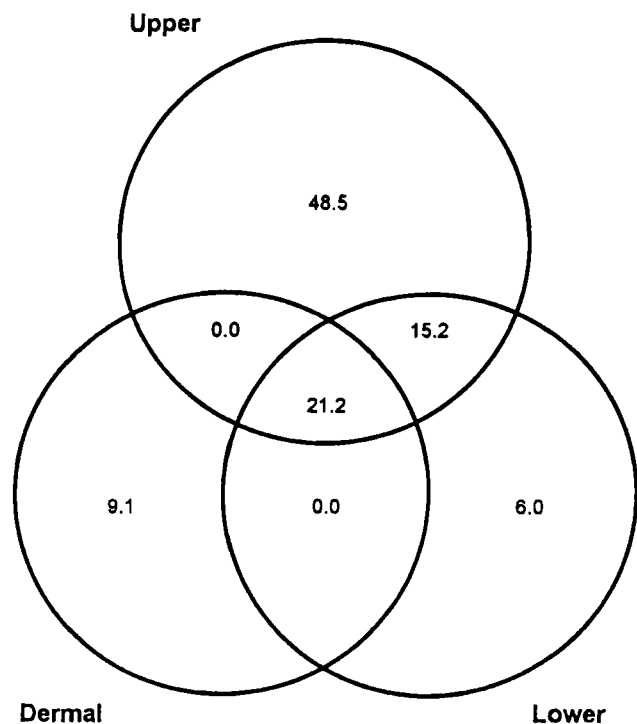
**FIGURE 1.** Distribution of upper and lower respiratory and skin symptoms among symptomatic animal-exposed subjects (n = 34).

TABLE IV. Multivariate Logistic Regression Modeling of Upper and Lower Laboratory Animal Allergy Symptoms Among Animal-Exposed Workers*

Variable	Odds ratio	95% C.I.
Associations with upper respiratory symptoms (N = 101)		
Number of positive skin tests	1.45	1.05–2.00
Associations with lower respiratory symptoms (N = 101)		
Age	1.09	1.01–1.16
Number of positive skin tests	1.65	1.05–2.59
Current smoking	3.03	1.43–6.41
Number of animal bites	1.91	0.99–3.66

*Number of positive skin tests = number of positive non-animal skin tests. Range is from 0 to 6. Number of animal bites = number of animal bites at work.

TABLE V. Multivariate Logistic Regression Modeling of Methacholine Reactivity Among Animal-Exposed Workers*

Variable	Odds ratio	95% C.I.
Association with methacholine reactivity ≤ 10 mg (N = 101)		
Number of positive skin tests	1.62	1.14–2.31
Current smoking	1.93	1.07–3.47
Association with methacholine reactivity ≤ 25 mg (N = 101)		
Number of positive skin tests	1.56	1.10–2.20
Current smoking	1.97	1.11–3.47

*Number of positive skin tests = number of positive non-animal skin tests. Range is from 0 to 6.

workers. Even so, the consensus is that a history of atopy is not of high enough predictive value to exclude people from animal-exposed work [Newill et al., 1986; Slovak and Hill, 1987], although such individuals may represent a population hypersusceptible to a variety of respiratory irritants. In our study, 49.5% of the animal workers reported a positive family history of allergy and 40% a personal history of allergy. The sensitivity and specificity of non-animal skin test positivity's association with LAA symptoms were 57% and 69%, respectively.

A review of the laboratory animal allergy literature reveals that response rates are not clearly reported in the majority of published studies [Botham et al., 1987; Gross, 1980; Lutsky and Neuman, 1975; Newman-Taylor et al., 1981; Sjostedt and Willers, 1993; Willers et al., 1992]. In several studies, the response rate among exposed subjects could be calculated as approximately 60% [Aoyama et al., 1992; Cockcroft et al., 1981; Kibby et al., 1989; Newill et

al., 1992]. Only a few studies reported excellent participation rates, slightly in excess of 80% [Venables et al., 1988; Beeson et al., 1983].

The epidemiologic definition of LAA used in this study is virtually identical to that used in the studies cited, basically work-related respiratory symptoms consistent with allergy. The epidemiologic definition is obviously nonspecific and may represent a combination of workers with immediate hypersensitivity reactions to animal antigens, workers with non-specific hyperreactive airways or otherwise sensitive mucosae, and workers with reactions to a variety of non-specific irritants in the workplace. Although the predictive value is low, it would seem advisable to advise atopic workers of their increased risk for LAA symptoms and of the advisability of decreasing aeroallergen exposure through a combination of improved ventilation, dust control measures, and personal respiratory protection. In the majority of research laboratories we studied on campus, there were few examples of clear procedures or protocols for handling laboratory animals, cages, wastes, etc. In cases where local exhaust systems, fume hoods, or ventilated work benches were found to be inadequate by our industrial hygienist, plans for dust control and remediation of ventilation were outlined for the investigators. In addition, these data support the recommendation of glove usage while handling laboratory animals as animal bites were significantly associated with lower respiratory tract symptoms (although bites are very possibly a marker for increased intensity of contact and inhalational exposure).

Methacholine reactivity at both 10 and 25 mg/ml was associated with non-animal skin test positivity and smoking status. Smoking was similarly associated with work-related respiratory symptoms. Unlike other recent studies [Das et al., 1992; Venables et al., 1985], we found no association between smoking status and either animal or non-animal skin test positivity and cannot thus implicate tobacco as increasing sensitization rates. Other possible explanations for this association might include synergistic airways irritation, increased antigen load through adsorption to inhaled smoke particles, some undetermined form of immunomodulation, or some other mechanism. Regardless of the mechanism, the implication for disease prevention is simply that workers exposed to lab animals as well as to other respiratory toxicants must be advised regarding the potential for increased toxicity and be assisted in smoking cessation, in addition to attention to dust control measures and the use of personal protective equipment.

ACKNOWLEDGMENTS

The authors are indebted to the University Occupational Health Service staff for data collection and for skillful secretarial work. This project was sponsored by a grant from the NIAID/NIH. Number:5-P50-AI19093-05.

TABLE VI. Estimated Odds Ratio and 95% C.I. for Those Significant Tests in Study of Laboratory Animal-Exposed Workers

	Respiratory symptoms	Respiratory symptoms	Dermal symptoms	Any LAA symptoms ^a
Hay fever	—	3.60 (1.09–11.90)	6.00 (1.62–22.24)	2.73 (1.02–7.29)
Family History	—	—	11.95 (1.47–97.31)	3.56 (1.47–8.61)
≥2 Skin tests	3.91 (1.47–10.42)	—	5.15 (1.42–18.89)	4.51 (1.69–12.01)

^aLAA symptoms = watery, burning, itching eyes; runny nose, sneezing; wheezing, shortness of breath, cough, chest tightness; hives or rash in association with laboratory animal exposure.

TABLE VII. Association of Responses With Index of Atopy in the Laboratory Animal-Exposed Group (N = 101)*

	p Value	Odds ratio (per unit of scale)	95% C.I.
Upper respiratory	.007	1.489	1.105–2.000
Lower respiratory	.009	1.587	1.102–2.286
Dermal	.001	1.861	1.229–2.815
Any LAA symptoms	<.0001	1.693	1.243–2.306

*Index of atopy = sum of hay fever, previous allergy, previous asthma, family history of allergy and ≥ non-animal skin test. Range of scale is from 0 to 5. The chi-square test for trend was used for computing p values.

REFERENCES

- Agrup G, Belin L, Sjostedt L, Skerfving S (1986): Allergy to laboratory animals in laboratory technicians and animal keepers. *Br J Ind Med* 43: 192–198.
- Aoyama K, Ueda A, Manda F (1992): Allergy to laboratory animals: An epidemiological study. *Br J Ind Med* 49:41–47.
- Beeson M, Dewdney J, Edwards R, Lee D, Orr R (1983): Prevalence and diagnosis of laboratory animal allergy. *Clin Allergy* 13:433–442.
- Bland S, Levine M, Wilson D, Fox N, Rivera J (1986): Occupational allergy to laboratory animals: An epidemiologic study. *J Occup Med* 28: 1151–1157.
- Botham P, Davies G, Teasdale E (1987): Allergy to laboratory animals: A prospective study of its incidence and of the influence of atopy on its development. *Br J Ind Med* 44:627–632.
- Chai H (1975): Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol* 56:323–325.
- Cockcroft A, Edwards J, McCarthy P, Andersson N (1981): Allergy in laboratory animal workers. *Lancet* April 827–830.
- Das R, Tager IB, Gamsky T, Schenker MB, Royce S, Balmes JR (1992): *J Occup Med* 34:53–60.
- Davies G, McArdle L (1981): Allergy to laboratory animals: A survey by questionnaire. *Int Arch Allergy Appl Immunol* 64:302–307.
- FauskerBler T, Tritschler J (1992): A review of epidemiologic methods applied in studies on laboratory animal allergy, with a discussion of the relation between prevalence and risk of an irreversible disease in a dynamic population. *Soz Praventivmed* 37:269–275.
- Ferris BG Sr (1978): American Thoracic Society Executive Committee, Epidemiology Standardization Project. *Am Rev Respir Dis* 118:1–120.
- Gross N (1980): Allergy to laboratory animals: Epidemiologic, clinical, and physiologic aspects, and a trial of cromolyn in its management. *J Allergy Clin Immunol* 66:158–165.
- Kibby T, Powell G, Cromer J (1989): Allergy to laboratory animals: A prospective and cross-sectional study. *J Occup Med* 31:842–846.
- Knudson RJ, Slatin RC, Lebowitz MD, Burrows B (1976): The maximal expiratory flow-volume. *Am Rev Respir Dis* 113:587–591.
- Lincoln T, Bolton N, Garrett Jr (1974): A. Occupational allergy to animal dander and sera. *J Occup Med* 16:465–469.
- Lutsky I, Neuman I (1975): Laboratory animal dander allergy: I. An occupational disease. *Ann Allergy* 35:201–205.
- Muller BA, Leick CA, Smith RM, Swelzer MT, Richerson HB (1993): Comparisons of specific and nonspecific bronchoprovocation in subjects with asthma, rhinitis and health subjects. *J Allergy Clin Immunol* 91:758–772.
- Newill CA, Evans III R, Khoury M (1986): Preemployment screening for allergy to laboratory animals: Epidemiologic evaluation of its potential usefulness. *J Occup Med* 28:1158–1164.
- Newill CA, Prenger VL, Fiske JE, Evans R, Diamond EL, Wei Q, Eggleston PA (1992): Risk factors for increased airway responsiveness to methacholine challenge among laboratory animal workers. *Am Rev Respir Dis* 146:1494–1500.
- Newman-Taylor AJ (1982): Laboratory animal allergy. *Eur J Respir Dis* 123:60–64.
- Newman-Taylor AJ, Myers JR, Longbottom JL, Sparkman D, Slovak AJM (1981): Immunologic differences between asthma and other allergic reactions in laboratory animalworkers. *Thorax* 36:299 (Abstract).
- SAS Institute Inc (1990): "SAS/STAT Guide for Personal Computers, Version 6 and Technical Report P-200, SAS/STAT Software: CALIS and LOGISTIC procedures." Cary, NC: SAS Institute, Inc.
- Sjostedt L, Willers S (1989): Predisposing factors in laboratory animal allergy: A study of atopy and environmental factors. *Am J Ind Med* 16: 199–208.
- Sjostedt L, Willers S (1993): A follow-up study of laboratory animal exposed workers: The influence of atopy for the development of occupational asthma. *Am J Ind Med* 24:459–469.
- Slovak AJM, Hill RN (1981): Does atopy have any predictive value for laboratory animal allergy? *Br J Ind Med* 44:129–132.
- Taylor G, Davies GE, Atloynyan REC, Morrow Brown H, Frankland AW, Morrison Smith J, Winch R (1976): Allergic reactions to laboratory animals. *Nature* 260:280.

United States Department of Agriculture (1990): "Animal Welfare Enforcement." Washington, DC: USGPO.

Venables KM, Topping MD, Howe W (1985): Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *Br Med J* 290:201–204.

Venables K, Tee R, Rosemarie Hawkins E, Gordon DJ, Wale CJ, Farrer NM, Lam TH, Baxter PJ, Newman-Taylor AJ (1988a): Laboratory animal allergy in a pharmaceutical company. *Br J Ind Med* 45:660–666.

Venables K, Upton JL, Rosemarie Hawkins E, Tee RE, Longbottom JL, Newman-Taylor AJ (1988b): Smoking, atopy, and laboratory animal allergy. *Br J Ind Med* 45:667–671.

Willers S, Hjortsberg V, Wihl JA, Orbek P (1992): Sensitization to laboratory animals and small airway hyperreactivity. *Indoor Environ* 1:82–87.