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OCCUPATIONAL ALLERGIES (JA POOLE, SECTION EDITOR)

Occupational Animal Allergy

Gregg M. Stave[1]

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Abstract
Purpose of Review This review explores animal allergen exposure in research laboratories and other work settings, focusing on causes and prevention.
Recent Findings (1) Consistent with the hygiene hypothesis, there is new evidence that early childhood exposure to pets produces changes in the gut microbiome that likely lead to a lower risk of allergy. (2) Anaphylaxis from laboratory animal bites occurs more frequently than suggested by prior literature. (3) Animal allergens represent an occupational hazard in a wide variety of work settings ranging from fields that work with animals to public settings like schools and public transportation where allergens are brought into or are present in the workplace.
Summary Exposure to animal allergens can result in allergy, asthma, and anaphylaxis. Animal allergy has been most studied in the research laboratory setting, where exposure reduction can prevent the development of allergy. Similar prevention approaches need to be considered for other animal work environments and in all settings where animal allergens are present.

Keywords Animal allergy · Animal bite anaphylaxis · Laboratory animal allergy · Occupational allergy · Occupational asthma

Introduction

Animal allergens are a significant occupational hazard in a wide variety of settings. Workers can develop dermal allergy, respiratory allergy, asthma, and anaphylaxis. In addition to the health consequences, these conditions can adversely employment and careers. Most of our understanding of the hazards and prevention of animal allergy comes from the experiences of research laboratories. In that setting, animal work continues to present a significant risk for the development of allergy and asthma. Occupational allergen exposure also occurs in other settings, such as veterinary practices, pet stores, and the agricultural sector. Due to the ubiquity of pet ownership and rodents in the environment, allergens are also found in the general environment and are brought into workplaces by people and pets.

This article is part of the Topical Collection on *Occupational Allergies*

✉ Gregg M. Stave
gms6@duke.edu

[1] Division of Occupational and Environmental Medicine, Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA

Lipocalins and Other Allergens

Animal allergens are proteins found in saliva, hair, dander, blood, and urine of rodents, rabbits, cats, dogs, horses, cows, and other species. Most of the common animal allergens are members of the lipocalin family, including mouse (Mus m 1), rat (Rat n 1), dog (Can f 1, Can f 2, Can f 4, Can f 6), and cat (Fel d 4, Fel d 7) [1•]. Most mammalian lipocalins are odorants and pheromone-binding proteins [2]. While varying in their sequence, the proteins have three structurally conserved regions and their three-dimensional structures are also similar. They share sequence homology with a schistosome protein, which may explain their allergenicity [3].

However, the primary cat allergen, Fel d 1, is a secretoglobin [4], and a major dog allergen, Can f 5, is a member of the kallikrein family [5]. The horse allergen Equ c 4 (latherin) is a surfactant protein [6••].

Cross-reactivity exists between rat and mouse urinary allergens, and the degree of cross-reactivity is likely to be dependent on the various epitopes being recognized on the major allergens from these two species. In one study in the UK, sensitization to mouse allergen was uncommon in the absence of sensitization to rats and sensitization to other animal species was less common among rat mono-sensitized individuals compared with those sensitized to both rat and mouse [7].

Can f 6, a dog allergen, cross-reacts with lipocalins from horse and cat and may contribute to sensitization and symptoms to more than one species [8]. Other lipocalins may have lower degrees of cross-reactivity [9•].

Genetic Predisposition

A number of studies have looked at the role of Human Leukocyte Antigen (HLA)/MHC in animal allergy as HLA class II molecules are involved in the presentation of allergen to the T cell. A small study of 26 laboratory technicians with animal allergy in Sweden compared with 75 controls showed that HLA-DR4 was more common than in controls, although this may have been due to an association with specific Gm locus genotypes [10]. In a larger cross-sectional study in the UK pharmaceutical industry involving 109 employees with allergy compared with 397 controls, HLA-DR7 was associated with rat allergen sensitization (odds ratio [OR], 1.82; CI, 1.12–2.97), respiratory symptoms at work (OR, 2.96; CI, 1.64–5.37), and, most strongly, sensitization with symptoms (OR, 3.81; CI, 1.90–7.65). HLA-DR3 was protective against sensitization (OR, 0.55; CI, 0.31–0.97) [11].

Immunology

Allergic symptoms occur when the balance of the T cell response favors Th2 cells. This leads to the production of interleukins (IL-4 and IL-5), which induce the production of IgE and eosinophils [12]. Noting that mammalian lipocalins have a limited ability to stimulate the cellular immune system, Virtanen et al. have proposed that "mammalian lipocalin allergens may be immunologically at the borderline of self and non-self" [9, 13].

High levels of allergen-specific IgG have been associated with clinical efficacy in immunotherapy studies [14]. Rat-specific IgG and IgG4 antibodies decrease the binding of IgE-allergen complex binding to B cells [15]. However, there is some uncertainty as to whether a modified Th2 response (IgG4 response in the absence of IgE) is protective from animal allergy. A prospective study conducted by Krop et al. followed 110 beginning animal workers for 2 years and found that IgG4 antibodies to rat and mouse allergens were present before the development of allergy [16]. Workers who became sensitized to mice actually had higher levels of IgG4, and higher IgG4 levels did not reduce symptoms [16].

Endotoxins

Endotoxin refers to the lipopolysaccharide (LPS) complex and associated proteins found in the outer layer of the cell wall of Gram-negative bacteria. Endotoxins have been shown to cause or exacerbate asthma and respiratory symptoms in farming and other occupational settings [17]. However, they appear to operate through a non-IgE-mediated mechanism involving IL-1, IL-6, IL-8, and TNF-α, triggering alveolar macrophages that carry specific endotoxin-binding receptors (CD14) [17].

In one study in the USA, endotoxin exposure was significantly associated with mouse-triggered symptoms in non-mouse-sensitized exposed workers [18]. A subsequent study of that setting revealed that endotoxin and mouse allergen concentrations were highly correlated during mouse-based experiments and mouse-care activities [19]. However, contradictory findings were observed in a recent study from the Jackson Laboratory, where atopic workers were more susceptible to, and non-atopic workers were protected from endotoxin-associated upper and lower respiratory symptoms [20]. Further research is required to understand the reason for this apparent discrepancy.

A recent cross-sectional study from Brazil compared employees from 92 workplaces where lab animal work was conducted with 53 where it was not and found that animal-exposed workplaces had higher concentrations of endotoxin, (median 34.2 endotoxin units (EU) per milligram of dust vs 10.2 EU/mg of dust ($p < 0.001$)). Animal facilities had higher concentrations of endotoxins. Endotoxin exposure above the median (20.4 EU/mg) was associated with increased reports of wheezing during the prior year (61% exposed to high compared to 29% exposed to low-endotoxin concentration ($p < 0.001$)) [21]. While the authors concluded that the difference in symptoms was due to endotoxins, they did not measure animal allergen concentrations, and it is possible that they have simply found a correlation between work in animal facilities and self-reports of wheezing, without sufficient evidence to attribute causation.

The Microbiome and the Hygiene Hypothesis

The "hygiene hypothesis" was proposed by David Strachan to explain an increase in observed allergy and asthma in the developed world [22]. Although the original hypothesis focused on the lack of exposure to infectious agents as a possible causal factor, the hypothesis was expanded by Agnes Wold to suggest that the increased illness might be attributed to changes in the intestinal flora [23]. It has been further modified to incorporate current understandings of immune regulation [24].

There is now increasing recognition of the role of the microbiome in the first year of life and the risk for allergy and asthma [25, 26]. Several recent studies have added to the understanding of the role of the microbiome in animal allergy. Early life exposure to two or more cats or dogs is

protective against allergic disease development [27]. Fujimura et al. sought to determine whether the distinct milieu of house dust associated with dog ownership could explain this phenomenon. They exposed mice to dog-associated house dust and found that they were protected against airway allergen challenge when compared with dust from homes without pets. This was associated with reduced Th2 cytokine production, fewer activated T cells, and a distinct gut microbiome composition highly enriched for Lactobacillus johnsonii. In a separate experiment, they determined that oral supplementation of mice with L. johnsonii protected them against airway allergen challenge [28••].

In a longitudinal study of 746 children in Canada, Tun et al. studied gut microbiota during infancy and pre- and post-natal pet exposure. Pet exposure enriched the abundance of Oscillospira and/or Ruminococcus, which have been negatively associated with childhood atopy and obesity. They also reported that among vaginally born infants whose mothers had received intrapartum antibiotic prophylaxis, Streptococcaceae were substantially reduced by pet exposure [29••].

Although still in the early investigative stage, it is possible that pre- or probiotic supplementation in infancy may reduce the risk for animal allergy or allergy and asthma generally [25].

Anaphylaxis

Anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by a rapid onset of airway, breathing, circulatory, or gastrointestinal problems, which is usually associated with skin and mucosal changes [30]. While a number of published articles mention that anaphylaxis is a concern, from 1983 through 2016, only eight cases of laboratory animal bite anaphylaxis were published in the English language world literature [31–36]. This included three cases from the USA, two from the UK, two from Canada, and one from Germany. The workers had worked with animals for 6 months to 20+ years. Six had a history of allergy or asthma. Among these cases, five involved rats and three involved mice. Of note, four had histories of previous animal bites that did not result in an anaphylactic response. All had uneventful recoveries, although one person required cardiopulmonary resuscitation and intubation. Only two were treated with epinephrine. Allergen testing was reported for seven, and all were positive. Some workers stopped working with animals or with the species that caused their anaphylaxis [37••]. An anaphylactic reaction following a needle injury that was used on rabbit tissue has also been described [38]. Animal bites from a mouse, hamsters, and guinea pigs outside of the occupational setting have also caused anaphylaxis [37••, 39–45]. In two cases involving hamsters, anaphylaxis was due to a novel allergen with cross reactivity with *Dermatophagoides pteronyssinus* (Der p) in hamster saliva [42].

However, anaphylaxis from laboratory animal bites occurs more frequently than suggested by this earlier literature. An online survey sent to 1272 laboratory animal care facilities identified by the National Institutes of Health Office of Laboratory Animal Welfare in the USA and completed by 198 organizations indicated that 15 had experienced at least one case of anaphylaxis between 2001 and 2016. Some organizations reported experiencing four cases. Where case reports were shared, cases involved bites from mice and rats, except for one case involving a needlestick with a syringe containing horse blood [37••].

Based on these published cases, it appears that anaphylaxis occurs frequently enough that it should be anticipated [37••, 46]. It is notable that, while atopy or respiratory allergy to animals may be risk factors for anaphylaxis, anaphylaxis following an animal bite may be the first indication of allergy. Anaphylaxis may also occur after a prior history of bites without an adverse reaction [37••]. After an episode of anaphylaxis, a review of allergy history and testing is helpful. Workers should be advised to carry injectable epinephrine [47]. It is also advisable to make injectable epinephrine available in locations where animal bites may occur [37••]. Epinephrine is the drug of choice for treating anaphylaxis, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis [48]. If epinephrine is available, it should be administered while awaiting emergency services [30].

Given the potentially life-threatening nature of anaphylaxis, workers experiencing anaphylaxis should be assigned to jobs that do not involve a risk of bites when possible. When this is not feasible, a review of work practices, administrative controls, engineering controls, and personal protective equipment (PPE) should be performed, preferably including a worksite visit.

Before returning to work, employees should also be asked about prior respiratory symptoms (allergy or asthma) or dermal allergy associated with animal work and, if present, these should also be addressed. Allergy testing (RAST or skin prick test) can provide helpful information.

For at-risk workers, appropriate work restrictions include not working alone when there is a risk of animal bites. Coworkers and/or first responders can be trained in how to recognize and address possible cases of anaphylaxis.

In the same survey, only about one third of respondents indicated that their organization had a protocol to treat anaphylaxis and fewer than two thirds of these incorporated treatment with epinephrine. Organizations that experienced a case of anaphylaxis were more likely to have a treatment protocol in place, although this was not universal [49].

Prevention of Laboratory Animal Allergy

Prevention of laboratory animal allergy requires reduction of exposure to allergens using the traditional hierarchy of controls: environmental, administrative, work practice, and finally, personal protective equipment (PPE) (Table 1). The goal is to minimize the requirement for PPE, but to use it when needed. Additionally, allergens need to be kept away from areas where animal work is not conducted, so that those not working with animals are not exposed.

In developing a prevention program, it should be recognized that the research environment is complex with movement of people and animals, variation in tasks, and the potential for exposure to animal allergens, endotoxin, and other hazards. Exposure varies by job title and task, with cage cleaning and washing potentially producing the greatest exposure [50–52]. Individuals performing similar tasks may also have widely different exposures depending on work practices and other factors [50, 51]. There is also an incomplete understanding of the process of sensitization. Heederik et al. pooled data from three studies to try and define an exposure response relationship for allergy to rats and concluded that "for atopic subjects, the risk increased little with increasing exposure, whereas for non-atopic subjects, a steadily increasing risk was observed" [53]. In a study at the Jackson Laboratory, Peng et al. found that variability and level of exposure together influence the allergen-specific immune response, with higher variability less likely to lead to sensitization [54].

Table 1 Approach to prevention of laboratory animal allergy

Environmental controls
Negative pressure environments
Local exhaust ventilation
Ventilated equipment (including individually ventilated cages)
Filter-topped cages
Downdraft tables
HEPA filter vacuums
Cage-changing stations
Robotic cage cleaning equipment
Bedding that reduces exposure
Administrative controls
Minimize animal use to extent feasible
Training and education of workers
Restricted access to animal rooms
Limit animal use to the animal facility (when not possible, limit animal transport to "dirty" corridors and minimize exposure during transport)
Restrict contaminated PPE to animal facility
Locker facilities that separate "clean" and "dirty" clothing and PPE
Work practice controls
Limit animal density
Work process design to reduce animal handling and exposure
Wet prep or HEPA vacuum for shaving
Room cleaning procedures that minimize exposure
Hand washing
Personal protective equipment (PPE)
Respirators—N95, N99, half-face, full-face, and powered air purifying respirators (PAPRs)
Gloves
Shoe covers
Hair covers
Protective clothing
• Lab coats
• Gowns
• Tyvek

An official safe working level has not been established. However, workers have developed allergic symptoms to mice at levels below 1.2 ng/m^3 [54]. Most facilities do not conduct environmental monitoring and those that do may conduct it only once or at varying periods (18 months to 3 years). The results may not represent typical conditions if workers pay greater attention to proper work practices during monitoring.

Once a worker develops animal allergy, the risk of developing allergies to additional species (secondary allergy) is high, with a 50% 10-year risk. In one program, this risk was present in an environment that was protective against development of primary allergy [55]. Secondary allergy may be due to cross-reactivity or new sensitization.

A variety of cage types and the use of cage changing stations can reduce allergen exposure [56]. There has been an increase in the use of individually ventilated cages (IVCs), although this use is far from universal. However, exposure occurs when these devices are unsealed and additional precautions are necessary [57]. In addition, these cages may not be appropriate for all studies. One assessment of IVCs that housed four mice per cage revealed a chronic low-grade reduction in oxygen concentration, from 21 to 20.5%. While this appears to be a minor change, the investigators noted that this was associated with increased red cells and platelets, decreased white cells, increased saccharin preference, and increased fluid consumption [58].

Employees often wonder whether respirators are necessary. If exposure cannot be adequately controlled with other methods, then respirators are needed. This is likely to be the case in the vast majority of workplaces today. In a survey of UK laboratory animal workers, for employees with less than 5 years of exposure, the use of respirators was associated with a lower prevalence of sensitization, regardless of the intensity of exposure [59•]. In the only published program that successfully prevented the development of primary animal allergy with an incidence of zero or near zero over many years, mandatory respirator use was a component of the comprehensive program [55, 60].

The choice of respirator will depend on the individual and the task. Respirators must be properly fitted to ensure that

there is an adequate seal. Disposable face masks, marked in the US as N95 or higher, are commonly used. The N95 designation indicates that the mask blocks 95% of particles that are 0.3 μm or larger. Alternative respirators include half-face, full-face, and powered air purifying respirators (PAPRs). However, surgical masks are not respirators as they do not create a seal, so they do not provide protection from allergens. In the USA, workers must be medically cleared to use respirators and fit testing is also required.

There is increasing interest in the use of a risk-based approach to reducing the need for respirators [61]. This approach requires air monitoring and utilizes a threshold level to distinguish high from low-exposure areas. There are numerous advantages in successfully identifying areas where the exposure risk is low, including savings on time, cost, and inconvenience. However, there is ongoing debate regarding the appropriate threshold. And given the complex and incompletely understood interaction between allergens and endotoxins in causing symptoms, it may be necessary to monitor endotoxin levels as well. While this approach is intriguing, it has not yet been demonstrated to prevent the development of primary or secondary animal allergy.

While the focus of prevention is on animal workers, support and administrative personnel who do not handle animals may also be at risk if allergens are not contained [62]. Prevention efforts may also benefit the family members of laboratory animal workers. Occupational laboratory animal allergens are detectable in the mattress dust of laboratory animal workers. Transfer of allergens via uncovered hair of animal workers is likely contributing to this phenomenon, which may be prevented by the use of hair covers [63].

While the use of engineering controls and the necessity of respirators may receive the most attention, it is critical to focus on work practices that reduce the risk of exposure to allergens, as well as bites and sharps injuries.

Although there will be challenges, many of the approaches to prevention of laboratory animal allergy could be incorporated into other settings where allergen exposure occurs. Just 25 years ago, most research laboratories conducted animal work without regard to allergen exposure.

Medical Surveillance

In order to monitor the health of employees and evaluate the success of a prevention program, it is necessary to perform medical surveillance. Medical surveillance should begin with a pre-placement assessment to identify risk factors and existing animal allergy. Periodic individual assessments, usually performed annually, should be used to identify previously undiagnosed allergy. Data from these surveillance assessments should be periodically analyzed to look for trends. In addition, workers should be encouraged to have an occupational medical evaluation if they have any symptoms that may represent allergy. Sample medical surveillance questionnaires have been published that can be used or adapted [12 Appendices C, D.]

To track the success of prevention efforts, it is helpful to track the prevalence (percent of workers with animal allergy at a point in time) and incidence (percent of new cases of animal allergy among those without prior allergy) over a period of time [64].

Other Work Settings

The prevalence of animal allergy in the research setting has ranged from 11 to 44% with a risk of asthma developing in 4 to 22% of those with animal allergy [12]. There are few studies that have reported on the prevalence of allergies in other settings. In a study of 59 workers in 24 pet shops in Sweden, one-third reported respiratory symptoms at work associated with exposure to rodents, birds, insects, or hay, and 29% were sensitized to work-related allergens, mainly rodents and insects [65]. A study of 51 workers in 20 pet shops in Ankara, Turkey, revealed that 25% of workers reported work-related symptoms, but only a third of these were sensitized to cats or dogs [66].

A study conducted at a veterinary animal hospital in the Netherlands quantified allergen and endotoxin exposure, but did not correlate these results with symptoms. In this setting, endotoxin levels were generally low, but allergen levels were high in some settings, with the highest allergen exposure (Fel d 1 and Can f 1) seen for student assistants in the intensive care unit. They also found significant allergen levels in the canteen likely due to the fact that pets were permitted in a separated area of the canteen [67]. In Iran, 100 animal workers from the veterinary school and animal husbandry service of a university medical school were compared with 50 controls. Symptoms were reported by 52 animal workers. Skin prick tests were positive in 36% of animal workers compared with 20% of controls [68].

A study of Danish farms revealed high levels of bovine allergens in stables, with up to 200-fold variability and also significant allergen levels in bedrooms [69]. Similarly, high levels of horse allergens have been found in horse stables [70]. In Finland, asthma caused by cow dander is a significant occupational problem for small family farms, although this is rarely reported in other countries [13].

General Environmental Exposure

Numerous studies have documented exposure to animal allergens in schools, daycare centers, public buildings, and public transportation [6]. It should be recognized that these

environments are also workplaces, so, for example, when allergens are identified as an issue in schools, teachers, administrators, and other staff may be affected along with students. When exposure to mouse allergen in inner city schools was associated with increased asthma symptoms and decreased lung function in students, [71•] this may also represent an occupational hazard. Pet allergens may similarly represent a problem in schools [72].

It is also common for allergens from pets carried on hair and clothing to be brought into workplaces. In an assessment of the carriage rate of allergens on various types of clothing, wearing a woolen sweater increased personal allergen exposure to cat allergen by a factor of 11 [73]. Washing frequency was also important [73]. A review of indoor allergens in schools and daycare centers revealed that upholstered furnishings and clothing are among the important reservoirs for dog and cat allergens, although allergens are also present in carpeting and on desks and chairs [74]. The number of pet owners among attendees is highly correlated with allergen levels [74]. Leather seats are less likely to retain allergens [75].

Future Research

While there have been extensive studies that have aided our understanding of how animal allergens produce allergy, there have been far fewer published studies of efforts to prevent allergy. There is also a need for a better understanding of the interaction between endotoxin and allergens in producing sensitization. More organizations with successful animal allergy prevention programs need to publish their experience. Outside of the laboratory setting, we need to implement control measures to reduce exposure and study their effects.

Conclusion

While it may be possible in the future to reduce the incidence of occupational allergy and asthma from animal allergens by altering the microbiome in infancy, for now, this remains a significant occupational health hazard. Animal work environments are highly varied, even within the same occupations. Exposure to animal allergens remains the most important risk factor for allergy, although there is a complex interplay with endotoxins in the work environment in precipitating symptoms. The most experience with prevention of animal allergies comes from the research laboratory environment. While continuing to enhance prevention efforts in that setting, it is time to apply some of the learnings from animal research settings to other animal workplaces. It will also be helpful to reduce the animal allergen burden in general workplaces, such as schools, offices, medical clinics, and hospitals.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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