Laboratory Animal Allergy: An Update

Robert K. Bush and Gregg M. Stave

Abstract

Allergic reactions are among the most common conditions affecting the health of workers involved in the care and use of research animals. Between 11 and 44% of the individuals working with laboratory animals report work-related allergic symptoms. Of those who become symptomatic, 4 to 22% may eventually develop occupational asthma that can persist even after exposure ceases. Allergic symptoms consist of rashes where animals are in contact with the skin, nasal congestion and sneezing, itchy eyes, and asthma (cough, wheezing, and chest tightness). The generation of immunoglobulin E (IgE) antibodies is a prerequisite for the production of allergic symptoms. The mechanism by which IgE antibodies develop is becoming clearer. The propensity to produce IgE is genetically determined, and pre-existing allergy may be a risk factor for the development of laboratory animal allergy (LAA). However, exposure to animal allergens is the major risk factor for the development of LAA. Techniques to measure the airborne concentration of laboratory animal allergens have been developed. Research on animal allergens themselves indicates that many of the mouse and rat urinary proteins belong to a family of proteins called lipocalins, which share sequence homology with antigens of the parasitic agent that causes schistosomiasis. The fact that parasite infections also trigger IgE antibody responses may account for the development of LAA in persons who have never had any previous allergy. The prevention of LAA should be a major goal of an effective health and safety program in the animal research facility, and it can be accomplished by education and training of employees, reduction of exposure (including the use of personal protective gear), and changes in facility design. Medical surveillance programs can also play a role in improving health of individuals working with laboratory research animals. Early recognition of symptoms and evidence of sensitization can lead to interventions to reduce exposure and thereby avoid the long-term health consequences of LAA.

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Epidemiology of Laboratory Animal Allergy (LAA[1])

Estimates of the number of individuals exposed to laboratory animals in their occupation vary considerably. Bland and colleagues (1987) estimated that 90,000 individuals were exposed to laboratory animals in the United States, and 32,000 workers were similarly exposed in the United Kingdom. Seward (1999) estimated that 40,000 to 125,000 individuals are exposed to laboratory animals in the United States.

The existence of different definitions of LAA used in published studies (reported symptoms vs. laboratory evidence of immunoglobulin E [IgE[1]]-mediated sensitivity) leads to significant variability in the reported prevalence (percentage of cases in the population) and incidence (percentage of new cases occurring in the population over a given period of time) of this occupational problem. Prevalence rates may also be affected if symptomatic workers discontinue work with laboratory animals. In addition, the sample size included in the study influences the results. In the United Kingdom, exposure to laboratory animals has consistently ranked in the top three causes of occupational asthma and comprises 5% of all cases reported to that country's surveillance of work-related and occupational respiratory diseases program since 1989 (Gordon 2001). These statistics are striking because laboratory animal workers comprise only a small portion of the total UK work force. In the United States, the National Institute of Occupational Safety and Health has formally recognized LAA as an occupational hazard since 1989.

The first reported cases of allergic symptoms due to laboratory animals occurred in the 1950s (Sorrel and Gottesman 1957). The high prevalence of this condition did not become apparent until cross-sectional epidemiological studies were conducted in the 1970s and -80s (Cockcroft et al. 1981; Gross 1980; Lutsky and Neuman 1975; Schumacher et al. 1981) (Table 1).

[1]Abbreviations used in this article: HEPA, high-efficiency particulate air; IFNγ, interferon-gamma; IgE, immunoglobulin E; IL, interleukin; LAA, laboratory animal allergy; MHC, major histocompatibility; PPE, personal protective equipment; RAST, radioallergosorbent test.

Table 1 Reported cases of allergic symptoms of individuals working with laboratory animals[a]

Study (year)[b]	Country	Facilities		Workers	
		No.	Type	No. evaluated	No. with allergic symptoms (%)
Lutsky and Newman (1975)	United States	39[c]		1293	181 (14%)
Gross (1980)	United States		Research	393	59 (15%)
Cockcroft (1981)	United Kingdom		Reseach	179	49 (27%)
Schumacher et al. (1981)	Australia		Research	121	39 (32%)
Slovak and Hill (1981)	United Kingdom		Pharmaceutical research	146	48 (30%)
Beeson et al. (1983)	United Kingdom		Pharmaceutical research	62	15 (22%)
Agrup et al. (1986)	Sweden		Research	101	30 (30%)
Bland (1986)	United States		Research	549	131 (23.9%)
Venebles et al. (1988)	United Kingdom		Pharmaceutical	133	59 (44%)

[a]Modified from Bush RK. 2001. Mechanisms and etiology of laboratory animal allergy. ILAR J 42:4-11.
[b]See text for complete references.
[c]Facilities that received questionnaires included 23 medical and veterinary schools, 9 research institutes, 5 pharmaceutical firms, and 2 commercial laboratory animal-producing facilities.

Gross (1980) observed that symptoms of affected individuals usually began within 6 mo of exposure and rarely occurred after 2 to 3 yr of employment. In that study, the percentages of workers affected by specific species were as follows: rats, 65%; rabbits, 72%; mice, 66%; and guinea pigs, 33%. Nasal symptoms preceded chest symptoms in 45% of the individuals, whereas 55% experienced nasal and chest symptoms simultaneously. Chest symptoms never occurred in the absence of nasal symptoms.

In Cockcroft and colleagues' (1981) evaluation, 49 of 179 individuals were symptomatic with mainly nasal symptoms. Skin testing was conducted and revealed a good correlation between the presence of rhinitis and positive skin tests to relevant laboratory animal allergens. Five individuals had positive skin tests to laboratory animal allergens but were asymptomatic.

In Schumacher and colleagues' (1981) study, of the 39 individuals who experienced respiratory symptoms or skin rashes, one third reported severe symptoms. Virtually all of these individuals had demonstrable sensitivity by positive skin tests to laboratory animal allergens.

Slovak and Hill (1981) examined 146 workers of whom 48 (30%) had a history of symptoms related to their laboratory animal exposure. Of the 48, 22 had positive skin tests and demonstrated rhinitis symptoms that progressed to asthma.

In a similar study of workers in the pharmaceutical industry in the United Kingdom, Beeson et al. (1983) reported that of the 15 workers with LAA, slightly more than half (8) had positive skin tests to animal allergens. Sixty-seven percent of the individuals were sensitive to allergens other than laboratory animals.

In Agrup and colleagues' (1986) evaluation, there was a high level of frequency of self-reported symptoms, but the number of individuals with symptoms was reduced when they were interviewed by clinicians. Nineteen of the 30 laboratory technicians with reported symptoms had positive skin tests or in vitro tests indicating sensitivity to laboratory animal allergens.

Laboratory animal exposure results in significant lost time from work. More than one third of individuals working at the US National Institutes of Health reported lost time from work due to their symptoms from laboratory animal allergy sensitivity (Bland et al. 1986). According to completed questionnaires, 131 of 549 individuals (23.9%) reported symptoms due to their occupational exposure to laboratory animals.

In perhaps the highest prevalence rate reported, Venables et al. (1988) found that 44% of 133 pharmaceutical workers in the United Kingdom had laboratory animal sensitivity. In a review of pooled data from reported studies, Hunskaar and Fosse (1990) found an overall prevalence of LAA of 20.9% in 4988 individuals. Subsequently, in a large series conducted in Japan (Aoyama et al. 1992), 1304 of 5641 (23.1%) workers had symptoms related to their laboratory exposure. This survey was conducted among 137 research facilities, 76 medical schools, 57 research institutes, and four breeding facilities. Rhinitis was the most common symptom. Seventy percent of individuals developed symptoms within 3 yr of exposure. The survey revealed sensitivity to a variety of animals for which the percentages of affected workers were as follows: sensitivity to guinea pigs, 31% of workers; to mice, 26.1%; to rats, 24.9%; to cats, 30.1%; to dogs, 24.9%; and to nonhuman primates, 23.6%. It is important to note that virtually any laboratory animal can cause occupational allergy al-

though the mammals listed above are the most commonly involved.

In another survey from Australia, Bryant and colleagues (1995) reported that 73 of 138 exposed individuals had symptoms of LAA. Of these individuals, 92% had positive skin tests to laboratory animal allergens; 23% of asymptomatic individuals also had positive skin tests to laboratory animal allergens. Bronchial hyper-responsiveness, a marker of asthma, was present in 21% of exposed individuals compared with 8% in a nonexposed control population.

From the United Kingdom, where good occupational disease reporting is available for workers in the laboratory animal field, 44% of 32,000 individuals indicated they had symptoms related to their work exposure in 1988. By 1994, this number had decreased to 31%. However, when skin testing was performed in those symptomatic individuals in 1988, only 13% had positive skin tests. In 1994, 10% had positive skin tests (S. Gordon, personal communication, 1999). In a recently reported preliminary study from the University of Wisconsin, 29 of 147 (19.7%) workers exposed to laboratory animal allergens in a research facility related allergic symptoms to their work exposure (Patel et al. 2000). However, of the 147 workers, only 12% had positive skin tests that correlated with histories suggestive of LAA.

As can be seen, prevalence and incidence rates may vary considerably based on whether a questionnaire is used to establish the presence of LAA or whether laboratory testing is required. The low prevalence of skin tests or in vitro tests showing IgE sensitivity may be related in part to the poor quality of skin testing and testing reagents available. Nonetheless, LAA does represent a significant health risk for the population of exposed individuals. Furthermore, few data are available on the number of individuals who end their employment due to LAA. Failure to capture this population in epidemiological studies could result in a significantly lower estimate of true prevalence or incidence (Monsó et al. 2000).

The overall prevalence of LAA varies from 11 to 44% (Seward 1999). The prevalence of asthma due to LAA ranges from 4 to 22% (Seward 1999). The wide range in these prevalence figures reflects the vigor with which the diagnosis of LAA was established (positive response to questionnaires vs. confirmatory medical evaluations). Nonetheless, LAA is common in the workplace where animals are used for research purposes.

In a study at a pharmaceutical company involving workers exposed to laboratory animals, the incidence of laboratory animal allergy was as high as 10.3% (Fisher et al. 1998). After the institution of a comprehensive prevention program, including environmental control measures and the use of personal protective equipment (PPE[1]) to reduce allergen exposure, the incidence decreased to 0. This decrease suggests that LAA is a preventable workplace hazard.

Workers who develop allergies to one animal species are at risk of developing allergy to other species (Goodno and Stave 2002). A work environment that may protect against the symptoms of an initial or primary allergy to one species may still leave workers at risk for subsequent allergy to another. Prevention of the initial allergy is the most successful approach to prevention of sequent allergy to other animals, but all aspects of the worker's exposure should be considered.

Symptoms of LLA

Symptoms of LAA are the result of the release of biochemical mediators and the generation of inflammation in the tissues induced by the IgE response. The nature and intensity of the symptoms are dependent on the level of exposure to the laboratory animal allergen by the individual. Once the worker has become sensitized (developed IgE antibodies to laboratory animal allergens), symptoms generally occur rapidly (within minutes) of exposure. Continued daily exposure can result in chronic symptoms that may require daily treatment. These symptoms can range from mild skin reactions to severe asthma. The most common symptoms are related to allergic reactions involving the nose and eyes (Aoyama et al. 1992; Cullinan et al. 1994) and are known as allergic rhinitis and allergic conjunctivitis, respectively. Nasal symptoms include congestion, runny nose, sneezing, and itching; ocular symptoms include redness and itchy watery eyes. Up to 80% of workers with LAA report nasal symptoms (Bush et al. 1998).

Skin reactions include hives at the site of contact with animal urine or dander as the result of scratches. Other rashes include maculopapular (measles-like) rashes, which are typically quite itchy and occur in about 40% of symptomatic individuals (Bush et al. 1998).

Asthma may affect 4 to 22% of symptomatic workers exposed to laboratory animals. Symptoms of asthma consist of cough, wheezing, and shortness of breath. It is important to recognize that symptoms related to laboratory animal exposure may continue for several hours or longer after exposure to the animals ceases. In addition, individuals may experience symptoms of asthma when exercising and when exposed to cold air, dust particles, or strong odors. This phenomenon, known as nonspecific airway hyperresponsiveness, occurs in other situations of allergen-induced asthma.

Systemic allergic reactions, known as anaphylaxis, can occur (albeit rarely) as a result of an animal bite (Teasdale et al. 1993) or from puncture wounds (e.g., needles contaminated with animal proteins) (Watt and McSharry 1996). These reactions can manifest by generalized itching, hives (urticaria), swelling (angioedema) of the lips, eyes, and/or extremities, respiratory distress due to edema of the larynx, hypotension (shock), or acute asthma attacks. These reactions are potentially fatal. Occasionally, a milder form of systemic reaction can manifest in which the allergic individual develops a maculopapular rash or hives under protective clothing as a result of a respiratory exposure to laboratory animal allergens.

Time from the onset of exposure to development of symptoms is variable but generally is within 3 yr of beginning employment. Approximately one third of individuals will develop symptoms in the first year and 70% within 3 yr. Workers who do not devleop symptoms in the first 3 yr remain at risk. In a study from the United Kingdom, the mean duration of employment before the onset of nasal symptoms was 214 days, 335 days for skin symptoms, and 365 for the development of chest symptoms (asthma) (Cullinan et al. 1994). Again, this estimate is quite variable depending on the individual study reported (Seward 1999).

Risk Factors for the Development of LAA

Epidemiological studies have been useful in determining factors that may lead to the development of LAA. The most important risk factor for an individual is the level of exposure to laboratory animal allergens. Methods have been developed that allow quantitative estimates of the exposure to laboratory animal allergens (Gordon 2001; Harrison 2001).

Some questions still exist as to whether individuals with coexisting allergies to substances outside the laboratory have an increased risk of developing LAA, although the majority of reported studies suggests it is an important risk factor. In the study by Gross (1980), one third of workers had no prior allergic disease before developing LAA. Schumacher and colleagues (1981) correlated the development of LAA with the presence of atopy (defined as positive skin test to one or more inhalant allergens). Slovak and Hill (1981) documented that atopy predisposes individuals to the development of asthma related to their animal exposure. Several other studies (e.g., Aoyama et al. 1992; Bland, et al. 1986; Botham et al. 1995; Bryant et al. 1995; Cullinan et al. 1999; Fisher et al. 1998; Fuortes et al. 1996) indicate that atopy is a risk factor for the development of LAA. In contrast, Heederik et al. (1999) found atopy to be a risk factor only for individuals exposed at low levels; and Renström et al. (1994) believe that atopy is not a significant risk factor but that total IgE level is. These latter investigators are from the same research group and share the same subject pool. In a review (Bush et al. 1998) based on the studies cited above, it was concluded that in individuals with a history of work-related symptoms and objective evidence of allergy as demonstrated by a positive skin test or in vitro test, the odds ratio for developing LAA was 3.35 in atopics compared with nonatopic workers.

Recent studies from Canada (Gautrin et al. 2000, 2001) showed that apprentices working in animal health technology facilities were at greater risk for developing LAA if they (1) were atopic, (2) had respiratory symptoms in the pollen season, (3) were sensitized to cat or dog allergens, (4) had baseline airway hyper-responsiveness, and/or (5) had an increasing number of hours of contact with laboratory animals.

The level of an individual's exposure to laboratory animal allergens certainly is a major factor in determining whether the worker develops LAA. Although most studies have shown that individuals who have coexisting allergies to other inhalant allergens are more at risk, some studies report different results. Of note is the study by Hollander et al. (1996), who found that sensitivity to mites or pollens was not associated with risk for developing LAA; however, sensitivity to cats and dogs was associated. Analysis of all available data suggests that pre-existing atopy is an important factor contributing to the development of LAA.

In many of these studies, the relation between atopy and the development of LAA suggests that a genetic predisposition to form IgE antibodies is a significant risk factor. The exact genetic cause has not yet been identified. Smoking has also been associated as a risk factor for the development of LAA. However, as with atopy, controversial data have arisen. Venables and colleagues (1988) reported a positive association between cigarette smoking and the development of LAA, as did Fuortes et al. (1996), and Cullinan et al. (1999). In contrast, Agrup et al. (1986) and Heederik et al. (1999) found no effect. Of note is the study by Fuortes et al. (1997), who reported that individuals with a smoking history had significantly greater declines in pulmonary function compared with nonsmokers. This finding would be an expected effect of tobacco smoke exposure in addition to the exposure to the laboratory animals. Tobacco smoke has been shown to elevate serum IgE levels. This increase could predispose an individual to an increased risk for LAA, although this possibility has not been proven.

Mechanism of LAA

LAA is a form of occupational allergic disease. Such allergic diseases are classified as immediate hypersensitivity reactions, or type 1, according to Gell and Combs (Shearer and Fleischer 1998). Immediate hypersensitivity reactions involve the production of IgE antibodies, which are formed in response to a variety of protein or glycoprotein antigens of which LAA is a typical example. Generation of IgE antibodies requires the central role of CD4+ T-helper lymphocytes. In the development of LAA, exposure to the allergens (antigens capable of eliciting any IgE antibody responses), such as mouse or rat urinary proteins, largely occurs through inhalation of these proteins into the lung. Some exposure may also occur through skin contact.

Development of IgE Antibodies

The first step in the process of the development of LAA consists of the production of IgE antibodies to the animal proteins or glycoproteins. This initial step is termed "sensitization." The allergens are taken up by antigen-presenting cells in the lung, which include monocytes, alveolar macrophages, and dendritic cells (Kiekhaefer et al. 2001). Dendritic cells and Langerhans cells in the skin serve a similar function and possess the properties necessary for the presentation of antigens to T-lymphocytes. For the antigen to

be recognized by the T-cell, it must first be processed into small peptide fragments and presented on the surface of the antigen-presenting cell in association with major histocompatibility (MHC[1]) class II proteins (Whitton 1998). Antigen-presenting cells capture and internalize the protein. They migrate to draining lymph nodes where the processed peptides are presented on the surface of the cell in association with the MHC class II molecules. Naive T-cells, through a T-cell receptor that has specificity for a particular antigenic peptide, recognize the complex of the antigen and the MHC class II molecules. For the naive T-cell to become activated, certain costimulatory signals are also necessary. The most common of these interactions is between the B7 molecule (B7.1 or B7.2) on the antigen-presenting cell and its counter ligand, CD28, on the T-cell (Figure 1) (Whitton 1998). The activated T-cell can then undergo multiple rounds of replication, which requires autologous production of the cytokine interleukin (IL[1])-2 and the surface expression of the IL-2 receptor, CD25. Initially, a multipotential population of T-cells (Th0) are produced. There are two types of effector cells, each with the potential to generate a selective and mutually exclusive array of cytokines, which dictate the type of immune response that may occur. The Th1-type lymphocytes preferentially secrete IL-2, interferon-gamma (IFNγ[1]), and tumor necrosis factor-α; and Th2-type cells produce IL-4, IL-5, IL-9, and IL-13 (Mosmann et al. 1986; Swain 1999) (Figure 1).

The particular type of immune response that is generated depends on a variety of factors, including the type and dose of antigen, the differential expression of B7.2 versus B7.1 costimulatory molecules, and the cytokine milieu present during the initial priming of the T-cells (Jaffar et al. 1999; Tsuyuki et al.1997). The most important factor appears to be the presence of particular cytokines. The Th2 cells are induced by the presence of IL-4, and Th1 cells are induced in the presence of IL-12. Elicitation of a Th2 response is the typical feature of immediate-type allergic diseases (Holt 1999). The genes that control the Th2-type of response have not been fully elucidated at present. However, clear-cut genetic influences do exist based on data from population studies.

A small portion of Th2 cells develop into memory T-cells, which can circulate for long periods of time. Subsequent exposure to the initial sensitizing antigen elicits a vigorous and rapid response from these memory T cells. Thus, once established, a Th2-response can continue for many years or be rekindled by subsequent re-exposure to the allergen that generated the initial response (Holt 1999).

The production of cytokines by Th2-type cells leads to the production of specific IgE antibodies. IL-4, which is a necessary signal to B lymphocytes, induces the synthesis of IgE antibodies by B-cells. A similar function has also been attributed to IL-13, which has approximately 30% homology with IL-4 and shares many of its biological activities. In contrast, IFNγ suppresses the formation of IgE antibody production. IgE antibody production, therefore, represents an excess of IL-4 and IL-13 and a relative absence of IFNγ. Although not fully elucidated, current theory holds that allergic disease results from a relative lack of production of IFNγ by individuals who have the atopic trait.

IgE antibody has unique biological characteristics. It is found in low concentrations in serum compared with immunoglobulins IgG, IgM, and IgA. IgE has the unique property of binding, through its Fc portion, to receptors found on mast cells and basophils. These cells, which contain histamine and other biochemical mediators, are found in abundance in tissues that are the site of allergic reactions. These sites include the skin, conjunctiva, respiratory system, and gastrointestinal tract.

Interaction between the specific allergen, such as rat or mouse urinary protein, triggers the release of preformed mediators, such as histamine, and the generation of other vasoactive biochemical mediators, such as leukotrienes and prostaglandins from mast cells and basophils. Furthermore, the release of chemokines, such as RANTES (regulated upon activation normal T- cell expressed and secreted) and eotaxin, results in the recruitment of inflammatory cells (particularly eosinophils) into the tissues. There, further release of leukotrienes and other mediators results in the typical inflammation seen in allergic reactions during the late-phase response. The biochemical mediators and inflammatory cells contribute to the allergic symptoms. Over time these events may lead to chronic disease states, such as asthma.

In summary, the mechanism underlying LAA involves a

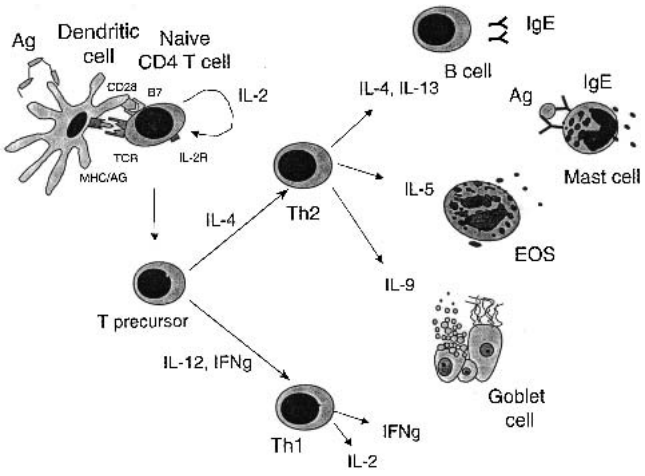

Figure 1 Antigen presentation to naive T-cells requires (1) recognition of antigen (AG)/major histocompatibility (MHC) complex by T-cell receptor (TCR), and (2) costimulatory signals provided through the interaction of CD28 and B7. Differentiation of T-precursor cells into Th1 or Th2 effector cells is influenced by the presence of interleukin (IL)-4 and IL-12. Th2-type cells contribute to antigen-induced airway inflammation through the generation of IL-4, IL-5, IL-9, and IL-13. Reprinted with permission from Kiekhaefer CM, Kelly EA, Jarjour NN. 2001. Antigen-induced airway disease. In: Bush RK, ed. Environmental Asthma. New York: Marcel Dekker. p 13-31.

complex series of events. Genetic factors may play a role in governing the ability of the individual to generate an allergic response. Through airborne or skin contact, the allergens produced by laboratory animals lead to their uptake by antigen-processing and -presenting cells. These cells in turn interact with T-lymphocytes and in the appropriate cytokine milieu lead to the generation of Th2 CD4+ T-helper cells. The Th2-cells then elaborate cytokines, such as IL-4 and IL-13, that are involved in the production of IgE. The production of IL-5 results in maturation and enhances the recruitment of eosinophils into sites of allergic reactions in the tissues. Finally, the interaction of allergens and IgE results in the immediate and late-phase allergic response that leads to the production of symptoms.

The Allergens

The role of the IgE antibodies in health is not completely understood. However, it is of interest that in the case of parasitic infections, specific IgE antibodies to parasite antigens arise in response to organisms that have a tissue migration phase. Interactions between parasitic antigens and IgE result in the degranulation of mast cells and recruitment of eosinophils into the site of the parasitic infection. Eosinophils have the capacity to kill parasites, such as schistosomes, in cultures. It is especially interesting to note that many of the allergens involved in laboratory animal allergies, such as mouse and rat urinary proteins and rabbit allergens (Baker et al. 2001), belong to a family of proteins termed lipocalins (proteins involved in the transport of low molecular weight compounds, such as urinary odorants involved in the sexual activity of rodents), which share sequence homology with schistosome antigens (Virtanen et al. 1999). This molecular mimicry between the urinary protein allergens of the mouse and rat and their close relation to schistosome allergens may account, in part, for the potency of these antigens in eliciting an IgE response in susceptible individuals (Virtanen et al. 1999).

Most major laboratory animal allergens have been identified and characterized (Table 2). The allergens from rats and mice cause most difficulty because they are the animals most often used in research facilities. At least three distinct mouse allergens have been identified and characterized (Price and Longbottom 1990; Robertson et al. 1996; Schumacher 1980; Siragenian and Sandberg 1979). The major mouse allergen Mus m 1, or mouse urinary protein, is a protein with a molecular weight of 19 kD. This allergen is found in the hair follicles and dander in addition to the urine. It is produced in liver cells, and males excrete four times more of the allergen than females. A second allergen, Mus m 2, is a 16 kD molecular protein found in the hair and dander but not in the urine. Mouse albumin is also allergenic in about 30% of mouse sensitive individuals.

Two rat allergens have been identified in the urine, saliva, and pellet (Bayard et al. 1996; Walls and Longbottom 1985). Rat n 1A was originally thought to be prealbumin, but more recent studies have demonstrated that both allergens are variants of an α_{2u}-globulin. Rat n 1B is also produced in the liver and is also androgen dependent. It can be produced by the salivary, mammary, and other exocrine glands (Bayard et al. 1996; Gordon et al. 2001b; Mancini et

Table 2 Laboratory animal allergens[a]

Animal	Allergen	MW[b] (kD)	Source	Biological function
Mouse	Mus m 1 (prealbumin)	19	Hair, dander, urine	Lipocalin-odorant binding protein
(*Mus musculus*)	Mus m 2	16	Hair, dander	Unknown
	Albumin		Serum	Serum protein
Rat	Rat n 1A/Rat n 1B	18.7	Hair, dander	Lipocalin-pheromone binding protein
(*Rattus norvegicus*)	(α_{2u}-globulin)		Urine, saliva	
	Albumin		Serum	
Guinea pig	Cav p 1		Hair, dander, urine	Unknown
(*Cavia porcellus*)	Cav p 2		Hair, dander, urine	
Rabbit	Ag 1 (Price and	17	Hair, dander, saliva	Possible lipocalin
(*Oryctolagus cuniculus*)	Longbottom 1990[c])		Hair, dander, urine	
	Ag 2 (Warner and Longbottom 1991)			
Cat	Fel d 1	38	Hair, dander, saliva	Unknown
(*Felis domesticus*)	Albumin		Serum	Serum protein
Dog	Can f 1	25	Hair, dander, saliva	Lipocalin cysteine protease inhibitor
(*Canis familiaris*)	Can f 2	19	Hair, dander, saliva	Lipocalin
	Albumin		Serum	Serum protein

[a]Adapted from Wood RA. 2001. Laboratory animal allergens. ILAR J 42:12-16.
[b]MW, molecular weight.
[c]See text for complete references.

al. 1989). Rat albumin also is an allergen in some rat allergic individuals.

Rabbit allergens are not as well characterized, but at least two allergens have been identified (Ohman et al. 1975; Warner and Longbottom 1991). One (Ag 1) is a 17 to 18 kD protein found in the saliva, urine, and dander (Price and Longbottom 1990). Recent observations of Baker and colleagues (2001) indicate that the allergen may be a member of the lipocalin family. The other allergen (Ag 2) is found in hair, dander, and urine (Warner and Longbottom 1991).

Guinea pig allergens have not been fully characterized, but two antigenic fragments, designated Cav p 1 and Cav p 2, have been identified. Both of these allergens are found in urine, hair, and dander (Ohman et al. 1975; Swanson et al. 1984; Walls et al. 1985).

The most important dog allergens are Can f 1 and Can f 2, which are produced in the hair, dander, and saliva (Konieczny et al. 1997; Larson et al. 1988; Schou et al. 1991; Spitzauer et al 1993). Can f 1 has a molecular weight of 25 kD, and Can f 2 has a molecular weight of 19 kD. Can f 1 has been shown to be a cysteine protease inhibitor (Virtanen et al. 1999). Both proteins appear to be members of the lipocalin family (Virtanen 2001).

Although cats are used only infrequently as laboratory animals, they are cause of significant allergy when they are kept as pets. Fel d 1 is produced primarily in the sebaceous glands from which it is secreted into the hair and fur (Wood 2001). It is also produced in salivary glands. It also appears to be influenced by testosterone production (Charpin et al. 1994). Approximately 20% of cat allergic patients are also sensitive to albumin. Recently a novel cystatin cat allergen has been identified from cat skin as a member of the cysteine proteinase inhibitor family (Ichikawa et al. 2001).

Other animals used in laboratories including gerbils, hamsters, cows, and sheep may also occasionally cause problems. The major allergens from some of these species, such as cattle (Bos d 2), have been identified as a member of the lipocalin family (Ruoppi et al. 2001). Horses can also be a potent source of allergen. Again, the allergenic Equ c 1 from horses belongs to the lipocalin family (Gregorie et al. 1996).

Although primates have been used in research facilities, few cases of sensitivity have been documented. There have been reported cases of allergy to the lesser bush baby and cottontop tamarin monkey (Petry et al. 1985). These allergens were principally identified in the animal's dander.

Exposure Assessment

Immunoassays have been developed that can assess the airborne concentrations of allergens from mice and rats (Gordon 2001). Typically they include inhibition assays involving human IgE (radioallergosorbent test [RAST[1]] inhibition). Other methods employ enzyme-linked immunoassays using monoclonal antibodies or polyclonal antibodies from animals such as rabbits or mice. Standardized method for assays, collection of samples, and elution techniques have yet to be developed; however, these quantitative measurements have proven useful in assessing individual exposure.

The principal route of exposure to animal allergens is inhalation. Direct skin and eye contact can also occur. Percutaneous exposures may result from animal bites, needle sticks, contaminated needles containing animal allergens or antigen contamination of wounds, and cuts on an individuals hand (Harrison 2001).

Studies of particle size distribution of allergens have shown that exposures involve a broad range of particle size. Airborne allergens consist of the dander and hair shed directly from the animal as well as particulates contaminated by the allergens through direct or indirect contact with animal urine, saliva, and so forth (Harrison 2001). The major concern is for respirable particles that do occur fairly typically (Bush et al. 1998). A significant portion of animal allergens are found on respirable particles (less than 5 micron) which may remain suspended in the air for extended periods of time.

Exposure levels are highly dependent on the number of animals in the facility and specific tasks performed by the workers in the facility (Bush et al. 1998; Harrison 2001). Typical exposure levels found in a laboratory animal facility are shown in Figure 2. It is important to understand that nanogram concentrations may elicit symptoms among sensitized individuals (Gordon and Newman Taylor 1999).

Recent evidence indicates that for individuals who are nonatopic, the risk of sensitization to rat urinary proteins increases with increasing intensity and duration of exposure, whereas for atopic subjects, the dose response relation is less steep (Heedrick et al. 1999). For those with atopy, a history of respiratory symptoms in the pollen season and the number of hours in contact with rodents also are determining factors for the risk of sensitization (Gautrin et al. 2000). Further investigations (working in an animal health facility) indicate that pre-existing lung function, airway hyperresponsiveness, and sensitivity to pets are associated with an increased risk for the development of occupationally related asthma (Gautrin et al. 2001).

Although increasing duration and level of exposure are risk factors for the development of sensitization and symptoms in nonatopic individuals, such exposure response relations do not exist for those with pre-existing allergy, especially to pets. Currently a threshold level of exposure cannot be precisely determined due to these factors and also because of lack of standardized methods for quantitating such exposure (Gordon 2001).

Occupational Health and Safety in the Laboratory Animal Facility

Prevention of LAA

Ultimately, the best approach to the problem of laboratory animal allergy is prevention. It can be achieved as has been

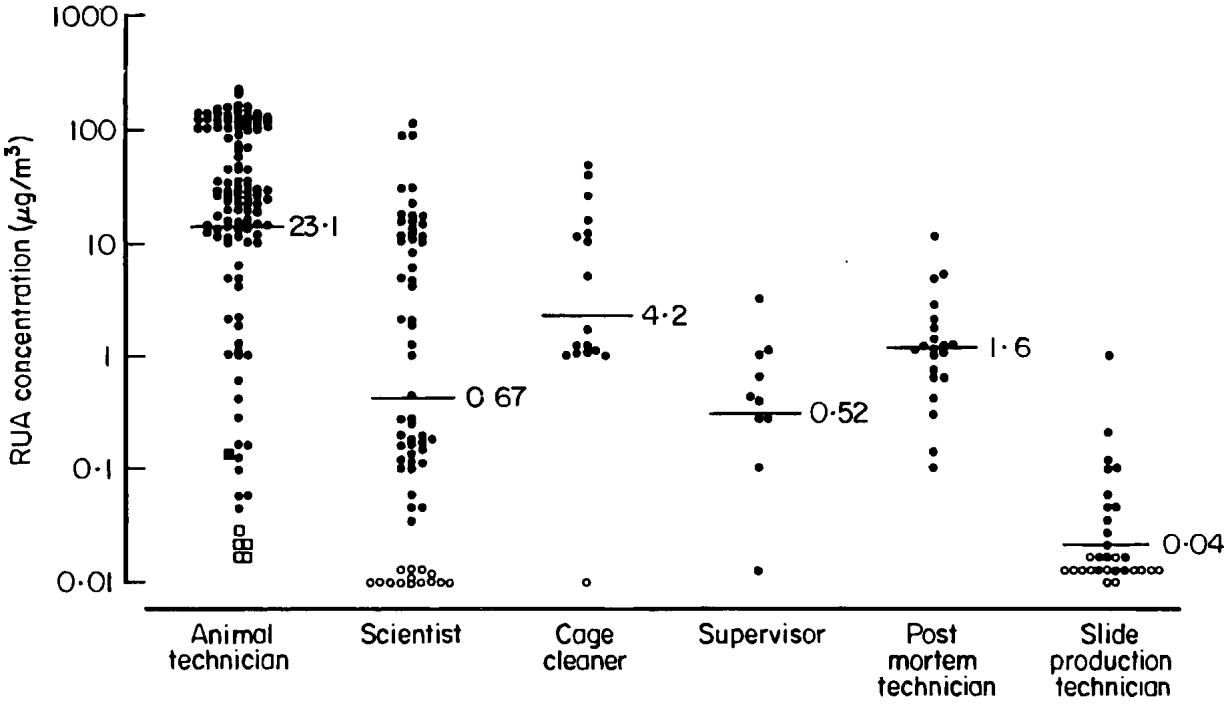

Figure 2 Rat urinary aeroallergen (RUA) exposure of a pharmaceutical workforce by exposure group. ○□, estimated exposure. ●■, measured exposure. ○●, animals housed in conventional cages. □■, animals housed in isolators. Reprinted with permission from Gordon S, Tee RD, Nieuwenhuijsen MJ, Lowson D, Harris J, Newman Taylor AJ. 1994. Measurement of airborne rat urinary allergen in an epidemiological study. Clin Exp Allergy 24:1070-1077.

demonstrated by Fisher and colleagues (1998). At total of 159 employees at a pharmaceutical research laboratory were enrolled in the program to reduce the incidence of LAA. The program consisted of education and training, modification of work practices such as controlling the animal stack density and instituting wet shaving practices, and engineering controls. The engineering controls that were implemented included the use of filter-top cages, high-efficiency particulate air (HEPA[1]) filtered room ventilation, increased room air exchange, and dust-free bedding. Individuals used PPE, including the mandatory use of respiratory protection (generally dust mist respirators). A medical surveillance program was included for symptom assessment and detection of sensitivity by RAST for animal allergens. The medical surveillance assessments were performed on an annual basis. In addition, regular housekeeping routines were established to ensure that the work place was as clean and free from animal allergens as possible. At the time of the institution of this comprehensive program, the annual incidence of laboratory animal allergy was approximately 10%. At the end of 5 yr, the incidence had been reduced to 0. This study suggests that laboratory animal allergy is potentially preventable. Subsequently, the annual incidence of LAA at that company has been maintained at close to 0 (Goodno and Stave 2002).

A well-designed LAA management program can be useful in achieving this goal (Appendices A and B). Important components of any program designed to reduce the risk of laboratory animal allergy should include proper training and education of the exposed individuals. The individual employed in the laboratory facility must know the proper techniques for working with animals and disposing of waste to reduce exposure. Training should include information on the allergic diseases, the symptoms, and the ways to control and minimize exposures.

Preplacement Evaluation

Preplacement medical evaluations may be helpful (Seward 2001). The extent of the evaluation depends on the cost and availability of such services. Questionnaires (e.g., Appendix C) can be used to assist placement of the worker in appropriate settings that can reduce or minimize the risk of developing laboratory animal allergy (Gordon et al. 2001a). It also provides the employees the opportunity to learn about their personal health risk and relationship to working with animals and to establish a baseline against which future changes in health can be measured.

Skin testing to animal allergens or in vitro assays such as the RAST to detect specific IgE antibodies may be performed in some instances. This would include testing to allergens with the actual laboratory animals to which the person will be exposed but may also include other allergens such as pollens, molds, and pet danders that if positive,

could indicate the employee's increased risk for sensitization to laboratory animal allergens (Seward 2001). In one prospective study, the combined use of RAST plus skin testing to animal allergens was 87.4% predictive of subsequent development of LAA after 2 yr (Botham et al. 1995). Most other studies have had less predictive value. RAST and skin tests are better utilized as diagnostic tests than as screening tests in asymptomatic workers.

As part of the medical surveillance, annual or semiannual evaluations using questionnaires may be conducted (e.g., Appendix D). If the worker starts to exhibit symptoms of laboratory animal allergy, further evaluation may be necessary.

Exposure Reduction

The techniques to reduce exposure include the following categories: (1) substitution, (2) engineering controls, (3) administrative controls, and (4) PPE. Substitution involves using fewer allergenic species (e.g., using female rats as opposed to male rats, using in vitro techniques as opposed to animals, or other methods). Engineering controls include improvement in ventilation (reviewed extensively by Harrison 2001) and improved caging systems (Gordon et al. 2001b). Administrative controls include workplace rules and procedures (e.g., limiting access to the animal care areas) and improved and required handling methods.

Examples of PPE include respirators, eye protectors, gloves, and clothing and footwear designed to reduce exposure. Dust mist respirators (not surgical masks, which provide no significant protection from LAA) for nonsymptomatic workers are relatively comfortable and readily used by workers. These items can remove up to 98% of rodent urinary allergens from the air (Sakaguchi et al. 1989). If employers choose to use respirators, they should also have a fully developed respiratory protective program that includes quality control, medical approval for use, and test fitting. Only respirators approved by the National Institute of Occupational Health and Safety should be used.

Gloves, gowns, and coverings are important to keep allergens off the skin. These items should be removed at the end of the work shift, when thorough hand washing and showering may also be appropriate. Latex gloves may be necessary where infection control is important. However, if this risk is minimal, nonlatex gloves can be substituted since sensitivity to latex is also a risk. Powdered latex gloves should be avoided because they have the strongest association with the development of latex allergy.

Prevention of laboratory animal allergy depends on control of the individual's exposure in the work environment. In addition to exposure control technologies, PPE should be considered where conditions require. Preplacement evaluation and periodic medical surveillance of workers can also be an important aspect of the overall occupational health program of the facility. Such medical surveillance programs have been demonstrated to reduce the risk of occupational asthma in other settings (Tarlo and Liss 2001). The emphasis on medical surveillance programs should be on counseling and early disease detection so that progressive impairments of the worker's health do not occur.

Evaluation and Treatment of the Individual with LAA

When individuals have allergic symptoms related to laboratory animal exposure, consultation with appropriate physicians should be considered so that an accurate diagnosis and effective management can be achieved. For animal facility personnel suspected of having allergic problems, the diagnosis of animal sensitivity is largely made on the basis of the history of symptoms in conjunction with exposure. The diagnosis is confirmed by the demonstration of specific IgE antibodies to the allergen in question.

Symptoms of allergic rhinitis include chronic congestion and rhinorrhea accompanied by sneezing, itchy nose or throat, and itchy eyes. To obtain a history of asthma, the individual should be asked about the following: wheezing, cough, chest tightness, or difficulty breathing that is episodic; colds; exposure to irritants such as cigarette smoke, odors, and cold air; and allergen exposure. Symptoms typically increase with exercise. Symptoms should clearly improve if asthma medications have been used.

To confirm a suspected diagnosis of LAA, appropriately performed skin tests or in vitro assays for the presence of IgE antibodies to laboratory animal allergens should be done (Bush 2001; Bush et al. 1998). If asthma due to LAA is suspected, it is important to perform lung function measurements (Bush 2001), which may include serial peak flow measurements obtained in and out of the workplace. As soon as a diagnosis of LAA or asthma has been confirmed, treatment should be directed toward removing the worker from continued exposure. Studies evaluating the clinical course of workers with occupational asthma after removal from exposure have shown that persistence of the symptoms frequently depends on the duration of symptoms before diagnosis (Bernstein et al. 1996). The longer patients have symptoms, the less likely they are to recover completely. With early diagnosis, prognosis is much better, lung function is preserved, and the degree of nonspecific bronchial hyper-responsiveness is reduced. In contrast, individuals who remain in the workplace for longer periods of time and experience deterioration of lung function develop chronic persistent asthma, which often requires continued medication use.

The use of PPE may be helpful in reducing or preventing symptoms; however, because nanogram concentrations of allergic exposure can induce symptoms, this approach may not provide sufficient protection. Pharmacological treatment of acute or chronic symptoms due to LAA is similar to treatment for individuals who have nonoccupational allergic disease (Bush 2001). Nonetheless, very highly sensitized individuals will continue to have symptoms and must avoid exposure to animal allergens com-

pletely. Immunotherapy to laboratory animal allergens has been performed, but these approaches may not prevent progression of symptoms and deterioration of lung function.

On rare occasions, an allergic worker may experience an anaphylactic reaction from an animal bite (Teasdale et al. 1993) or from needle punctures contaminated with laboratory animal allergens (Watt and McSharry 1996). Because these reactions can progress rapidly and become potentially fatal, physicians may recommend that the sensitized worker carry a self-administered form of epinephrine (e.g., EpiPen® or Ana-Kit®). In appropriate circumstances, it may be helpful to instruct coworkers in emergency procedures such as cardiopulmonary resuscitation.

Summary

As noted in *Occupational Health and Safety in the Care and Use of Laboratory Animals* (NRC 1997), prevention of the development of LAA should be the aim of all facilities engaged in the use of laboratory animals. Cooperation between facility management and workers and the implementation of good industrial hygiene measures aimed at preventing exposure to inhalant material have the potential for reducing LAA. Workers should be educated continually about the importance of adhering to appropriate procedures that reduce exposure. Preplacement screening of hired workers for allergy to other antigens such as pollens, molds, and animal danders may be considered before assigning employees to specific jobs in an effort to reduce risks for development of laboratory animal sensitivity. Comprehensive surveillance programs for detecting and monitoring workers at increased risk for sensitization may reduce the frequency of laboratory animal allergies or prevent its progression.

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Appendix A

Laboratory Animal Allergy Management Program Outline

1. Policy and Goals
   a) Institutional commitment
   b) Organization
   c) Accountability and responsibility
   d) Goals and priorities
2. Exposure Assessment
   a) Characterization of allergens (e.g., sources, exposure vectors, life-cycle analysis)
   b) Characterization of exposure (e.g., by job description, activity, and location)
   c) Identification of at-risk employee populations
3. Exposure Control
   a) Identification and evaluation of industrial hygiene control methods and ASHRAE[†] recommendations for particulate control
   b) Engineering controls
   c) Administrative controls
   d) Personal protective equipment
4. Facility Design and Operation
   a) Integration of LAA[†] management into new facility design and existing facility renovation process (e.g., design, modeling, testing, commissioning)
   b) Testing and evaluation of equipment and systems critical for aeroallergen control
   c) Preventive maintenance for control equipment and systems
5. Equipment Performance
   a) Performance standards for new purchases and existing equipment
   b) Equipment certification in accordance with consensus national standards
   c) Equipment monitoring (HEPA[†] filtration units and ventilation system performance)
   d) Environment surveillance
   e) Evaluation of allergen control methods' effectiveness
6. Administrative Controls
   a) Goals: Reducing (i) the number of employees at risk of exposure, and (ii) exposures by direct and indirect contact, specifically inhalation and percutaneous exposures
   b) Proper use and maintenance of equipment and installed systems
   c) Management of room occupancy (people and animals)
   d) Zoning of facility for animal use
   e) Monitoring of work environment
   f) Training and education of workers
   g) Monitoring of worker health status
7. Education and Training
   a) Formal orientation: Risk assessment and hazard recognition
   b) Written guidelines and codes of practice
   c) Periodic refresher training
   d) Hazard communication (e.g., signs, posters, information pamphlets)
   e) On-the-job training (work practices to reduce exposure)
   f) Written emergency response procedures
   g) Record keeping
8. Occupational Health and Safety
   a) Management that is consistent with traditional hazards (e.g., asbestos, formaldehyde) and medical conditions and diseases
   b) Characterization of exposure (see text, Exposure Assessment)
   c) Identification of employees at risk (i.e., exposed to allergen) (see text, Exposure Assessment)
   d) Medical surveillance (e.g., with defined procedures, frequency, populations)
   e) Consultation with appropriate physicians (allergist, pulmonologist, or occupational medicine specialist) if allergic symptoms develop
   f) Policy and practices for management of employees diagnosed with LAA
   g) Medical record keeping
9. Information Management
   a) On-line employee access to appropriate Program components
   b) Computer links to pertinent web sites
10. Emergency Procedures
    a) Written emergency response plans
    b) Medical preparedness for anaphylactic reactions
11. Program Evaluation
    a) Identification and tracking of total costs associated with program
    b) Periodic program audit
    c) Workplace surveys
    d) Trend analysis
    e) Ongoing review of goals and status
    f) Annual report

[†]Abbreviations: ASHRAE, American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc.; HEPA, high-efficiency particulate air; LAA, laboratory animal allergy. Reprinted with permission from Harrison DJ. 2001. Contolling exposure to laboratory animal allergens. ILAR J 42:17-35.

Appendix B

Summary of Recommendations to Reduce Exposure to Animal Allergens in the Workplace and Prevent Animal-induced Asthma and Allergies*

- Increase the ventilation rate and humidity in the animal-housing areas.
- Ventilate animal-housing and -handling areas separately from the rest of the facility.
- Direct airflow away from workers and toward the backs of the animal cages.
- Install ventilated animal cage racks or filter-top animal cages.
- Perform animal manipulations within ventilated hoods or safety cabinets when possible.
- Avoid wearing street clothes while working with animals. Leave work clothes at the workplace to avoid potential exposure problems for family members.
- Keep cages and animal areas clean. Take particular care to control exposures during cleaning.
- Use absorbent pads for bedding. If these are unavailable, use corncob bedding instead of sawdust bedding.
- Use an animal species or sex that is known to be less allergenic than others.
- Reduce skin contact with animal products sush as dander, serum, and urine by using gloves, laboratory coats, and approved particulate respirators with face shields.
- Provide training to educate workers about animal allergies and steps for risk reduction.
- Provide health monitoring and appropriate counseling and medical follow-up for workers who have become sensitized or have developed allergy symptoms.

*Adapted from US Department of Health and Human Services, National Institute for Occupational Safety and Health. 1998. Preventing Asthma in Animal Handlers (Publication 97-116). Cincinnati: NIOSH. Reprinted with permission from Harrison DJ. 2001. Controlling exposure to laboratory animal allergens. ILAR J 42:17-35.

Appendix C
Laboratory Animal Allergy Questionnaire – INITIAL

Demographic Information

1. Name: _____ _____ _____
   Last First Middle Initial

2. Social security number: _____

3. Birth-date: _____/_____/_____ 4. Age: _____ 5. Sex: M F (circle one)
   Month Day Year

6. Today's Date: _____/_____/_____
   Month Day Year

7. Race: (circle one) Asian Black Hispanic/Latino White Other _____

8. Current Job Title: _____

   Where do you work? (Specific Location)

   Building: _____

   Room: _____

   Date you began this job: _____/_____ Date you began with this organization: _____/_____
   Month Year Month Year

9. Highest Education completed: (check one)
   _____ Grade School (elementary)
   _____ High School
   _____ Some College
   _____ College
   _____ Masters degree
   _____ DVM, DDS, MD PhD

Current Allergic Symptoms

10. Have you experienced any of the following symptoms on a regular basis?
(Do NOT answer "YES" if these symptoms are associated with a cold, flu, or other illness) **YES / NO**

Please indicate year of onset, whether the symptom is present now, and the times at which you are most troubled by the symptom.

	Year of Onset	Present now?	Spring	Summer	Fall	Winter	No Particular Season	Home	Work	Vacation	No Difference	Go to # 11
Watery or itchy eyes	_____	___	___	___	___	___	___	___	___	___	___	
Runny or stuffy nose	_____	___	___	___	___	___	___	___	___	___	___	
Sneezing spells	_____	___	___	___	___	___	___	___	___	___	___	
Frequent cough	_____	___	___	___	___	___	___	___	___	___	___	
Difficulty swallowing	_____	___	___	___	___	___	___	___	___	___	___	
Sputum production (excessive mucous)	_____	___	___	___	___	___	___	___	___	___	___	
Sinus problems	_____	___	___	___	___	___	___	___	___	___	___	
Frequent colds	_____	___	___	___	___	___	___	___	___	___	___	
Hives	_____	___	___	___	___	___	___	___	___	___	___	
Swelling of lips or eyes	_____	___	___	___	___	___	___	___	___	___	___	
Eczema	_____	___	___	___	___	___	___	___	___	___	___	
Wheezing/ chest tightness	_____	___	___	___	___	___	___	___	___	___	___	

If you answer "YES" to the following questions, please complete the additional questions in the enclosed boxes. Thank you.

Atopic History

11. Do you think you have ALLERGIES? **YES / NO**

If YES:

To what are you allergic: _____

What symptoms do you have when your allergies act up?

_____

12. Have you ever had HAY FEVER? **YES / NO**

If YES:

At what age did you first develop hay fever? _____

When was the last time you were troubled by hay fever? _____/_____
Month Year

13. Has a physician ever told you that you have ALLERGIES? **YES / NO**

14. Have you ever had a SKIN TEST for allergies (not TB)? **YES / NO**

If you were skin tested, to what were you allergic?

_____

15. Have you ever received ALLERGY SHOTS? **YES / NO**

16. Have you ever taken MEDICATIONS FOR ALLERGIES? **YES / NO**

If YES:

What medications? _____

How Often? _____

17. Has a physician ever told you that you have ASTHMA? **YES / NO**

18. Have you ever had an attack of wheezing that made you short of breath? **YES / NO**

If YES:

At what age did you have your first attack? _____

Are you still occasionally troubled by these attacks? YES / NO

Do you currently take medications for these attacks? YES / NO

19. Are you allergic or sensitive to things that cause skin rashes? **YES / NO**

If YES:

What causes rashes? _____

20. Is there anyone in your immediate family with ALLERGIES or ASTHMA? **YES / NO**

Father	Allergies	Asthma	Both
Mother	Allergies	Asthma	Both
Sister	Allergies	Asthma	Both
Brother	Allergies	Asthma	Both
Child	Allergies	Asthma	Both

Home Environment

21. Have you EVER had HOUSEPETS? **YES / NO**

If YES:

Which animals? For how long?

___Dogs _____
___Cats _____
___Other (specify):
_____ _____
_____ _____

Are you (or were you) allergic to them? **YES / NO**

Do you have **housepets** now? **YES / NO**

22. Do you smoke cigarettes? **YES / NO**

If YES:

On average, how many do you smoke per day? _____

For how many years have you smoked? _____

If NO:

Did you smoke cigarettes in the past? **YES / NO**

For how many years? _____

When did you quit? (Month/Year) _____

23. Do other members of your household smoke? **YES / NO**

24. Did your parents smoke when you were living at home? **YES / NO**

25. Are you taking any medications on a regular basis? **YES / NO**

Please list **ALL** medications (including herbal or vitamin supplements) you are currently taking on a regular basis and how often you take them.

_____
_____
_____

OCCUPATIONAL HISTORY / Current Exposure Information

26. Have you worked with laboratory animals before this job? **YES / NO**

If YES:

For how long? (total years) _____

What types of animals? _____

Were you allergic to any of the animals with which you worked? YES / NO

If **YES,** what type of animal? _____

When was the onset of allergy? (Year or Month/Year) _____

27. In your current job do you handle animals or their tissue, body fluids, or cages? **YES / NO**

28. Do you work in the animal room at least once a week? **YES / NO**

If YES:

How many days per week do you work with the lab animals or their cages? (circle one)

< 1 1 2 3 4 5 More ____

During these days, **how many hours per day** (on the average) do you work with lab animals or their cages? (circle one)

<1 1 2 3 4 5 6 7 8 More ___

If NO:

Over the past 24 weeks (about six months) **during how many weeks** have you had lab animal contact? _____

During these weeks, **how many days per week** have you worked with lab animals?

<1 1 2 3 4 5 More ____

On these days, **how many hours per day** have you worked with lab animals?

<1 1 2 3 4 5 6 7 8 More___

29. How many hours per week do you usually have contact with the following species?
(circle one choice for each listing)

	Hours per week						
Guinea Pig	0	<1	1-5	6-10	11-15	16-20	21 or more
Hamster	0	<1	1-5	6-10	11-15	16-20	21 or more
Dogs	0	<1	1-5	6-10	11-15	16-20	21 or more
Cats	0	<1	1-5	6-10	11-15	16-20	21 or more
Rat	0	<1	1-5	6-10	11-15	16-20	21 or more
Rabbit	0	<1	1-5	6-10	11-15	16-20	21 or more
Marmosets	0	<1	1-5	6-10	11-15	16-20	21 or more
Primates	0	<1	1-5	6-10	11-15	16-20	21 or more
Mice	0	<1	1-5	6-10	11-15	16-20	21 or more
Other _____(specify)	0	<1	1-5	6-10	11-15	16-20	21 or more

30. How many hours per week are you usually involved in the following activities?
(circle one choice for each listing)

	Hours per week						
Handle dirty cages	0	<1	1-5	6-10	11-15	16-20	21 or more
Return clean cages	0	<1	1-5	6-10	11-15	16-20	21 or more
Receiving animals	0	<1	1-5	6-10	11-15	16-20	21 or more
Breeding room	0	<1	1-5	6-10	11-15	16-20	21 or more
Holding room	0	<1	1-5	6-10	11-15	16-20	21 or more
Gavage or other dosing	0	<1	1-5	6-10	11-15	16-20	21 or more
Weighing	0	<1	1-5	6-10	11-15	16-20	21 or more
Sacrifice/Necropsy	0	<1	1-5	6-10	11-15	16-20	21 or more
Isolators	0	<1	1-5	6-10	11-15	16-20	21 or more
Change bedding	0	<1	1-5	6-10	11-15	16-20	21 or more
Other animal room housekeeping	0	<1	1-5	6-10	11-15	16-20	21 or more
Isolated organ or tissue experiments	0	<1	1-5	6-10	11-15	16-20	21 or more
Using animals or tissues/fluids **outside** animal facility	0	<1	1-5	6-10	11-15	16-20	21 or more

31. When working with lab animals or their cages how often do you do the following?
(check one choice for each item)

	Never	Less than <1/2 time	Most of the time	Always
Wear gloves	____	____	____	____
Wear a dust/mist respirator	____	____	____	____
Wear other respirator	____	____	____	____
Wear a gown/Tyvek suit	____	____	____	____
Wear hair bonnets	____	____	____	____
Wear shoe covers	____	____	____	____
Wash hands after handling animals	____	____	____	____
Wear eye protection	____	____	____	____

32. **Do you get any of the following symptoms from working with laboratory animals or their cages? (Or have you ever had any of the symptoms in the past from working with laboratory animals or their cages. In other words, if you were not able to wear personal protective equipment, would you probably get these symptoms?).** **YES / NO**

If YES:

Which of the symptoms do you have? (please check all that apply)

___Sneezing spells
___Runny or stuffy nose
___Watery or itchy eyes
___Coughing spells
___Wheezing/Chest tightness
___Shortness of breath
___Skin rashes or hives ___

If NO, Go to Question # 33

Does personal protective equipment eliminate these symptoms? **YES / NO**

Which of the following species causes any of these problems?

___Guinea pig
___Hamster
___Dogs
___Cats
___Mouse
___Rat
___Rabbit
___Marmosets
___Primates
(Type: _____)
___Bedding Only
___Other: _____

How soon after exposure to lab animals do these symptoms start? (circle one)

Less than 10 minutes	10 minutes to 1 hour	1 to 8 hours	More than 8 hours

How long do they last?

Less than 10 minutes	10 minutes to 1 hour	1 to 8 hours	More than 8 hours	For the duration of exposure

Do you take any medicines for these symptoms? **YES / NO**

33. **Are there any lab animals with which you cannot work because of allergy problems?** **YES / NO**

If YES:

Which animal species? _____

How long have you been allergic to this (these) species? _____

34. **Have you ever changed jobs or working habits because of symptoms from handling animals?** **YES / NO**

Please explain: _____

35. **Aside from your own work, are lab animals used by others in the same room where you work?** **YES / NO**

Appendix D

Laboratory Animal Allergy Questionnaire – FOLLOW-UP

Important: This form should be completed only by employees who have completed an INITIAL questionnaire in the past. The INITIAL questionnaire should be used as a baseline when evaluating responses to this questionnaire.

Demographic Information

1. **Name:** _____ _____ _____ **SSN:** _____
   Last First Middle Initial

2. **Today's Date:** _____/_____/_____
   Month Day Year

3. **Current Job Title:** _____

4. **Since your last questionnaire, have you changed job title?** **YES / NO**

If YES:

Date of change (month/year) _____

Where do you work? (Specific Location)

Building: _____

Room: _____

Current Allergic Symptoms

5. **Have you developed any of the following symptoms since you completed the last questionnaire?** **YES / NO**

(Do not answer YES if the symptoms are associated with colds, influenza, or other acute illness)

If YES, please indicate year of onset, whether the symptom is present now, and the times at which you are most troubled by the symptom.

	Year of Onset	Present now?	Spring	Summer	Fall	Winter	No Particular Season	Home	Work	Vacation	No Difference
Watery or itchy eyes	_____	___	___	___	___	___	___	___	___	___	___
Runny or stuffy nose	_____	___	___	___	___	___	___	___	___	___	___
Sneezing spells	_____	___	___	___	___	___	___	___	___	___	___
Frequent cough	_____	___	___	___	___	___	___	___	___	___	___
Difficulty swallowing	_____	___	___	___	___	___	___	___	___	___	___
Sputum production (excessive mucous)	_____	___	___	___	___	___	___	___	___	___	___
Sinus problems	_____	___	___	___	___	___	___	___	___	___	___
Frequent colds	_____	___	___	___	___	___	___	___	___	___	___
Hives	_____	___	___	___	___	___	___	___	___	___	___
Swelling of lips or eyes	_____	___	___	___	___	___	___	___	___	___	___
Eczema	_____	___	___	___	___	___	___	___	___	___	___
Wheezing/ chest tightness	_____	___	___	___	___	___	___	___	___	___	___

Atopic History

If you answer "YES" to the following questions, please complete the additional questions in the enclosed boxes. Thank you.

6. Since your last questionnaire, have you developed ALLERGIES? **YES / NO**

If YES:

To what are you allergic: _____

What symptoms do you have when your allergies act up?

_____

7. Since your last questionnaire, has a physician told you that you have ALLERGIES? **YES / NO**

8. Since your last questionnaire, have you developed hayfever? **YES / NO**

9. Since your last questionnaire, have you had a SKIN TEST for allergies (not TB)? **YES / NO**

If you were skin tested, to what were you allergic?

_____

10. Since your last questionnaire, have you received ALLERGY SHOTS? **YES / NO**

11. Since your last questionnaire, have you taken MEDICATIONS FOR ALLERGIES? **YES / NO**

If **'YES,'** what medications? _____

How Often? _____

12. Since your last questionnaire, has a physician told you that you have ASTHMA? **YES / NO**

13. Since your last questionnaire, have you had an attack of wheezing that made you short of breath? **YES / NO**

Do you currently take medications for these attacks? YES / NO

14. Are you allergic or sensitive to things that cause skin rashes? **YES / NO**

If **'YES,'** what causes rashes? _____

Home Environment

15. Since your last questionnaire, have you gotten any house pets? **YES / NO**

What type? _____

Are you allergic to them? **YES/NO**

16. Do you smoke cigarettes? **YES / NO**

If YES:

On average, how many do you smoke per day? _____

For how many years have you smoked? _____

If NO:

Did you smoke cigarettes in the past? **YES / NO**

For how many years? _____

When did you quit? (Month/Year) _____

17. Do other members of your household smoke? **YES / NO**

18. Are you taking any medications on a regular basis? **YES / NO**

If YES, please list **ALL** medications you are currently taking on a regular basis and how often you take them.

_____

_____

_____

_____

Current Exposure Information

19. In your current job do you handle animals or their tissue, body fluids, or cages? **YES / NO**

20. Do you work in the animal room at least once a week? **YES / NO**

If YES:

How many days per week do you work with the lab animals or their cages? (circle one)

< 1 1 2 3 4 5 More ____

During these days, **how many hours per day** (on the average) do you work with lab animals or their cages? (circle one)

<1 1 2 3 4 5 6 7 8 More ___

Go to next page

If NO:

Over the past 24 weeks (about six months) **during how many weeks** have you had lab animal contact? _____

During these weeks, **how many days per week** have you worked with lab animals?

<1 1 2 3 4 5 More ____

On these days, **how many hours per day** have you worked with lab animals?

<1 1 2 3 4 5 6 7 8 More___

21. How many hours per week do you usually have contact with the following species?
(circle one choice for each listing)

	Hours per week						
Guinea Pig	0	<1	1-5	6-10	11-15	16-20	21 or more
Hamster	0	<1	1-5	6-10	11-15	16-20	21 or more
Dogs	0	<1	1-5	6-10	11-15	16-20	21 or more
Cats	0	<1	1-5	6-10	11-15	16-20	21 or more
Rat	0	<1	1-5	6-10	11-15	16-20	21 or more
Rabbit	0	<1	1-5	6-10	11-15	16-20	21 or more
Marmosets	0	<1	1-5	6-10	11-15	16-20	21 or more
Mice	0	<1	1-5	6-10	11-15	16-20	21 or more
Primates	0	<1	1-5	6-10	11-15	16-20	21 or more
Other _____(specify)	0	<1	1-5	6-10	11-15	16-20	21 or more

22. How many hours per week are you usually involved in the following activities?
(circle one choice for each listing)

	Hours per week						
Handle dirty cages	0	<1	1-5	6-10	11-15	16-20	21 or more
Return clean cages	0	<1	1-5	6-10	11-15	16-20	21 or more
Receiving animals	0	<1	1-5	6-10	11-15	16-20	21 or more
Breeding room	0	<1	1-5	6-10	11-15	16-20	21 or more
Holding room	0	<1	1-5	6-10	11-15	16-20	21 or more
Gavage or other dosing	0	<1	1-5	6-10	11-15	16-20	21 or more
Weighing	0	<1	1-5	6-10	11-15	16-20	21 or more
Sacrifice/Necropsy	0	<1	1-5	6-10	11-15	16-20	21 or more
Isolators	0	<1	1-5	6-10	11-15	16-20	21 or more
Change bedding	0	<1	1-5	6-10	11-15	16-20	21 or more
Other animal room housekeeping	0	<1	1-5	6-10	11-15	16-20	21 or more
Isolated organ or tissue experiments	0	<1	1-5	6-10	11-15	16-20	21 or more
Using animals or tissues/fluids **outside** animal facility	0	<1	1-5	6-10	11-15	16-20	21 or more

23. When working with lab animals or their cages how often do you do the following?
(check one choice for each item)

	Never	Less than <1/2 time	Most of the time	Always
Wear gloves	_____	_____	_____	_____
Wear a dust/mist respirator	_____	_____	_____	_____
Wear other respirator	_____	_____	_____	_____
Wear a gown/Tyvek suit	_____	_____	_____	_____
Wear hair bonnets	_____	_____	_____	_____
Wear shoe covers	_____	_____	_____	_____
Wash hands after handling animals	_____	_____	_____	_____
Wear eye protection	_____	_____	_____	_____

24. Do you get any of the following symptoms from working with laboratory animals or their cages? (Or have you ever had any of the symptoms in the past from working with laboratory animals or their cages. In other words, if you were not able to wear personal protective equipment, would you probably get these symptoms?). **YES / NO**

If YES:

Which of the symptoms do you have? (please check all that apply)

___Sneezing spells
___Runny or stuffy nose
___Watery or itchy eyes
___Coughing spells
___Wheezing/Chest tightness
___Shortness of breath
___Skin rashes or hives

Does personal protective equipment eliminate these symptoms? YES / NO

Which of the following species causes any of these problems?

___Guinea pig
___Hamster
___Dogs
___Cats
___Mouse
___Rat
___Rabbit
___Marmosets
___Primates
Type _____
___Bedding Only
___Other: _____

How soon after exposure to lab animals do these symptoms start? (circle one)

Less than 10 minutes	10 minutes to 1 hour	1 to 8 hours	More than 8 hours

How long do they last?

Less than 10 minutes	10 minutes to 1 hour	1 to 8 hours	More than 8 hours	For the duration of exposure

Do you take any medicines for these symptoms? YES / NO

If NO, Go to Question # 33

31. Are there any lab animals with which you cannot work because of allergy problems? YES / NO

If YES, which animal species? _____

How long have you been allergic to this (these) species? _____

32. Have you changed jobs or working habits because of symptoms from handling animals? YES / NO

33. Aside from your own work, are lab animals used by others in the same room where you work? YES / NO