Epidemiology of laboratory animal allergy

Hayley L. Jeal, Meinir G. Jones and Paul Cullinan

Department of Occupational and Environmental Medicine, National Heart and Lung Institute, Imperial College, 1b Manresa Road, London SW3 6LR, UK

Abstract

Laboratory animal allergy is common and an important occupational health issue for the research, pharmaceutical and toxicological sectors. In most settings where there is regular contact with laboratory animals – chiefly small mammals – the prevalence of specific sensitisation is around 15% and the prevalence of clinical allergy around 10%. These figures probably underestimate the true risk of disease since epidemiological studies of the disease have been beset by response and survivor biases. Allergen exposure appears to be the most important modifiable risk factor, but the effects of such exposure seem to be modified importantly by individual susceptibility. Laboratory animal research shows no signs of becoming less common, and an increasingly susceptible (atopic) population is likely to be recruited into such work. Future studies should be designed to take into account the inherent biases of occupational epidemiology, to study in detail the immunological mechanisms that underlie sensitisation and tolerance, and to identify early biomarkers of each.

Introduction

Human allergy to furred animals has a history, presumably, that is as long as that of the domestication of wild beasts. With a general increase in atopy it is probably more common now than it has ever been. Animal allergy in an occupational, laboratory setting on the other hand is a far more recent phenomenon, reflecting the development of vivisection as a means of studying human biology and responses to toxins and pharmaceuticals.

Early descriptions of laboratory animal allergy were in case report form only and are reviewed by Hunskaar and Fosse [1]. An interesting example is given by Sorrell and Gottesman [2] who in 1957 reported a single case of mouse allergy in a female research worker after she developed rhinitis at work. She was treated by specific immunotherapy with an autogenous extract, after which she was able to continue working with mice for up to 4 h at a time.

In 1961 Rakja identified, on the basis of skin and exposure tests, ten cases of laboratory animal allergy at the Karolinska Hospital in Sweden [3] and suggested that

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hypersensitivity to laboratory animals was not as uncommon in research laboratory workers as might previously have been thought. It was not until the 1970s, however, that proper epidemiological studies of laboratory animal workers were carried out and a better idea of the scale of the occupational problem was determined. Over the subsequent 35 years laboratory animal allergy has been the subject of extensive epidemiological study and is now universally recognised as an important occupational health issue. With the possible exception of baker's asthma, it is the best understood of all the occupational respiratory allergies.

Causes, species and allergens

The contemporary use of animals for research purposes is dominated by the pharmaceutical, toxicological and academic sectors. In 2007, for example, just over 3.2 million scientific procedures were carried out on animals in the United Kingdom; 83% included rodents. The total number was a 6% rise over the previous year, due mainly to an increase in the use of genetically modified mice in scientific experiments.

A bewildering variety of animal species are used in laboratory-based research (Tab. 1). Most procedures use mammalian species and, as the figures above suggest, most of these now involve mice because of the relative ease of genetic manipulation in that species. Other commonly used mammals include rats, guinea pigs, hamsters and ferrets, cats and dogs, pigs, sheep and goats. Non-human primate research is far less common; interestingly human allergy to other primates appears to be very rare.

Commonly used non-mammalian species include insects, amphibians and fish; allergic responses to the last two of these appear to be extremely rare. A wide variety of species of insects have been identified as causing occupational allergy: fruit flies, cockroaches, locusts, grasshoppers, bumblebees, mites, spiders and chironomid midges. Birds are occasionally used in research, chiefly in behavioural studies.

Table 1 lists commonly used species and their associated allergens. The majority of the major mammalian allergens belong to a family of proteins known as lipocalins [4]. The sequence identity of lipocalin allergens often falls below 20% but they have a similar three-dimensional structure and contain between one and three structurally conserved regions [5]. Lipocalins also share biological functions that predominantly relate to the transport of small hydrophobic ligands such as vitamins and pheromones. Interestingly, lipocalins share a sequence homology with schistosome proteins and it is possible that molecular mimicry may be responsible for the high rates of sensitisation to lipocalin allergens in the workplace.

Laboratory animal workers may also be exposed to other types of allergen in the workplace. These include allergens in animal or fish food (such as mealworms or corn cob), natural rubber latex (gloves), moulds, pollens, enzymes, antibiotics and several sensitising chemicals

Table 1. Animal species (and associated allergens) commonly used in laboratory research

Species	Allergens	Mol. mass (kDa)	Source
Mammalian			
Mouse (*Mus musculus*)	Mus m 1 (prealbumin)	19	Hair, dander, urine
	Mus m 2	16	Hair, dander, urine
	Albumin	68	Serum
Rat (*Rattus norvegicus*)	Rat n 1 Rat n 2	21	Hair, dander, urine
	(α_{2u}globulin)	17	Hair, dander, urine
	Albumin	67	Serum
Guinea pig (*Cavia porcellus*)	Cav p 1 Cav p 2	20	Hair, dander, urine
		17	Hair, dander, urine
Hamster (*Cricetus cricetus*)	Unknown	-	-
Ferret (*Mustela putorius furo*)	Unknown	-	-
Rabbit (*Oryctolagus cuniculus*)	Ory c 1	17	Hair, dander, saliva
	Ory c 2	21	Hair, dander, urine
Cat (*Felis domesticus*)	Fel d 1	38	Hair, dander, saliva
	Fel d 4	19.7	Saliva
	Albumin	65–69	Serum, dander, saliva
Dog (*Canis familaris*)	Can f 1	25	Hair, dander, saliva
	Can f 2	19	Hair, dander, saliva
	Albumin	67	Serum
Pig (*Sus domesticus*)	Unknown	-	-
Sheep (*Ovis aries*)	Unknown	-	-
Goat (*Capra hircus*)	Unknown	-	-
Other			
Fruit fly (*Drosophila melanogaster*)	Unknown	-	-
Locust (several species)	Unknown	-	-
Cockroach (several species)	Bla g 2	36	Faeces, saliva and
	Bla g 4	21	body of cockroach
	Bla g 5	23	

Clinical characteristics of laboratory animal allergy

Laboratory animal allergy has clinical characteristics typical of an immediate-type hypersensitivity to a protein aeroallergen. Symptoms develop after a latent period of exposure that is generally between 3 and 24 months. Upper respiratory symptoms of rhinitis and itchy eyes are almost universal and may be accompanied by asthma and by urticarial skin responses to animal scratches or abrasions. In the early stages of disease there is noticeable improvement when away from the workplace. With continuing exposure a hypersensitive state tends to develop with symptoms provoked by increasingly smaller exposures [6] and any improvement away from work becoming less apparent. Under these conditions standard treatments for asthma and rhinitis are relatively ineffective. Conversely, the avoidance of exposure to the causative allergen generally results in considerable – or complete – improvement.

As with its symptomatology, the immunopathology of laboratory animal allergy is typical of a type 1 allergic response. The development of sensitisation is complex and involves interaction of antigen-presenting cells and Th2 lymphocytes, which secrete IL-4, IL-5, IL-9 and IL-13 cytokines leading to an allergic response, with associated specific IgE response that may be detected by serum assay or skin prick testing. With appropriate test methods for all relevant allergens the detection of an IgE response is almost wholly sensitive. Thus, the false-negative rate is very low, and a negative result to both skin prick testing and serum assay effectively rules out the diagnosis.

Disease frequency

There are several ways in which the prevalence or incidence of laboratory animal allergy may be estimated. Each has particular drawbacks but all probably underestimate the true frequency of disease. The reasons for this include:

- Specific sensitisation to animal proteins may be clinically unapparent and thus detectable only through skin prick testing or by the measurement of serum-specific IgE antibodies. Survey methods that do not include such techniques will lead to an underestimation of the true frequency of sensitisation.
- The tools – generally self-completed questionnaires – that are used to determine the frequency of laboratory animal allergy in clinical or workplace populations may be insensitive; either intrinsically as they may not include all relevant questions or because participants may be reluctant to disclose full information. While high sensitivity is desirable in obtaining a true estimate of disease prevalence, specificity is also important, particularly in deriving unbiased estimates of exposure-response relationships [7].

- Epidemiological methods that do not include all or a very high proportion of the eligible population are likely to suffer from a responder bias. The direction of this bias in the context of laboratory animal allergy is not known but it is the experience of the authors that symptomatic workers are less likely to participate in surveys.
- The use of cross-sectional survey to measure the prevalence of laboratory animal allergy probably incurs a risk of survivor bias, an example of a healthy worker effect. Employees who have developed laboratory animal allergy may be more likely than others to seek alternative employment or, within the workplace, to move to jobs that entail less (or no) exposure to the allergens that incite their symptoms [8]. The first process (selection out of the workforce) will result in a cross-sectional population whose disease experience is healthier than is truly the case; the second (selection within the workplace) may lead to erroneous estimates of exposure-response relationships.

If conducted carefully, cohort studies provide not only a measure of the incidence of laboratory animal allergy but potentially also an account of any (internal) selection, and thus an unbiased estimate of exposure-response relationships. In practice they have rarely if ever been entirely successful in these respects; they are certainly far less common than cross-sectional designs.

As with the case of potential responder bias, the size of any 'healthy worker' effect in the animal laboratory setting is unknown. There are several probable determinants that include the relatively short latency period for the induction of laboratory animal allergy and, once disease has developed, the very brief interval between exposure and the elicitation of symptoms. Once established and under conditions of continuing exposure, laboratory animal allergy displays other characteristics of an immediate-type hypersensitivity, in particular the incitement of symptoms at increasingly low concentrations of allergen exposure. Each of these factors permits an obvious relationship between exposures at work and the manifestations of disease and together they are likely to have an important influence on employment behaviour. More individual factors that are likely also to impact on retention within a job or a workplace include the severity of symptoms – which appears to be variable – and the attitudes of employers. For the most part, those who employ laboratory animal workers have a more enlightened view of occupational disease among their employees than is generally the case. Thus, many laboratory animal workers with a specific occupational allergy are afforded an unusual degree of flexibility in their work.

Cross-sectional surveys

The most common approach to measuring the frequency of laboratory animal allergy is to estimate its prevalence through the use of a cross-sectional survey of a

workforce. Table 2 provides a comprehensive but succinct summary of published results from 29 such surveys. The numbers of employees included range from 62 to over 5500; where information is available response rates between 61% and, in some cases, 100% are reported.

The reported prevalences of 'allergic symptoms' vary widely from around 10% ('any symptoms') to over 50%. There is similar if less pronounced variability in the estimated prevalences of specific sensitisation. Such variation has at least three sources: true variation reflecting differences in site- or population-specific risk factors; between-study inconsistency in the definition and measurement of 'allergy'; and variation in the study populations reflecting, as above, different survival patterns.

Perhaps the most important of these is the second. Very few published cross-sectional surveys provide sufficient information on the constitution of their surveyed population; even the most basic information, such as on the duration of employment, is frequently lacking. Thus, it is generally very difficult to judge to what extent the reported findings reflect true disease incidence rather than the effects of important survival processes. Even the apparently consistent – and certainly plausible – observation that upper respiratory symptoms (rhinitis) are more common than symptoms of asthma may in part be a result of employees with asthma re-locating at a greater frequency than those with rhinitis alone.

Few cross-sectional surveys have attempted to address this problem. Exceptions include a study of research workers in the United Kingdom [8] in which analyses were restricted to those who had not had exposure to laboratory animals prior to their current employment, and surveys by Hollander et al. [27] and Heederik et al. [28] in which analysis was confined to employees with less than 4 years exposure to laboratory animals. Although imperfect, these techniques probably lessen the impact of any healthy worker effect and may lead to associations that approximate those observed in cohort studies.

A recent ecological examination of prevalence estimates from 15 cross-sectional surveys concluded that the prevalence of occupational asthma – but not of occupational rhinitis – among laboratory workers had declined by about 50% between 1976 and 2001 [34]. This decline was not, however, evident in those studies where workers were exposed to rats, mice, rabbits or guinea pigs. Comparisons such as these should be viewed cautiously since, as above, studies in this field rarely share a common methodology. Thus, it is not possible to account for the several biases inherent in cross-sectional epidemiology, particularly perhaps those that relate to survival pressures.

Cohort studies

Cohort ('longitudinal') studies circumvent many of the difficulties associated with cross-sectional surveys. In particular, if they are carried out carefully, they have

Table 2. Prevalence studies from cross-sectional surveys (English language publications).

						Prevalence of allergic symptoms (%)			Prevalence of sensitisation: SPT or IgE (%)		
Study/year	**Country**	**Facility**	**Species***	**N (% response)**	**Average duration of exposure**	**Any**	**Chest**	**Eye/ nose**	**Mouse**	**Rat**	**Any/other**
Lincoln 1974 [9]	US	Research	M, R, Rb, Gp, H	238 (NA)	NA	11%	5%	9%	NA	NA	10% (SPT)
Lutsky 1975 [10]	US	Mixed	M, R, Rb, Gp, C, D, H	1293 (NA)	NA	15%	10%	15%	NA	NA	NA
Taylor 1976 [11]	UK	Research, pharma	LA	474 (NA)	NA	23%	9%	17%	NA	NA	NA
Gross 1980 [12]	US	Research	M, R, Rb, Gp	399 (100%)	NA	15%	8%	15%	NA	NA	NA
Cockcroft 1981 [13]	UK	Research	M, R, Gp, Rb, S	179 (61%)	NA	27%	12%	25%	NA	NA	16% (SPT)
Davies 1981 [14]	UK	Research, pharma	LA	585 (NA)	NA	20%	3%	11%	NA	NA	NA
Schumacher 1981 [15]	Australia	Research	M	121 (82%)	3 years	32%	4%	24%	33%	-	-
Slovak 1981 [16]	UK	Pharma	LA	146 (NA)	NA	30%	10%	23%	NA	NA	15% (SPT)
Beeson 1983 [17]	UK	Pharma	M, R, Gp, Rb	62 (83%)	NA	24%	5%	21%	5%?	11%	32% (IgE)?

Table 2 (continued)

						Prevalence of allergic symptoms (%)			Prevalence of sensitisation: SPT or IgE (%)		
Study/year	**Country**	**Facility**	**Species***	**N (% response)**	**Average duration of exposure**	**Any**	**Chest**	**Eye/ nose**	**Mouse**	**Rat**	**Any/other**
Agrup 1986 [18]	Sweden	Research	M, R, Rb, Gp, H, C	101 (100%)	NA	30%	20%	10%	18%?	18%	any:19% (SPT+IgE): Rb: 11%, Gp: 26%, C: 31%
Bland 1986 [19]	US	Research	R, Rb, Gp, C	549 (93%)	NA	24%	NA	NA	NA	NA	NA
Lutsky 1986 [20]	Israel	Research	R, M, Rb, Gp	90 (NA)	9 years	7%	4%	7%	NA	NA	NA
Platts-Mills 1987 [21]	UK	Research	R	213 (NA)	NA	17%	10%	7%	-	12% (SPT)	-
Venables 1988 [22]	UK	Pharma	R, M, Rb, Gp	138 (87%)	9 years	44%	11%	37%	NA	NA	26%
Venables 1988 [23]	UK	Mixed	R, M, Rb, Gp	296 (NA)	8 years	47%	13%	NA	NA	NA	17% (SPT)
Aoyama 1992 [24]	Japan	Research, breeding	R, M, Gp, Rb, H, C, D, P, Mn	5641 (64%)	NA	23%	6%	18%	NA	NA	NA
Cullinan 1994 [8]	UK	Research	R	323 (88%)	21 months	31%	10%	22%	-	10% (SPT)	-
Bryant 1995 [25]	Australia	Research	LA	130 (NA)	NA	56%	22%	NA	NA	NA	NA

Hollander 1996 [26]	Netherlands	Research, pharma,	R	458 (77%)	11years	19%	6%	17%	-	18% (SPT)	-
Hollander 1996 [26]	Netherlands	Research, pharma,	M	377 (77%)	10years	10%	3%	9%	10% (SPT)	-	-
Hollander 1997 [27]	Netherlands	Research, pharma	R	398 (77%)	NA	20%	NA	NA	-	17% (SPT)	-
Heederik 1999 [28]	Sweden	Research, training	R	74 (82%)	<4 years	-	3%	12%	-	5%	-
Heederik 1999 [28]	Netherlands	Research, pharma, training	R	219 (77%)	<4years	-	5%	15%	-	8%	-
Heederik 1999 [28]	UK	Research, pharma	R	357 (88%)	<4 years	-	9 (3%)	10%	-	4%	-
Lieutier-Colas 2002 [29]	France	Research	R	113 (100%)	NA	39%	4%	34%	-	12%	-
Ruoppi 2004 [30]	Finland	Research	R, M	156 (61%)	6 years	47%	26%	42%	NA	NA	NA
Jeal 2006 [31]	UK	Research	R	689 (96%)	8 years	22%	NA	NA	-	11%	-
Krakowiak 2007 [32]	Poland	Vets	R, M, H, Rb, Gp	200 (NA)	NA	NA	10%	14%	16% (SPT)	17% (SPT)	H: 6%, Gp: 13%, Rb: 5%
Hewitt 2008 [33]	New Zealand	Research	LA	50 (NA)	11 years	22%	4%	18%	4%	2%	Gp: 2%

* M, mouse; R, rat; Rb, rabbit; Gp, guinea pig; H, hamster; D, dog; C, cat; S, sheep; Mn, monkey; LA, laboratory animals unspecified; SPT, skin prick test.
NA, not available.

the ability to examine the determinants of employees' movements within or out of a workforce. Furthermore (see below), they allow the measurement of relevant workplace exposures, a particular advantage in an immunological disease such as laboratory animal allergy where it is probably the case that very early exposures determine the risk of sensitisation.

However, cohort studies are far more difficult to conduct well, and tend to be far more expensive, than cross-sectional surveys. Probably for these reasons they have been far fewer in number. Occasionally (e.g. [35, 36]) cohort studies are embedded within routine surveillance schemes, potentially a far more efficient approach – and certainly one that is underused.

Eleven published cohort studies are summarised in Table 3 with estimates of disease and sensitisation incidence rates where these are available. As with the cross-sectional surveys described earlier, the response rates for several are low – a serious problem with any cohort design.

Some studies have been of very short duration and probably have produced underestimates of true incidence rates. A further important limitation of many studies is that they incorporate participants with previous occupational exposure to laboratory animals. This effectively negates much if not all of the advantage of a longitudinal approach over the cross-sectional survey. Some [35, 43] have restricted analyses to, or included analysis of, newly exposed employees and so gained valuable insights. In a longitudinal study of pharmacological research employees in the United States for example [35], the estimated incidence rate of laboratory animal allergy was about 2.3 per 100 person years. In an analysis confined to employees without prior exposure to laboratory animals, however, the estimated incidence rate was about twice as high, suggesting an important degree of 'selection out' in that workforce.

A note of further caution in relation to estimated incidence rates for laboratory animal allergy in warranted. The immunological nature of this short-latency condition is reflected in a high incidence of disease shortly after first exposure – and probably a diminishing risk thereafter, under conditions of continuing similar exposure. If this is true then rates derived across a longitudinal survey may hide differential annual rates; few, if any, studies have been large enough to examine this in any detail.

Surveillance schemes

Alternative methods of measuring the frequency of laboratory animal allergy depend on routine surveillance statistics. Several countries – notably Finland, the UK and France but also South Africa and parts of Spain, Canada and Australia – have established surveillance schemes for occupational asthma. Each measures disease that is newly recognised and reported by specialised physicians, usually in occupational

Table 3. Estimated incidence rates of laboratory animal allergy from longitudinal studies.

						Estimated incidence of allergic symptoms per 100 person years			Estimated incidence of sensitisation (SPT or IgE) per 100 person years
Study/year	**Country**	**Facility**	**Species***	**n (% of eligible population)**	**Duration of follow–up**	**Any**	**Chest**	**Eye/ nose**	
Davies 1983 [37]	UK	Pharma	M, R, Rb, Gp	148 (100%)	1 year	15	2	NA	NA
Botham 1987 [36]	UK	Pharma	R, M, Gp, Rb	383 (NA)	Variable	12–37	NA	NA	NA
Kibby 1989 [38]	US	Research	LA	169 (70%)	2 years	6.5	NA	NA	NA
Das 1992 [39]	US	Training	LA	29 (55%)	7 months	0	0	0	NA
Renstrom 1995 [40]	Sweden	Training	M, R, Rb, H, Ho, P, Ch	38 (100%)	18 months	6	2	5	5
Kruize 1997 [41]	US	Pharma	LA	99 (44%)	10 years	1.9	0.8	1.4	NA
Fisher 1998 [42]	US	Pharma	LA	159 (NA)	≤5 years	0–10	NA	NA	NA
Cullinan 1999 [43]	UK	Research	R	342 (80%)	7 years	–	3.5	7.3	4.1
Gautrin 2001 [44]	Canada	Training	M, R, Rb	373 (89%)	44 months	–	2.7	–	NA
Rodier 2003 [45]				387 (93%)			–	9.6	
De Meer 2003 [46]	Netherlands	Research	M, R, Rb, Gp,	105 (NA)	2 years	6	NA	NA	NA
Elliot 2005 [35]	US	Pharma	LA	495 (82%)	12 years	2.3		3	1.32

* M, mouse; R, rat; Rb, rabbit; Gp, guinea pig; H, hamster; D, dog; C, cat; S, sheep; Ho, horse; P, pig; Ch, chicken; LA, laboratory animals unspecified; SPT, skin prick test.
NA, not available.

or respiratory medical practice; in some instances the schemes are closely linked to compensation claims. They are of course entirely dependent on the presentation of disease by an employee and its recognition and reporting by an appropriate specialist. Surveillance in this manner certainly leads to an underestimate of the true incidence of occupational asthma; in the case of laboratory animal allergy this is enhanced by the omission of cases without overt asthma.

Some surveillance schemes can be linked to national workforce denominators to estimate occupation-specific incidence rates (Tab. 4). Such denominators are rarely, if ever, specific to laboratory animal workers. Hence the rates from which they are derived are a further underestimate of the true job-specific incidence. In the UK, for example, the annual incidence rate of occupational asthma among 'laboratory assistants and technicians' was estimated to be 0.24/1000, based on a workforce of 127478. A subsequent exercise to establish a more specific estimate of the size of the laboratory animal-exposed workforce produced a figure of between 12000 and 17300 employees working with small mammals. From these were derived new estimates of annual disease incidence of 1.26/1000 and 2.54/1000 for occupational asthma and occupational rhinitis, respectively [47].

Analysis of reports from surveillance schemes in different countries also affords the possibility of international comparisons (Tab. 4). Where they are available (but see above), estimated annual incidence rates vary between 17 and 79 cases per

Table 4. Numbers of total cases of occupational asthma and laboratory animal asthma with estimated annual incidence rates per million workers from surveillance schemes in seven different countries.

	All occupational asthma		Laboratory animal asthma		Laboratory animal asthma as a proportion of all cases
Scheme	**No. of cases**	**Annual incidence**	**No. of cases**	**Annual incidence**	
UK (1989–1990) [48]	1985	20	50	188	2.5%
France (1996–1999) [49]	2178	24	27	NA	1.2%
Finland (1989–1995) [50]	2602	17	52	116	2.0%
South Africa (1997–1999) [51]	324	18	3	NA	0.9%
Quebec (1992–1993) [52]	287	42–79	19*	329**	7%
Catalonia, Spain (2002) [53]	174	NA	7	NA	4%
Australia† (1997–2001) [54]	170	NA	4	NA	2.4%

*Occupational asthma to 'laboratory and farm animals' in **'agricultural and related service industries'
† Victoria and Tasmania
NA = not available

million workers; the last (highest) figure, however, also includes agricultural workers. The proportions of all registered cases of occupational asthma that are attributed to laboratory animal exposures are remarkably consistent between approximately 1% and 7%, the lowest figure being for three provinces in South Africa.

Aside from the professional surveillance schemes above, estimates of the incidence of laboratory animal allergy may be made from counts of claims for statutory compensation or, through the courts, for personal injury. The obvious weaknesses in each of these is likely to compound the problems of under-ascertainment described above.

Risk factors

The imperative to reduce the incidence of laboratory animal allergy has produced a focus on the study of modifiable risk factors. The most important of these is believed to be allergen exposure within the workplace. Most allergen exposure-response studies have, like those of disease frequency, been carried out in cross-sectional occupational populations. A summary of these ($n = 18$) together with the findings of five cohort studies is displayed in Table 5. In addition, where it is available, information on disease latency is provided. The evidence that laboratory animal allergy is usually a condition of short latency is both consistent and strong.

Allergen exposure

'Exposure' has, in most cases, been assessed by job title and only occasionally by direct measurement of airborne allergen. The use of 'zoning' techniques whereby employees in different jobs are grouped by their likely exposures (e.g. into 'scientist', 'animal technician' and 'other') allows job title to be a good, albeit broad, proxy of direct measurement [55]. Where proxies are used as the main indicator of exposure, it is helpful if they are supplemented by quantitative exposure information. Neither approach, however, has proved to be a good indicator of the variability in exposure 'quality'; the exposure of animal technicians, for example, who carry out the day-to-day care of animals, is likely to be more consistent than that of scientists whose experimental protocols generally cause a far more variable exposure pattern.

In general it has been more difficult in cross-sectional surveys to demonstrate any relationship between allergen exposure – however defined – and disease risk. The reasons for this have been discussed above and probably relate primarily to survival processes including those that determine survival within a particular job within a workplace. In a survey of UK research workers [8], no relationship between disease prevalence and current exposure was observed; however, such was evident when exposure at the time of onset of disease was examined, suggesting that employees

Table 5. Cross-sectional and cohort studies of the relationship between exposure and the risk of laboratory animal allergy.

Study/year	Species*	*n*	Exposure measurement	Latency	Exposure-response
Cross-sectional surveys					
Taylor 1976 [11]	Mixed	474	ND	"No increase in incidence of LAA after 2 years"	ND
Gross 1980 [12]	Mixed	399	Frequency of entry into animal house	Average 11 months. "LAA most likely to occur within 6 m and rarely >2–3 years"	ND
Cockcroft 1981 [13]	Mixed	179	Job category	High exposed groups < medium exposed	ND
Schumacher 1981 [15]	M	121	Frequency/ duration of exposure	usually <1 year	Neither frequency nor duration of exposure significantly related to sensitisation or symptoms.
Slovak 1981 [16]	Mixed	146	Job category	Asthma: 66% ≤3 years	Asthma cases confined to high exposure group
Beeson 1983 [17]	Mixed	62	Duration of exposure	ND	No significant difference in duration of exposure between LAA and non-LAA cases
Bland 1986 [19]	Mixed	549	Job category, frequency	ND	Dose effect for frequency in low/moderate but not in high exposure group. No. of species handled is a risk factor for LAA
Platts-Mills 1987 [21]	R	213	Job categories	Mean 2.5 years	Sensitisation: 0% (low exposure), 6% (medium), 20% (high). Duration is less important than exposure
Venables 1988a [22]	Mixed	138	Job category, duration of exposure	ND	Non-significant inverse trend by duration of exposure for prevalence of LAA
Aoyama 1992 [24]	Mixed	5641	Job category, frequency, # species	33% ≤1 year, 70% ≤3 years	Prevalence of LAA increased with higher frequency of exposure and with increasing # species handled. No significant association with job categories

Cullinan 1994 [8]	R	323	Aeroallergen measurement	ND	Prevalence of LAA symptoms related to intensity of exposure. Stronger in atopic subjects
Hollander 1997 [27]	R	398	Aeroallergen measurement	ND	In those exposed <4 years – prevalence of sensitisation in low, medium and high exposure groups were 4.1, 5.0 and 7.2 times higher than control group. Exposure –response relationship steeper in atopics
Fisher 1998 [42]	Mixed	159	Intensity of exposure	ND	High exposure not a significant predictor of LAA
Heederik 1999 [28]	R	650	Aeroallergen measurement	ND	Risk of sensitisation increased with exposure intensity. Atopics had elevated risk of sensitisation at low allergen exposures.
Lieutier-Colas 2002 [29]	R	113	Aeroallergen measurement	ND	No relationship between rat exposure and development of sensitisation or symptoms
Ruoppi 2004 [30]	R, m	156	Frequency of handling	ND	Exposure-response relationship between intensity of exposure and development of respiratory disease.
Jeal 2006 [31]	R	689	Job category, # rats handled	ND	High-exposure attenuation of exposure–response relationship for sensitisation and symptoms
Krakowiak 2007 [32]	Mixed	200	Frequency	ND	Exposure-response relationship for symptoms (OR 50.2; 95% CI, 2.84; 884.99)
Cohort studies					
Davies 1983 [37]	R	142	ND	Symptoms within 0.5–12 years – rhinitis preceded asthma	ND
Kibby 1989 [38]	Mixed	450	Aeroallergen measurement	ND	Duration unrelated to LAA Positive association between LAA and intensity of exposure (PR=1.75; 95% CI, 1.06–2.39; p=0.03) Positive association between LAA and weighted job exposure (PR=1.58; 95% CI 1.00–2.50)

Table 5 (continued)

Study/year	Species*	n	Exposure measurement	Latency	Exposure-response
Cullinan 1999 [43]			Aeroallergen measurement	Median: skin, eye/nose 12 months, chest 18 months	In those exposed <2 years, exposure related to development of symptoms – but attenuated at highest exposure. Relationship stronger in atopics.
Rodier 2003 [45]	Mixed	417	Time in contact	ND	Contact time associated with the incidence of rhinoconjuctivitis in dose-dependent manner
Eliott 2005 [35]	Mixed	495	Frequency of handling	ND	Risk of LAA increased with duration of exposure to animals and work in animal-related tasks

LAA, laboratory animal allergy

with symptoms had moved away from jobs of higher exposure. Similar factors presumably explain why duration of exposure appears irrelevant [38] – or even inversely related to risk [22].

Many cohort studies of laboratory animal employees have been set up to examine exposure-response relationships and thus have done so with greater attention to detail. Some [43] have had this aim as primary, others [36, 42] in order to examine changes in disease incidence in relation to primary preventive programmes. Broadly, their findings suggest that higher allergen exposure intensities are related to the risk of laboratory animal allergy – with some important modifying influences (see below). What is far less clear is the detail of such a relationship and in particular the existence – and level – of any threshold of exposure below which there is no measurable risk. This is a problem common to any immunological outcome, reflecting in part the wide range of individual susceptibility. Arguably this is an issue that will not be amenable to further epidemiological study.

A recent and interesting observation is that the relationship between exposure intensity and risk, which is almost certainly non-linear, may also not be monotonic. Thus, there is some evidence [31, 43] that at highest exposures there is a degree of attenuation in risk; this may reflect qualitative differences in exposure (e.g. 'constant' vs 'intermittent'), differences in exposure route or even a phenomenon of high-dose 'immunotolerance'. The last of course – if established with certainty – would have interesting implications for occupational health practice.

Atopy

Atopy, the tendency to develop immediate-type immune responses to environmental aeroallergens, is a well-documented risk factor for the development of laboratory animal allergy [8, 13, 19, 27], its relative risk being of the order of 3.0–4.0 [8, 13, 19, 27, 41]. Cross-sectional studies generally report higher risk estimates than do those of longitudinal design, perhaps a reflection of co-sensitisation. In addition, atopic employees are more likely to develop occupational asthma as a result of exposure [13, 41], and are more likely to be absent from work or transferred to another job because of symptoms of laboratory animal allergy [41]. Indeed, the latter observation suggests that survival is further influenced by atopic status, in which case its true relative risk may be higher than is commonly measured. The onset of symptoms from laboratory animals following first exposure is probably shorter in atopic employees than it is in those who are not atopic [36, 41]. For example, Kruize et al. [41] reported that the mean latency for laboratory animal allergy was significantly shorter in atopics (45 months) than in non-atopics (109 months).

Furthermore, atopy may confer quantitative differences in the response to allergen exposure in the laboratory. Several studies suggest a stronger exposure response for the development of laboratory animal allergy in atopic than non-atopic workers

[8, 27, 28, 41, 43], although this is not an entirely consistent observation and probably dependent on both exposure levels and any definition of atopy. Differences may also reflect lower outcome rates – and thus less statistical power in non-atopic subgroups. Kruize et al. [41] reported similar exposure-response patterns in atopic and non-atopic groups, but a stronger relationship in those who were atopic. Similarly, other studies suggest interactions between allergen exposure and atopy whereby, in general, exposure-response relationships are steeper for workers with atopy-associated risk factors [8, 27]. Heederik et al. [28], on the other hand, reported a flatter association in atopic workers; this finding probably reflects exposures above an important threshold for atopic workers who, at the lowest level of exposure, had a more than threefold increase in risk of allergy.

Clearly atopy is a strong risk factor in the development of laboratory animal allergy and the question arises as to whether it could be used as a predictive tool. In their longitudinal study of pharmaceutical research workers, Botham et al. [36] observed that laboratory animal workers who developed symptoms during their first year of exposure were mainly atopic, but that the majority of atopic subjects remained non-symptomatic during the first year of exposure. The number of atopics becoming symptomatic in the second and third year of exposure was small with an increasing proportion of non-atopics developing laboratory animal allergy. Similarly, Slovak and Hill [56] in an examination of several different methods of defining 'atopy' concluded that none had sufficiently high predictive sensitivity or specificity. A more recent study has essentially confirmed these findings [57]; although atopy is strongly associated with the development of laboratory animal allergy, its predictive value is low and most employees with atopy – currently a high proportion of laboratory animal workers – will not develop a specific sensitisation. Thus, the exclusion of atopic people from working with laboratory animals seems to be insufficiently discriminatory as a factor to be considered as a means of screening for susceptible individuals.

Human leucocyte antigen

There have been few studies investigating the association of HLA genes and laboratory animal allergy. The first of two relatively small studies found statistically significant associations with HLA-B15, -DR4 and (inversely) -B16 and sensitisation to rat urine [58]. The second reported an excess of HLA-DR4, -DR11 and -DRw17 in human T lymphocyte responses to the major mouse allergen, Mus m 1 [59].

In a relatively large case ($n = 109$) referent ($n = 397$) analysis of a cross-sectional survey of pharmaceutical researchers, HLA-DR7 was associated with sensitisation, respiratory symptoms at work and most strongly with the combination of sensitisation and symptoms [60]. HLA-DR3 was found to be protective against sensitisation. Furthermore, amino acid analyses of HLA-DR7 and -DR3 indicated a biologically

plausible explanation for the associations found. There was no evidence of any modification by exposure of the association between HLA-DR7 and sensitisation to rat urinary protein, or respiratory symptoms at work.

In the same study, the risk estimate of being sensitised to rat urinary protein was almost doubled in the presence of HLA-DR7; this risk was lower than those associated with atopy (fivefold) or a crude estimate of exposure (fourfold). These figures suggested that approximately 40% of occupational asthma in that population study could be attributed to HLA-DR7; in comparison, attributable proportions for atopy and daily work in animal house were 58% and 74%, respectively.

Conclusion

Laboratory animal allergy is common and an important occupational health issue for the research, pharmaceutical and toxicological sectors. In most settings where there is regular contact with laboratory animals – chiefly small mammals – the prevalence of specific sensitisation is around 15% and the prevalence of clinical allergy around 10%. These figures probably underestimate the true risk of disease since epidemiological studies of the disease have been beset by response and survivor biases. Allergen exposure appears to be the most important modifiable risk factor; however, the effects of such exposure seem to be modified importantly by individual susceptibility. Laboratory animal research shows no signs of becoming less common and an increasingly susceptible (atopic) population is likely to be recruited into such work. Future studies should be designed to take into account the inherent biases of occupational epidemiology, to study in detail the immunological mechanisms that underlie sensitisation and tolerance, and to identify early biomarkers of each.

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