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IN-DEPTH REVIEW

Prevention of laboratory animal allergy

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Background	Laboratory animal allergy (or LAA) is an important threat to the occupational health of those who work with rats, mice and other species.
Aim	This review examines the risk factors for LAA and the effectiveness of control measures.
Methods	A literature review was performed.
Results	An extensive literature was identified regarding LAA and the use of control measures. The contribution that these measures can make to the overall effectiveness of an occupational health and safety programme is discussed in the context of the literature currently available.
Conclusion	The incidence of this disease can be reduced by effective, integrated health risk management, with the conscientious use of engineering, procedural and personal control measures.
Key words	Allergen exposure; health surveillance; immunology; laboratory animals; occupational allergy prevention and control; occupational asthma; sensitization.
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Introduction

Laboratory animal allergy (LAA) is a common health problem in pharmaceutical research workers. The aetiology of LAA is well established and it is generally accepted that approximately one-third of exposed people may develop symptoms of LAA—see review articles [1,2]. The most common symptoms are rhinitis, conjunctivitis and contact urticaria; ~10% of workers may experience the most serious symptom of asthma. A personal history of allergy to common environmental allergens (atopy) and exposure to the animals are considered the most important risk factors for the development of allergy. What is of concern is that despite this knowledge, there continues to be a high prevalence of this disease throughout the western world [3–7]. This article will therefore focus on strategies for the prevention of LAA.

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Method

The medical and scientific literature was searched using Medline (PubMed) and employing the key search terms 'laboratory animal allergy' and 'occupational asthma'.

Epidemiology and clinical features

When no special prevention strategies have been employed, the numbers of newly developing cases of LAA in exposed populations in the first years of animal work vary between 5 and 40% [8–10]. Pooled data from 13 studies revealed a consistent picture of symptom distribution [1]. Of 10 people with symptoms of LAA, about eight will have rhinoconjunctivitis (range 53–100%), about four will have skin reactions (13–70%) and about three or four will have asthma (13–71%). Studies of the incidence of new symptoms suggest this 2:1:1 ratio of symptoms remains typical [11,12]. There is inevitably overlap between symptoms, and most subjects have more than one affected target organ; for example, asthma rarely occurs in the absence of the prior development of rhinoconjunctivitis [12,13]. More than 60% of cases of LAA (and almost all asthmatic individuals) will have specific IgE to animal allergens

detectable by a positive skin prick test or a serological test [14]. In cases of asthma with no specific IgE to laboratory animals, the symptoms may be due to reactions to other agents that are present in the working environment, e.g. dust, ammonia, formaldehyde or disinfectants. Anaphylactic reactions are a rare manifestation of LAA that have been reported in association with both rat and mouse bites [15,16] and a puncture wound from a needle used on a rabbit [17].

Risk factors for LAA

Animal allergens are found in the urine, fur, saliva and serum of laboratory animal species such as rats, mice, guinea pigs, rabbits and ferrets [18]. Contamination of the occupational environment may occur by the allergens becoming airborne or being carried on clothing and other surfaces. All personnel who work directly or indirectly with animals and their waste products (including maintenance workers, waste disposal workers and other infrequent visitors to animal facilities) are therefore at risk of developing LAA.

Most workers who develop LAA do so within the first 3 years of exposure [1,7]. During this time, their immune systems may be primed to produce specific IgE antibodies to one or more animal allergens and subsequent exposure may provoke clinical symptoms. The time-course of these events and the influence of genetic and environmental factors on the development of (and the manifestations of) disease, is still being established. One study suggests that the average latency period between first exposure and the development of symptoms is shortest for nasal symptoms and longest for chest symptoms [19]. However, there is great variation between individuals in the length of the latency period before allergy is expressed clinically.

Influence of atopy

Atopic individuals are up to 11 times more likely to become sensitized (i.e. produce specific IgE antibodies) to animal allergens than non-atopics [20,21] and, hence, have an increased risk of experiencing symptoms of LAA, including asthma. Atopy may also influence the time-course of symptoms; in a retrospective study, atopics were found to develop LAA after a median time of 2.2 years and non-atopics after a median time of 8.2 years [7]. It would therefore seem that if atopics become sensitized, they are at risk of developing a more severe form of the disease and at a faster rate. It is important to note that atopy is not a sufficiently good predictor of LAA to be used in pre-placement selection [7,8,22,23]. In a cross-sectional study of 323 workers exposed to rats [19], two-thirds of the atopic people who remained in jobs with a high intensity of exposure were not sensitized to rats at the time of the study [14].

Influence of exposure

There are now convincing data from three European cross-sectional and prospective studies demonstrating that the risk of sensitization to rodents—and the development of symptoms of LAA—increases with increasing exposure [19,20,24]. These data, from 650 rat exposed subjects, have been pooled [25] and show that for atopic workers, those exposed to low levels of rat allergen for only a few hours per week are three times more likely to be sensitized than non-exposed workers. This risk did not increase significantly with higher intensity or duration of exposure. However, in contrast, the risk for non-atopic workers increased significantly with increased intensity of exposure. This result implies that the lowest possible exposures observed in this study were sufficient to sensitize atopics, whereas the risk for sensitizing non-atopic workers becomes significant only at higher concentrations of rat allergen. A direct, positive association between exposure to animal allergens and the occurrence of symptoms (particularly chest symptoms) has also been observed.

There is also interesting direct and indirect evidence that sensitization to allergens may occur at exposure levels lower than that required to provoke symptoms. Whilst no formal exposure measurements were conducted, the prospective study of Botham and co-workers demonstrates that measures designed to reduce exposure to animal allergens succeeded in reducing the incidence of reported symptoms, but did not affect the incidence of those with specific IgE to animal allergens [7]. A similar observation has also been made amongst those working with enzymes in the detergent industry [26]. A prospective study of 458 workers exposed to mice suggests that the risk of sensitization relative to a low exposure reference group (e.g. those working with mouse tissue) begins to increase at exposures >5 ng/m^3; the exposure level provoking symptoms in this study population was apparently two to three times higher (S. Gordon, unpublished data). A parallel study of rat-workers did not show such a clear relationship [19].

Implementation in the workplace

Legal requirements

LAA is universally recognized as a significant health problem and formal health and safety advice for this specific occupational problem now exists in some countries. Examples of this are the National Institute for Occupational Safety and Health (NIOSH) Hazard Alert Notice in the USA [27] published in 1998 and the Health & Safety Executive (HSE) Guidance Note EH76 in the UK [28] published in 2002. The principal elements of an occupational health and safety programme as

recommended by NIOSH and HSE are shown in Table 1. These documents are complementary to existing legislation such as Control of Substances Hazardous to Health (COSHH) Regulations 2002 in the UK and they offer examples of good practice. Where comprehensive programmes designed to reduce exposure to animal allergens have been introduced, a reduction in the incidence of allergy has been observed [7,29].

In the UK, the HSE are currently undertaking an inspection of all 260 animal establishments to ensure compliance with COSHH and the Management of Health and Safety at Work Regulations. The planned visits have initially focused on academic institutions. In the 35 institutions visited by December 2002, the standard of compliance was reported to be good. However, deficiencies, where they existed, involved problems with local exhaust ventilation and/or respiratory protective equipment (such as failure to test, to ensure proper use, etc.) and health surveillance and management arrangements (Dr T. Erlam, HSE, personal communication); so far, 13 Improvement Notices have been served. It is anticipated that all university visits will be completed during 2003 and that inspection of research establishments and pharmaceutical industry premises will commence in 2004.

Controlling exposure to animal allergens

The main aim of allergy prevention strategies should be to reduce airborne allergens in the worker's breathing zone, but consideration should also be given to controlling exposure to allergens by routes such as ingestion, skin absorption and percutaneous injury. Control measures should be designed to reduce both the intensity and the duration of exposure. Several studies have described the intensity of exposure associated with common tasks in the absence of control measures [30–32] and the relative exposure of typical husbandry tasks is shown in Table 2. Exposure control should be achieved through a combination of engineering, procedural and personal controls and more than one control measure may be required to reduce allergen exposure sufficiently for very high exposure tasks.

Table 1. Principal elements of an occupational health and safety programme

NIOSH	
1.	Administrative procedures
2.	Facility design and operations
3.	Exposure control methods
4.	Education and training
5.	Occupational health services
6.	Equipment performance testing
7.	Information management networks
8.	Emergency procedures
9.	Program evaluation and audit
HSE, EH76	
1.	Implementation of a health and safety management system
2.	Risk assessment
3.	Prevention and control of exposure
(a)	Ventilation
(b)	Systems of work
(c)	Personal protective equipment
(d)	Welfare facilities
4.	Maintenance, examination and testing of controls
(a)	Ventilation
(b)	Respiratory protective equipment
5.	Health surveillance
6.	Information, instruction and training

Engineering controls

Animal facilities should be designed to incorporate engineering controls wherever practicable. There is relatively little evidence that specific building systems (such as ventilation or architect design) may reduce exposure to allergens, but it is generally assumed that ventilation design may contribute to a reduction in particle counts. However, design features that act to direct allergen-contaminated air away from personnel or communal areas may be effective in reducing widespread contamination by airborne allergens throughout an animal unit. A one-way airflow system in an animal holding room that was equipped with sliding perforated screens, behind which the cage racks and exhaust vents were situated, has been shown effectively to reduce the allergen levels in the centre of the room [33]. Similarly, the use of pressure gradients within an animal unit (e.g. having the animal holding rooms at negative pressure to corridors) can assist in the localization of animal allergens to specific areas.

Task-specific, local exhaust ventilation is the principal

Table 2. Relative exposures of typical husbandry tasks

Relative exposure	Task
Low	Procedures *post mortem* or with tissues
	Procedures on unconscious animals
	Procedures involving few animals
	Automated cage cleaning
Medium	Cleaning within animal unit
	Indirect contact in animal room
	Feeding animals
High	Injections and other invasive procedures
	Shaving fur
	Handling animals
	Box changing
	Disposal of soiled litter
	Changing filters of local exhaust ventilation or room ventilation
	Washing cages

control method, as it is usually very effective and easy to install and implement at relatively little cost. Task ventilation includes biosafety cabinets, fume cupboards and ventilated workstations that use down-draft or back-draft systems [2,34]. Careful selection of equipment and maintenance and training in its use is very important, as misuse can compromise the effectiveness of the systems. Airborne allergen measurements have shown that leaving the front of a ventilated work station raised to facilitate the transfer of cages into the hood seriously compromised its effectiveness in allergen containment [35].

Tasks such as emptying soiled cages and handling animal waste have the potential to expose workers to high aeroallergen levels. Automated systems for these tasks can greatly reduce ambient levels of allergen and are becoming more widely available [36]. These systems are, however, only a realistic, cost-effective option for large facilities.

Cage design can make a valuable contribution to aeroallergen control. The replacement of open-top cages with filter-top cages reduces allergen concentrations by >75% [37,38]. More recently, individually ventilated cage (IVC) systems have become available [39]; these cages can be maintained at either negative or positive pressure to the environment. The use of IVCs means that stock density can be increased without necessarily increasing ambient levels of aeroallergen. Several studies have shown that IVCs can reduce background aeroallergen levels [35,39–42], particularly when operated at negative pressure to the environment. The production of IVCs with highly effective seals in the cage lid may mean that the cages can be maintained at positive pressure (i.e. microbiological integrity of animals maintained), with minimal leakage of allergens [42]. The choice of such equipment should, however, always take into account animal welfare considerations, as well as factors such as ergonomic design.

The cost of measures to reduce allergen exposure, such as robots and sophisticated ventilation, may be prohibitive, whilst their ability to reduce the incidence of allergy is uncertain. No studies of the cost-effectiveness of allergen control programmes have been reported.

Procedural controls

The first consideration should be to minimize the number of people exposed. This may be achieved by situating the facility away from non-animal workers and, within the facility, segregating animal work from other work. The use of individual security or entry passes, set boundaries and the categorization of 'clean' and 'dirty' work areas, facilitates control of the spread of contamination. Procedural controls can be implemented to ensure that the work is carried out in a way that minimizes aeroallergen levels and prevents spread of allergens into the environment. Examples of these are to use, wherever appropriate, female or juvenile animals instead of adult males, as male animals secrete more allergens in their urine [43,44] and working with them may increase the risk for LAA [20]. Also, when animals are housed in open-top cages, where practicable stock density should be minimized because there is a direct relationship between stock density and allergen levels [31,37]. Additionally, as litter type may influence the airborne dissemination of allergens, this factor should be considered when selecting environmental enrichment or bedding material. Procedural controls are also important in the cleaning of the unit, in the handling of contaminated documents and clothing and in the disposal and handling of animal waste and litter.

Personal controls

The focus of personal control measures is on individual behaviour. This includes guidance on the correct use of personal protective equipment, general hygiene, changing routines for protective clothing, provision of information and training. The effective use of respiratory protection is an important component of any control strategy [7,29] and for most people, a properly fitted half-face particle filter respirator (SPF 2 grade) will be adequate. Air-stream respirator helmets, with which filtered air is delivered to the operator, can be very effective and have been shown to relieve symptoms of LAA in sensitized workers [45].

Measurement of airborne allergens

Whilst exposure standards have been set in some countries for respiratory sensitizers such as flour and formaldehyde, there is currently no occupational exposure standard for laboratory animal allergens. Because of the serious health effects and the considerable variation in the susceptibility of individuals, it is most likely that when a standard is set it will be a 'maximum permissible level'. One serious obstacle at present is the lack of a standardized method to quantify rodent allergens. Recent studies have shown that the type of assay employed may influence the results obtained by up to three orders of magnitude [46,47]. Whilst assays that utilize monoclonal antibodies to measure major rodent allergens (such as Rat n1) offer excellent sensitivity and standardization, it is important to note that animal room dust is a complex mixture of allergens and exposure to other allergens (e.g. albumin) will not be measured. The number of workplaces performing exposure measurements has grown. The data generated have proven to be useful for the validation of risk assessments, the objective assessment of control measures and for the education of staff. It is likely that approved methods to quantify airborne exposure to rat and mouse allergens will be

available within 5 years and a requirement to measure exposure in the workplace will then follow.

Effectiveness of control measures

Where comprehensive measures have been introduced to reduce personal exposure to allergens, a decrease in the incidence of reported symptoms of allergy to very low levels has been seen [7,29]. This suggests that, in the majority of workers, LAA can be prevented by effective control of allergen exposure. The pooled study by Heederik *et al.* [25] demonstrated that, in order to reduce the risk of sensitization to rat proteins, the control of exposure must be even more rigorous, as the increase in risk of sensitization increased most markedly between the 'no exposure' category and the next highest category. It would therefore seem that airborne exposure must be virtually eliminated in order for sensitization to be prevented in most people [7,24,26]. Even stringent exposure control methods may be insufficient to prevent sensitization in all workers and therefore health surveillance is required.

Health surveillance

It is not feasible to predict, prior to exposure, who will develop allergy; atopy is a poor predictor and immunological tests to measure specific IgE add little [7]. However, pre-placement assessment is a valuable opportunity to gather baseline data, assess vulnerability and provide information on prevention of allergy. Occasionally, candidates will report pre-existing LAA (possibly from pets) and, if they have a history of asthma or anaphylaxis, they may not be suited to animal work.

Regular health surveillance provides an opportunity to raise awareness of LAA and investigate any symptoms that occur. In some jurisdictions, health surveillance is a requirement for all those who are significantly exposed [28]. Although annual review is typical, more frequent review may be appropriate in the first 2 years of exposure, when the risk of disease is greatest [1]. The most important part of surveillance is recent history supported by a questionnaire [48]. Lung function tests and specific IgE measurements are used by some centres, but although they help to reinforce the educational message, their value as routine screening tests is unproven.

Management of symptoms

Rhinoconjunctivitis and urticaria are a nuisance and, if not effectively managed, may make it very difficult for the affected person to continue to work with the animals. The frequency and intensity of symptoms can be reduced if exposure to allergens is reduced. However, subjects who have developed sensitivity to one type of fur animal are at increased risk of developing allergies to others. In a study of 100 subjects diagnosed with occupational asthma and followed up after a mean 5.8 years after ceasing exposure, significantly more subjects had developed symptoms against other animals [49].

The workplace management of LAA should be focused on the reduction of exposure to a clinically insignificant level (i.e. when the LAA sufferer is free of symptoms in the absence of treatment). This can usually be achieved by changes in working practices or redeployment away from the relevant animal. Only in the most extreme cases should the affected persons have to leave their employment.

Conclusion

Recent evidence has made it clearer that the development of LAA is most influenced by exposure to allergens and even low levels of exposure may still pose a risk. This has important implications for the prevention of laboratory animal allergy and the design of effective control strategies. First, resources must be focused on those control measures (or combinations of control measures) that will have most impact in reducing exposure to undetectable levels. Secondly, sufficient effort must be employed in the education and training of workers exposed to allergens. Only if workers properly understand the risks can they do their utmost to make sure that they correctly use control measures and, hence, minimize their personal exposure. It is also of note that the recent HSE inspections in the UK have illustrated that approximately one-third of establishments are failing to comply fully with long-established health and safety legislation. There is therefore the need to be constantly vigilant and periodically to check that the systems put in place to combat LAA continue to work effectively.

Key messages

- Exposure standards are not yet available, but current studies may lead to their introduction in the next few years.
- Allergy is one of many hazards faced by those in animal science. To be effective, the management of all such hazards (e.g. microbiological safety, ergonomic hazards) should be integrated.
- New technology is contributing to improved control of allergen. Many of these new technologies are costly and their value to the control strategy has yet to be fully determined.
- Traditionally, the principal role for occupational health has been to manage the health surveillance programme. The preventive role of health surveillance is limited and the true value of occupational health lies in its contribution to the development and

implementation of integrated and comprehensive risk management programmes.

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