

New insights into laboratory animal exposures and allergic responses

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Purpose of review

To update the epidemiology of laboratory animal allergy, identify new exposures in the laboratory animal workplace, discuss complexities in the exposure–response relationship, and review the immunology of symptomatic and allergic responses.

Recent findings

Laboratory animal allergy remains a common occupational hazard of research scientists, technicians and animal handlers. The epidemiology is typical of a stable workforce: incidence is low, although prevalence is high. Risk factors of atopy, current exposures, and sensitization to cats or dogs incompletely predict disease. Exposures include a complex, potent mixture of allergens, biological adjuvants such as endotoxin and irritants. The dose–response relationship between laboratory animal exposure, sensitization and symptoms is hard to define: cross-sectional studies identify most sensitized workers in moderate laboratory animal exposure, not in the highest exposure. Exposure assessments based on workday averages underestimate exposure peaks that may be significant for symptoms and disease. Although we have assumed that workers without symptoms are not sensitized to laboratory animal allergens, recent data demonstrate that many asymptomatic workers do make laboratory animal-specific immune responses that may be necessary to prevent symptomatic disease.

Summary

Understanding laboratory animal exposures and disease must include exposures other than allergen, and responses other than allergic disease.

Keywords

endotoxin, exposure measurement, laboratory animal allergy, laboratory animal asthma

Abbreviations

HLA	human leukocyte antigen
LAA	laboratory animal allergy
PST	prick skin test
RAST	radioallergosorbent test

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Introduction

Laboratory animal allergy (LAA) is a model system to study the exposures and host factors that contribute to the risk for work-related allergy and symptoms, as well as interventions that may lead to prevention. There are several paradoxical aspects to both responses and exposures that should guide further research. The first is that although work-related skin, upper and lower respiratory symptoms are common, typically less than half of symptomatic workers are also sensitized to the laboratory animal in question. So not all symptoms reflect LAA. Second, dose–response relationships between animal allergen and symptoms or sensitization are not linear. Rather, in cross-sectional prevalence studies, workers in the highest exposure group have a lower frequency of symptoms or sensitization compared with moderately exposed workers. As most workers will have been exposed to laboratory animals before the job in which they are evaluated, which exposure should we measure to determine the risk of sensitization: past, present, or exposure at the time of symptom onset? Are mean or peak exposures the most relevant to trigger symptoms or immune responses? Exposure–response assessments are complicated by the healthy worker effect, in that symptomatic workers remove themselves from the triggering allergen or exposure, leaving behind healthy unaffected workers. The unhealthy worker effect also shapes this relationship, in that symptomatic workers who are committed to their jobs will alter their workplace exposures so as to limit symptoms. A number of recent papers have described new occupational exposures important to consider in symptomatic laboratory animal workers. Together, these factors introduce nuances of exposure that complicate our ability to model explanatory exposure–response relationships.

Epidemiology

The epidemiology of LAA is typical of a stable workforce: incidence is low, although prevalence is high. It is difficult to estimate the onset of disease because most workers have

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laboratory animal exposure before the current job, and may not have reported previous symptoms. Many epidemiological studies are hampered by low participation rates, which raise questions about the generalizability of the results. Case findings also depend on how allergy is measured [by symptoms, prick skin test (PST), or radioallergosorbent test (RAST)], and which groups of workers are examined (all exposed or just symptomatic). Overall, approximately twice as many workers report symptoms when working with laboratory animals than are sensitized to them, although symptomatic workers who do not show current evidence of specific IgE antibodies to laboratory animals are at an increased risk of becoming sensitized.

One recent study [1] examined the incidence of LAA and allergy symptoms in a longitudinal study of pharmaceutical workers between 1991 and 2003. Of 792 enrolled workers, complete data on symptoms, RASTs, and typical work exposures with at least two visits were available for 305 individuals (38.5%). Of these, the incidence of LAA, based on positive RASTs and symptoms, was 1.32/100 person-years (py). The incidence of laboratory animal symptoms alone was twice that at 2.22/100 py. Those without exposure to laboratory animals before their current jobs had the highest rates of allergy at 4.26/100 py. Workers aged 18–28 years, those with more than 6 h per week of laboratory animal exposure, and 1–3 years of follow-up were also at higher risk. Work with mice or rats was associated with the highest rates of sensitization, both with and without symptoms. These rates are similar to an earlier study [2] using SWORD reports of laboratory animal-associated asthma and rhinitis from 1999 to 2000 in the United Kingdom, based on exposed population data from 207 out of 296 research institutions (70%) using laboratory animals and responding to a questionnaire. The authors calculated an annual incidence rate of 1.56/1000 workers for occupational asthma, and 2.54/1000 for occupational rhinitis to laboratory animals. Rates were highest for insect work (2.35/1000 and 21.1/1000), and work with birds (23.9/1000 and 14.4/1000), although the case numbers were low.

The same pharmaceutical medical surveillance program [1] evaluated the progression of self-reported symptoms to laboratory animals among workers enrolled during a comparable time period [3]. Of these, 603 (76%) completed two or more questionnaires, had an average of 5.2 years of previous work with laboratory animals, and contributed 2527 py of surveillance, or a mean of over 4 years per subject. Workers were divided into prevalent cases with at least one laboratory animal-associated symptom at baseline ($n = 108$) and 47 incident cases of laboratory animal symptoms reported during the course of the study. Of the 108 workers with baseline symptoms, most had more than one symptom, and the frequency

of those with asthma symptoms rose from 20% initially to 35% at the final visit [hazard ratio 9.4; (4.2, 20.9), compared with incident cases]. Workers with baseline laboratory animal symptoms were more likely to be female, perform more job tasks, have physician-diagnosed allergy, hayfever, or a history of allergy shots, and to be non-smokers. The variables not contributing to risk for laboratory animal symptoms included age, race, years of employment in a particular job, years of previous work with animals, number of follow-up years, hours per week in animal rooms, history of asthma, pet ownership, and cigarette smoking. The reported use of personal protective equipment was high in all worker groups, and did not distinguish between those with and without symptoms.

Risk factors

Risk factors for symptoms or sensitization to laboratory animals have been replicated in a number of studies, but are incompletely characterized, as their presence predicts at best 60% of sensitized workers. Predictors typically include markers of atopy, physician diagnosis of hayfever or asthma, some measure of exposure to laboratory animals, and sensitization to furred pets. One recent study [4] evaluated 200 veterinarians, working at small animal clinics in a metro area in Poland, by questionnaire, PST, total serum IgE, specific IgE to cats, dogs and laboratory animals, as well as to latex and several common disinfectants. Asthma was assessed by histamine challenge, and the peak expiration flow rate was measured before and hourly after occupational exposure to laboratory animals in those with symptoms suggesting occupational asthma.

Almost 60% of these veterinarians were atopic on the basis of one or more positive skin tests, and rates of LAA were high: 123 out of 200 or 61.5% were allergic to one or more laboratory animals by PST or specific IgE, most commonly to rats or mice. PSTs were more sensitive in detecting LAA than serum-specific IgE, as 89 out of 123 sensitized workers (72.4%) had positive PST, compared with 63 out of 123 (51%) with detectable laboratory animal-specific IgE. Twenty per cent were allergic to natural rubber latex, and 11% had IgE to disinfectants (ethylene oxide, phthalic anhydride, formalin/formaldehyde, or chloramine T), indicating that other allergens need to be considered when evaluating symptomatic laboratory animal workers. Laboratory animal sensitization was most closely associated with work-related respiratory symptoms: 14 out of 19 with chest symptoms; 23 out of 27 with nasal symptoms; 25 out of 33 with eye symptoms; but only three out of six with skin symptoms were sensitized to laboratory animals.

Workers who were sensitized to laboratory animals were more likely to be men, report previous contact with or be

sensitized to cats or dogs, and have chest or eye symptoms at work, compared with non-sensitized workers. Whether male sex was associated with specific jobs or exposures was not explored in that paper. Subjects with laboratory animal asthma or rhinitis ($n = 25$) were also more likely to be men, and describe more intense laboratory animal exposure, such as spending 11 years or more of working with laboratory animal, and having daily contact with laboratory animals. They were also more likely to have atopic risk factors such as a family history of atopy, elevated specific IgE to cats or dogs, and total IgE greater than 100 kU/l. When 14 veterinarians with work-related chest symptoms were monitored at the beginning and end of a typical work day by peak flow rates and the provocative concentration of histamine causing a 20% fall in forced expiratory volume in 1 s, both fell at the end of the work challenge to make the diagnosis of occupational asthma. In contrast, peak flow rate monitoring or histamine challenge obtained during a work period, and compared with results obtained during a period away from work, did not show sufficient differences to establish a diagnosis of occupational asthma.

Many groups have worked to develop diagnostic models that better predict the risk of sensitization to laboratory animal allergens, although results have been somewhat disappointing. This suggests that currently defined personal and exposure variables only partly explain the process, and highlights the need for further research in this area. A model of predictive variables for high molecular weight occupational sensitization [5] was developed using 579 Dutch laboratory animal workers (77% participation) and 427 Dutch bakers (75% participation), and then validated in 357 British laboratory animal workers (88% participation). Out of nine original risk factors, the authors identified four as significant in the final model. These predictors included work-related symptoms, more than 38 working hours per week, specific IgE to one or more common allergens, and total IgE of 100 kU/l or greater, each modified by the type of work (laboratory animal versus baker) and weighted to provide a predictive score. Age, sex, personal history of atopic symptoms, previous exposure to high molecular weight allergens, and smoking status were ultimately not helpful factors in the final model. The authors used mouse or rat-specific IgE-RAST as a marker of laboratory animal sensitization that, nonetheless, missed sensitized workers potentially identified by PSTs. If all risk factors were present, the model predicted a 60% probability of laboratory animal sensitization. Applying the model to the British laboratory animal workers (the validation set) showed reasonable discrimination between sensitized and non-sensitized workers (area under the curve from a receiver operated curve 0.76; 95% confidence interval 0.68–0.83); when sensitivity is 70%, and specificity is 75%.

Exposures

Exposures in laboratory animal work are complex and incompletely characterized, likely to be multifactorial, and include more than just recognized allergens. New allergens (storage mites, collagenase) and adjuvant exposures (endotoxin) have recently been described. How we measure exposure may also be important, in that peaks of exposure, which may be most important for the outcomes of interest, are missed in whole-shift sampling.

Estimating an exposure–dose relationship is also difficult because of the characteristics of the workforce. The laboratory animal workforce appears to reflect both a healthy worker effect in the highly exposed such as animal handlers (symptomatic workers leave jobs with high allergen exposure, leaving unaffected workers behind), and an unhealthy worker effect in the less exposed such as researchers and scientists (symptomatic workers stay in their jobs, but modify exposures to limit symptoms). Both of these effects impair our ability to characterize the relationship between work exposures, symptoms, and sensitization accurately.

Typically, the relative risks for sensitization do not show a linear association with increasing exposures indicated by $\mu\text{g}/\text{m}^3$, or hours per week of laboratory animal work [6,7]. The highest prevalence of laboratory animal-related sensitization is consistently found in those with moderate, but not the highest, exposures. Similarly, when workers are separated into those who are laboratory animal sensitized, and those who are not, the incidence of symptoms does not generally track well with increasing categories of laboratory animal exposure.

Airborne endotoxin has recently been measured together with animal allergen in the laboratory animal workplace, both in animal facilities and research laboratories, and associated with laboratory animal symptoms. One study [8] created individual subject exposure variables for mouse allergen and endotoxin based on typical work tasks reported by each subject, weighted by the time spent each week in each work task, and normalized to the volume of air breathed. Air concentrations were sampled during specific job tasks, rather than averaged over the course of the work day. The relationships between workplace exposures to animal allergens and endotoxin, and laboratory animal-related symptoms, differed based on the allergic status of the worker; atopic workers are more likely to report laboratory animal-associated symptoms, even those not sensitized to laboratory animals, than non-atopic workers. Although endotoxin was not associated with laboratory animal sensitization nor laboratory animal symptoms when the cohort was analysed as a whole, separation of the workforce into mouse allergic and non-mouse allergic demonstrated

different exposure–symptom patterns of response. Daily endotoxin exposures were the strongest predictors of laboratory animal symptoms in non-mouse sensitized workers, whereas any work with mice (rather than actual airborne mouse allergen concentrations) predicted laboratory animal symptoms in mouse-sensitized workers. Here too, atopy and asthma contributed an equal risk of symptoms in both mouse-allergic and non-mouse-allergic workers.

Further characterization of endotoxin and mouse allergen exposures in mouse facilities and research laboratories indicated that peak exposures to either do not always correlate [9[•]]. Airborne endotoxin peaked during mouse experiments in the animal facility, whereas mouse allergen concentrations were highest during direct mouse work throughout mouse research laboratories. Endotoxin and mouse allergen concentrations correlated moderately during direct research work with mice and mouse care activities, although neither associated with any specific sized particles. Most particles sampled were submicron in size, and the possible health effects of these deserve further study. Real-time particle counts showed marked peaks and valleys during the course of each task, findings that are lost in 8-h time-weighted averages. As peak, rather than mean, exposures may be more important for both symptom generation and for sensitization, sampling should also account for time-related variations.

Other exposures should also be considered in symptomatic laboratory animal workers. In a subset (40/65) of laboratory animal workers with work-related rhinitis, 17 (43%) were sensitized to storage mites or dust mites [10]. Evidence of mites was detected in 21 out of 22 dust samples from litter, straw, feedstuffs, and dust from storages of animal food. An allergy to collagenase [11] was recently reported in a laboratory technician also sensitized to laboratory animals, who exposed mice to the nebulized protein. Laboratory animal allergens have been detected on the surgical caps of laboratory animal workers [12], and on their mattresses and pillows, with levels similar to those of pet owners. The implication is that personal protective equipment can also serve as a reservoir of animal allergens that may be transferred to the home.

Immunology

We have previously assumed that symptomatic workers respond immunologically to airborne laboratory animal allergen, and medical evaluation was focused on symptomatic workers. Skin test-negative but symptomatic workers were felt to be incorrectly classified as non-sensitized because of limitations of skin or enzyme-linked immunosorbent assay tests, or because they were mucosally but not systemically sensitized and the responsive organ system had not been examined. Immune responses to workplace allergens are, however, more complicated

than they seem initially. A recent well-designed cross-sectional study of rat-exposed pharmaceutical workers [13^{••}] evaluated 685 out of 719 employees (96%) by questionnaire, PSTs, and rat-specific IgE, IgG and IgG₄ by laboratory developed RAST and enzyme-linked immunosorbent assay, respectively. Exposure was classified by the maximum number of rats ever handled in one day: 0, 1–10, 11–50, more than 50, based on the assumption that maximum exposure was important, and may have occurred in the past. Rat-specific IgE showed 96% concordance with the rat PSTs. The prevalence of rat-specific IgE increased with the number of rats ever handled up to 11–50, but was reduced in those handling or having handled more than 50 rats a day. The prevalence of rat-specific IgE was greater in atopic workers than in non-atopic workers, but showed the same pattern of reduction at the highest level of daily rat exposure. Positive rat IgG and IgG₄ were set at stringent levels: an optical density reading within the top quartile. By these criteria, 25% of the workers having handled 1–10 and 11–50 rats a day had rat IgG, and 20% had rat IgG₄. In the highest exposure group, a third of workers had rat-specific IgG and IgG₄. These data indicate that many exposed workers make an immunological response to rats, although most are asymptomatic. Workers in the higher two exposure categories and with longer periods (≥ 3 years) of rat work were more likely to make rat-specific IgG and IgG₄, and less likely to make rat-specific IgE. An interesting finding was that workers with the highest rat exposure had higher ratios of rat-specific IgG₄:IgE compared with those with lower exposures, and were more likely not to have chest symptoms. This finding of increased specific IgG and IgG₄ and reduced specific IgE has been termed a modified T helper cell type 2 response, and is also detected with specific immunotherapy.

Similar results have been published for mouse-exposed laboratory animal workers [14–16], although a comparable study of 529 rat-exposed workers reported different findings [17]. Higher serum levels of rat IgG₄ in those workers were associated with atopy, positive rat PSTs, and allergic respiratory symptoms to rats independent of the cumulative exposure to rats. When workers were grouped into those with rat exposure of less than 4 years, or more than 4 years, atopic workers exposed to rats for more than 4 years showed an inverse relationship between increasing exposures and sensitization; those with the highest cumulative exposures had the lowest prevalence of positive rat PSTs, and were less likely to report allergic respiratory symptoms to rats. Ratios of rat-specific IgG₄:IgE were not reported in that study, which might explain these latter findings.

The relationship between home pet exposures, pet sensitization, and pet-specific IgG antibody titres in children are supportive of these conclusions. One study of 226

children aged 12–14 years found that more children in the highest Fel d 1 exposure group had cat-specific IgG and were not sensitized to cats compared with those in lower exposure households [18]. Similar results were published by Hesselmar and colleagues [19]. Both papers interpreted these findings as indicative of clinical tolerance, a modified T helper cell type 2 immune response, in children with high levels of exposure to cats: results similar to those in laboratory animal workers with high exposures to rats and mice.

Taken together, these results indicate that, depending on how mouse or rat-specific antibodies are measured, a large proportion of exposed workers will recognize and respond to laboratory animal allergens. A smaller proportion of workers will become symptomatic, and be classified with allergic disease, based on evidence of laboratory animal-specific sensitization. It is, however, possible that the lack of symptoms or disease requires active recognition of the allergen, which, in normal individuals, sets in motion a process of tolerance marked by laboratory animal-specific IgG or IgG₄. It may be the inadequate or dysfunctional recognition of allergen, that which results primarily in laboratory animal-specific IgE, which is the cause of symptoms and disease [20].

A further risk of laboratory animal sensitization is conferred by specific human leukocyte antigen (HLA) types that more effectively bind rodent lipocalin allergens [21]. Of 512 rat-exposed pharmaceutical workers (71%) who were HLA typed, 115 were rat sensitized. Similar to other studies, sensitized workers were less likely to have worked in the highest exposure job category. HLA-DRβ1*07 was associated with a risk of rat sensitization, odds ratio (OR) 1.82 (1.12, 2.97), and work-related chest symptoms, OR 2.96 (1.64, 5.37), $P < 0.001$, whereas HLA-DRβ1*03 was protective, OR 0.55 (0.31, 0.97). There was no evidence that the HLA effect was modified by the extent of laboratory animal exposure. The differences in sensitization risk were attributed to changes in the specific HLA peptide-binding groove, in which the hydrophobic peptides of HLA-DRβ1*07 potentiate the binding of Rat n1, whereas the positively charged residues of HLA-DRβ1*03 repel the binding of Rat n 1, and the subsequent recognition or response to rat allergen.

Prevention

Allergic disease in the laboratory animal workplace is currently defined as work-related allergic symptoms, laboratory animal sensitization, and evidence of asthma or rhinosinusitis. Primary prevention recommends a reduction of relevant exposures to levels below which no new allergic disease would be detected. The exposure–response relationship for LAA is, however, not well defined. Clearly, some workers with high exposures make laboratory animal-specific IgG titers

not linked to disease, and others make laboratory animal-specific IgE in settings of lower exposures. We have limited longitudinal data on symptomatic workers not sensitized to laboratory animals; we have as yet not identified those characteristics that protect from symptom progression or lung function decline. Furthermore, more than laboratory animal allergen is active in this exposure–disease equation; also included are endotoxin, storage mites, collagenase, and other protein allergen exposures that may need to be controlled. Most exposure control efforts have looked at work shift time-weighted average exposures, and have not addressed peak typical or intermittent exposures that may be more important in triggering sensitization or symptoms. Most predictive models have not defined levels or durations of exposures likely to cause disease that are applicable to all laboratory animal workplaces. Whereas most identified risk factors are personal features of workers, primary prevention implies control of all relevant exposures. Therefore which exposures are most important, and how we should control them, are unanswered questions.

A number of exposure control strategies, typically related to cage design and storage, have been shown to reduce airborne animal allergens, although the effect of these changes on worker outcomes have usually not been evaluated. The addition of perforated Makrolon plastic curtains in front of animal racks reduced airborne Mus m1 in an animal facility [22], filter topped animal cages reduced exposure to laboratory animal allergens and endotoxin 50-fold [23], and the addition of vented cages with filtered exhaust ports resulted in further reductions. High animal allergen exposure tasks have been defined as those involving the direct handling of animals, cage changing, disposal of soiled litter, changing exhaust filters in animal rooms, and cage wash. Jobs associated with medium exposures to laboratory animal allergens included cleaning in the animal unit, indirect contact in animal rooms, and feeding animals. Low exposure tasks included procedures with animal tissue, and unconscious or dead animals [24]. High allergen exposures do not, however, necessarily correlate with the highest prevalence of disease. The most compelling evidence that reducing exposure to animal allergens can diminish disease was shown in a 2002 study from Sweden [25]. Airborne mouse allergen was measured before and after engineering interventions, and was shown to be significantly reduced by changing to automated cage dumping and cleaning, using ventilated cage changing wagons, keeping mice in ventilated cabinets, handling animals only on ventilated benches, and using a centralized vacuum cleaner. After these interventions, the levels of mouse urinary allergen IgE in two workers became undetectable. Whether other relevant exposures responsible for these effects were also controlled with these changes was not measured in that study.

Conclusion

The laboratory animal workplace remains fruitful ground to study the exposure–response relationships necessary for the onset of allergic disease. The following questions remain: The dose of what exposure? How should we measure it? What is the relevant outcome (antibodies or symptoms, or both)? Recent research indicates that we are not measuring all relevant exposures, or appropriately modeling the associations between these exposures and disease. Understanding the patterns of response to laboratory animal allergens associated with tolerance, symptoms, or disease will be as important as better measurement, and from there, better control of relevant laboratory animal exposures.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 207).

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A detailed description of the associations between mouse allergen, endotoxin, and particulates in different settings of the laboratory animal workplace.