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Prevalence and diagnostic values of laboratory animal allergy among research personnel

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Abstract

Background: Laboratory animal allergy (LAA) has not been sufficiently investigated, although LAA is a relatively common work-related condition and important occupational hazard.

Objective: This study aimed to evaluate the prevalence of LAA and analyze the diagnostic value of serum specific IgE (sIgE) using the skin prick test (SPT) as a comparative standard.

Methods: Korean laboratory animal researchers who attended an annual symposium were requested to answer questionnaires regarding demographic characteristics, laboratory animal exposure, and symptoms related to laboratory animal exposure. A total of 213 participants underwent a SPT with mouse and rat epithelial allergen extract. We measured sIgE against rodent urine, epithelium, and serum allergens from 63 participants. SPT outcome served as the comparison method.

Results: Among 223 participants, 213 had direct/indirect exposure to mice or rats, and 30% and 14% of them complained of allergic symptoms after exposure to mouse and rat, respectively. Sensitization rates were 28% for mouse epithelium and 23% for rat epithelium. Compared to a positive SPT with wheal ≥ 3 mm, presence of sIgE against rodent allergens showed a higher positive predictive value of 87–91% at a cut-off level of 0.35 KUA/L. Agreement between SPT and sIgE test was determined to be fair to moderate.

Conclusion: Sensitization and allergy to mouse and rat were prevalent among laboratory personnel in Korea. When evaluating cases of potential LAA, the sIgE test can provide added diagnostic value if the skin test is positive. Careful interpretation of two tests is required to accurately diagnose LAA.

Key words: Allergy; Laboratory animal; Prevalence; Serum specific IgE; Skin prick test

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Introduction

Laboratory animal allergy (LAA) is an occupational allergic disease seen among people engaged in the care or use of laboratory animals. The prevalence of LAA varies based on the composition of the study population and the method used for diagnosis; nonetheless, it may affect up to 46% of exposed laboratory workers and result in considerable socioeconomic burden.[1-6] LAA can affect almost any organ system with a wide range of symptoms, including rhinoconjunctivitis, asthma, and skin symptoms, or a combination of these.[3-6] Rodents, in particular mice and rats, are widely used in scientific and medical research studies and can cause sensitization with subsequent allergic diseases.[7,8] While prevalence rates for mouse allergies have ranged from 10–32%, rat allergies have been similarly reported to be 12–31% of laboratory personnel.[1,9] In recent years, the number of rodents used for research has risen sharply in Korea and in the world, and consequently, LAA has received increasing attention.[10,11]

Therefore, it is necessary to accurately determine the prevalence of LAA and assess whether (i) the diagnostic test helps patients prevent exposure to any allergic substance and (ii) provide appropriate treatment to improve their health status and quality of life. Thus, our study was designed to evaluate the prevalence of LAA among personnel handling laboratory animals in Korea and to assess the value of two modalities, skin prick test (SPT) and allergen-specific IgE (sIgE), for determining mouse and rat allergies.

Material and Methods

Study subjects

This cross-sectional study was conducted during the 2018 annual symposium of the Korean Association of Laboratory Animal Science (KALAS) held during 18-20th July 2018. Initially, 223 subjects were enrolled in this study, but we excluded 10 subjects as they did not report recent exposure to mice or rats. Thus, the remaining 213 subjects were invited to enroll in the study and relevant data from this group was used for analysis. Enrolled participants were administered a questionnaire and underwent a SPT and blood sampling for sIgE against mouse and rat allergens. Participants who had administered medications that could influence the SPT results such as antihistamines, systemic corticosteroids, and tricyclic antidepressants within a week were excluded before enrollment. The study protocol was approved by the institutional review board of our institution (IRB: GAIRB2018-094) and all individuals gave informed consent to participate.

Questionnaires

Subjects were asked to answer a questionnaire that obtained information on demographic characteristics, medical history, history of laboratory animal exposure, and allergic symptoms during exposure to laboratory animals. Exposure to mouse and rat was queried as handling and working with or near rodents (direct exposure) or as contact with a person who had direct exposure (indirect exposure). Participants were regarded as having a LAA if they suffered from allergic symptoms during working hours or after direct/indirect contact with laboratory animals. Allergic symptoms such as rhinitis and conjunctivitis were defined as follows: rhinitis, one or more of the following symptoms, namely, rhinorrhea, sneezing, nasal congestion, postnasal drip, or itchy nose; conjunctivitis, one or more of the following symptoms, such as red, swollen, or itchy eyes with or without tears.

Skin prick test

Subjects who had been exposed to mice and rats underwent skin prick test (SPT) using rodent allergens such as mouse and rat allergen extract (Lofarma, Milano, Italy). SPT was administered to each subject, and the test used 1% histamine solution and diluent as positive and negative controls, respectively. The SPT was scored as positive under three conditions, namely, (i) Any wheal larger than that of negative control; (ii) allergen-induced mean wheal diameter (MWD) ≥ 3 mm; (iii) ratio of mean wheal diameter between allergen and histamine (A/H ratio) ≥ 1. The allergen sensitization rates were calculated using a positive SPT of a wheal 3 mm or greater.

Specific IgE measurement

We excluded 12 subjects with false positive SPT results responding to negative control of SPT and 15 subjects who did not consent to have their blood drawn. Specific IgE measurement was performed in 63 subjects who had tested positive in SPT. A positive SPT was defined as any wheal larger than that of negative control. Serum sIgE against urinary, epithelial, and serum allergens from mouse and rat were measured using the ImmunoCAP® kit (Thermofisher, Uppsala, Sweden) (**Figure 1**).

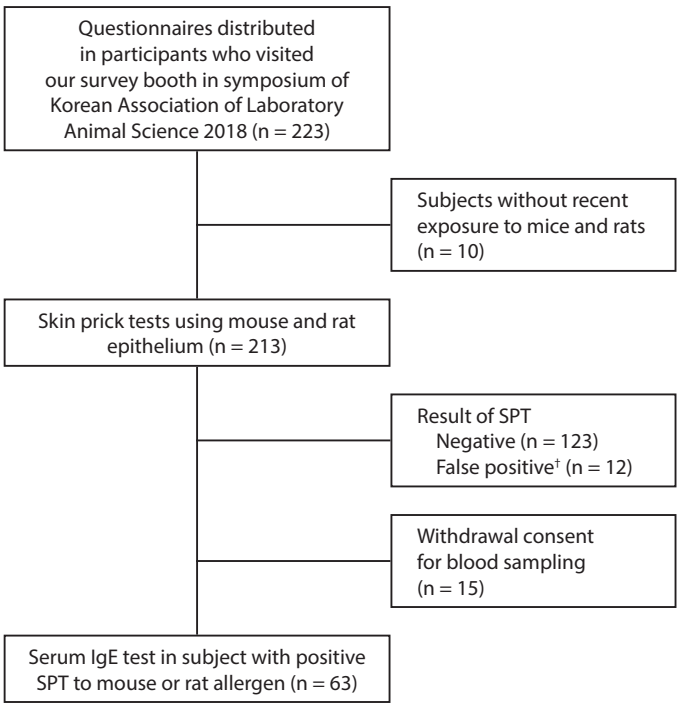

Figure 1. Participant flowchart.
SPT, Skin prick tests; sIgE, serum specific IgE. †False positive is a result that responds to negative control of SPT.

Statistical analysis

Continuous variables are expressed as medians (interquartile ranges) due to non-normally distributed data. Categorical variables are expressed as absolute numbers and percentages. Continuous variables were compared using the Mann–Whitney *U*-test. Categorical variables were analyzed using the Chi-squared test. Two-by-two tables were used to calculate percent positive predictive value (PPV), negative predictive value (NPV), sensitivity (SN), and specificity (SP). Cohen's kappa and overall agreement were calculated to compare sIgE test results against those of SPT, which was used as the reference standard.[12] Kappa values were interpreted as almost perfect (0.8–1.0), substantial (0.6–0.8), moderate (0.4–0.6), fair (0.2–0.4), and poor (< 0.2).[12] All statistical analyses were carried out using SPSS Version 19 (SPSS, Chicago, IL, USA). A p value less than 0.05, using a two-tailed analysis, was considered significant.

Results

Baseline characteristics of laboratory animal personnel in Korea

Demographic characteristics of the study subjects are listed in **Table 1**. LAA during exposure to mouse were reported by 64 participants (30.0%) while 29 (13.7%) reported LAA to rat exposure. In the study subjects who were exposed to rats, LAA group was older (33 vs 28 years, $p = 0.024$) and had a longer duration (6.5 vs 3.0 years, $p = 0.018$) of occupation as compared to non-LAA group. Among the 64 subjects who developed a LAA to mice, the most common ever-diagnosed allergic disease was allergic rhinitis (54.7%), followed by allergic conjunctivitis (25.0%), asthma (14.1%), atopic dermatitis (14.1%), chronic urticaria (12.5%), food allergy (4.7%), and drug allergy (4.7%). Allergic rhinitis, allergic conjunctivitis, and asthma were more prevalent in subjects who developed LAA during exposure to mouse compared to subjects without LAA (54.7% vs. 29.5%, $p < 0.001$; 25.0% vs. 12.1%, $p < 0.024$; 14.1% vs 3.4%, $p < 0.007$; respectively). Among 29 subjects who showed LAA to rats, the most common ever-diagnosed condition was allergic rhinitis (62.1%), followed by chronic urticaria (20.7%), allergic conjunctivitis (10.3%), asthma (10.3%), atopic dermatitis (10.3%), food allergy (6.9%), and drug allergy (6.9%). Allergic rhinitis and chronic urticaria were more prevalent in subjects who developed LAA during exposure to rat compared to subjects without LAA (62.1% vs. 33.0%, $p < 0.004$; 20.7% vs. 4.9%, $p < 0.008$; respectively).

Allergic symptoms during exposure to laboratory animals

As shown in **Table 2**, rhinitis (67.2%) was the most common symptom among the 64 subjects allergic to mouse, followed by itchy skin (64.1%), cough (48.4%), conjunctivitis (40.6%), skin rash (28.1%), urticaria (23.4%), sputum (17.2%), chest discomfort (12.5%), wheezing (9.4%), dyspnea (7.8%), and angioedema (6.3%). Among the 29 subjects allergic to rat, the most frequent allergic symptom during exposure was itchy skin (69.0%), followed by rhinitis (58.6%), cough (37.9%), urticaria (31.0%), skin rash (24.1%), conjunctivitis symptom (17.2%), chest discomfort (17.2%), dyspnea (13.8%), wheezing (10.3%), sputum (6.9%), and angioedema (3.4%).

Table 2. Allergic symptoms during exposure to mouse or rat.

	Subjects allergic to mouse (n = 64)	Subjects allergic to rat (n = 29)
Rhinitis symptom*	43 (67.2)	17 (58.6)
Itchy skin	41 (64.1)	20 (69.0)
Cough	31 (48.4)	11 (37.9)
Conjunctivitis symptom†	26 (40.6)	5 (17.2)
Skin rash	18 (28.1)	7 (24.1)
Urticaria	15 (23.4)	9 (31.0)
Sputum	11 (17.2)	2 (6.9)
Chest discomfort	8 (12.5)	5 (17.2)
Wheezing	6 (9.4)	3 (10.3)
Dyspnea	5 (7.8)	4 (13.8)
Angioedema	4 (6.3)	1 (3.4)

Data are shown as frequency (%). *Rhinitis symptoms are defined as one or more of rhinorrhea, sneezing, nasal congestion, postnasal drip, and itchy nose, †Conjunctivitis symptoms are defined as one or more of red, swollen, and itchy eyes with or without tears.

Table 1. Demographic characteristics of the study subjects.

	Subjects exposed to mouse (n = 213)		*P*-value*	Subjects exposed to rat (n = 211)		*P*-value*
	LAA to mouse (n = 64)	Non-LAA (n = 149)		LAA to rat (n = 29)	Non-LAA (n = 182)	
Age, years	29.5 [26.0-34.0]	28.0 [25.0-34.5]	0.443	33.0 [27.0-38.0]	28.0 [25.-33.3]	**0.024**
Female (%)	41 (64.1)	95 (63.8)	1.000	18 (62.1)	117 (64.3)	0.837
Duration of occupation, years	4.6 [1.6-9.0]	3.0 [1.3-8.3]	0.170	6.5 [3.0-9.8]	3.0 [1.1-8.0]	0.018
Ever diagnoses of allergic diseases						
Allergic rhinitis	35 (54.7)	44 (29.5)	**0.001**	18 (62.1)	60 (33.0)	**0.004**
Allergic conjunctivitis	16 (25.0)	18 (12.1)	**0.024**	3 (10.3)	31 (17.0)	0.586
Asthma	9 (14.1)	5 (3.4)	**0.007**	3 (10.3)	11 (6.0)	0.416
Atopic dermatitis	9 (14.1)	23 (15.4)	0.838	3 (10.3)	29 (15.9)	0.582
Chronic urticaria	8 (12.5)	7 (4.7)	0.075	6 (20.7)	9 (4.9)	**0.008**
Food allergy	3 (4.7)	9 (6.0)	1.000	2 (6.9)	10 (5.5)	0.672
Drug allergy	3 (4.7)	4 (2.7)	0.431	2 (6.9)	5 (2.7)	0.247
Family history of allergic diseases	25 (45.5)	50 (38.2)	0.414	10 (50.0)	64 (39.0)	0.469

Data are shown as median [interquartile range] or frequency (%). **P*-value < 0.05 is shown as boldface in comparing variables between subjects with mouse allergy and those without it or between subjects with rat allergy and those without it.

Results of SPT with mouse and rat epithelial allergen extract

Overall sensitization rates of mouse and rat epithelium were 28% and 23%, respectively. As shown in **Table 3**, among the 201 subjects who underwent SPT using commercially available mouse epithelium allergen extract, the LAA group showed higher MWD and A/H ratio compared to those of the non-LAA group (median [interquartile range, IQR]: 3.0 [0.0-5.0] mm vs 0.0 [0.0-0.0] mm, $p < 0.001$; 0.5 [0.0-0.9] vs 0.0 [0.0-0.0], $p < 0.001$, respectively). The proportion of subjects with a positive SPT result was also higher in the LAA group than in the non-LAA group (53.3% vs. 17.0% for MWD ≥ 3 mm, $p < 0.001$; 25.0% vs. 6.4% for A/H ratio ≥ 1, $p < 0.001$; respectively). Among 199 subjects who underwent SPT using commercially available rat epithelium allergen extract, the LAA group also showed higher MWD and A/H ratio compared to those of the non-LAA group (2.8 [0.0-5.0] mm vs 0.0 [0.0-0.0] mm, $p = 0.001$; 0.4 [0.0-0.9] vs 0.0 [0.0-0.0], $p < 0.001$, respectively). The proportion of subjects with a positive SPT result was also higher in the LAA group than in the non-LAA group (50.0% vs. 18.1% for MWD ≥ 3 mm, $p < 0.001$; 21.4% vs. 7.0% for A/H ratio ≥ 1, $p = 0.025$; respectively).

Performance of sIgE for mouse and rat allergen compared to the SPT

We collected blood samples from 63 participants who had tested positive for SPT for mouse or rat allergens. We used cut-off levels of SPT wheal size ≥ 3 mm and sIgE ≥ 0.35 kU/L to compare test performance and evaluated the diagnostic performance of sIgE against rodent allergens from 3 different allergenic sources, such as urine, epithelium, and serum. SPT was considered the clinical standard (**Table 4**). When compared to SPT, sIgE for the three different allergens showed acceptable PPV (87.2–90.6% for mouse allergen and 81.0-82.4% for rat allergen), but rather low NPV (45.2-62.5% for mouse allergen and 53.3-66.7% for rat allergen). The SN for mouse allergen ranged from 63.0% to 87.0%, and the SP ranged from

Table 3. Results of skin prick test with mouse and rat epithelial allergen extracts.

	SPT with mouse allergen (n = 201)		*P*-value*	SPT with rat allergen (n = 199)		*P*-value*
	LAA to mouse (n = 60)	Non-LAA (n = 141)		LAA to rat (n = 28)	Non-LAA (n = 171)	
MWD, mm	3.0 [0.0-5.0]	0.0 [0.0-0.0]	**< 0.001**	2.8 [0.0-5.0]	0.0 [0.0-0.0]	**0.001**
A/H ratio	0.5 [0.0-0.9]	0.0 [0.0-0.0]	**< 0.001**	0.4 [0.0-0.9]	0.0 [0.0-0.0]	**< 0.001**
Positive results						
MWD ≥ 3mm	32 (53.3)	24 (17.0)	**< 0.001**	14 (50.0)	31 (18.1)	**< 0.001**
A/H ratio ≥ 1	15 (25.0)	9 (6.4)	**< 0.001**	6 (21.4)	12 (7.0)	**0.025**

Data are shown as median [interquartile range] or frequency (%). *P-value < 0.05 is shown as boldface in comparing variables between subjects with mouse allergy and those without it or between subjects with rat allergy and those without it.
MWD, mean wheal diameter provoked by allergen; A/H ratio, allergen/histamine ratio of mean wheal diameter

Table 4. Comparison of characteristics in sIgE compared to SPT for mouse and rat allergens*

	PPV%	NPV%	SN%	SP%	Overall agreement (%)†	Kappa index
Mouse allergen						
Positive if sIgE for						
Urine ≥ 0.35 kU/L	90.6	45.2	63.0	82.4	68.3	0.360
Epithelium ≥ 0.35 kU/L	85.1	62.5	87.0	58.8	79.4	0.466
Serum ≥ 0.35 kU/L	87.2	50.0	73.9	70.6	73.0	0.394
Rat allergen						
Positive if sIgE for						
Urine ≥ 0.35 kU/L	81.0	66.7	82.9	63.6	76.2	0.471
Epithelium ≥ 0.35 kU/L	82.4	55.2	68.3	72.7	69.8	0.382
Serum ≥ 0.35 kU/L	81.8	53.3	65.9	72.7	68.3	0.356

*By blood sampling from 63 patients who came out positive for SPT, we measured sIgE for urine, epithelium, and serum of mouse and rat. We compared sIgE results with SPT as the clinical gold standard. †Agreement is a percentage of overall results (SPT ≥ 3 mm and sIgE ≥ 0.35 kU/L) where both tests have either both positive and negative results. SPT, skin prick test; sIgE, serum specific IgE, PPV, positive predictive value; NPV, negative predictive value; SN, sensitivity; SP, specificity

58.8% to 82.4%. The SN for rat allergen ranged from 65.9% to 82.9%, and the SP ranged from 63.6% to 72.7%. Overall agreement and kappa index between SPT and sIgE tests ranged from 68.3–79.4% and 0.360-0.466 for mouse allergen, and from 68.3–76.2% and 0.356–0.471 for rat allergen, respectively.

Discussion

Laboratory animal personnel can come in to contact with organic material from rodents in multiple ways. They had attendant risks of allergic sensitization according to the nature and intensity of exposure with rodent allergens including dander, saliva, urine, and serum.[1,8] Such exposure to sensitizing agents in the workplace can lead to allergic diseases.[13,14] Depending on the population studied and the diagnostic methods used, the prevalence of sensitization and allergy symptoms due to rodents has shown wide variation, but LAA has not been extensively studied in Korea.[1,10]

In this study, up to one-third of the participants suffered from allergy symptoms upon exposure to mice (30.0%) or rats (13.7%), and rhinoconjunctivitis was the most common allergic manifestation, followed by cough and dermatologic symptoms such as rash and urticaria. Further, questionnaire-based reporting of sensitization to rodents by qualitative and quantitative measures was higher in the symptomatic group (LAA) than in the non-symptomatic group. Similarly, several cross-sectional studies have also reported that 10–47% of exposed personnel have laboratory animal allergies that often manifest as rhinoconjunctivitis, asthma, and skin reactions such as hives and rashes.[3-6]

Prevalence of sensitization to mouse and rat allergens has been reported in 4–18% of laboratory personnel.[5,15-20]; however, we found much higher levels of sensitization in our cohort (28% for mouse epithelium and 23% for rat epithelium). Thus, these findings from cross-sectional surveys of laboratory personnel are concerning and warrant special attention on LAA in Korea.

Structured questionnaires and diagnostic tests, such as allergen specific IgE measurements and lung function tests, have been used for screening and identification of LAA. Allergen-specific IgE measurements can be determined using the SPT or the sIgE assay. SPT, commonly used for detecting the causative allergen, remains the gold standard for *in vivo* assessment of allergen-specific IgE. In line with previous studies in laboratory workers and community populations, our results with SPT showed higher SP and NPV (data not shown).[21,22]

Measurement of sIgE levels has been used as an alternative to SPT for identifying the causative allergen for multiple reasons, including those related to operator technique, underlying medical conditions, or adverse reactions.[23] Compared to SPT, the PPV for sIgE against mouse and rat was higher than the NPV, even though SN and SP varied depending on the allergen source used. Our analyses demonstrated that combined results of sIgE for rodent allergens were similar to those of sIgE for the individual components (data not shown). Taken together, our data indicate that the high PPV of rodent sIgE can be used to add diagnostic value (i.e., ruling in) in cases where the skin test for evaluating LAA is positive.

A comparison of the two methods has been reported previously.[24,25] Good strength of agreement between SPT and sIgE has been observed for aeroallergens such as house dust mites, trees, grasses, weeds, and pets, including cat and dog.[24] Nevertheless, some studies have revealed a discrepancy between these two tests.[25] Our study found that both SPT and sIgE provided fair-to-moderate agreement, depending on the source of rodent allergens. The discordance between the SPT and the sIgE assays can be explained by differences in the composition of the allergens used. Previous studies showed wide variations in compositions of SPT reagents and their IgE binding capacity. There were also differences in allergenic potency and concentration of the major allergens, leading to inconsistent results even when the same extract was used.[26,27] Therefore, the quality of allergen extracts used in SPT and sIgE is of main significance to ensure a diagnostic accuracy to allergic diseases.

There are several limitations to this study. First, we could not evaluate the clinical relevance of LAA using challenge tests. We enrolled participants who visited an annual symposium and relied on self-reported questionnaire data to describe allergic conditions. Second, asymptomatic sensitization, a risk factor for subsequent allergy development, may have affected our results. Lastly, the results of the two diagnostic tests might have been influenced by allergens from other sources or cross-reactivity between mouse and rat allergens. To overcome these limits, component-resolved diagnostics may be needed to identify the patient's reactivity to specific allergenic protein components. Additional studies are required to investigate whether allergen component analysis can add value to LAA diagnosis in routine clinical practice.

Nevertheless, the strengths of this study are as follows. To the best of our knowledge, this is the first study of researchers from various research institutes in Korea, and the results of this study would be of value to healthcare providers and health authorities as it can help to identify the unmet need of prevention and countermeasures against LAA. Moreover, we evaluated the performance of sIgE against rodent allergens from different allergen sources and compared the results to those from SPT, which is the current gold standard. Our findings suggest that the sIgE assay could be an adjunct tool in the accurate identification of LAA but that additional larger-scale studies are needed to draw a definite conclusion.

In summary, our data indicate that LAA affects about one third of all personnel exposed to laboratory animals and that raising awareness and strategies to control LAA are warranted. sIgE tests can be used along with SPT to detect LAA among symptomatic personnel. Detailed interpretation of both SPT and sIgE measurement, despite the relative difference in performance, can help adequate assessment of LAA.

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References

1. Bush RK, Wood RA, Eggleston PA. Laboratory animal allergy. J Allergy Clin Immunol. 1998;102(1):99-112.
2. Vandenplas O, Suojalehto H, Cullinan P. Diagnosing occupational asthma. Clin Exp Allergy. 2017;47(1):6-18.
3. 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(1): 41-7.
4. Davies GE, McArdle LA. Allergy to laboratory animals: a survey by questionnaire. Int Arch Allergy Appl Immunol. 1981;64(3):302-7.
5. 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(3):545-54.
6. 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(10):667-71.
7. 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(10):660-6.
8. Jones M. Laboratory Animal Allergy in the Modern Era. Curr Allergy Asthma Rep. 2015;15(12):73.
9. Corradi M, Ferdenzi E, Mutti A. The characteristics, treatment and prevention of laboratory animal allergy. Lab Anim (NY). 2012;42(1):26-33.
10. Feary J, Cullinan P. Laboratory animal allergy: a new world. Curr Opin Allergy Clin Immunol. 2016;16(2):107-12.
11. Zastrow M. Why South Korea is the world's biggest investor in research. Nature News. 2016;534(7605):20.
12. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
13. Palmberg L, Sundblad BM, Lindberg A, Kupczyk M, Sahlander K, Larsson K. Long term effect and allergic sensitization in newly employed workers in laboratory animal facilities. Respir Med. 2015;109(9):1164-73.
14. Simoneti CS, Ferraz E, de Menezes MB, Bagatin E, Arruda LK, Vianna EO. Allergic sensitization to laboratory animals is more associated with asthma, rhinitis, and skin symptoms than sensitization to common allergens. Clin Exp Allergy. 2017;47(11):1436-44.
15. Hewitt RS, Smith AD, Cowan JO, Schofield JC, Herbison GP, Taylor DR. Serial exhaled nitric oxide measurements in the assessment of laboratory animal allergy. J Asthma. 2008;45(2):101-7.
16. Krakowiak A, Wiszniewska M, Krawczyk P, Szulc B, Wittczak T, Walusiak J, et al. Risk factors associated with airway allergic diseases from exposure to laboratory animal allergens among veterinarians. Int Arch Occup Environ Health. 2007;80(6):465-75.
17. Schumacher MJ, Tait BD, Holmes MC. Allergy to murine antigens in a biological research institute. J Allergy Clin Immunol. 1981;68(4):310-8.
18. Cullinan P, Lowson D, Nieuwenhuijsen 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(9):589-92.
19. Heederik D, Venables KM, Malmberg P, Hollander A, Karlsson AS, Renstrom A, et al. Exposure-response relationships for work-related sensitization in workers exposed to rat urinary allergens: results from a pooled study. J Allergy Clin Immunol. 1999;103(4):678-84.
20. Platts-Mills TA, Longbottom J, Edwards J, Cockroft A, Wilkins S. Occupational asthma and rhinitis related to laboratory rats: serum IgG and IgE antibodies to the rat urinary allergen. J Allergy Clin Immunol. 1987;79(3):505-15.
21. Chong LK, Ong MJ, Curtin-Brosnan J, Matsui EC. Skin test sensitivity to mouse predicts allergic symptoms to nasal challenge in urban adults. Allergy Asthma Proc. 2010;31(6):472-6.
22. Sharma HP, Wood RA, Bravo AR, Matsui EC. A comparison of skin prick tests, intradermal skin tests, and specific IgE in the diagnosis of mouse allergy. J Allergy Clin Immun. 2008;121(4):933-9.
23. de Vos G. Skin testing versus serum-specific IgE testing: which is better for diagnosing aeroallergen sensitization and predicting clinical allergy? Curr Allergy Asthma Rep. 2014;14(5):430.
24. Calabria CW, Dietrich J, Hagan L. Comparison of serum-specific IgE (ImmunoCAP) and skin-prick test results for 53 inhalant allergens in patients with chronic rhinitis. Allergy Asthma Proc. 2009;30(4):386-96.
25. de Vos G, Nazari R, Ferastraoaru D, Parikh P, Geliebter R, Pichardo Y, et al. Discordance between aeroallergen specific serum IgE and skin testing in children younger than 4 years. Ann Allergy Asthma Immunol. 2013; 110(6):438-43.
26. Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology task force report on 'dose-response relationship in allergen-specific immunotherapy'. Allergy. 2011;66(10):1345-59.
27. Pagani M, Antico A, Cilia M, Calabro D, Poto S, Pecora S, et al. Comparison of different diagnostic products for skin prick testing. Eur Ann Allergy Clin Immunol. 2009;41(1):23-31.