

The characteristics, treatment and prevention of laboratory animal allergy

Massimo Corradi, MD, Elisabetta Ferdenzi, MD & Antonio Mutti, MD

Laboratory animal allergy (LAA) is a pervasive problem that affects up to one-third of laboratory animal personnel. An immediate hypersensitivity reaction can be triggered by contact with antigens present in urine, hair, dander and saliva of laboratory animals. The authors provide an overview of the epidemiology, triggering mechanisms, diagnosis, treatment and risk factors of LAA. They also discuss primary and secondary prevention measures that can be taken to reduce LAA morbidity and to allow personnel suffering from LAA to safely continue to do their jobs.

An allergy is characterized by a hypersensitivity reaction to stimuli that have no effect on most people. This exaggerated response of the immune system may be initiated by immunological mechanisms (in most cases, immunoglobulin E (IgE) antibodies) or may be non-immunological. Laboratory animal allergy (LAA) is caused by an immunological hypersensitivity reaction to high-molecular-weight antigens that are present in laboratory animals' urine, dander and saliva. All laboratory animal facility personnel who regularly come in contact with laboratory animals, such as technicians, researchers, cleaning staff, veterinarians and even administrative staff, are at risk of developing LAA. Generally, most epidemiological studies indicate a LAA prevalence ranging from 6% to 44% (refs. 1–10; **Table 1**) and an incidence ranging from 9% to 30% (refs. 11–20; **Table 2**). Prevalence and incidence data vary widely because the diagnosis is not uniformly defined: some diagnoses are made solely on the basis of symptoms, whereas others also require a positive skin test or confirmation of the presence of laboratory animal allergen-specific IgE antibodies.

In 1998, the US National Institute for Occupational Safety and Health (NIOSH) estimated that one-third of the ~2 million people who constantly work with laboratory animals may develop allergic symptoms and that 10% of these people may develop bronchial asthma²¹. Clinical manifestations of LAA include cutaneous, ocular, nasal and pulmonary symptoms that can vary in intensity from mild to severe. The most common

symptoms are rhinitis and allergic conjunctivitis, present in 80% of people with LAA, and cutaneous reactions occur in almost 40% of people with LAA²²; asthma is present in 4–22% of those with LAA^{11,23}.

The clinical features of LAA include manifestation of symptoms after exposure to laboratory animal allergens; a latency period between exposure and the appearance of symptoms; low prevalence of the disease and dependence on individual predisposing factors; and a very specific response to sensitizing agents. Here, we provide an overview of LAA progression, symptoms, diagnosis and treatment. We also outline the host- and work environment-related risk factors associated with developing LAA. We also provide primary and secondary prevention strategies that can be implemented to reduce LAA morbidity and to allow personnel suffering from LAA to safely continue to do their jobs.

OVERVIEW OF LAA

Progression

LAA is usually caused by an immunological hypersensitivity reaction, which consists of three phases. The first is the exposure phase, during which lab animal antigens are recognized by the immune system. Allergens can come into contact with the body through inhalation, through the skin or through mucosa. Exposure is often caused by the inhalation of airborne allergens that are present in the laboratory animal facility environment. Contact with animal antigens can also occur outside enclosed facilities, because they can be transported on clothing and hair and later mobilized. This may explain

Department of Clinical Medicine, Nephrology and Health Sciences, University of Parma, Parma, Italy. Correspondence should be addressed to M.C. (massimo.corradi@unipr.it).

TABLE 1 | Prevalence of LAA symptoms among laboratory animal personnel in previously published studies¹⁻¹⁰

Reference	Year of publication	Location of study	Personnel surveyed	Personnel with LAA symptoms	Prevalence of LAA
1	1992	Japan	5,641	1,304	23%
2	1999	Northern Europe	650	36	6%
3	1997	Holland	99	19	19%
4	2002	Northern Italy	45	5	11%
4	2002	Central Italy	80	9	11%
5	2010	US	369	78	21%
6	2000	US	147	29	19%
7	2004	Holland	529	77	15%
8	1981	UK	146	48	30%
9	2009	Canada	414	72	17%
10	1988	UK	138	60	44%

the presence of sensitization to laboratory animal allergens in children of exposed personnel²⁴.

The second phase is a pre-allergy sensitization phase, during which the body produces specific IgE antibodies against animal proteins and glycoproteins. Sensitization does not seem to be correlated with peak cumulative exposure, so even 1–2 h per month of exposure may lead to sensitization^{5,25}. In more than 600 people exposed to laboratory animal antigens, there was clear evidence of a relationship between the amount of exposure and the presence of sensitization, especially in subjects without a genetic predisposition to LAA². Another study found that more intense exposure led to a higher prevalence of sensitization²⁶. In a 2-y longitudinal study of 110 newly hired personnel that developed sensitization to laboratory animal antigens, the number of hours of contact with the animals correlated with both the degree

of sensitization and the concentration of lab animal-specific IgE antibodies. There was a similar correlation with the concentration of immunoglobulin G4 antibodies, however, which could suggest that a modified Type 2 helper T cell (T_H2) response was occurring in these individuals; this response has a protective effect against developing sensitization^{19,20}.

The final phase, called the disease phase, is characterized by clinical allergic manifestations with the release of inflammatory mediators and the development of inflammation. A review of 13 studies of LAA detected that disease onset consistently occurred within 3 y of starting work with laboratory animals^{17,27}. The symptoms of this phase include sneezing and rhinitis with nasal discharge, conjunctival lacrimation, photophobia and eyelid swelling. These symptoms frequently overlap; for example, asthma rarely occurs in the absence

TABLE 2 | Incidence of LAA symptoms among laboratory animal personnel in previously published studies¹¹⁻²⁰

Reference	Year of publication	Location of study	Personnel with LAA symptoms	Incidence of LAA
11	1999	US	—	15%
12	1987	UK	383	12%
13	1995	UK	218	13%
14	1999	UK	342	30%
15	1983	UK	585	19%
16	2005	US	495	9%
17	2000	US	417	9%
18	1979	US	399	15%
19	1989	US	69	13%
20	2011	Holland	110	20%

Ref. 11 did not state the number of personnel with LAA symptoms.

of previous rhinitis²⁸. Clinical signs in already sensitized subjects occur within a few minutes of exposure to allergens and spontaneously resolve within hours. Rhinoconjunctivitis, although mild, may indicate the future development of asthma²⁹. Bronchial asthma is manifested by wheezing, dyspnea, dry cough and chest tightness. These symptoms may persist for several days and cause frequent nocturnal awakenings. Although we found no data specifically concerning occupational asthma and LAA, it is known that the prognosis of occupational asthma is worse if exposure to the causative agent continues³⁰. Anaphylactic reactions are rare but possible and are typically induced by animal bites or contaminated needles^{31–33}.

Diagnosis and treatment

LAA is diagnosed when the symptoms listed above are present and appropriate diagnostic investigations result in positive outcomes³⁴. The diagnoses of rhinitis, conjunctivitis and urticaria are often only clinical, whereas a diagnosis of asthma requires instrumental confirmation (a reversible spirometry test or bronchial methacholine reactivity test). Documented antigen-specific sensitization to lab animal-associated allergens is not mandatory for a diagnosis of LAA, but it is highly recommended for a more reliable diagnosis. LAA can be treated by pharmacologically treating LAA-associated symptoms directly. No vaccine is available for LAA.

RISK FACTORS

Host-related factors

The search for risk factors implicated in the development of LAA has resulted in numerous independent studies with differing results. Risk factors that have been strictly associated with characteristics of the host include atopy, sensitization to laboratory animal allergens, smoking of tobacco and a history of respiratory diseases.

Atopy, defined as a genetic predisposition to develop allergic diseases as a result of contact with or ingestion, injection or inhalation of allergens, is considered the main risk factor for LAA. Although some isolated studies have found that atopy weakly correlates with the development of LAA¹⁸, most studies have found a strong correlation between atopy and either the development of lab animal sensitivity or clinical manifestations of LAA^{13,35–39}. It is estimated that atopic personnel have a risk of developing sensitivity that is 10 times greater than that of non-atopic personnel²³. In addition, more atopic individuals develop sensitization (75% in 2 y) than do non-atopic individuals (24% in 2 y)¹². In non-atopic subjects, the risk of sensitization to rat urinary protein increases with exposure, whereas in subjects with atopy to animal antigens (e.g., dog and cat antigens) and to other non-aerodispersed antigens, only exposure to low doses increases the risk of

sensitization, and the dose-response relationship is less clear². A recent review concluded that the estimated odds ratio for the development of LAA in atopic subjects compared with non-atopic subjects was 3.35 (ref. 37). Non-atopic individuals exposed to laboratory animals for at least 2 h per week had an increased risk of developing LAA, but the risk was even greater in atopic subjects³. Furthermore, when personnel do develop LAA, the disease is often clinically more severe in atopic subjects than in non-atopic subjects²³.

Sensitivity to laboratory animal allergens is not only a sign of the preclinical disease phase but also a predisposing factor for the development of LAA^{27,40}. Sensitization to laboratory animal allergens can be determined by carrying out a skin prick test for mouse and rat urinary proteins or by testing the blood for the presence of laboratory animal antigen-specific IgE. A prospective study correctly predicted 87.4% of the subjects who subsequently developed LAA on the basis of combined results of skin tests and the presence of allergen-specific IgE¹⁴. In a group of seven unrelated studies, 51–69% of subjects with LAA had a positive response to the prick test²⁷. It has been claimed that an individual's total level of IgE may be used as an indicator of his or her risk of developing LAA⁴¹. Sensitization to laboratory animals, mainly rats, may arise in subjects who are not occupationally exposed to animals because of a cross-reaction with allergens from cats and dogs⁴⁰. A prospective study on a cohort of 417 newly recruited apprentices working in animal enclosures found that a positive result on a skin test for pet allergens is also a risk factor for LAA development^{17,42}.

Tobacco smoke has been associated with the development of LAA in some studies^{10,14,39}, but the evidence is slight; others have found no such effect^{2,43}. Cigarette smokers have a probability of developing LAA leading to asthma that is 1.5–3 times greater than that of non-smokers²². Exposure to tobacco smoke can increase serum IgE levels⁴⁴, which may predispose an individual to LAA. Lung function declines more in previous smokers exposed to laboratory animals than in subjects who have never smoked⁴⁵. Pre-existing bronchial hyper-reactivity is an additional risk factor for the development of LAA³⁰.

Environmental factors

In addition to host characteristics, factors in the work environment also can influence the development of LAA. A dry environment favors the volatility of antigens. Studies of the distribution of particulate sizes have demonstrated a high prevalence of particles measuring 5–15 µm in diameter, although the diameter of a substantial fraction of particulates is less than 4 µm (ref. 46). However, the antigens produced by laboratory animals are highly allergenic, and so

even antigen concentrations on the order of parts per billion in laboratory facility environments can induce symptoms in sensitized subjects^{22,47,48}.

The type of allergens contained in the environment and the intensity and duration of exposure to the environment can greatly affect risk of developing LAA. Male rodents excrete higher levels of urinary allergens than female rodents, probably owing to the spontaneous nephropathy with proteinuria that develops with age in male rats⁴⁹. Many of these allergens belong to the lipocalin family of proteins, whose sequences are similar to those found in parasites (e.g., schistosoma) and are similarly capable of causing IgE-mediated reactions⁵⁰. Hamsters and guinea pigs seem to be less allergenic laboratory animals¹⁶.

Intensity of exposure has emerged as a likely risk factor for LAA. Several epidemiological studies have indicated a linear relationship between exposure to high-molecular-weight antigens and the development of sensitivity and occupational allergic diseases such as LAA^{22,44,50}. This positive relationship seems to be especially present in non-atopic subjects^{13,26}. The presence of sensitization and of LAA-triggering symptoms was more pronounced in personnel whose jobs required high levels of exposure to antigens³⁷. The relationship between antigen exposure and risk may differ for the development of sensitization versus LAA. For example, although the risk of sensitization increases with increased exposure to rats, the risk of LAA does not²⁶. Studies have shown that sensitization can occur at lower environmental antigen levels than those capable of triggering LAA^{36,51}. Antigen concentrations of $<3 \text{ ng/m}^3$ and $<5 \text{ ng/m}^3$ are associated with a low risk of developing sensitization and LAA, respectively⁵².

Risk of developing LAA may also increase with length of exposure to laboratory animal antigens. LAA typically develops in affected employees within the first 3 y of exposure²², although the period of latency is less for the development of symptoms of rhinitis versus asthmatic symptoms⁴⁷. There is a wide range of individual variability that can affect the latency period, however, especially in non-atopic subjects.

PREVENTION

It is not possible to establish an environmental antigen concentration below which there is no risk of developing an allergy³⁷. Still, prospective studies have found that reducing allergen exposure can reduce both the incidence and prevalence of LAA²³. Primary and secondary prevention measures are required to control laboratory animal personnel's exposure to allergens. A preventive program including educational measures, engineering controls, administrative rules and health monitoring can greatly reduce the incidence of LAA²⁹.

Primary prevention measures

Primary prevention measures are effective in reducing the incidence and prevalence of LAA and in reducing symptoms in people who have already developed the disease. Primary prevention measures may be divided into technical and organizational categories. Technical approaches include eliminating the substance, changing the substance and containing the substance by means of systems engineering. Organizational approaches include administrative controls, behavioral regulations and requiring the use of personal protective equipment (PPE).

The Occupational Safety and Health Act (OSHA)⁵³ requires employers to provide a safe and healthy workplace for their employees. Various strategies can be used to reduce occupational exposure to laboratory animal allergens. Engineering controls are a preferred approach because they are effective and because they do not rely on routine human implementation and intervention. Process automation using robotics has been successfully implemented at some larger animal facilities in order to improve efficiency while reducing both operating costs and occupational hazards (e.g., allergen exposure). Use of automated cage-handling and vacuum-bedding systems addresses occupational health concerns and helps to reduce on-the-job injuries, potentially reducing compensation claims and future litigation.

By far the most effective practice to reduce allergen exposure is to house mice in negatively pressurized individually ventilated cages (IVCs) and to change cage bedding using pressurized ventilated changing tables^{12,15,17,22,36,54-56}. IVC systems, in which HEPA-filtered air is supplied to the individual filter-top cages and exhausted air is captured, provide an effective barrier that protects animals from airborne contaminants and contains cage-borne aeroallergens, thus reducing the aeroallergen levels in the ambient room⁵⁷. Using IVC systems in the negative pressure mode allows greater containment of cage-borne aeroallergens. When one type of IVC was used at positive, neutral or negative pressure in relation to ambient room pressure, mouse urinary aeroallergens in the ambient room were reduced by 58%, 97% and almost 99.6%, respectively, in comparison with conventional open-top caging⁵⁸. Another study reported a 75% reduction in ambient room aeroallergen levels when a negative-pressure IVC was used instead of a positive-pressure IVC⁵⁹. Similarly, when a different IVC system was evaluated, positive-pressure operation (1.5 ng/m^3) led to higher ambient levels of rat urinary aeroallergens in the room than negative-pressure (0.1 ng/m^3) or background-pressure (1.0 ng/m^3) operation⁶⁰.

Organizational measures to prevent exposure to laboratory animal allergens can be implemented through employee training. It is essential to have

dedicated zones within the facility for manipulating animals. Additionally, when possible, less allergenic animals should be used: guinea pigs and hamsters are less allergenic than rats and mice, female rats and mice are less allergenic than males and young males are less allergenic than adult male rats and mice. Reducing the number of animals per room, handling animals under a hood and maintaining a vacuum in empty cages are all good working practices that can reduce allergen exposure⁵².

Good housekeeping practices are also essential. As inhalation is the main route of exposure, control measures should be aimed at containing particulates. Dry sweeping should be avoided, as it may re-suspend aeroallergens that have settled on the floor. Because animal proteins are soluble in water, moist cleaning methods should be used to avoid the resuspension of particles. The animal room should be constructed to facilitate effective cleaning, for example, by including rounded coping where the floor and walls meet and constructing surfaces to be smooth and washable. Some facility rooms are equipped with special air showers for personnel that prevent dust and particulates from spreading to adjacent rooms. Enclosures should be cleaned by a limited number of formally identified and dedicated technical staff members.

Personnel should wear a full tracksuit (closed at the neck, wrists and ankles) with a hood or other dedicated clothing and closed-toed shoes or boots⁶¹. If disposable clothing is to be used, it should be supplied (in sufficient numbers and appropriate sizes) in closed cabinets near the entrance of the enclosure. Alternatively, clothing can be supplied for short periods of about one week, before being washed by a specialized laundry informed about the risk of allergic sensitization. Employees should be provided with individual lockers for storing their personal clothing. In the case of reusable clothing, employees should be provided with a locker that has separate compartments for personal and working clothing. It is preferable for personnel not to wear contact lenses or personal items, such as bracelets and rings, that could be a vehicle for allergens. PPE, such as vinyl gloves, gowns, overalls, shoe covers, goggles, masks and ventilated helmets, should be worn to limit contact with allergens, respiratory or cutaneous penetration of allergens and dispersion of allergens outside the workplace. The integrity and efficacy of all PPE should be verified prior to use. Respiratory protective equipment includes filtering face piece (FFP3) respirator masks with a THP3 filter^{61,62} and N95 air purifying respirators^{63,64}, the use of which is regulated by the European Union's Directive on Personal Protective Equipment⁶⁵ or OSHA⁶⁶ in the US. Masks should be supplied in various sizes, and fit tests using a test aerosol such as saccharin should be carried out to verify that the respirator fits properly and provides

a tight seal. All protective masks should be disposable. Ideally, masks should be changed every day, although they may be replaced weekly. The simultaneous use of systems to reduce the concentrations of environmental allergens and of appropriate PPE can reduce levels of specific IgE to near zero⁶⁷.

Secondary prevention measures

The aims of secondary prevention measures are to identify LAA in personnel during its preclinical stages and to prevent it from evolving into overt disease. Organizational measures of secondary prevention include implementing medical surveillance programs and changing the assignments of personnel who are found to be at risk of developing LAA.

Occupational physicians can implement measures of secondary prevention by making regular preventive examinations of all professionals who come in contact with laboratory animals^{8,62,68}. Periodic examinations are usually annual, but may also be every 6 months in those most at risk, particularly during the first 3 y of employment (the period during which personnel are at greatest risk for the development of LAA). Preventive examinations should include taking a medical history, conducting a physical examination, including respiratory function testing, and providing relevant information to patients.

Specific and validated questionnaires are available to help in the evaluation of anamnestic symptoms. Some authors believe that careful history-taking is the best means of making the most of periodic examinations^{9,38}. The medical history should include the presence of a personal or family history of atopy, the presence of a personal history of smoking, the presence of respiratory or skin diseases and, most importantly, the presence of previous manifestations of LAA.

The physical examination should cover the respiratory tract, conjunctiva and skin. Spirometry should be performed at an early stage; the test can provide baseline functional values that can subsequently be used for comparative purposes, and abnormal values can be used for diagnostic purposes. A methacholine test is not recommended at an early stage in low-risk patients but might be helpful in high-risk patients, such as those with asthma, and for subsequent comparisons with later tests. For example, two spirometry or methacholine tests performed at different times may both give results that are within normal limits, but comparing the results of the two tests can help to identify a decline in lung function⁷. Skin prick tests or assays of animal antigen-specific IgE are not necessary but could be used to identify patients who are already sensitized by previous animal antigen exposure. Carrying out skin tests for common and ubiquitous inhaled allergens on all personnel is recommended, however, as a means of evaluating their atopic status. Measurement

of fractional exhaled nitric oxide (FeNO) has recently been used to diagnose and monitor bronchial asthma⁶⁹, because an increase in FeNO level seems to predict the onset of illness. FeNO levels are higher in subjects with LAA than in controls⁷⁰ and increase during the work week in sensitized subjects⁷¹. Determining FeNO levels may therefore be a less invasive and more rapid means of complementing spirometry than a methacholine test for evaluating lung inflammatory responses in patients at risk of developing LAA.

Patients should be informed of any risk factors for allergic events, of work tasks that expose them to greater risk of developing LAA, of the most appropriate measures of prevention and of clinical signs that may precede the onset of allergy symptoms. Should early clinical signs, such as mild rhinoconjunctivitis, appear, patients should schedule an additional visit with the physician so that necessary preventive measures may be taken.

Following the periodic preventive visit, four clinical scenarios may emerge. Patients without atopic respiratory, eye or skin disease can be considered at low risk of developing LAA and may continue working without limitation. Patients that are atopic, as determined by a positive skin prick test or the presence of IgE for ubiquitous inhaled antigens, must be considered at high risk. Although atopy has previously been considered a precluding factor when determining suitability for work with animals, a study of 323 personnel exposed to rats found that two-thirds of those employed in high-risk positions did not develop sensitization²². Therefore, the presence of atopy is not itself sufficient to preclude a person from continuing to perform tasks that require contact with laboratory animals. It should, however, necessitate increased personal prevention measures, such as increased use of PPE, and more frequent health surveillance^{46,52,72}. If the patient has not developed LAA after first 3–4 y, such precautions may be reduced.

A patient may be sensitized to animal antigens but may show no clinical signs of disease. This preclinical condition may have some value in predicting the development of LAA, but, if it was to be used as an indicator of allergy risk, it would incorrectly include two-thirds of patients³⁷. Sensitized patients who remain exposed to antigens show a greater decline in lung function⁷³, however, so it would be prudent to remove asymptomatic but sensitized personnel from high-exposure environments. Patients who are sensitized should also be considered at greater risk of serious reactions, such as anaphylaxis after an animal bite, and appropriate measures of resuscitation should be readily available. Sensitized personnel should only be allowed to continue to work after applying strict limitations or requirements, such as limiting the activities associated with an increased risk of inhalation or bites and requiring the use of respiratory devices and skin protection.

If the patient is found to have a respiratory, eye or skin disorder as a result of LAA, his or her disorder should be treated directly. As an example, we can consider a patient with bronchial asthma. There is no evidence indicating that asthmatic patients cannot work in an animal facility, because they may not necessarily develop asthmatic LAA and their asthma may not worsen. However, asthmatics (whether atopic or not) are at high risk, and so it is useful to investigate the degree to which the disease is controlled. If it is well controlled, an employee may be considered eligible for work but should only be given very low-risk duties and be required to make constant use of PPE. The physician should explain the additional risk that the work may have on the patient's illness. These patients should be regularly monitored, as often as every 6 months. The prognosis of immunological occupational asthma is worse if exposure to the causative agent is maintained³⁰. If the asthma is not easily controlled, or if there is a previous diagnosis of asthma or rhinitis induced by the sensitizing agent in question, the patient should be considered unsuitable for work with laboratory animals. Highly skilled personnel and researchers may still be considered eligible for positions involving contact with laboratory animals with particularly stringent requirements, such as minimizing the time of exposure; using PPE to protect respiratory, ocular and nasal mucous membranes and high-index protective devices (for example, a ventilated helmet); and carrying out in-depth physical examinations at shorter intervals (e.g., every 3 months) in order to confirm the effectiveness of the measures taken.

Medico-legal aspects

In the absence of both a generally shared 'approved code of practice' and a safe threshold of exposure to animal allergens, employers must follow the International Commission on Occupational Health (ICOH) guidelines⁷⁴, the aim of which is to draw general laws concerning health and safety at work based on good clinical practice, for the prevention of LAA. As respiratory sensitizers, animal allergens are subject to these regulations and employers are required to assess the health risk arising from working with laboratory animals and their waste products (risk assessment) to decide what precautions are needed, to prevent or control exposure to animal allergens, to ensure that control measures are used and properly maintained, to carry out appropriate health surveillance and to ensure that employees are properly informed, trained and supervised.

The duties of employers are generally qualified by the phrase 'as far as is reasonably practicable'⁷⁴. In other words, an employer must balance the risk and severity of harm against the financial and other costs of introducing control measures to prevent it. If an accident occurs, an employer may not be found to have acted illegally

if the 'best current practice' was used and reasonably practicable steps were taken to control the hazard. As the guideline requires employers to reduce exposure to animal allergens 'as far as is reasonably practicable', thus accepting that sensitization to animal allergens may still occur, it is essential to detect sensitized patients early. This will make it possible to adopt suitable measures to reduce or eliminate their exposure to animal allergens and monitor their health. There is now a large body of evidence indicating that the sooner a patient with occupational asthma is removed from exposure to the causative agent, the better his or her prognosis.

CONCLUSIONS

The manifestations, diagnosis and treatment of LAA do not differ from those of common allergic respiratory and skin diseases not induced by laboratory animals. However, the risk factors are well known, and the incidence and severity of LAA can be reduced by implementing appropriate preventive measures. Engineering and organizational primary prevention measures effectively reduce the concentration of environmental antigens, reducing exposure levels and thus the incidence and prevalence of LAA. Occupational physicians are the key figures of secondary prevention: they can provide appropriate health surveillance and information and training to patients, although they often face difficult choices in terms of preventive diagnostics.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Received 15 May 2012; accepted 27 July 2012
Published online at <http://www.labanimal.com/>

- Aoyama, K. *et al.* Allergy to laboratory animals: an epidemiological study. *Br. J. Ind. Med.* **49**, 41–47 (1992).
- Heederik, D. *et al.* Exposure-response relationship for work-related sensitization in workers exposed to rat urinary allergens: results from a pooled study. *J. Allergy Clin. Immunol.* **103**, 678–684 (1999).
- Kruize, H. *et al.* Respiratory allergy in laboratory animal workers: a retrospective cohort study using pre-employment screening data. *Occup. Environ. Med.* **54**, 830–835 (1997).
- Laresse Filon, F. *et al.* Prevalence of occupational allergy to laboratory animals in two towns of northern and central Italy [in Italian]. *Med. Lav.* **93**, 87–94 (2002).
- Pacheco, K.A. *et al.* Gene-environment interactions influence airways function in laboratory animal workers. *J. Allergy Clin. Immunol.* **126**, 232–240 (2010).
- Patel, N.J., Olson, P., Lumby, D., Fine, J.P. & Bush, R.K. Laboratory animal allergy (Abstract). *J. Allergy Clin. Immunol.* **105**, S372 (2000).
- Portengen, L., Hollander, A., Doekes, G., de Meer, G. & Heederik, D. Lung function decline in laboratory animal workers: the role of sensitisation and exposure. *Occup. Environ. Med.* **60**, 870–875 (2003).
- Slovak, A.J. & Hill, R.N. Laboratory animal allergy: a clinical survey of an exposed population. *Br. J. Ind. Med.* **38**, 38–41 (1981).
- Suarthana, E. *et al.* The Dutch diagnostic model for laboratory animal allergen sensitization was generalizable in Canadian apprentices. *J. Clin. Epidemiol.* **62**, 542–549 (2009).
- Venables, K.M. *et al.* Laboratory animal allergy in a pharmaceutical company. *Br. J. Ind. Med.* **45**, 660–666 (1988).
- Seward, J.P. Occupational allergy to animals. *Occup. Med.* **14**, 285–304 (1999).
- Botham, P.A., Davies, G.E. & Teasdale, E.L. 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 (1987).
- Botham, P.A., Lamb, C.T., Teasdale, E.L., Bonner, S.M. & Tomenson, J.A. Allergy to laboratory animals: a follow up study of its incidence and of the influence of atopy and pre-existing sensitisation on its development. *Occup. Environ. Med.* **52**, 129–33 (1995).
- Cullinan, P. *et al.* Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. *Eur. Respir. J.* **13**, 1139–1143 (1999).
- Davies, G.E. *et al.* Allergy to laboratory animals: a retrospective and a prospective study. *Br. J. Ind. Med.* **40**, 442–449 (1983).
- Elliott, L., Heederik, D., Marshall, S., Peden, D. & Loomis, D. Incidence of allergy and allergy symptoms among workers exposed to laboratory animals. *Occup. Environ. Med.* **62**, 766–771 (2005).
- Gautrin, D., Infante-Rivard, C., Ghezzi, H. & Malo, J.L. Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. *Am. J. Respir. Crit. Care Med.* **163**, 899–904 (2001).
- Gross, N.J. Allergy to laboratory animals: epidemiologic, clinical and physiologic aspects, and a trial of cromolyn in its management. *J. Allergy Clin. Immunol.* **66**, 158–165 (1980).
- Kibby, T., Powell, G. & Cromer, J. Allergy to laboratory animals: a prospective and cross-sectional study. *J. Occup. Med.* **31**, 842–846 (1989).
- Krop, E.J., Doekes, G., Heederik, D.J., Aalberse, R.C. & van der Zee, J.S. IgG4 antibodies against rodents in laboratory animal workers do not protect against allergic sensitization. *Allergy* **66**, 517–522 (2011).
- National Institute of Occupational Safety and Health. *Alert: Preventing Asthma in Animal Handlers* (DHHS (NIOSH) Publication No. 97-116) (NIOSH, 1998).
- Bush, R.K., Wood, R.A. & Eggleston, P.A. Laboratory animal allergy. *J. Allergy Clin. Immunol.* **102**, 99–112 (1998).
- Bush, R.K. Assessment and treatment of laboratory animal allergy. *ILAR J.* **42**, 55–64 (2001).
- Krakowiak, A., Szulc, B. & Górski, P. Allergy to laboratory animals in children of parents occupationally exposed to mice, rats and hamsters. *Eur. Respir. J.* **14**, 352–356 (1999).
- Pacheco, K.A. *et al.* Airborne endotoxin predicts symptoms in non-mouse-sensitized technicians and research scientists exposed to laboratory mice. *Am. J. Respir. Crit. Care Med.* **167**, 983–990 (2003).
- Cullinan, P. *et al.* Work-related symptoms sensitization and estimated exposure in workers not previously exposed to laboratory rats. *Occup. Environ. Med.* **51**, 589–592 (1994).
- Hunnskaar, S. & Fosse, R.T. Allergy to laboratory mice and rats: a review of the pathophysiology, epidemiology and clinical aspects. *Lab. Anim.* **24**, 358–374 (1990).
- Ruoppi, P., Koistinen, T., Susitaival, P., Honkanen, J. & Soininen, H. Frequency of allergic rhinitis to laboratory animals in university employees as confirmed by chamber challenges. *Allergy* **59**, 295–301 (2004).
- Elliott, L., Heederik, D., Marshall, S., Peden, D. & Loomis, D. Progression of self-reported symptoms in laboratory animal allergy. *J. Allergy Clin. Immunol.* **116**, 127–132 (2005).
- Paggiaro, P.L. *et al.* Prognosis of occupational asthma. *Eur. Respir. J.* **7**, 761–767 (1994).
- Hesford, J.D., Platts-Mills, T.A. & Edlich, R.F. Anaphylaxis after laboratory rat bite: an occupational hazard. *J. Emerg. Med.* **13**, 765–768 (1995).

32. Teasdale, E.L., Davies, G.E. & Slovak, A. Anaphylaxis after bites by rodents. *Br. Med. J. (Clin. Res. Ed.)* **286**, 1480 (1983).
33. Watt, A.D. & McSharry, C.P. Laboratory animal allergy: anaphylaxis from a needle injury. *Occup. Environ. Med.* **53**, 573–574 (1996).
34. Meijer, E., Grobbee, D.E. & Heederik, D. Detection of workers sensitised to high molecular weight allergens: a diagnostic study in laboratory animal workers. *Occup. Environ. Med.* **59**, 189–195 (2002).
35. Bland, S.M., Levine, M.S., Wilson, P.D., Fox, N.L. & Rivera, J.C. Occupational allergy to laboratory animals: an epidemiologic study. *J. Occup. Med.* **28**, 1151–1157 (1986).
36. Bryant, D.H., Boscatto, L.M., Mboloi, P.N. & Stuart, M.C. Allergy to laboratory animals among animal handlers. *Med. J. Aust.* **163**, 415–418 (1995).
37. Bush, R.K. & Stave, G.M. Laboratory animal allergy: an update. *ILAR J.* **44**, 28–51 (2003).
38. Davies, G.E. & McArdle, L.A. Allergy to laboratory animals: a survey by questionnaire. *Int. Arch. Allergy Appl. Immunol.* **64**, 302–307 (1981).
39. Fuortes, L.J. *et al.* Epidemiologic assessment of laboratory animal allergy among university employees. *Am. J. Ind. Med.* **29**, 67–74 (1996).
40. Jeal, H. & Jones, M. Allergy to rodents: an update. *Clin. Exp. Allergy* **40**, 1593–1601 (2010).
41. Renström, A., Malmberg, P., Larsson, K., Sundblad, B.M. & Larsson, P.H. Prospective study of laboratory-animal allergy: factors predisposing to sensitization and development of allergic symptoms. *Allergy* **49**, 548–552 (1994).
42. Gautrin, D., Ghezzi, H. & Malo, J.L. Rhinconjunctivitis, bronchial responsiveness, and atopy as determinants for incident non-work-related asthma symptoms in apprentices exposed to high-molecular-weight allergens. *Allergy* **58**, 608–615 (2003).
43. Agrup, G. & Sjöstedt, L. Contact urticaria in laboratory technicians working with animals. *Acta. Derm. Venereol.* **65**, 111–115 (1985).
44. Herr, C.E. *et al.* Exposure to air pollution in critical prenatal time windows and IgE levels in newborns. *Pediatr. Allergy Immunol.* **22**, 75–84 (2011).
45. Fuortes, L.J. *et al.* Prospective epidemiologic evaluation of laboratory animal allergy among university employees. *Am. J. Ind. Med.* **32**, 665–669 (1997).
46. Wood, R.A. Laboratory animal allergens. *ILAR J.* **42**, 12–16 (2001).
47. Gordon, S., Tee, R.D., Lawson, D., Wallace, J. & Newman Taylor, A.J. Reduction of airborne allergenic urinary proteins from laboratory rats. *Br. J. Ind. Med.* **49**, 416–422 (1992).
48. Hollander, A., Heederik, D. & Doekes, G. Respiratory allergy to rats: exposure-response relationships in laboratory animal workers. *Am. J. Respir. Crit. Care Med.* **155**, 562–567 (1997).
49. Renström, A., Karlsson, A.S., Malmberg, P. & Larsson, P.H. & van Hage-Hamsten, M. Working with male rodents may increase risk of allergy to laboratory animals. *Allergy* **56**, 964–970 (2001).
50. Vandoren, G. *et al.* Different forms of alpha 2u-globulin in male and female rat urine. *Eur. J. Biochem.* **134**, 175–181 (1983).
51. Jones, M.G. Exposure-response in occupational allergy. *Curr. Opin. Allergy Clin. Immunol.* **8**, 110–114 (2008).
52. Gordon, S. & Preece, R. Prevention of laboratory animal allergy. *Occup. Med. (Lond)* **53**, 371–377 (2003).
53. Occupational Health and Safety Act. Title 29 U.S.C. §651 *et seq.* (1970).
54. Carosso, A. & Romano, C. Aspetti normativi e medico-legali [Italian]. *J. Allergy Clin. Immunol.* (in the press).
55. Gautrin, D., Ghezzi, H., Infante-Rivard, C. & Malo, J.L. Incidence and determinants of IgE-mediated sensitization in apprentices. A prospective study. *Am. J. Respir. Crit. Care Med.* **162**, 1222–1228 (2000).
56. Gordon, S., Fisher, S.W. & Raymond, R.H. Elimination of mouse allergens in the working environment: assessment of individually ventilated cage systems and ventilated cabinets in the containment of mouse allergens. *J. Allergy Clin. Immunol.* **108**, 288–294 (2001).
57. Clough, G., Wallace, J., Gamble, M.R., Merryweather, E.R. & Bailey, E. A positive, individually ventilated caging system: a local barrier system to protect both animals and personnel. *Lab. Anim.* **29**, 139–151 (1995).
58. Gordon, S., Wallace, J., Cook, A., Tee, R.D. & Newman Taylor, A.J. Reduction of exposure to laboratory animal allergens in the workplace. *Clin. Exp. Allergy* **27**, 744–751 (1997).
59. Reeb-Whitaker, C.K. Control strategies for aeroallergens in an animal facility. *J. Allergy Clin. Immunol.* **103**, 139–146 (1999).
60. Ziemann, B., Corn, M., Ansari, A.A. & Eggleston, P. The effectiveness of the Duo-Flo BioClean unit for controlling airborne antigen levels. *Am. Ind. Hyg. Assoc. J.* **53**, 138–145 (1992).
61. Fisher, R., Saunders, W.B., Murray, S.J. & Stave, G.M. Prevention of laboratory animal allergy. *J. Occup. Environ. Med.* **40**, 609–613 (1998).
62. Slovak, A.J., Orr, R.G. & Teasdale, E.L. Efficacy of the helmet respirator in occupational asthma due to laboratory animal allergy (LAA). *Am. Ind. Hyg. Assoc. J.* **46**, 411–415 (1985).
63. Coffey, C.C. *et al.* Fitting characteristics of eighteen N95 filtering-facepiece respirators. *J. Occup. Environ. Hyg.* **1**, 262–271 (2004).
64. Reponen, T., Lee, S.A., Grinshpun, S.A., Johnson, E. & McKay, R. Effect of fit testing on the protection offered by n95 filtering facepiece respirators against fine particles in a laboratory setting. *Ann. Occup. Hyg.* **55**, 264–271 (2011).
65. European Commission. *Personal Protective Equipment Directive (89/686/EEC)* (European Commission, 1989).
66. Code of Federal Regulations, Title 29, Part 1910, Subpart I—Personal Protective Equipment.
67. Thulin, H., Björkdahl, M., Karlsson, A.S. & Renström, A. Reduction of exposure to laboratory animal allergens in a research laboratory. *Ann. Occup. Hyg.* **46**, 61–68 (2002).
68. Goodno, L.E. & Stave, G.M. Primary and secondary allergies to laboratory animals. *J. Occup. Environ. Med.* **44**, 1143–1152 (2002).
69. Moore, W.C. & Pascual, R.M. Update in asthma 2009. *Am. J. Respir. Crit. Care Med.* **181**, 1181–1187 (2010).
70. Adisesh, L.A. Exhaled and nasal nitric oxide is increased in laboratory animal allergy. *Clin. Exp. Allergy* **28**, 876–880 (1998).
71. Hewitt, R.S. Serial exhaled nitric oxide measurements in the assessment of laboratory animal allergy. *J. Asthma* **45**, 101–117 (2008).
72. Demange, V. *et al.* Associations of airway inflammation and responsiveness markers in non asthmatic subjects at start of apprenticeship. *BMC Pulm. Med.* **10**, 37 (2010).
73. Portengen, L., de Meer, G., Doekes, G. & Heederik, D. Immunoglobulin G4 antibodies to rat urinary allergens, sensitization and symptomatic allergy in laboratory animal workers. *Clin. Exp. Allergy* **34**, 1243–1250 (2004).
74. International Commission on Occupational Health International code of ethics for occupational health professionals. (International Commission on Occupational Health, Rome, Italy 2002).

Copyright 2013® by Nature America, Inc.