

Laboratory Animal Allergy: A British Perspective on a Global Problem

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Abstract

In the United Kingdom, laboratory animal allergy (LAA) has been recognized as an important occupational disease for nearly 25 yr. However, introduction of health and safety legislation (e.g., the Control of Substances Hazardous to Health Regulations of 1988) and an increasing knowledge of the factors that contribute to the etiology of this disease have had surprisingly little impact on the prevalence and incidence of LAA over the last 10 to 20 yr. Studies of the relation between exposure to animal allergens and the development of LAA reveal that the risk of disease increases with increasing intensity of exposure. Current evidence suggests that animal allergens are very potent, and substantial decreases in allergen exposure are therefore necessary before a reduction in symptoms will be observed. In the United Kingdom, it is unlikely that an Occupational Exposure Limit will be set for animal allergens in the near future, partly because an adequately standardized assay for quantifying exposure is not yet available. Prevention of LAA in the future will probably be driven by the needs of the industry and will most likely rely on the adoption of guidelines describing “best practise,” which incorporate sophisticated engineering methods of controlling exposure to animal allergens.

Key Words: exposure-response relation; health and safety; laboratory animal allergy; occupational asthma

Introduction

The importance of laboratory animal allergy (LAA¹) as an occupational disease was recognized in the United Kingdom nearly 25 years ago. In 1976, the British Society for Allergy

and Clinical Immunology published preliminary survey results indicating that 23% of 474 participating animal workers experienced one or more symptoms consistent with LAA (Taylor et al. 1976). This percentage was substantially greater than the contemporary reports from the United States, where the prevalence rate of LAA was found to be less than 15% (Lincoln et al. 1974; Lutsky and Neuman 1975). More detailed cross-sectional epidemiological studies of four pharmaceutical companies in the early 1980s confirmed that the prevalence rate of LAA in the United Kingdom varied between 19.5 and 30% (Beeson et al. 1983; Cockcroft et al. 1981; Davies and McArdle 1981; Slovak and Hill 1981). The prevalence rate observed in such studies may be influenced by a number of factors including the stability of the work force (the so-called “healthy worker effect”; Venables et al. 1988; Sjöstedt et al. 1993) and the practices used with animals. However, a common study observation was that approximately one in 10 individuals exposed to laboratory animals experience asthma, the most serious symptom of LAA. Subsequent studies have suggested that there has been relatively little change in the high prevalence rate of this disease in the United Kingdom over the last 20 yr despite increased awareness of the factors that can influence the disease (Cullinan et al. 1994; Venables et al. 1988). The etiology of LAA and its continuing high prevalence are remarkably consistent throughout the Western world (Aoyama et al. 1992; Bryant et al. 1995).

LAA in the United Kingdom

Number of People Exposed

The exact number of people currently exposed to laboratory animals in the United Kingdom is unknown. Although statistics are kept by the Home Office on the number of license holders and the number of experiments performed on live animals (information published annually by Her Majesty’s Stationery Office), there is no accurate record of the true number of people occupationally exposed to laboratory animals. In the 1980s, it was estimated that 32,000 people were in regular contact with laboratory animals (Cockcroft et al. 1981). A more accurate postal survey suggests the current figure is closer to 15,000 (A. Draper, Imperial College School of Medicine, National Heart & Lung Institute, London, UK, personal communication, 2000).

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¹Abbreviations used in this article: COSHH, Control of Substances Hazardous to Health; HSWA, Health and Safety at Work Act; IgE, immunoglobulin E; LAA, laboratory animal allergy; MEL, maximum exposure limit; OES, occupational exposure standard; RAST, radioallergosorbent test; RIDDOR, Reporting of Injuries, Diseases and Dangerous Occurrences Regulations; SWORD, Surveillance of Work-related and Occupational Respiratory Disease.

Incidence Rate

Very few studies have been published of the incidence rate of LAA. In the United Kingdom, there has been one prospective study of laboratory animal workers (Cullinan et al. 1999). From a cohort of 355 newly employed workers, 36 developed work-related chest symptoms, an incidence of 3.5 per 100 person years. (A person year is sum of the number of years each member of a population has been afflicted by a certain condition [e.g., years of treatment with a certain drug].) The incidence rates of work-related eye/nose and skin symptoms were 7.3/100 person years ($n = 84$) and 4.8/100 person years ($n = 59$), respectively.

The best national estimate of the incidence rate of asthma caused by laboratory animal species in the United Kingdom can be obtained from the Surveillance of Work-related and Occupational Respiratory Disease (SWORD¹) project. This voluntary surveillance scheme was established in 1989 and is funded by the Health and Safety Executive. Initially, 90% of the chest clinics in England, Scotland, Wales, and Northern Ireland, and nearly 400 occupational physicians, submitted monthly reports of newly diagnosed cases of occupational respiratory disease. A change in the reporting system was introduced in 1992 to maintain interest in reporting cases to the scheme. Reports are now submitted by a “core” group of physicians at chest clinics, and other physicians are selected at random and report only on cases seen during the previous month. With the exception of Finland and Sweden, few other countries operate reporting schemes for occupational diseases. In the United States, a surveillance scheme instituted in 1987 by the National Institute for Occupational Safety and Health is operating in some states. For additional information regarding the Sentinel Event Notification System for Occupational Risks (“SENSOR”), see Jajosky et al. (1999) and Becklake et al. (1999).

From the SWORD data, it is clear that in the United Kingdom, asthma is the most commonly reported occupational respiratory disease, and it consistently accounts for approximately 28% of all cases reported to the scheme. It is generally accepted that this number is likely to be an underestimate of the true incidence of occupational asthma. Meredith and colleagues (1991) suggest that the minimum incidence rate of occupational asthma in the general population is 22 per million people employed per year. The number of the cases of occupational asthma attributable to laboratory animals is shown in Table 1 (J. D. Meyer, Occupational Disease Intelligence Network, University of Manchester, Manchester, UK, personal communication, 1999) and is about 5% of the total cases of occupational asthma reported. However, when the number of cases of occupational asthma attributable to laboratory animals is expressed in relation to the number of people exposed to animals, the estimated rate of asthma for this profession is 204 per million people employed per year (Meredith et al. 1991). This occupational group therefore has an increased risk for occupational asthma of approximately 10 times that of the general working population, but only one third that experienced by spray paint

Table 1 Occupational asthma caused by laboratory animal allergy in the United Kingdom: Incidence rate of asthma compared with compensation rates

Year	SWORD ^a project	Industrial injuries' disablement benefit
1989/1990	48	NA ^b
1991/1992	84	20
1993/1994	90	17
1995/1996	90	22
1997/1998	47	12

^aSWORD, Surveillance of Work-related and Occupational Respiratory Disease.

^bData not available.

workers, another group with a high risk of occupational asthma. In the first 10 yr of SWORD, laboratory animals have remained among the most common agents initiating asthma (Meyer et al. 1998).

Associated Attitudes

LAA is generally perceived to be an important occupational health problem in the United Kingdom, and this view is strongest among occupational health physicians, chest physicians, and other health and safety professionals. The introduction of more stringent health and safety legislation in the 1980s, which is discussed in more detail below, has played a key role in changing the perspective of professional groups toward this disease. Attitudes toward LAA have changed more quickly in large institutions and the pharmaceutical industry than in academia. If a casual attitude toward LAA still persists at a “user” level, it is most likely due to lack of education and/or lack of support from higher management. The use of basic control measures makes good sense for the health of both staff and animals.

There is now a trend toward centralizing biomedical services. Many new large facilities are designing their premises to accommodate the problem of LAA. Safety and management features that have been widely adopted include improved ventilation systems and limiting the access of personnel to animal units and animal holding rooms. The use of swipe card entry systems also facilitates the identification of individuals for health surveillance schemes. In addition, it is becoming less common for animal experimentation to occur at locations distant from the main animal facility, and procedure rooms and laboratory space are now more frequently located within the animal facility.

Although such measures are helpful, they are relatively insignificant in preventing LAA on their own. It is still necessary to change everyone's attitude further regarding the

hazards that laboratory animals represent. Only when it becomes unacceptable to enter an animal unit, even briefly, without following current best practice (as it now is to handle radioactive chemicals without appropriate protection), will the incidence rate of LAA reach its lowest level.

Legislation Relevant to LAA in the United Kingdom

In the current absence of either a “safe” threshold of exposure or publication of an “Approved Code of Practice” for the control of animal allergens, legislation for the prevention of LAA in humans rests with general health and safety at work laws. The following discussion is a very brief overview of key features of the British health and safety system that are relevant to this disease. More detailed information is available in a comprehensive review by Dolan (1999) or on the Health and Safety Executive web page (<http://www.open.gov.uk/hse/>).

Law

The basis of British health and safety law is the Health and Safety at Work Act (HSWA¹), which describes the general responsibilities employers have for their employees and the public and employees’ responsibilities for themselves and each other (HSWA 1974). The wide-ranging legislation covers many aspects of the work facilities and activities practiced within those facilities that may influence the health, safety, and welfare of all those on the premises. The duty of the employer as outlined in the HSWA is, however, qualified with the phrase, “so far as is reasonably practicable.” In other words, an employer must balance the risk and severity of harm against the cost (financial and otherwise) of introducing control measures to prevent it (see also additional discussion below). If an accident occurs, an employer may not be found to have acted illegally if the employer used “best current practise” and can prove that reasonably practicable steps were taken to control the hazard. The HSWA is enforced by the Health and Safety Executive.

Regulations

The next “layer” of British law comprises the Regulations, which are legally binding and not qualified with the phrase, reasonably practicable. Regulations are intended to clarify specific risks further and specify actions that must be taken to reduce those risks. Most relevant to the prevention of LAA are the Control of Substances Hazardous to Health (COSHH¹) Regulations (COSHH 1999) and the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (RIDDOR¹) (RIDDOR 1995).

The COSHH Regulations were introduced in 1988 and have been regularly updated, most recently in 1999. These

regulations constitute the main legal framework to protect people against health risks from hazardous substances used at work. As respiratory sensitizers, animal allergens are subject to these regulations, and employers are therefore required to (1) assess the risk to health arising from working with laboratory animals and their waste products (risk assessment); (2) decide on what precautions are needed; (3) prevent or control exposure to animal allergens; (4) ensure that control measures are used and maintained properly; (5) carry out appropriate health surveillance (and keep records for 40 years); and (6) ensure that employees are properly informed, trained, and supervised. The Health and Safety Executive office advises that although the assessment of risk is the responsibility of the employer, it may be delegated to a suitable representative. The office recommends a systematic approach and involvement of the employees actually performing the tasks. If a risk is trivial, no action is required. However, if risks to health are perceived, then further action is required to address points 2 through 6 above. The assessment should be recorded in sufficient detail to show how decisions about risks and precautions were defined. The assessment should also include a date for the next review, which is usually (1) when there is a significant change in practice, (2) when there is reason to believe that the assessment is no longer accurate, or (3) at no less than 5-yr intervals. It is clearly important to keep the workforce fully informed of the outcome of the risk assessment and to train them in appropriate safety measures.

For LAA, the most important aspect of the COSHH Regulations is arguably the provision of adequate health surveillance. Because British law offers an employer the flexibility of reducing exposure to animal allergens as far as is reasonably practicable and hence accepts that sensitization to animal allergens may still occur, it is of paramount importance that the sensitized individuals are detected at the earliest stage possible. Early detection will ensure that suitable measures are taken to reduce or eliminate their exposure to animal allergens and to monitor their health. There is now a large body of evidence indicating that the sooner an individual with occupational asthma is removed from exposure to the initiating agent, the better the prognosis.

The RIDDOR were introduced in 1985 and were updated in 1995 (effective April 1, 1996). As the name implies, these regulations require the reporting of work-related accidents, diseases, and dangerous occurrences to the local area office of the Health and Safety Executive, usually by completion of an accident report form. In the context of LAA, for example, an anaphylactic episode would constitute a “major injury,” and a new case of occupational asthma would constitute a “reportable disease.”

Approved Codes of Practice

The Approved Codes of Practice provide practical examples of good practice and advice on legal compliance. Employers risk prosecution for not complying with relevant provisions

of approved codes of practice (e.g., control of carcinogens and control of biological substances [COSHH AcoP 1995]).

Guidance Notes and Chemical Hazard Alert Notices

Guidance notes and chemical hazard alert notices are issued to provide advice on interpretation and implementation of the law. They can be specific to a particular health and safety problem of an industry. Following these written announcements is not compulsory, but employers who do so will normally be doing enough to comply with the law. Publication of a guidance note about LAA is expected in the second half of 2000 (Health and Safety Executive 2000).

Powers of the Health and Safety Executive

After a report of a dangerous incident or case of occupational asthma under the RIDDOR, the Health and Safety Executive will instigate an inspection of the animal facility involved. Between August 1996 and February 1997, 16 facilities were visited in southeast London, and the following observations were made (Morris and Roberts 1999). More educational establishments ($n = 13$) than research establishments ($n = 3$) were studied as previous data from incidents reported under the RIDDOR suggested that academia had significantly lower standards than the industrial sector. A total of 1015 workers were employed at the sites, including 118 handlers and 897 researchers. The most common areas requiring improvements were risk assessment, health surveillance, and training. The difference between the two sectors was particularly apparent in the provision and enforcement of health surveillance. All of the research establishments, but only 15% of the educational institutions, identified and ensured that those employees with significant exposure to animal allergens received health surveillance. The most effective arrangement for managing the system was to have one person with overall responsibility who also incorporated a method of monitoring and auditing the service. The Health and Safety Executive-recommended health surveillance program was summarized as a pre-employment health questionnaire, examination, and lung function test, with a follow-up questionnaire

administered 6 weeks, 6 months, and 1 year after initial exposure. All of the research establishments provided this program except for the 6-week follow-up questionnaire. However, two educational institutions offered no service whatsoever, and the 11 others did not routinely offer lung function tests or follow-up during the first year of employment (Table 2).

The most common outcome after a visit is that the Health and Safety Executive provides advice on which the institution then acts. Infrequently, an Improvement or Prohibition Notice may be served, after which an institution must make specified changes to practices within a given time. In rare cases, an institution may be prosecuted. During the 6 months of the Morris and Roberts (1999) study, two improvement notices were issued to educational institutions with no health surveillance systems, and one case was prosecuted.

It is widely recognized that the RIDDOR are underused. It is thought that the Health and Safety Executive office is informed of only 10% of the cases reported to SWORD involving occupational asthma due to laboratory animals (A. Morris, Health and Safety Executive, London, UK, personal communication, 2000). Increased funding to implement "spot checks" and more widespread dissemination of the Health and Safety Executive inspection outcomes would increase the profile of LAA and provide those involved in the prevention of LAA extra authority to implement changes.

Legislation and the Individual with LAA

Should the criminal law system (e.g., the HSWA and COSHH Regulations) fail to prevent an individual from developing occupational asthma, then there is the recourse of social and civil law.

Social Law

Occupational asthma due to LAA became a prescribed industrial disease in the United Kingdom in 1982 (Department of Health and Social Security, Command 8121). This means that laboratory animals are formally recognized as a cause of occupational asthma, and subjects with this disease are therefore entitled to claim compensation from the government for their disability. The Industrial Injuries Disablement Benefit

Table 2 Content of UK health surveillance programs^a

Sector	Pre-employment			Follow-up		
	Questionnaire	Examination	LFT ^b	6 weeks' questionnaire	6 months' questionnaire	Annual questionnaire
Education ($n = 13$)	11	11	5	0	2	11
Research ($n = 3$)	3	3	3	1	3	3

^aInformation kindly supplied by Dr. Andrew Morris (Health and Safety Executive [<http://www.open.gov.uk.hse/>]).

^bLFT, lung function test.

is a “no fault compensation” scheme, intended to compensate individuals for their disability, not for loss of earnings. It is therefore a graded benefit that is subject to review. Whether the initial diagnosis of occupational asthma is made through health surveillance in the workplace or by an individual’s general practitioner, the subject will be assessed for the extent of disability by the Benefits Agency. In Table 1, the number of cases of occupational asthma attributable to laboratory animals reported to SWORD and the number of cases receiving compensation are shown. Only 20 to 25% of the cases of occupational asthma caused by LAA and reported to SWORD have been compensated. The reasons for this low rate of compensation are not known but may reflect (1) a lack of knowledge by the individuals and clinicians treating them, (2) the effort required to obtain relatively little money, or (3) that subjects are insufficiently disabled to qualify (to be eligible, subjects must be 14% or more disabled, i.e., regularly use an inhaler).

Civil Law

Those who do successfully claim statutory compensation are still entitled to sue their employers for civil compensation in the courts. If the employer is shown to have been negligent, then a successful claim means that any Industrial Injuries Disablement Benefit already paid out may have to be paid back by the claimant.

Exposure as a Risk Factor for LAA

Because there is a good understanding of the allergens that trigger LAA, the etiology of the disease, and the factors that influence its development (as discussed elsewhere in this volume ([Bush 2001; Wood 2001]), the prime goal should now be prevention. Strategies for the prevention of LAA should be based on a thorough understanding of the relation between the intensity of exposure to aeroallergens and the magnitude of risk of disease. Only then can procedures to avoid animal allergens be properly assessed.

Indirect Evidence

Information indicating that exposure to animal allergens is the most important risk factor for developing LAA has come from several sources. Indirect evidence is available from the work of Botham and colleagues, who have reported on the effect of introducing mandatory control measures within a British pharmaceutical company. In 1980 and 1981, the incidence rate of LAA (defined as symptoms reported in an annual health surveillance questionnaire) was 37% among those in their first year of exposure to animals. In 1982, a code of practice was introduced within the company to reduce exposure to animal allergens. Although no exposure measurements were taken, it is very probable that the mandatory use of face masks and air-fed helmets reduced exposure to

animal allergens. These control measures were supported by requirements to restrict the movement of animals and contaminated material through the unit and an education program for all staff (Botham and Teasdale 1987). By 1982, the incidence rate of self-reported symptoms of LAA was reduced to 20%, and additional reductions were seen in 1983 (10%) and 1984 (12%) (Botham et al. 1987). A subsequent report published in 1995 documented that the annual incidence rate of self-reported symptoms had remained the same, at approximately 10%. However, an important observation was that the rate of sensitization to laboratory animals (presence of specific immunoglobulin E [IgE¹] antibodies) was three- to fourfold higher, suggesting that control measures may protect against the development of symptoms but not of sensitization (Botham et al. 1995).

Similar studies have also been conducted in the United States (Fisher et al. 1998; Fuortes et al. 1997). It is encouraging that these too show that improved work practices, including education programs and the mandatory use of respiratory protection, can greatly reduce or possibly eliminate the incidence of LAA.

Exposure-Response Relations

The relation between exposure to rodent allergens and the development of LAA has been examined by groups from North Europe, both independently and through collaboration (Cullinan et al. 1999; Heederik et al. 1999; Hollander et al. 1997). Cross-sectional studies of workers exposed to rat allergens have consistently found a relation between the intensity of exposure and an increased risk of developing LAA.

In the study from The Netherlands, 117 Dutch subjects who had worked with rats for 4 yr or less and who had had current or recent exposure to rats were grouped into three categories or exposure zones (Hollander et al. 1997). The “low” category was defined as those working with low numbers of rats or where the rats were housed in isolators. The “high” category comprised those who worked in areas of high stock density or performed high-exposure tasks such as the handling of contaminated bedding or the rats themselves. Quantification of rat airborne allergens revealed that the exposure of the high group was 28-fold greater than that of the low group and sixfold greater than that of the medium group. Of the study population, 79% had “medium” exposure to rats. The internal reference group consisted of 86 workers from the same sites who had never worked with rats or with only their tissue. The prevalence of sensitization to rats (defined as a positive skin prick test response) was increased 4.1-, 5.0-, and 7.2-fold for the low-, medium-, and high-exposure group workers, respectively, when compared with that of the internal reference group. When exposure was expressed as a product of the intensity and duration of exposure (measured in hours per week) and after stratifying for atopy, the exposure-response relation was even more striking. Among atopic subjects, the prevalence rate ratio for sensitization was 7.3 for those in the low exposure category,

9.5 for the medium category, and 15 for the high-exposure category.

In the UK study, 342 newly employed laboratory animal workers with no previous exposure to rats were followed prospectively (Cullinan et al. 1999). A nested case-referent analysis was used to examine the exposure-response relation. Exposure to rats was expressed in terms of job title and validated by aeroallergen analysis. Four exposure categories were established among which the population was nearly equally divided. The lowest exposure category comprised those indirectly exposed to rats and was used as a referent group. As the exposure increased, the risk of disease increased (Table 3). The relation was strongest when the analysis was confined to those cases occurring within their first 2 yr of employment. Atopy was found to increase the odds ratio for developing a positive skin prick test to rat urine and for developing chest symptoms, but it did not increase the risk of eye and nose symptoms.

The Cullinan et al. (1999) study highlights the importance of exposure in influencing the development of LAA. Of particular note is that the risk increases very rapidly at relatively low allergen concentrations (Table 3). A 600-fold increase in rat allergen exposure (when measured by radio-allergosorbent test [RAST¹] inhibition) was associated with a sixfold increased risk of developing a positive skin prick test. When translated into job titles, this is the approximate difference between the exposure of slide production workers who work with rat tissue and that of animal technicians with direct exposure to rats. This result indicates that controlling exposure to animal allergens is likely to be the most effective way of reducing the incidence and prevalence of LAA and implies that a considerable reduction of exposure is necessary. To achieve this magnitude of reduction in exposure, a combination of control measures must be adopted.

As part of a European collaborative study, the British and Dutch data were pooled with similar independent data from Sweden (Heederik et al. 1999). Analysis of the pooled total

of 650 rat-exposed subjects suggests that atopic workers who are exposed to low levels of rat allergen for only a few hours per week are three times more likely to be sensitized than nonexposed workers. This risk did not increase significantly with higher intensity or duration of exposure. However, in contrast, the risk for nonatopic workers increased significantly with increased intensity of exposure. This result implies that the lowest exposures observed in this study were sufficient to sensitize most atopics, whereas the risk for sensitizing nonatopic workers becomes significant only at higher concentrations of rat allergen. In effect, the exposure-response curve for atopics can be thought of as “shifted to the left.”

Taken together, the data from Europe support the observation that there is a direct, positive association between exposure to animal allergens and the risk of disease. This relation is particularly strong in the first few years of employment and for those health endpoints that are related to, or are markers of, specific IgE production (i.e., a positive skin prick test, chest symptoms). It appears that a risk of disease exists even at low levels of allergen exposure, especially for atopic individuals, and even stringent exposure control methods may be insufficient to prevent sensitization in all workers.

Toward a Threshold for LAA

Occupational Exposure Limits

In the United Kingdom, occupational exposure limits for hazardous substances are set by the Health and Safety Executive on the recommendation of the Advisory Committee on Toxic Substances (“ACTS”) and its Working Group on the Assessment of Toxic Chemicals (“WATCH”). There are two types of limit: maximum exposure limits (MELs¹) and occupational exposure standards (OESs¹). Both types of limit are concentrations of hazardous substances in the air,

Table 3 Relation between exposure and response. Odds ratios (ORs^a) and confidence intervals (CIs) of risk for four categories of exposure for cases occurring within 2 yr of first employment^b

RUP ^c exposure (µg/m ³)		New work-related symptoms		SPT ^c
Category	GM ^c (95% CI)	Eyes/nose OR (95% CI)	Chest OR (95% CI)	OR (95% CI)
1	0.05 (0.04-0.07)	1	1	1
2	0.12 (0.06-0.23)	3.0 (0.8-10.9)	2.4 (0.2-38.2)	3.0 (0.3-29)
3	1.26 (0.86-1.85)	3.7 (1.1-12.2)	5.5 (0.5-65.1)	6.0 (0.6-57.1)
4	30.36 (21.67-42.55)	3.2 (0.9-11.5)	4.6 (0.3-77.4)	5.7 (0.6-53)
Atopy		0.4 (0.2-1.0)	2.7 (0.8-9.7)	2.9 (1.1-7.9)

^aIndependent ORs derived from conditional logistic regression.

^bAdapted from Cullinan P, Cook A, Gordon S, Nieuwenhuijsen M J, Tee R D, Venables K M, McDonald J C, Newman Taylor A J. 1999. Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. *Eur Respir J* 13:1139-1143.

^cGM, geometric mean; RUA, rat urinary aeroallergen; SPT, skin prick test.

averaged over a specified period of time: long-term (8 hr) and short-term (15 min). A MEL is set for substances that may cause the most serious health effects, such as cancer and occupational asthma. For these substances (e.g., high molecular weight respiratory sensitizers), the threshold level of exposure for the key health effect either is unknown or a threshold has been identified but at concentrations not yet routinely achievable in the workplace. An OES is set at a level where there is no known risk to health on the basis of daily exposure. OESs have been set for a wide range of chemicals (e.g., ammonia, ethanol, silica). There is currently no "safe" exposure limit (i.e., OES) in the United Kingdom for respiratory sensitizers; however, MELs have been published for some low molecular weight respiratory sensitizers such as complex platinum salts, isocyanates, anhydrides, and glutaraldehyde (EH40: occupational exposure limits; Health and Safety Executive Books 2000). A MEL has been proposed for total inhalable flour dust of 10 mg/m³ (8-hr time-weighted average), and this exposure limit is currently at the consultative stage. In the United Kingdom, there are no plans to introduce a similar exposure limit for animal allergens, in part because of the lack of a standardized method for quantifying exposure.

Measurement of Airborne Animal Allergens

The airborne dust levels in animal facilities are generally low, and it is therefore not possible to quantify exposure to animals by gravimetric means (Nieuwenhuijsen et al. 1994). Animal allergens are carried on a range of amorphous particles with no distinct morphology. Thus, the only means of objectively quantifying exposure to animal airborne allergens is to elute the allergens from the filter and then measure their concentration in the eluate by using specific immunoassays.

Several methods for quantifying animal airborne allergens have been described, and the main ones use antibodies from humans, rabbits, or mice (monoclonal antibodies). In

1997, a study was published that compared two methods of measuring rat urinary aeroallergen (Renström et al. 1997a). When air samples were measured using each assay and the values compared, a large systematic difference was observed. The RAST inhibition method (which uses specific IgE antibodies from rat-sensitized humans) resulted in values between seven- and 3000-fold higher (median, 316-fold) than the enzyme-linked immunosorbent assay method, which used monoclonal antibodies to the major rat urinary allergen. A more extensive study has confirmed this large discrepancy between different types of assay to measure rat aeroallergens (Hollander et al. 1999). In decreasing order of importance, the contributory factors were the specificity of the antibodies (800-fold), elution protocol (10-fold), assay design (inhibition style increased values sevenfold), urine standard (two-fold), and method of collection (1.2-fold) (Renström et al. 1999). Interestingly, the differences between the assays for quantifying mouse aeroallergens were much smaller and varied by between two- and sixfold. These differences probably existed because the assays were more similar in design and all used antiserum to mouse urine that had been raised in rabbits.

If a standard method is developed for the measurement of animal allergens, all stages of the collection of the air sample, elution of the filter, and immunoassay of the eluate must be standardized. An optimized method for the collection and elution of air samples in animal facilities has been described (Gordon et al. 1992). The method utilizes a Seven Hole sampling head, polytetrafluoroethylene (or Teflon) filters (1.2 μm pore size), and elution of the filter in a test tube with buffer containing 0.5 % v/v Tween 20. The development of a standardized immunoassay is more problematic because numerous factors (summarized in Table 4) must be taken into account.

Assays Using Monoclonal Antibodies

Monoclonal antibodies are antibodies that have been produced so that they originate from one cellular source (i.e.,

Table 4 Summary of the advantages and disadvantages of currently available immunoassays to quantify animal allergens

Assay type	Advantages	Disadvantages
Sandwich assay— monoclonal antibodies	Very specific and sensitive, good standardization	Measures only one component
RAST ^a inhibition	Uses human IgE ^a , measures all relevant allergens	Standardization requires care
Sandwich assay— polyclonal antibodies	Specific and sensitive, widely applicable	Standardization requires care

^aRAST, radioallergosorbent test; IgE, immunoglobulin E.

clone). By definition, all of the antibodies are identical and recognize only one part of an antigen (i.e., epitope). Assays that use monoclonal antibodies are very specific, sensitive, and reproducible. They have been applied widely and successfully to the measurement of environmental animal allergens such as cat (Fel d 1) and dog (Can f 1). A key feature of this type of “sandwich” assay is that it detects only one type of protein (or allergen), which must be large enough to contain two spatially separate epitopes. It is therefore important for the protein to be stable and a good “marker” protein (i.e., it is preferably a major allergen and its concentration in dust is consistent under a wide range of conditions).

An assay using monoclonal antibodies is available for measuring the major rat allergen, Rat n 1 (Renström et al. 1997b), but careful consideration is necessary before it is adopted as the assay of choice. Although Rat n1 is present in accumulated and airborne dust (Gordon et al. 1996), many other allergens of importance have been described in rat urine (Gordon et al. 1993) and rat serum (Gordon et al. 1997). Rat n 1 is the main allergenic constituent of the urine of adult male rats and is not excreted in significant amounts by female rats. The relation of Rat n 1 to allergens from other sources (e.g., pelt) is not known. It therefore appears that the monoclonal antibody assay may not quantify all of the relevant exposure. Very little is known about how the allergenic composition of dust varies under different working practices. The wide variation in values obtained between RAST inhibition and the monoclonal antibody assay suggests that other allergens are also important.

When adopting a standard method for the quantification of rat allergens, it is also important to consider whether it is desirable to establish a method for rat that in time could also be applied to quantify mouse aeroallergens. Because the immune system of a mouse will not recognize mouse allergens as foreign, an alternative species must be used to raise the antibodies. It is technically more difficult to establish monoclonal antibodies using other species.

Assays Using Polyclonal Antibodies

Polyclonal antibodies are heterogeneous mixes of antibodies that recognize many different antigens and their epitopes. Polyclonal antibody sources that have been used for measuring animal allergens have come from rabbits immunized with animal allergens or humans sensitized by occupational exposure to laboratory animal species. Standardization of these assays is possible with care, provided that large quantities of antiserum are collected and the biological potency of each new batch of antigen is compared.

Quantification of exposure to animal allergens by RAST inhibition represents the other extreme to that of monoclonal antibody production. The use of serum from individuals sensitized to the species of interest ultimately offers unparalleled clinical relevance of the exposure data, but at the cost of reduced sensitivity and poor standardization over the long term. Polyclonal antibody assays using antisera raised in rabbits (or other species) are a compromise, yet may offer the

best chance of obtaining a standard method for the following reasons:

- The technology to raise antiserum is more widely available than either human allergic sera or monoclonal antibody (hybridoma) technology.
- Polyclonal assays, when optimized, are both sensitive and specific.
- Polyclonal assays will quantify total and relevant allergen exposure if the immunizing agent is selected with care.
- Polyclonal assays are adaptable to quantify any type of antigen. Comparison of data between animal species and across a broad range of respiratory sensitizers is therefore theoretically possible.
- Adequate standardization is possible if large pools of antiserum are collected and appropriate controls are applied.

This type of assay has been described for the measurement of rat and mouse airborne allergens (Hollander et al. 1999). Long-term standardization of these assays is now required.

Question: What is “Reasonably Practicable”? Answer: A Balance of Risk, Severity, and Cost

Interpretation of this phrase, “reasonably practicable,” is particularly important for laboratory animal allergens because it is recognized that as with other respiratory sensitizers, complete elimination of all allergenic material may not be possible and sensitization may still occur in very susceptible individuals. Because individuals who do become sensitized are at a much greater risk of developing the most severe form of LAA, which includes asthma, more specific guidance on what is reasonably practicable is now needed. At a minimum, steps should be taken to prevent asthma and reduce the prevalence of other symptoms of LAA. Ideally, exposure to laboratory animal allergens should be reduced sufficiently to prevent sensitization in the first place. However, such decisions should be based on consideration of a number of factors.

Asthma and anaphylaxis as caused by LAA can be life threatening. Although anaphylaxis due to needle stick injuries or bites in sensitized individuals is rare (Hesford et al. 1995; Watt and McSharry 1996), asthma is much more common and affects approximately 5 to 10% of the exposed population. In addition, those with severe asthma can be seriously disabled, which can ultimately result in loss of occupation and income. It is well documented that continued exposure to respiratory sensitizers after the onset of occupational asthma may result in persistent asthma and the risk of permanent disability. An employer therefore should balance these risks of mortality and morbidity with the cost of prevention of LAA.

There have been no published studies to date on the cost-effectiveness of preventing LAA. The financial cost of prevention would include expenditures for health surveillance, education, provision of personal protective equipment, and

other control measures, as well as the potential cost of replacing and/or relocating highly trained staff. Other significant factors, the value of which cannot be so easily priced, are the loss of health and income inevitably experienced by individuals with severe LAA. There is also an important "morality factor." Given our extensive knowledge of LAA, is any level of risk acceptable?

Although our knowledge of the etiology of LAA has progressed significantly in some areas, there is still no reliable way of identifying at pre-employment those who will go on to develop LAA. It is therefore important that measures are taken to protect all workers. Current evidence suggests that it is feasible to reduce exposure in the workplace to such an extent that a decrease in the prevalence of symptoms will be observed. It is also apparent that this reduction can be obtained only by a combination of strategies (Harrison 2001; Seward 2001). However, if exposure to animal allergens is reduced so that the prevalence of symptoms is decreased, one unconfirmed report suggests that the number of people sensitized may remain the same (Botham et al. 1995). It is theoretically possible that people with "silent" allergy (i.e., sensitized but not necessarily experiencing symptoms) will be missed by health surveillance unless a test for specific IgE is routinely undertaken.

Summary and Concluding Statements

In the United Kingdom, allergy to laboratory animals has been recognized as an important occupational disease for nearly 25 yr. Legislation was introduced in 1988 to control the use of hazardous substances, including respiratory sensitizers, in the workplace. Despite this action, from an estimated total exposed population of 15,000 individuals, approximately 30 new cases of occupational asthma attributable to laboratory animals are reported to SWORD each year. There is currently no evidence to suggest that the incidence of LAA is decreasing either in the United Kingdom or in the rest of the Western world.

This situation is perhaps surprising when we consider how much is now known about the disease and the means to prevent it. Rat urine appears to be a very potent respiratory sensitizer (Heederik et al. 1999), and substantial reductions in airborne levels of animal allergens are needed before an improvement in disease prevalence will become apparent (Cullinan et al. 1999).

If the prevention of laboratory animal allergy is to advance in the United Kingdom, it is likely that progress will be driven by the needs of the "industry," rather than through legislative means. To comply with current British law, and in the absence of an enforceable exposure standard, employers must (1) undertake risk assessments of the hazards, (2) offer and administer an effective health surveillance scheme for exposed staff, (3) educate the staff about the risks, and (4) offer adequate protective or control measures consistent with what is considered to be reasonably practicable. Because there is no apparent decline in the prevalence of this disease,

it is now time to reconsider what is reasonably practicable. It is unlikely that an occupational exposure limit will be published in the foreseeable future, therefore control of this occupational disease is best achieved by following guidelines describing best practice. In addition to incorporating the requirements under the COSHH Regulations, it is anticipated that greater reliance should and will be placed on the use of engineering control measures such as ventilated cage systems and ventilated workstations, particularly for high-level exposure tasks.

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