

Health surveillance of workers exposed to laboratory animal allergens

P. J. Nicholson¹, G. V. Mayho², D. Roomes³, A. B. Swann⁴ and B. S. Blackburn⁵

¹Occupational Health, P&G, Whitehall Lane, Egham, Surrey TW20 9NW, UK, ²Pfizer UK Ltd, Sandwich, Kent CT13 9NJ, UK,

³GlaxoSmithKline plc, Employee Health Management, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK,

⁴Occupational Health, Imperial College London, South Kensington Campus, London SW7 2AZ, UK, ⁵West Berkshire Occupational Health, 21 Craven Road, Reading RG1 5LE, UK.

Correspondence to: A. B. Swann, Occupational Health, Imperial College London, South Kensington Campus, London SW7 2AZ, UK. Tel: +44 (0)20 7594 6301; e-mail: a.swann@imperial.ac.uk

Background	Laboratory animal allergy (LAA) remains prevalent among workers exposed to laboratory animals. Pre-placement and health surveillance procedures vary between different employers.
Aims	To determine evidence-based strategies for pre-placement and periodic health assessments for workers exposed to laboratory animals.
Methods	Literature was searched systematically using Medline and EMBASE for articles published in all languages up to the end of May 2010. Evidence-based statements and recommendations were graded according to a modified Royal College of General Practitioner's star system.
Results	Hundred and nine studies were identified from the literature search; 59 of these were accessed for critical appraisal and 50 contributed to the evidence statements.
Conclusions	We recommend that laboratory animal workers should have a baseline health assessment that includes a health questionnaire, face-to-face assessment and spirometry. Identification of specific immunoglobulin E to common aero-allergens and to domestic and laboratory animal allergens may be used to identify workers who would benefit from further advice about managing their exposure, where risk assessment indicates that this might be prudent. Thereafter health surveillance should be performed by administering an appropriate health questionnaire, covering upper and lower respiratory, eye and skin symptoms on exposure, and wheals with animal scratches. The questionnaire should be administered at increased frequency for the first few years, the frequency being determined by a risk assessment. Where a worker develops new symptoms suggestive of LAA or where an asthmatic employee experiences deterioration either in symptoms or in control, they should be assessed further and a multi-cause multidisciplinary investigation performed.
Key words	Evidence based practice; health surveillance; laboratory animal allergy; occupational asthma.

Introduction

Occupational asthma and rhinitis are common in people who work with laboratory animals, with estimated incidences of 1.56 and 2.54/1000 employees/year, respectively [1]. Since case numbers derive from voluntary reporting schemes and rely on doctor diagnosis, they are likely to be underestimates. For this review, we refer to 'laboratory animal allergy' (LAA) and take this to encompass all manifestations of allergy as defined by each of the individual papers reviewed.

Health and Safety Regulations in the UK and other countries require employers to undertake health surveillance of employees working with substances that can harm health, where significant exposure cannot be reli-

ably prevented by engineering and procedural controls and where acceptable means to detect harm exist. Work with laboratory animals meets these criteria. There is however little guidance available on how health surveillance can be undertaken effectively.

A survey of practices (unpublished data) in the pharmaceutical and higher education sectors by two of this paper's authors (G.V.M. and A.B.S.) found wide variation that did not necessarily reflect evidence. While evidence-based guidelines were published by the British Occupational Health Research Foundation (BOHRF) for the identification and management of occupational asthma (recently updated (2)), they were specific to asthma and excluded studies that used the term 'allergy'

rather than ‘asthma’. These factors prompted this review that aims to produce evidence-based guidelines for workers exposed to laboratory animal allergens.

While we have focused on health surveillance, it is important to emphasize employers’ duties to provide safe working environments, training and communication with workers.

Methods

The methodology is one of ‘best evidence synthesis’, summarizing the literature and drawing conclusions on the balance of evidence based on quality, quantity and consistency. Although the methodologies employed in the reviewed studies varied, this should not invalidate the choice of methodology for this review.

A systematic electronic search was conducted using Medline and Embase for original research published from 1966 to the end of May 2010. It included search strings with keywords relevant to laboratory animal allergies (search limits = ‘English language’ and ‘human’ and search terms = ‘laboratory animal’ and ‘rhinitis’ or ‘dermatitis’ or ‘asthma’ or ‘allergy’). Narrative reviews were excluded except for citation tracking. The abstracts were circulated among the five authors to select relevant papers for full review. The literature search identified 109 potentially relevant studies, 59 being appraised and 50 included in the evidence review. Each author undertook detailed assessment of 10–11 papers using a common template and presented to the group for open discussion. Findings of the review are presented in the form of ‘evidence statements’ with each statement being linked to the main supportive sources of evidence.

The strength of evidence supporting statements in boxes 1–3 was graded using the Royal College of General Practitioner’s three-star system, modified in 2008 by the Swedish Council on Technology Assessment in Health Care report for scientific studies, as shown in Table 1.

Results

The reported prevalence of LAA varies widely from ~10 to 55% among workers exposed to laboratory animal

allergens in different study populations [3–13]. This variation arises from differences in defining and ascertaining LAA, in study populations, and in site-specific risk factors, e.g. species handled and exposures.

Both occupational and personal risk factors are purported (Box 1). While exposure to laboratory animal allergens is a risk factor for the development of LAA, there is no reproducible threshold. Different studies report different durations of exposure (from 2 to >38 h/week) that increase risk [12,14–17]. Some researchers report a dose–response relationship between symptoms and the following markers of exposure:

- exposure categories or airborne levels of urinary allergen [11,18–21],
- increased frequency of exposure and number of animals handled [6,22],
- increased duration of exposure to animals and work in animal-related tasks [8,9,17,23,24] and
- number of species handled [6,8,25].

Box 1. Associations and risks

- *** Exposure to laboratory animal allergens is associated with the risk of developing LAA.
- *** LAA is more likely with increasing exposure to laboratory animal allergens.
- *** Most workers who develop symptoms do so within 3–4 years of starting work and particularly within 1–2 years.
- *** Atopy is associated with an increased risk of LAA.
- *** Sensitization or allergy to pet cats or dogs is an independent risk factor for developing LAA.
- *** Excluding atopics is a very inefficient approach in the control of LAA.
- ** Atopics develop symptoms earlier than non-atopics.
- ** Smoking is not an independent risk factor for the development of LAA.
- * Gender is not an independent risk factor for the development of LAA.
- * Age is not an independent risk factor for the development of LAA.

Table 1. Modified Royal College of General Practitioner’s three-star system

Evidence grade		Definition
***	Strong	Conclusion supported by at least two independent studies with high quality or a good systematic review
**	Moderate	Conclusion supported by one study with high quality and at least two studies with medium quality
*	Limited	Conclusion is corroborated by at least two studies with medium quality
	Insufficient	No conclusions can be drawn as no study meets quality criteria
	Contradictory	No conclusions can be drawn as the findings of studies of similar quality contradict one another

Quality assurance was provided by peer review of the final draft by an expert working group and by two independent reviewers (RP and KV).

Most workers who develop symptoms do so within 3–4 years of starting work, particularly within 1–2 years [5,6,11,13,15,19,22,26,27,29–31]. LA rhinitis can develop following exposure of only a few weeks [31]. LAA can also occasionally present after many years work with laboratory animals [6,11,29–35].

Most studies find atopy, however defined, to be an independent risk factor for developing specific immunoglobulin E (IgE) to laboratory animal allergens [5,13,28,36] and for developing LAA [4–16,19,20,22,27,28,29–44]. Two studies [25,45] have not shown an association between atopy and development of sensitization or LAA, although the authors of one considered their study underpowered [25]. Other studies report that atopy increases the risk of developing asthma but not rhinitis [3,21,25,26,40,46]. Sensitization or allergy to pet cats or dogs is an independent risk factor for LAA [4,8,13,23,27,32]. Atopics develop symptoms earlier than non-atopics [12,31].

Most studies found no association between cigarette smoking and the risk of developing LAA [4,5,8,10,11,18,25,26,32,33] although some have [19,36,39,44].

Few studies investigated age. Four studies demonstrated that age is not a risk factor [10–12,18]. One study reported younger age to be a risk factor [8], whereas another reported increasing age as a risk [39].

Few studies have investigated gender as a contributory factor, most consistently reveal no gender variation [4,8,10,12,18]. A few studies have suggested that either males [11,32] or females [24] are at increased risk of sensitization or symptoms.

Several studies considered the effect of excluding atopic individuals from work and concluded this was an inefficient strategy. Two studies estimated that four atopics would need to be excluded to prevent one case of LAA [20,47]. Others noted such a policy would only avert half of cases of asthma and a third of rhinitis [22,26,48] resulting in incorrect decisions in one-third of the population [28].

LAA may cause cutaneous and/or respiratory symptoms that can interfere with an individual's ability to continue in their job (Box 2). Symptoms are most commonly upper respiratory symptoms [7,8,19,20,24–26,41,44] that may precede or coincide with the onset of asthma [3,5,17,26,30]. Laboratory animal rhinitis and asthma often occur co-morbidly [26,27,29,30,36,48]. Symptoms can occur in the absence of demonstrable specific IgE to laboratory animal allergens [3–5,7,10,11,22,26,27,31,49,50]. Sensitization to house dust or storage mite is common, may be work related, and may account for allergic symptoms in the absence of specific IgE to laboratory animal allergens [4,49]. Exposure to these mite allergens and other airborne particulates, e.g. endotoxins [41,50] occurs particularly in workers handling soiled bedding or feed.

Box 2. Clinical and occupational outcomes

- *** Upper respiratory (nasal and eye) symptoms occur more frequently than skin symptoms or asthma.
- *** Laboratory animal rhinitis and laboratory animal asthma frequently occur co-morbidly.
- *** Laboratory animal rhinitis either precedes or coincides with the onset of laboratory animal asthma.
- *** Skin prick or serological tests for animal allergens can be positive or negative in those with work-related respiratory symptoms and who are exposed to laboratory animals.
- *** Work-related respiratory symptoms in workers exposed to laboratory animals can be caused by agents other than laboratory animal allergens, e.g. house dust or storage mite or endotoxins.
- * Some workers who develop LAA can continue work with reduced animal contact or with the aid of respiratory protective equipment and/or prophylactic medication.

Proportionately more workers who developed LAA ceased work with the animals causing their symptoms than workers without LAA [29,35,47]. Some workers who developed LAA could continue work with reduced animal contact [26] or with the aid of respiratory protective equipment and/or prophylactic medication [29].

Discussion

The studies into LAA are heterogeneous with regard to study populations, animal species, degrees of exposure, methods of assessing exposure, defining atopy and establishing a diagnosis of LAA. Most studies were cross-sectional and provide little information on the natural history of LAA. The recommendations based on this review account for these points and recognize that many of the studies preceded the introduction of stricter statutory health and safety requirements and improvements in animal research and welfare. The recommendations also recognize the dearth of research evidence that demonstrates health surveillance is effective.

With regard to pre-placement health assessment, atopic individuals are at greater risk of developing LAA. However, its predictive value is low; it is inappropriate to exclude atopics from animal work. They will benefit from being identified at pre-placement stage so they can be counselled on their risk and given information and training specific to their circumstances, e.g. information on how to recognize signs of LAA on top of existing atopic disease or training in the use of additional personal controls such as use of a powered respirator.

We found little research that assessed the effectiveness of health surveillance programmes in averting new cases

of LAA. However, a well-designed programme should provide a means to identify new cases of LAA earlier than would be likely with passive reporting, creating opportunity for interventions that may prevent disease progressing or becoming established. Surveillance is a direct means beyond occupational hygiene measurements to assess the effectiveness of engineering and procedural controls. It also provides opportunity to remind and reinforce messages to workers on individual risks of LAA and the importance of complying with control measures to minimize allergen exposure. We therefore consider surveillance worthwhile with an expectation that it will contribute towards prevention.

There is no consistently reproducible no-observable-effect threshold for exposure (or exposure surrogates) to laboratory animal allergens. Since increased risk of LAA has been shown to occur down to exposures of 2 h/week, health surveillance should be conducted on workers whose exposure is typically 2 h or more a week. We emphasize that this should not be interpreted as an absolute cut-off and a proper, situation-specific assessment of risks, which includes intensity, duration and nature of exposure, degree of allergenicity of animal involved and specific work activity should define the threshold.

Many studies have found that laboratory animal allergen exposure can lead to the development of LAA. The broad search (allergy versus asthma) did not find evidence that LAA evolves differently from occupational asthma attributable to other agents, so the BOHRF health surveillance recommendations are valid. Health surveillance for laboratory animal workers should be modelled on the BOHRF [2] guidelines (Box 3)—accepting that clinicians, employers and workers must exercise their judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines, taking into account individual circumstances and patients' wishes.

Baseline health assessment, against which future pathophysiological changes will be assessed, should include symptom enquiry, face-to-face assessment and spirometry. Serological or skin prick tests for IgE specific to common aero-allergens and domestic and laboratory animal allergens may help identify those at increased risk. They (and their employer) can then be advised on the nature of the risk and on additional control measures to manage their exposure. The need for these tests should be based on an assessment of personal risk factors (e.g. past and family history of atopy, current atopic status, past occupational history, presence of domestic pets) and occupational exposure.

Thereafter health surveillance should be performed by an appropriate health questionnaire, covering eye, skin and upper and lower respiratory symptoms on exposure, and wheals with animal scratches. The additional value of spirometry for ongoing health surveillance has not been demonstrated [2] but it is useful in the diagnostic assess-

Box 3. BOHRF guidelines [2]

- ★★ Health practitioners should provide workers at risk of occupational asthma with health surveillance at least annually and more frequently in the first years of exposure.
 - ★★ Health practitioners should provide more frequent health surveillance to workers who develop rhinitis when working with agents known to cause occupational asthma and ensure that the workplace and working practices are investigated to identify potential causes and implement corrective actions.
 - ★★ Health practitioners should take measures to protect workers diagnosed with occupational asthma from further exposure to its cause in the workplace.
 - ★★ The likelihood of improvement or resolution of symptoms or of preventing deterioration is greater in workers who avoid further exposure to the causative agent.
- Good practice point: Health practitioners should assess whether skin prick or serological tests add value as part of the health surveillance of workers exposed to agents that cause IgE-associated occupational asthma in assessing the effectiveness of the control of exposure.

ment of people with lower respiratory symptoms and in monitoring people with asthma.

The frequency of continuing surveillance should be based upon risk assessment and be proportionate to it. Employers should determine, with advice from competent occupational health professionals, the frequency of surveillance necessary taking into account the working environment, hierarchy of control measures and health

Box 4. Summary of health surveillance recommendations

- The specific scope, content and periodicity of screening should be determined by an assessment of exposure risk. As a general guide, anyone exposed to animal allergens for more than 2 h/week should be included in a programme.
- Individuals new to animal work should be screened more frequently during their first few years of exposure.
- Screening should include enquiry into symptoms of skin disease, upper and lower respiratory tract symptoms, and conjunctivitis.
- Asthmatics should additionally be screened to identify exacerbation of symptoms or deterioration in control.
- Workers reporting symptoms should be assessed by an experienced occupational physician.

profiles of individual workers. It may be that some individuals' health surveillance is conducted more (or less) frequently than for others working alongside. Since nasal symptoms may develop within a few weeks of exposure and since most workers who develop symptoms do so within 3–4 years of starting work (and particularly within 1–2 years), we recommend that more frequent health surveillance is conducted in the first few years, starting as soon as 3 months.

Those workers with current asthma should also have an assessment of their respiratory function sufficient to identify any deterioration in symptoms or in control, at the same intervals. This may include peak expiratory flow rate or spirometry performed by a competent person.

Where a worker reports new symptoms suggestive of LAA or deterioration in symptoms or control of pre-existing allergic disease, they should be referred quickly to a qualified, experienced occupational physician. Investigation should include history and clinical assessment, determining any temporal relationship between symptoms and exposure to laboratory animal or common aeroallergens. Serological or skin prick tests should be performed to detect IgE specific to laboratory animal allergens and common aeroallergens. Further advice on management may be sought from clinicians with expertise in occupational allergy. Investigation of workers reporting symptoms suggestive of asthma should also include serial peak flow measurements [2].

Individuals who become sensitized to LA allergen should be counselled on their risk. Consideration should be given to restricting exposure, reviewing and reinforcing their training and use of personal protective equipment. In cases of occupational rhinitis (which may precede occupational asthma typically by one year), questionnaires and clinical assessment should be performed more frequently and if symptoms remain uncontrolled, removal from exposure may have to be considered.

Where an individual develops asthma attributable to laboratory animal work, they should be counselled on the risk from further exposure to the causative agents and provided with appropriate risk assessment-derived protective measures, as early avoidance of exposure leads to better health outcomes. Where new-onset asthma is confirmed but is not work related, surveillance should continue as recommended for workers with asthma.

Any new case of LAA should trigger a multidisciplinary, multicausal investigation with a review of health data trends, occupational hygiene data, the effectiveness of engineering and other controls to ensure these are adequate to protect the individual and other workers.

Where statutory or voluntary reporting instruments are in place, cases of disease should be reported and affected workers advised regarding eligibility for compensation.

We were not able to ascertain any body of evidence relating to the efficacy and efficiency of screening tools nor

could we find a respiratory questionnaire validated explicitly for use in health surveillance of workers who are exposed to workplace asthmagens. These are areas that would benefit from specific research.

Key points

- There exists wide variation in health surveillance policies and practice among occupational health services that monitor the health of those working with laboratory animals.
- Surveillance programmes should include all exposed or working in close proximity to laboratory animals for 2 or more hours/week and should identify atopics and individuals sensitized to domestic or laboratory animals to counsel them on their increased risk of developing laboratory animal allergy.
- Periodic surveillance should be conducted more frequently for the first few years of work.

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Conflicts of interest

P.N. participated because of his previous research into occupational asthma. His employer firmly believes that ending animal research is beneficial for consumers, animal welfare, and industry and is committed to continuing leadership in developing non-animal alternatives, with the goal to ultimately eliminate all animal research.

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