

Controlling Exposure to Laboratory Animal Allergens

D. J. Harrison

Abstract

Laboratory animal allergy (LAA) is a significant occupational disease that may affect up to one third of personnel exposed to laboratory animals. Research has characterized the relative risks of exposure in terms of intensity, frequency, and duration associated with given tasks and work areas in the animal facility. Studies have shown that reduced exposure to animal allergens can reduce the incidence of LAA and relieve symptoms among affected workers. A combination of measures to eliminate or control allergen exposure, including engineering and administrative controls and personal protective equipment, have been integral components of effective LAA management programs. This article provides a comprehensive review of exposure control options, considerations, and “best practices” relative to laboratory animal allergen in the context of traditional industrial hygiene methods.

Key Words: administrative controls; aeroallergen; engineering controls; exposure control; health and safety; laboratory animal allergy; personal protective equipment; ventilation

Introduction

Controlling occupational exposure to animal allergens can be a formidable challenge, encompassing a broad range of considerations and often involving an array of solutions. The objective of exposure control is to prevent or minimize occupational exposure to laboratory animal allergens, thus reducing the incidence and prevalence of allergic disease while relieving symptoms among those employees who are sensitive. No clearly established threshold for allergen exposure supports a minimum safe exposure level; however, prospective studies indicate that reduced exposure will reduce symptoms and decrease the incidence of laboratory animal allergy (LAA¹) (Bush 2001a; Bush et al. 1998; Fisher et al. 1998;

Gordon 2001; Lindqvist et al. 1996; Seward 1999, 2001; Wood 2001). To this end, exposure control is an essential factor in the prevention and management of LAA (Botham et al. 1995; Bush 2001a; Eggleston and Wood 1992; Fisher et al. 1998; Gordon 2001; Gordon and Newman Taylor 1999; Powell 1994; Seward 2001; Wood 2001; Wood and Eggleston 1992).

As described in the literature, most laboratory animal species have multiple allergen sources (i.e., hair, dander, urine, saliva, and serum), each of which warrants due consideration where exposure is concerned (Bush 2001; Bush et al. 1998; Gordon 2001; Seward 2001). For example, rodent urinary allergens are predominantly hazardous as contaminants on inhaled airborne particulate; however, direct contact with the skin should also be avoided. The type of animal, cage or enclosure, and bedding, as well as environmental conditions in the cage and room, all affect exposure. Of greater significance, however, are the various tasks associated with the care and use of laboratory animals and their respective implications for exposure and biological dose. Like many occupational hazards, the intensity (or concentration) of allergen exposure, along with duration and routes of entry, are significant factors in allergic disease. They are also most often a direct function of particular tasks and job responsibilities.

Given the significance of LAA, animal allergens warrant control and management consistent with traditional occupational hazards. Occupational exposure to animal allergens occurs predominantly through inhalation of airborne allergens (aeroallergens), which makes exposure control largely an exercise in particulate control. In this sense, controlling allergen exposure is not unlike controlling many other airborne hazards. Worker exposure is directly related both to the amount of aeroallergens that reach the breathing zone of the worker and to the duration of the exposure. Exposure controls must therefore reduce the transfer of allergens into the breathing zone and/or the length of exposure. Understanding the sources of allergens, routes of exposure, and work practices that influence exposure allows for application of specific control measures that can effectively mitigate exposure.

The conventional hierarchy for exposure control of occupational hazards includes (1) engineering controls, (2) administrative controls, and (3) personal protective equipment (PPE¹). This approach appropriately recognizes the significant value of engineered protection afforded by proper facility design, local ventilation, and other engineered controls. Administrative controls, including work practices and

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¹Abbreviations used in this article: CFD, computational fluid dynamics; HEPA, high-efficiency particulate air; IVC, individually ventilated caging; LAA, laboratory animal allergy; PPE, personal protective equipment; RPE, respiratory protective equipment; RUA, rat urinary aeroallergen.

training, address the human element, which is a key factor in any exposure control strategy. PPE is the last line of defense for protecting the worker. Although it can be effective in reducing exposure, it is the most imposing type of control from the worker's perspective and is often difficult to implement and manage. Despite the emphasis on rank order, an effective exposure control strategy invariably embraces all three methods to a given extent, as noted in *Occupational Health and Safety in the Care and Use of Research Animals* (NRC 1997).

An additional aspect of occupational exposure that warrants attention is control of indirect exposure. Allergen exposure stemming from occupational sources experienced by individuals who are not directly involved in the care and use of laboratory animals should be controlled as well. Such fugitive exposures warrant consideration in a comprehensive exposure control plan.

Exposure Assessment

Fundamental to exposure control are the identification and characterization of exposure sources. In the case of laboratory animals, the source is certainly no mystery: Animals shed, excrete, and secrete material containing allergenic proteins. Aeroallergens consist of dander and hair shed directly from the animal, as well as particulate contaminated by allergens through direct or indirect contact with the animal, urine, saliva, and so forth (Bush 2001a,b; Bush et al. 1998; Clough et al. 1995; Gordon and Newman Taylor 1999; Reeb-Whitaker et al. 1999; Wood 2001). Virtually any material in contact with laboratory animals (most notably bedding) can be contaminated with allergens. Studies of particle size distributions have shown that allergen contamination can be found in all particle size ranges (Gordon and Newman Taylor 1999; Platts-Mills et al. 1986; Reed et al. 1999; Swanson et al. 1990). Although various studies have identified specific size ranges of aeroallergens, the range in a given environment will basically reflect source types (i.e., animals and bedding), types and levels of activity, the effectiveness of any control measures, and aerosol physics. Aeroallergens in the range of 5 to 15 μm in aerodynamic diameter are typical, although a significant percentage of aeroallergens is found on respirable particulate (less than 4 μm), which may remain suspended in air for extended periods of time. Controlling fugitive particulate generation from the animal and its immediate environment is critical for aeroallergen control in the worker's environment.

Particle size is a significant factor in deposition within the respiratory tract, which, along with aeroallergen concentration and time of exposure, will determine the dose. Individual biological response to allergen exposure depends on a complex combination of factors beyond route of exposure (site of deposition) and dose, including relative health, genetic predisposition, exposure, and disease history, as discussed elsewhere in this volume (Wood 2001). These factors, specifically the health status of the exposed population (e.g.,

symptomatic, asymptomatic, atopic), can have an impact on the relative effectiveness of any control measure. Although most, if not all, of the controls discussed below can result in some degree of a *mathematically* significant reduction in allergen exposure, whether the same reduction is *biologically* significant (i.e., reduces the incidence of disease or the onset of symptoms) may vary within the exposed population.

Routes of Exposure

The principle route of exposure to animal allergens is inhalation of aeroallergens. Direct skin and eye contact can also be a common route of exposure and, occasionally, ingestion. Percutaneous exposures may result from animal bites, needle punctures contaminated with animal allergens, or allergen contamination of wounds. Different routes of exposure often elicit symptoms relative to the site of exposure through somewhat unique disease mechanisms. Skin exposure may result in hives but is generally not a significant factor in the onset of asthma, which is typically caused by inhalation of aeroallergens. Similarly, the risk of anaphylaxis is much greater from an animal bite than from other routes of exposure. These topics are discussed in greater detail elsewhere in this volume (Bush 2001b; Wood 2001).

Inhaled aeroallergens preferentially deposit in the various regions of the respiratory system with some implication for disease symptoms. Particles greater than approximately 10 μm typically deposit in the mucosal linings of the head airways or nasopharyngeal region (upper respiratory tract). Particles in the range of about 4 to 10 μm more often deposit in the lung airways or tracheobronchial region (thoracic region). Particles less than approximately 4 μm are likely to penetrate deeply into the lung and deposit in the pulmonary, or alveolar, region of the lung, where gas exchange takes place. A general exception are ultrafine (0.001- to 0.01- μm) particles, which can have relatively significant deposition in the upper respiratory tract (high diffusion coefficient) and the tracheobronchial region (Brownian motion), especially for particles less than 0.001 μm (Hinds 1999).

It should be noted, however, that particle behavior in the respiratory system depends on a number of factors, including particle size, particle density, rate of respiration, volume and flow rate of inhaled air, and whether breathing is by mouth or nose. The preceding description of respiratory deposition pertains to nose breathing. During mouth breathing, which is the result of nasal obstruction or increased physical activity, inhaled air completely bypasses the nasal passages and can significantly increase the portion of inhaled particulate penetrating to the thoracic region of the lungs (Johnson and Swift 1997).

Generally speaking, particles greater than 10 μm have limited stability in the air; however, they can be an important source of occupational exposure depending on activity and worker proximity to the source (Hinds 1999). Inhalation draws air in through the nose or mouth from the immediate region of the face, also known as the breathing zone. During

this process, most airborne particles in the breathing zone will be drawn toward the nose or mouth and inhaled, but larger particles will escape due to inertia. Inhalation studies have shown that aspiration efficiency is roughly 50% for particles of about 20 to 30 μm but decreases progressively to about 20% for particles 140 μm in size (Johnson and Swift 1997; Vincent 1995, 1999). Hand-to-nose activity can also be a significant factor in the transfer of allergens to the breathing zone, including a disproportionate number of larger particles that perhaps would not be inhaled otherwise (Lewis et al. 1999). In addition to its influence on the site of deposition, particle size may also have an even more significant impact on biological dose. A 5.0- μm droplet may contain up to 1000 times more allergens than a 0.5- μm droplet (Reed et al. 1999). Although aspiration efficiency may decrease substantially for larger particles, high-exposure activities that yield not only higher particulate concentrations but also larger particles in the breathing zone can place workers at greater risk for exposure, sensitization, and allergic symptoms.

Despite being relatively large in terms of respirable particulate, a 50- μm particle is at the threshold of recognition with the naked human eye. The dot over the letter “i” has a diameter of about 400 μm , and the average human hair is about 70 μm in diameter. It is important to understand that the vast majority of aeroallergens in the animal room environment are too small and insufficiently concentrated to be seen. It is equally important to understand that laboratory animal allergens are often potent sensitizers, and nanogram concentrations (parts per billion) may elicit symptoms among sensitized individuals (Bush et al. 1998; Gordon and Newman Taylor 1999).

Measurement of Aeroallergens

Allergen monitoring allows for the measurement of worker exposure and characterization of the work environment, both of which can be very useful when implementing control measures. Monitoring is also necessary to quantify and evaluate the relative effectiveness of control measures. Various sampling and analysis techniques are documented throughout the literature (Bush et al. 1998; Gordon et al. 1996, 1997a; Hollander et al. 1999; Ohman et al. 1994; Price and Longbottom 1988; Reed et al. 1999; Renström et al. 1997a,b). Variations in sampling methods and materials for conducting both personal and area sampling reflect national and international standards, sampler efficiency, and demonstrated performance, as well as geographic availability of equipment and personal preferences (Hinds 1999; Lippman 1999; Reed et al. 1999; Vincent 1995, 1999). The two primary techniques for allergen analysis, the radioallergosorbent test inhibition assay and the enzyme-linked immunosorbent assay, are documented and compared in the literature and discussed in detail elsewhere in this volume (Bush 2001 a,b; Gordon 2001; Gordon et al. 1997a; Hollander et al. 1999; Reed et al. 1999; Renström et al. 1999; Renström et al. 1997b; Seward 2001).

Aeroallergen monitoring entails traditional particulate sampling techniques: A calibrated sampling pump is used with one of various sampling heads available (depending on size-selective preferences) fitted with a filter (generally polytetrafluoroethylene, or Teflon, 1 μm pore size). Flow rates are generally 1 to 5 L/min for personal sampling and 20 to 60 L/min or more for area sampling. This wide range in flow rates reflects the situational need to sample much greater volumes of air from the ambient room environment to collect detectable quantities of allergen. The filters are then eluted and assayed using the radioallergosorbent test inhibition or enzyme-linked immunosorbent assay methods. Aeroallergen concentrations are typically reported in terms of nanograms (ng) or micrograms (μg) of allergens per cubic meter (m^3) of air, as opposed to particulate mass per unit volume of air (i.e., the gravimetric method). Perhaps the single largest drawback for both analysis methods is the lack of standardized antibody pools and protocols, followed by availability of a test laboratory to perform the analysis. Variability in sampling and analysis currently makes it difficult, if not scientifically invalid, to compare results obtained using different techniques.

Research findings have correlated breathing zone particle counts with mouse allergen levels during higher exposure activities, which suggests that particle counting may be useful as a surrogate monitoring method to characterize the relative effectiveness of source control measures (Kacergis et al. 1996). However, a direct relation between allergen levels and particle concentrations would be valid only if the allergenic quality of respective particles is the same. For example, breathing zone particle counts could be comparable when dumping soiled bedding and filling cages with clean litter, but the respective allergen concentrations would obviously differ. It should be noted that no correlation has been documented for ambient room particle concentrations and allergen levels, perhaps due to variation of particle sources (i.e., allergenic quality of particles).

Characterizing Exposure

Numerous studies have characterized the environmental distribution of allergens throughout a facility as well as tasks that increase allergen exposure (Eggleston et al. 1989; Hollander et al. 1998; Nieuwenhuijsen et al. 1994; Ohman et al. 1994; Turner et al. 1993). Research by Eggleston et al. (1989) demonstrated the relative high risk for allergen exposure associated with given tasks and work areas in the animal facility. Gordon and colleagues' (1994) research of rat urinary aeroallergen (RUA¹) exposure among animal technicians, cage cleaners, and other workers shows the increased risk of exposure associated with given job descriptions and tasks (Figure 1). Aeroallergen exposure during these high-risk activities can be 10 times greater than ambient concentrations. Bush and colleagues (1998) profiled job classifications (handlers, users, and unexposed) against symptoms of LAA to show the predictive nature of higher exposure tasks

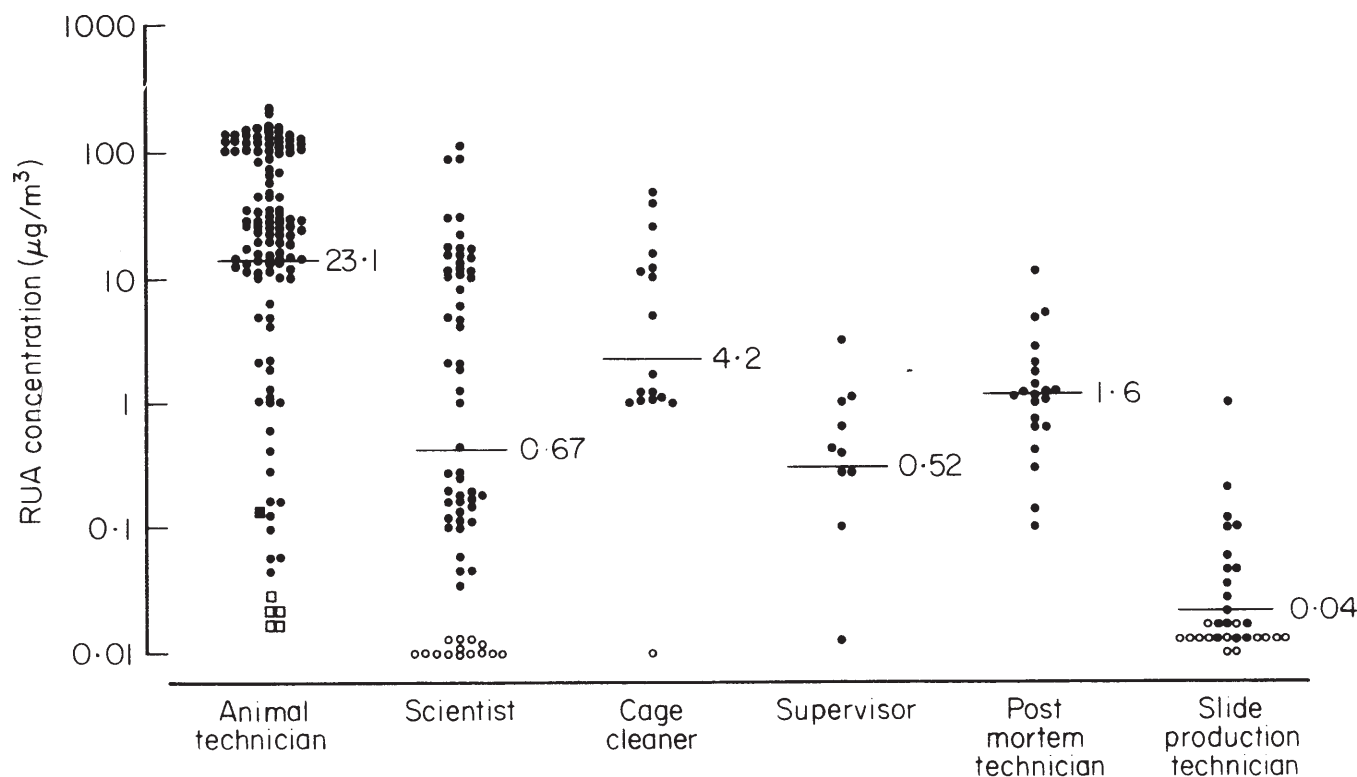


Figure 1 Rat urinary aeroallergen exposure of a pharmaceutical workforce by exposure group. $\square$, estimated exposure. $\blacksquare$, measured exposure. $\circ$, animals housed in conventional cages. $\blacksquare$, animals housed in isolators. Reprinted with permission from Gordon S, Tee RD, Nieuwenhuijsen 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.

for increased risk of sensitization and allergic symptoms. Handlers responsible for cage cleaning and animal care were at greatest risk, followed by users such as investigators, students, and technicians involved in experimental animal use. Research has also documented the fugitive migration of aeroallergens from animal facilities to adjacent rooms and buildings (Ohman et al. 1994). Findings suggest that the vectors for such movement can be both air currents (smaller particulates) and contaminated people and material (settled and adhered particulates).

Implementation of Controls

After identifying and characterizing exposure sources, it is necessary to identify appropriate control methods, evaluate them in terms of costs and benefits, and implement and monitor them, as described in Table 1. The feasibility of a given control strategy, specifically an engineered control, may well depend on the status of planned or existing facilities. Regardless, it is important to consider all options and weigh the total long-term impacts of LAA against the cost of implementing given controls. Such long-term impacts include direct and indirect costs (e.g., worker compensation, increased insurance premiums, sick time, loss of trained personnel, loss of

expertise, low morale, and the rehiring and retraining of personnel) as well as ethical and regulatory considerations. Respiratory protection may be an attractive short-term solution; however, costs over an extended period might exceed a one-time engineering modification to install local exhaust ventilation. In implementing allergen controls it is important to remember that, as previously mentioned, no minimum safe level of exposure has been identified, nanogram concentrations may elicit symptoms, and some research suggests that any exposure to animal allergens may induce disease (Bush et al. 1998).

Engineering Controls

Engineering controls encompass a variety of strategies that can significantly reduce occupational exposure if effectively implemented. They include material substitution, process substitution, isolation or enclosure, and ventilation. Engineering controls are preferred not only because of their effectiveness, but also because they do not rely on routine human implementation and intervention. This preference is reflected in multiple US federal regulations for exposure control of regulated occupational hazards: Engineering controls are *required* to the extent feasible, and only if they are not

Table 1 Recommended approach for the application of laboratory animal allergen exposure controls^a

1. Identify and characterize allergen hazards.
2. Identify allergen exposure sources.
3. Characterize allergen sources.
4. Characterize worker exposure to allergen sources.
5. Characterize air movement (for aeroallergens).
6. Identify exposure control options.
7. Select appropriate exposure control(s), based on total costs, ethics, applicable compliance requirements, and so forth.
8. Implement exposure controls.
9. Monitor control performance.
10. Maintain control systems.

^aAdapted from Burton DJ. 1997. General methods for the control of airborne hazards. In: DiNardi SR, ed. *The Occupational Environment—Its Evaluation and Control*. Fairfax VA: AIHA Press. p 829-846.

sufficient to control exposure may other methods such as PPE be used.

Engineering controls should be integrated into the animal facility design to the extent feasible. Design and equipment changes during the construction phase are costly, as are renovations and retrofitting. Often the most significant drawback of engineering control solutions is the capital investment. Design and system changes introduced after construction invariably cost more and may prove extremely difficult, if not impossible, to implement if they require an interruption or shutdown of operations.

Although engineering controls traditionally focus on the capture and removal of airborne contaminants, material and process substitutions are preferred methods to reduce exposure. Regarding ventilation control, source control is recognized as the single most effective means to control exposure and is also often the most efficient and cost-effective means. The American Society of Heating, Refrigerating and Air-Conditioning Engineers recommends the following precedence for exposure control of airborne particulate: (1) enclosure, (2) local exhaust, (3) general or dilution ventilation, and (4) PPE (ASHRAE 1997).

Material Change or Substitution

Material substitution generally involves replacement of a material harmful to health with a less hazardous or toxic material. Although substituting animals can reduce exposure, feasibility may be subject to research or production requirements. Various bedding options, however, may offer some legitimate substitutes to help reduce aeroallergen levels.

Animals. Just as allergen production varies across laboratory animal species, research has also revealed variations between sexes, strains, and ages. Allergen variation between animal strains is not well characterized; however, certain mouse strains (e.g., C57BL/6J mice) have been observed to produce higher levels of allergens than others (Reeb-Whitaker et al. 1999). Mature male animals, specifically rats, secrete greater concentrations of allergens in their urine, which has also been observed in mice and cats (Bush et al. 1998; Gordon and Newman Taylor 1999; Lorusso et al. 1986; Sakaguchi et

al. 1990; Schumacher 1987). To the extent feasible, animal substitution with a less allergenic species or strain, juvenile or younger animals, or females is recommended.

Bedding. Absorbent, noncontact pads can significantly reduce allergen exposure by containing allergens in the pads. Gordon and colleagues (1992) measured worker exposure during clean-out of open top cages containing absorbent pads, woodchips (graded shavings), and sawdust (grade 6 wood-flakes) and found that allergen levels were reduced up to 68% with the noncontact pads. Sakaguchi and coworkers (1990) observed a 57% reduction in aeroallergens by switching from woodchip to corncob bedding. Ideally, contact bedding should be highly absorptive, contaminant free, and dust free, which will help control aeroallergen generation from the cage, cost and feasibility notwithstanding. Options and considerations regarding contact and noncontact bedding are described by Novak and Lamborn (1998, 1999). Perkins and Lipman (1995) describe the relative performance of representative contact bedding types with respect to the cage microenvironment, including effect of ammonia.

Process Change or Substitution

Process change is often pursued to reduce costs through improved efficiency: equal or better performance with reduced consumption of material, manpower, utilities, or all three resources. Changing a given process may offer significant opportunities to reduce aeroallergen exposure in the animal facility and likewise reduce the direct and indirect costs associated with LAA. However, building or changing installed systems requires considerable planning and may involve a significant capital investment. Automation through the use of robotics is an example of process substitution that has been successfully implemented at some larger animal facilities to improve efficiency while reducing both operating cost and occupational hazards (e.g., allergen exposure and repetitive motion disorders). Although engineered process change is often viewed on the scale of a cage washing operation, it need not be extremely extensive or expensive to be effective (e.g., vacuuming clippers and high-efficiency particulate air [HEPA¹] filters).

Process automation. Automation, in the form of robotic cage washing and waste handling systems, has been implemented in a growing number of animal facilities. System components for robotic cage washing and waste handling typically include robots, a pneumatic waste disposal and bedding dispenser system, and an indexing tunnel washer system, as shown in Figure 2. Benefits of this system include decreased labor costs (minimum 50% reduction in manpower), increased capacity, decreased space requirements, and removal of workers from a high-level aeroallergen exposure and ergonomically hazardous environment. Implementation may require extensive interface and commissioning requirements, significant initial maintenance, equipment modification (e.g., existing cage types), and operational delays and interruptions during construction and commissioning. Thorough design and operational planning for both new construction and retrofitting is essential for successful implementation.

The prototype for the system described by Klein and colleagues (1998) was initiated in 1995 at the Karolinska Institute in Stockholm, Sweden. This prototype and a second such system are fully operational in Karolinska facilities, and a third has been planned into a new facility currently being designed (G. Lustig, Karolinska Institute, personal communication, 2000). Automated systems of this and similar designs have been commissioned at 13 animal facilities in

Sweden and three facilities in the United Kingdom. As of this writing, three robotic cage wash and vacuum bedding systems are under construction in the United States, including Stowers Institute in Kansas City, Missouri, and Baylor College of Medicine, Houston, Texas; and four other systems are planned. Return on investment (“payback”) for the prototype project at Karolinska Institute was 4 yr, and long-term savings are estimated to be approximately \$75,000 annually (Lustig 1998). The increased initial investment for the automated systems at Baylor College of Medicine has been calculated to be about \$1M (71% increase), with an estimated payback in about 4 yr, including annual savings of at least \$150,000 in labor (Faith 2000).

Cleaning methods. Allergenic proteins are water soluble, and wet methods enhance the cleanup of walls, floors, and other horizontal surfaces. To promote effective cleaning, the animal room should be constructed to facilitate good housekeeping, including rounded floor corners and walls (“coping”) and smooth, washable surfaces. It is important to avoid dry-sweeping, which will resuspend aeroallergens that have settled to the floor. Likewise, although vacuuming can be effective for cleaning floors and other surfaces, the exhaust air from individual vacuum units can cause significant resuspension of settled aeroallergen. If used, vacuum units should have HEPA filtration. A central vacuum system with filter and exhaust components external to the animal room

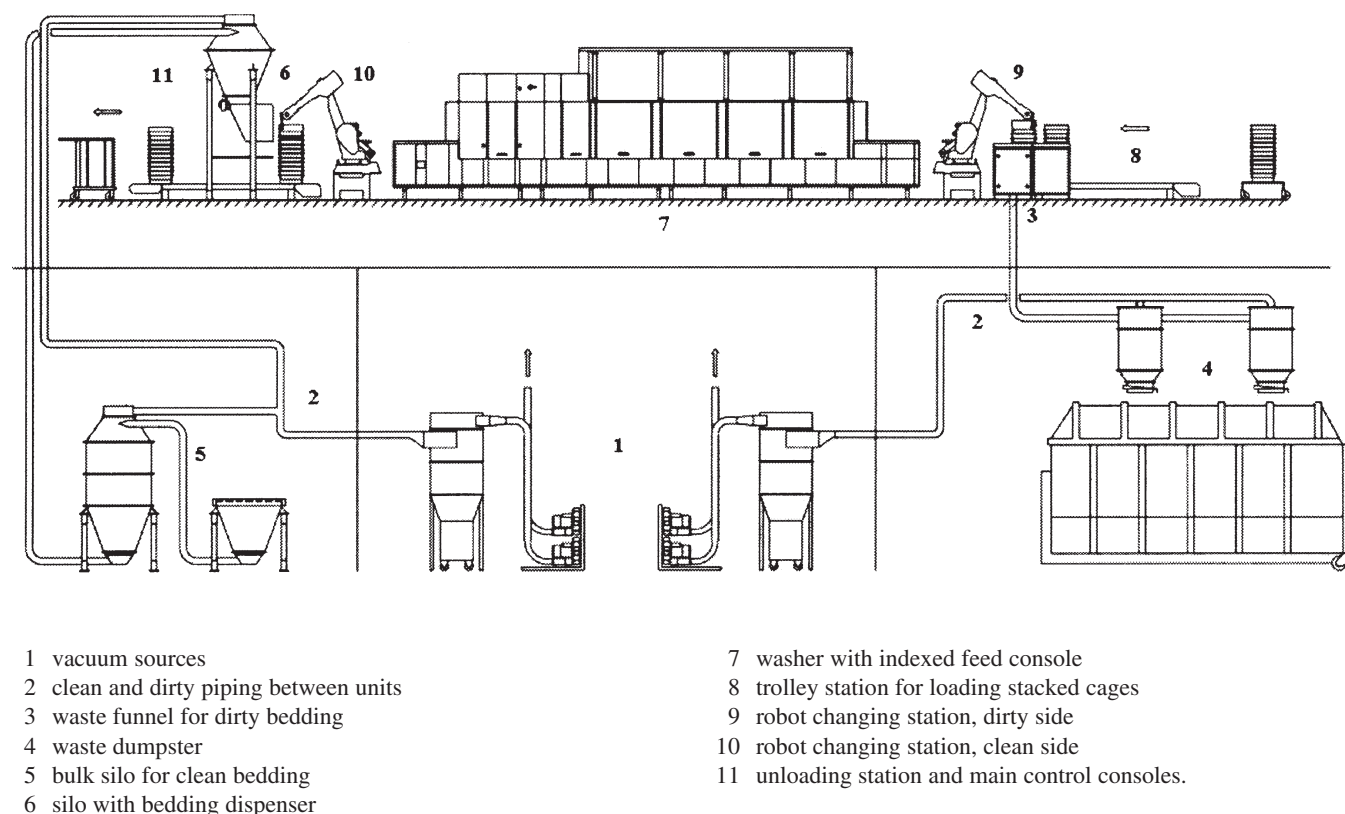


Figure 2 Robotic cage washing and waste handling system. Reprinted with permission from Gunnar Lustig of Karolinska Institute, Stockholm, Sweden, and Steve Westfall of Tradeline, Inc.

can completely exhaust captured contaminants with minimal impact on the room environment and is among the best options for effective room cleanup.

An evaluation of the exposure associated with manual dumping of dirty bedding versus vacuum removal revealed no significant difference in the normalized total dose experienced by workers (Gordon et al. 1997b). The explanation for these counterintuitive results was that although there was a 50% reduction in the intensity of allergen exposure, it took workers twice as long to remove litter with the vacuum. Efficiency at performing such a task would undoubtedly improve with experience, however, and variations in work practices and equipment performance may have influenced the results. Questions also remain regarding peak intensities and whether vacuuming disturbed the bedding similar to cage dumping.

Isolation or Enclosure

Isolation or enclosure, whereby a process is physically isolated or contained to control exposure, is a fundamental engineering control that should be attempted after substitution has been considered. All processes are basically open or closed. Conventional caging without tops is an example of an open system (within a closed system—the room). In this case, contaminants from the open cage can freely migrate into the room environment. Closing an open system through physical isolation or enclosure is a classic emission control method. The automated robotic system described above includes isolation of the process to mitigate worker exposure. Isolation may also be accomplished in terms of time, for example, performing high-exposure tasks with the fewest workers present (although this method is generally considered an administrative-type control). The benefits of isolators and ventilated caging for the care and use of animals are well documented in the literature (Dillehay et al. 1990; Huerkamp 1993; Huerkamp and Lehner 1994; Lipman 1992; Lipman et al. 1993; Walzer et al. 1989), and Lipman (1999) provides an excellent overview of commercially available static and ventilated animal caging systems. Research has also demonstrated the effectiveness of such systems for reducing ambient aeroallergen levels and worker exposure.

Filter tops. Fitting conventional, nonventilated cages with fine mesh or paper filter cage tops can significantly reduce ambient aeroallergen levels. Gordon et al. (1992) observed a 75% reduction in RUA concentrations when rats were housed in filter top cages compared with conventional open top cages, as shown in Figure 3. Under similar conditions, Reeb-Whitaker et al. (1999) observed an 84% reduction, Sakaguchi et al. (1990) reported a 90% decrease in airborne allergen, and Hollander et al. (1998) associated filter tops with a decrease as great as 94% in ambient allergen levels.

Allergen containment aside, filter tops can significantly affect cage ventilation performance and the cage micro-environment in terms of carbon dioxide and ammonia concentrations and relative humidity (Baer et al. 1997; Lipman 1992, 1999; Lipman et al. 1992; Memarzadeh 1998; Reeb et

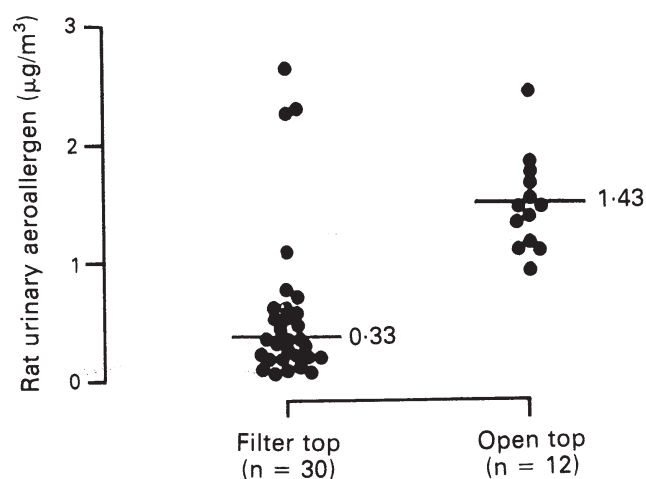


Figure 3 Comparison of cage design. Rat urinary aeroallergen concentrations measured when 30 rats were housed on woodchip bedding in filter top and open top cages, excluding those measurements made on cleaning out days for the open top cages. The geometric mean (GM) is indicated. Reprinted with permission from Gordon S, Tee RD, Lowson D, Wallace J, Newman Taylor AJ. 1992. Reduction of airborne allergenic urinary proteins from laboratory rats. *Br J Ind Med* 49:416-422.

al. 1997). These effects warrant consideration of bedding type (Perkins and Lipman 1995), room ventilation and temperature, and relative humidity as detailed in *Ventilation Design Handbook on Animal Research Facilities Using Static Microisolators* (Memarzadeh 1998).

Individually ventilated caging. Cage systems in which filtered air is supplied to and exhausted or captured from individual cages provide an effective barrier to protect animals from airborne contaminants in the room environment. This cage design has also proved effective for containing cage-borne aeroallergens, thus reducing ambient room aeroallergen levels (Clough et al. 1995). Gordon et al. (1997b) observed reductions of 58%, 97%, and at least 99.6% in ambient room mouse urinary aeroallergens when one type of ventilated caging was operated positive, neutral, and negative to ambient room pressure, respectively, compared with conventional open top caging. Similarly, Ziemann and colleagues (1992) evaluated a different individually ventilated caging (IVC¹) system and found higher ambient room RUA levels during positive pressure operation (1.5 ng/m³) compared with negative pressure (0.1 ng/m³) and background (1.0 ng/m³) (Ziemann et al. 1992). Reeb-Whitaker et al. (1999) reported a 75% reduction in ambient room aeroallergen levels when ventilated caging was operated under negative versus positive pressure configuration.

The relative effectiveness of IVC in controlling aeroallergen levels, specifically in the positive pressure mode, varies by manufacturer; however, few published data are available for the ever-growing variety of designs and systems on the market. Tu and colleagues (1997) demonstrated

performance variability (most notably cage leakage) among three commercially available IVC systems. Systems designed to scavenge positive pressure air escaping from the cage, including a canopy exhaust scavenging system, may effectively provide barrier protection for the animals and prevent contaminants, including aeroallergen, from entering the macroenvironment. However, studies to validate the performance of such systems have not been published.

Operating IVC in the negative pressure mode clearly affords greater containment of cage-borne aeroallergens. However, protection of animals from cross-contamination remains a valid question. Several studies have explored this concern, and research is ongoing. Clough et al. (1995) reported an IVC system that reduced the spread of viable airborne bacteria (reported as colony-forming units into rodent cages) by 94.3% when it was operated under negative pressure, compared with a 99.9% reduction under positive pressure. Reeb-Whitaker et al. (1999) reported a significant reduction in colony-forming units measured in the cage when operating an IVC system under negative pressure, but only when it was used in conjunction with a ventilated changing table.

Cubicles or modules. Independent of animal research trends to reduce costs, improve space efficiency, and improve disease and genetic containment, the advent of isolated cubicles and modular rooms offers opportunities to reduce worker exposure to aeroallergens and control the spread of aeroallergens throughout a facility. Properly designed cubicle animal rooms, incorporating one-way air flow and displacement ventilation configurations (discussed below), have proved effective for reducing ambient aeroallergen levels, improving room air quality, and decreasing worker exposure and symptoms (Curry et al. 1998; Lindqvist et al. 1996). Portable mass-air displacement systems with HEPA-filtered exhaust can effectively control the spread of aeroallergens to adjacent spaces while providing effective biocontainment.

Static pressure zones. The use of pressure differentials to control contamination is common in many animal facilities. Unfortunately, cascading pressure decreases designed to protect animals from airborne contaminants can enhance the spread of aeroallergens throughout a facility. Properly designed air locks and negative pressure “sinks” adjacent to animal rooms can effectively control aeroallergen migration into nonanimal areas.

Ventilation

Ventilation is a basic control method intended to improve the work environment (e.g., reduce exposure to airborne hazards) by supplying and/or exhausting air to reduce the concentration of airborne contaminants in ambient air or capture contaminants at or near their source. General, or dilution, ventilation is used to dilute room contaminants (e.g., carbon dioxide, particulate, aeroallergen) to acceptable levels while heating or cooling the work environment and maintaining humidity at desired levels. Local exhaust ventilation is used to remove contaminants at their source, thus preventing migration into the room environment and subsequent worker

exposure. In the animal room, general ventilation of the macroenvironment can have a significant impact on the animal cage microenvironment (except where individually ventilated caging is used). This consideration has been perhaps the most significant factor in guidance for ventilation design and operation in the animal room and is reflected in parameters and designs intended to mitigate thermal stratification and ensure adequate ventilation of animal cages, primarily for the benefit of the animals. Current performance-based standards emphasize efficient, cost-effective ventilation to ensure not only adequate ventilation of the animal microenvironment but also a suitable macroenvironment for workers (NRC 1996a).

General or dilution ventilation. General ventilation is used to control room temperature and humidity and to maintain airborne room contaminants at acceptable levels. Raterman (1996) describes the appropriate application of general ventilation for airborne contaminant control under conditions that include low concentrations of contaminants released into the work environment at uniform rate and adequate distances between workers and contaminant sources to allow sufficient dilution to safe levels.

General ventilation is *not* considered the appropriate primary control method for specific high-level exposure activities in the animal room; local exhaust ventilation is more effective (and more economical). However, a properly designed and maintained general ventilation system is important to ensure a healthful, comfortable environment for animals (closed or open caging) and workers by providing properly conditioned air, efficiently removing heat loads, controlling odors, and reducing ambient aeroallergen levels. With respect to aeroallergen, animal density, cage type, and the effectiveness of any local exhaust controls will have a direct impact on the ability of general ventilation to effectively maintain a satisfactory ambient environment.

Ventilation system design. Perhaps the most important consideration regarding general ventilation is that a given ventilation rate does not ensure adequate ventilation of static animal cages or the animal room (Besch 1980; Memarzadeh 1998; Morse et al. 1995; NRC 1996a). Sufficient air volume, measured in air changes per hour, must be distributed throughout the room in effective airflow patterns to mix and dilute the air to provide acceptable ventilation. This mixing of the air, termed ventilation efficiency or ventilation effectiveness, is a function of multiple factors including air volume, velocity, and temperature; ventilation configuration and diffusion patterns; ventilation system balance; room configuration and spatial dimensions; and room heat loads.

Conventional mixing ventilation systems, including high-supply-in/low-exhaust-out configurations, are intended to minimize thermal stratification within the animal room while diluting and removing air contaminants. System evaluations and computer modeling, however, indicate that specific designs and configurations may produce lower ventilation efficiencies, caused by re-entrainment and recirculation of contaminated air and dead air zones (Hughes et al. 1996; Reeb-Whitaker et al. 1999). A system similar in design, but

modeled to provide single-pass ventilation, has been validated for a relatively open kennel facility, reducing air stagnation and re-entrainment (Hughes and Reynolds 1995; Reynolds 1994; Reynolds and Hughes 1994). With respect to static, nonventilated animal cages, however, research has shown that enhanced thermal ventilation efficiency of the room utilizing high-level exhaust systems may adversely affect cage ventilation efficiency (Memarzadeh 1998). Design engineers and facility managers should consult *Ventilation Design Handbook on Animal Research Facilities Using Static Microisolators* (Memarzadeh 1998) as appropriate.

Innovative ventilation designs have been developed to improve the dilution and removal of airborne contaminants, control thermal stratification, and improve overall room air quality significantly. Three such systems are the one-way airflow system, the central soffit system, and displacement ventilation. The one-way airflow system isolates animal racks within rigid perforated polycarbonate curtains. Clean air, which is supplied by a central duct in the room, flows through holes in the curtain, moves across the animal racks, and is exhausted at the ceiling within the curtained module. This type of system has been demonstrated to be effective in several studies, in which it reduced airborne particulate levels by as much as 95% (Hunskar and Fosse 1993; Lindqvist et al. 1996; Yamauchi et al. 1989). The concept of a central soffit system, or air capture and containment system, depicted in Figure 4, is to optimize the capture of warmer contaminated air at the ceiling and reduce air recirculation (Hughes and Reynolds 1997; Hughes et al. 1996). This system has supply air diffusers and exhaust vents in a single integrated overhead unit, or soffit, located at the ceiling. Centrally supplied fresh air follows natural circulation patterns as it warms, flows upward carrying contaminants, and is extracted at the soffit by exhaust ducts. Advantages of this type of system may include increased floor space, decreased energy consumption, and prefabrication. Displacement ventilation provides cool air at low velocity near the floor, and the air rises as heat is gained from room sources (i.e., personnel, animals, and equipment). Thermal lift carries the warm, contaminated air toward the ceiling where it is exhausted by high-extraction vents. This single-pass concept has been demonstrated to improve air quality (Breum and Skotte 1992; Kristensson and Lindqvist 1993), and computer modeling suggests it may provide optimal ventilation for cubicle configurations (Curry et al. 1998).

Additional considerations during design of the ventilation system are operational flexibility and life-cycle capacity needs. For example, a system designed specifically to optimize ventilation in static microisolators with high supply and low exhaust may not be optimal if the caging were replaced with IVC. Consequently, some animal facilities have been constructed or renovated with both high and low exhaust. Centralized air handling systems capable of servicing (supply and exhausting) forced cage ventilation, such as IVC, offer many potential advantages including (1) decreased heat-load in the room from animals and equipment, (2) decreased maintenance in terms of numbers and frequency (e.g., filters,

fans), and (3) increased reliability through system redundancy (if designed as such). It is important to compensate for anticipated life-cycle degradations in initial heating, ventilating, and air conditioning specifications, including full filter load conditions. Some facilities have increased initial ventilation specifications to provide as much as 125% of calculated needs to ensure adequate performance throughout the life of the system, accommodate future ventilation needs, and minimize future impacts on animal facility operations (D. G. Green, Imperial College of Science, Technology, and Medicine, London, UK, personal communication, 1998).

Validation of ventilation performance. The *Guide for the Care and Use of Laboratory Animals* recommendation of 10 to 15 fresh air changes per hour in the animal room is an acceptable *general* guideline, but it should not be expected to be appropriate for all circumstances. The *minimum* required ventilation should be calculated based on the cooling load necessary to control the room heat load, which should then be adjusted to accommodate other factors, including odor control, particle and gas generation, and allergen control (NRC 1996a). Although underventilation holds implications for environmental conditions and the health of animals and workers, overventilation can waste energy and money. If the appropriate ventilation rate cannot be attained (e.g., fixed system, degraded capability), operational adjustments (e.g., reduced animal density) should be made to achieve adequate environmental conditions. As noted above, where static microisolators are concerned, cages with filter tops may be affected by different room airflow conditions, which should be considered when calculating room ventilation requirements.

Because ventilation efficiency is critical for control of the macroenvironment, including removal of ambient aeroallergen, and may hold significant implications for the microenvironment, it is important to validate the performance of installed or planned systems. Although in this discussion the concern is efficient removal of aeroallergens, ventilation efficiency can also have a major impact on operating costs. Traditional methods to demonstrate air flow and movement include smoke or fog, chemical tracer gas, air velocity anemometers, and other measuring techniques in a scaled environment. Computational fluid dynamics (CFD¹), an advanced three-dimensional mathematical technique for modeling fluid flow (gas or liquid), heat transfer, and diffusion, has become an accepted, effective tool for evaluating and validating animal room ventilation efficiency (Curry et al. 1998; Hughes and Reynolds 1997; Hughes et al. 1996; Memarzadeh 1998; Reynolds and Hughes 1994). CFD predictions for animal room ventilation performance have been validated with strong correlation, both qualitatively and quantitatively (Hughes and Reynolds 1995; Morse et al. 1995; Reynolds 1994). Computer simulations for more than 100 different room configurations are contained in the *Ventilation Design Handbook on Animal Research Facilities Using Static Microisolators* (Memarzadeh 1998). These simulations were created using numerical methods based on CFD and validated by more than 13 million experimental data values.

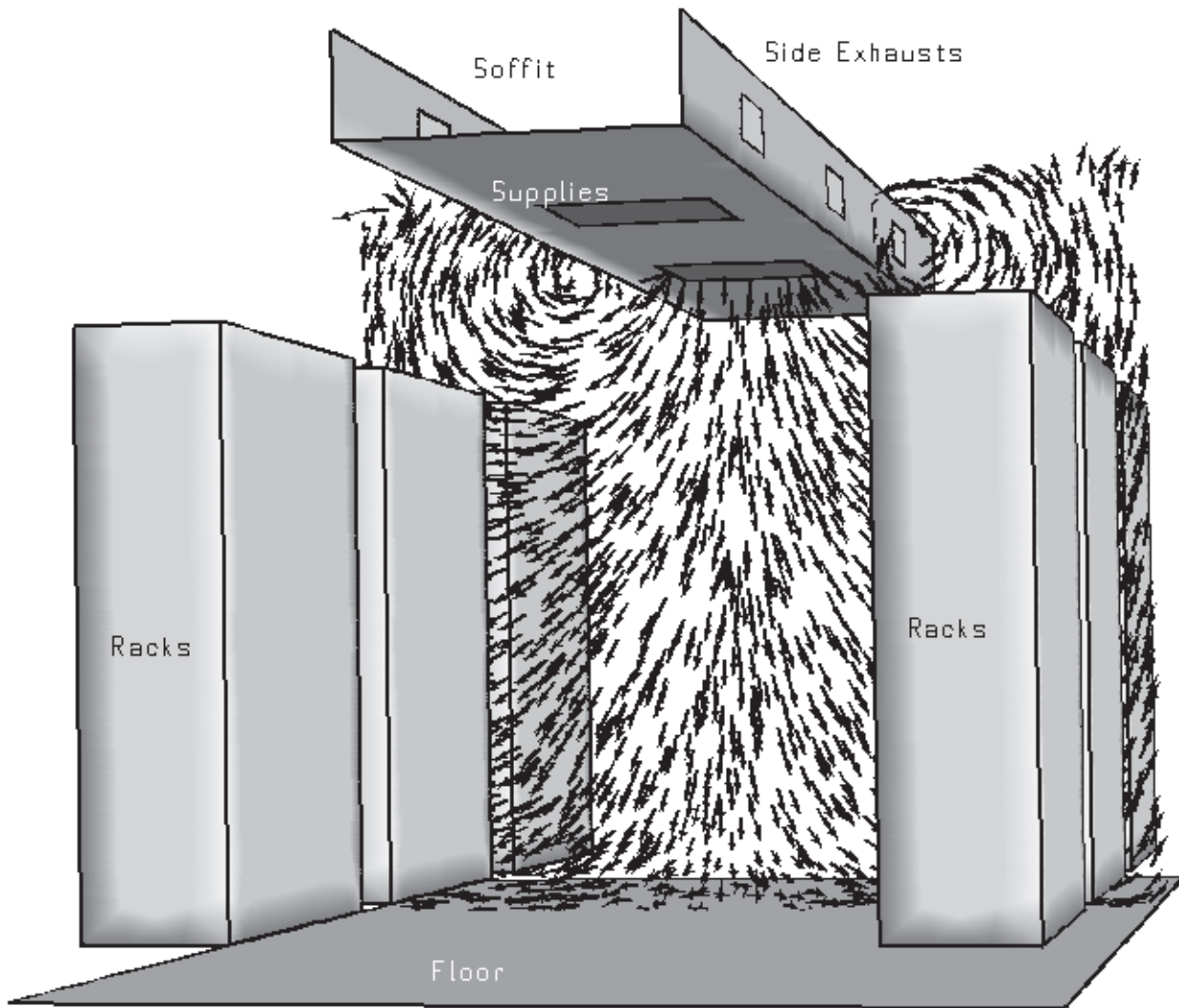


Figure 4 Computational fluid dynamic (CFD) model depicting air velocity in a small animal holding room with six racks of mice. Isometric view of velocity vectors on a plan cut through the supply diffuser of an air capture and containment system, which features two laminar flow supply diffusers at the bottom of a central soffit and six exhaust grills on the sides. Reprinted with permission from Scott Reynolds, Computer Aided Engineering Solutions, a division of Bearsch Compeau Knudson Architects and Engineers, Binghamton NY.

Using CFD can save considerable time compared with comprehensive scale model studies and can generally be performed for less than 10% of the cost (Hughes and Reynolds 1995). Useful for evaluations, renovations, and new construction, CFD modeling can also be a valuable tool to evaluate various designs and configurations in advance of construction (animal facility or scale model), optimizing the return on investment and operating costs, as well as environmental conditions in the room. In Figure 4, an isometric view of velocity vectors is depicted on a plan cut through the supply diffuser of an air capture and containment system in a small animal holding room, as modeled by CFD. CFD modeling results such as this are typically produced in color, which illustrates speed as well as direction. Similar results typically depict particle tracks and temperature contours as well.

Validation of ventilation performance can also be an important consideration where experimental research is concerned. Just as variability in sampling and analysis prohibits the direct comparison of results obtained using different techniques, ambient room environmental data obtained under different ventilation efficiencies may not be comparable. For example, differences observed in ambient aeroallergen concentrations between rooms with different configurations and/or system designs might outwardly implicate variations in cage type, equipment performance, or work practices, whereas differing ventilation efficiencies may play a significant role in the results. Likewise, because ambient concentrations of aeroallergens are generally low, an inefficient ventilation system could produce an undue concentration of contaminants, result in misleading data, and possibly mask variability in equipment performance.

Optimized room humidity. Aeroallergen studies have shown that ambient allergen levels are negatively correlated with room humidity levels—As humidity increases, aeroallergen levels decrease (Edwards et al. 1983; Jones et al. 1995). This correlation reflects the effect of adsorbed and absorbed liquid molecules on particles. Particles subject to greater relative humidity generally have an increased adhesive force, weigh more, and agglomerate with other small particles causing accelerated settling. Jones and colleagues (1995) observed a sixfold reduction in ambient aeroallergen levels as room humidity increased from 15 to 65%. However, worker comfort and fungal growth considerations suggest an optimal humidity level more in the range of 40 to 50%; and it is important to consider potential effects on animal health (e.g., the development of “ring tail” in rodents (NRC 1996b). Managers of facilities with static microisolators should consider data in the Ventilation Design Handbook on Animal Research Facilities Using Static Microisolators, which indicate that increased-supply air temperatures resulting in lower relative humidity led to lower ammonia generation in animal cages (Memarzadeh 1998).

Filtered room exhaust air. Exhaust air from animal facilities can be a relatively significant source for indirect, or secondary, exposure to aeroallergens. An additional consideration in the use of general (dilution) ventilation therefore should be filtering the air before discharge into the outdoor environment. Although many facilities supply HEPA-filtered air to the animal room, the treatment of exhaust air may be overlooked. Depending on the heating, ventilating, and air conditioning configuration, “best maintenance practices” should include nominal filtration of exhaust air (e.g., 30% efficient filters) to improve the performance and life expectancy of exhaust system components (e.g., motors, bearings). Where indirect allergen exposure is a concern, higher-efficiency filters could be used to reduce the discharge concentration of particulate and aeroallergens further. Some facilities, such as the Karolinska Institute, filter incoming supply air at a relatively reduced efficiency (e.g., 80% filters) but control the discharge from room sources by filtering exhaust air at a relatively high efficiency (e.g., 90% filters) (G. Lustig, personal communication, 1997). This action provides the dual benefit of controlling the most significant source of on-site biological hazards while also controlling aeroallergens that could expose employees outside the animal room and entrain in supply air. HEPA filtration is recommended in the *Guide for the Care and Use of Laboratory Animals* (NRC 1996) to remove airborne particulate before recycling air into the animal room, primarily to prevent the spread of disease but also, appropriately, to remove aeroallergens.

Local exhaust ventilation. Local exhaust ventilation is the classic method of contamination control and is, in the case of high-exposure tasks in the animal room, most appropriate. Local exhaust systems capture aeroallergens with low volumes of air removed at relatively high velocity precisely at the source before they migrate throughout the room environment. This method of control requires much less

airflow than general (dilution) ventilation and reduces air conditioning costs. Two basic conditions dictate the relative effectiveness of local exhaust ventilation: (1) The process must be enclosed as much as possible, and (2) the air exhaust rate must be sufficient to capture contaminants.

Ventilated work stations. Ventilated equipment is common in many research facilities to prevent cross-contamination between animals and the surrounding environment and is typically used in conjunction with isolators and IVC to protect animal health. Where aeroallergen control is also a concern, protection of both the animals and workers can be achieved through alternative equipment designs and capture schemes. Typical activities requiring ventilation control to protect animals include animal transfer (cage changing) and cage dumping or cleaning. Additional activities that put workers at risk include animal manipulation and necropsy.

Local ventilation may exhaust directly from the room or incorporate air filters to recycle the air back into the room. Ductless systems, including fume hoods, biosafety cabinets, and ventilated changing tables, are often attractive because in addition to containing biohazards, they are relatively easy to retrofit and are highly mobile. Nevertheless, these systems can add significant heat load to the room, and loss of integrity or failure of the filtration system can recycle contaminants back into the room. More than other engineering controls, ventilated equipment must be used and maintained properly to provide effective containment.

Traditional horizontal flow equipment, which blows clean air over the bench and open cage into the room, provides little or no protection for the worker. Depending on the containment desired to protect animals and workers, a conventional fume hood, a class I biosafety cabinet, or a laminar flow class II biosafety cabinet would be appropriate for animal transfer and manipulation. Of these three options, only a class II cabinet, or a similar laminar flow design, would provide protection for both animal and worker (provided the cabinet has been properly tested and maintained and used correctly, of course). The same equipment may be used for necropsy; however, ductless systems may not be appropriate where volatile liquids, such as chemical fixatives, are used.

An alternative local control used for animal procedures, including necropsy, is the ventilated laboratory bench, designed to provide either downdraft or backdraft (Skoke 1995). The downdraft system draws air through a perforated work surface at a face (capture) velocity typically 50 to 100 ft/min to capture aerosols and vapors. Designs include a square or rectangular bench surface (e.g., 750 × 500 mm) and a procedure table with exhaust perforations at the perimeter, in an island or peninsula configuration. Backdraft designs pull air across a solid work surface into perforations or slots in a plenum perpendicular to the table, with slot velocities as great as 2000 ft/min. Although the downdraft design has been demonstrated to be effective in some allergen control applications (D. G. Green, personal communication, 1998; G. Lustig, personal communication, 1997), they require even air flow across the work surface and numerous factors may compromise effectiveness, including room and ventilation

configuration, animal size, and work practices (NRC 1997). A vertical sash, constant-volume fume hood, with three accessible sides and exhausted through a rear grille and an overhead duct, has been designed for primate and small animal perfusion and should effectively control aeroallergen exposure (Klein et al. 1997). Consistent with most local exhaust ventilation systems, the effectiveness of downdraft and backdraft systems should be evaluated based on demonstrated performance before managers rely on these systems for hazard control.

Cage dumping usually requires no contamination protection and can be accomplished under the negative air environment of a class I-style cabinet fitted with a waste container or through slotted extraction vents in close proximity to the waste container to contain fugitive particulate and gases. Gordon et al. (1997b) reported a 95% reduction in RUA exposure when rats were handled in a ventilated cabinet compared with the open bench. In two studies that compared changing cages in a nonventilated environment versus within a portable ventilated table, the latter system reduced workers' allergen exposure by 57% (Kacergis et al. 1996) and 55% (Reeb-Whitaker et al. 1999). In Figure 5, various ventilation options to reduce the risk of exposure are illustrated.

Administrative Controls

Engineering controls can provide some of the most significant reductions in animal allergen exposure; however, human

elements, including work practices, the maintenance of systems, and use of equipment, can be important factors that influence exposure during the care and use of laboratory animals. This second tier of controls, commonly referred to as administrative controls, addresses human factors that affect exposure and place significant responsibility for exposure control on the worker. Administrative controls tend to focus more on reducing the duration of individual exposures; and because human intervention is required, they can be difficult to implement and maintain. Although some work practices are conditionally feasible based on resources and facility design (e.g., job rotation and zoning), certain administrative controls are always appropriate (e.g., maintenance, personal hygiene, and housekeeping) and others may be required (e.g., training and education).

Facility Zoning

Foresight during design planning and the establishment of specific areas, or zones, for the care and use of animals within a facility can help minimize allergen exposure for all personnel (Lindqvist et al. 1996). A significant factor in facility aeroallergen control concerns the proximity of animal rooms, animal holding areas, procedure rooms and laboratories, and the corresponding implications for animal and personnel movement. Although work practices and procedures intended to accommodate the movement of animals and personnel to and from contaminated areas may be dictated, compliance is often difficult to enforce. Designing the facility to minimize

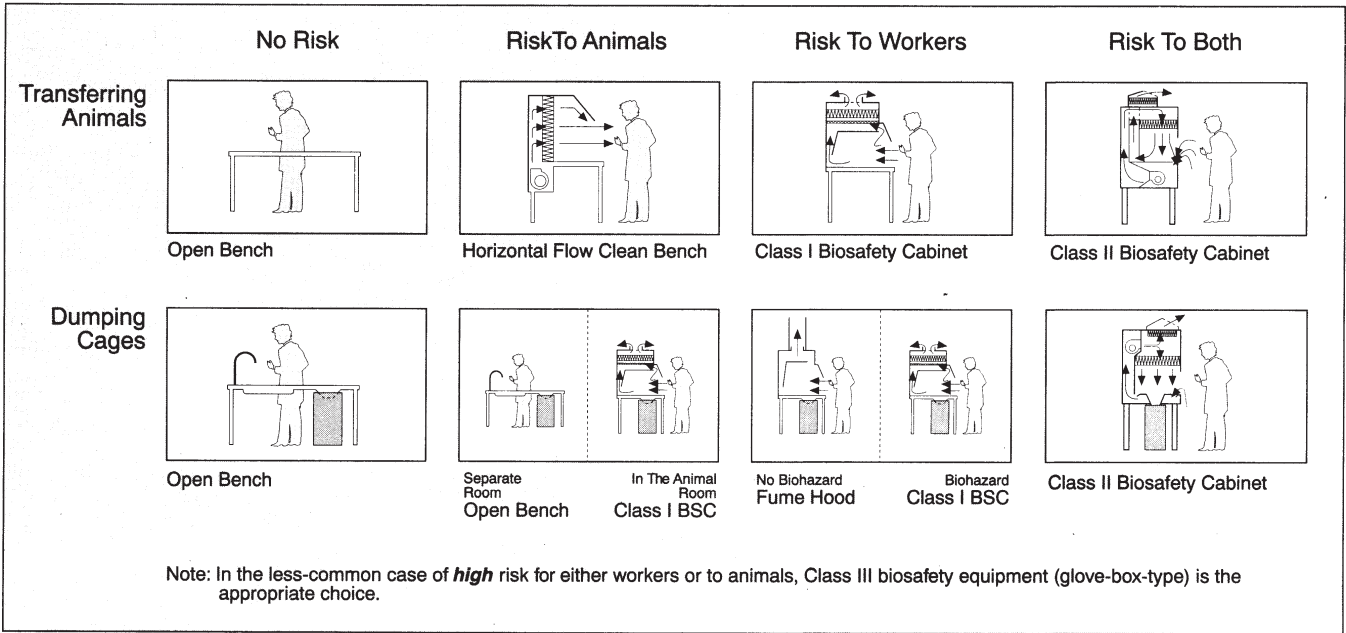


Figure 5 Suggestions for equipment selections based on type of operation and the nature of the risks. Reprinted with permission from ACUMEN. 1995. Selecting animal-transfer stations and cage dumping units for research facilities. Vol 3, no 2. Sanford ME: The Baker Company. p 3.

animal movement (e.g., procedures room in, or directly adjacent to, animal rooms) will enhance compliance and help reduce fugitive exposures. This approach embraces the philosophy that personnel who are not employed to work with animals, such as administrative personnel, should not be exposed to allergens or put at risk for developing LAA or experiencing disease symptoms. Movement of animals throughout the facility should be minimized. If transport is necessary, the animals should be placed in clean, covered, preferably ventilated carriers that contain fresh bedding. Animals should be maintained and manipulated in a negatively ventilated environment in the laboratory.

Facility zoning might include three major areas: (1) animal rooms, (2) rooms and laboratories for animal procedures, and (3) administrative and nonanimal use areas. Within such a scheme, animal use and movement would be unrestricted within the animal facility; however, animals and tissue could be taken only into the research laboratory and manipulated under containment. Personnel who leave the animal facility to enter the research laboratory or administrative areas or to leave the facility would be required to change out of contaminated clothing. Additionally, access to given areas could be restricted based on job description, thus ensuring an acceptably low risk of exposure for appropriate personnel.

Animal Density

The concentration of aeroallergens in ambient room air is a function of production and removal, and in given circumstances, relatively high animal densities can exceed the capacity of a conventional ventilation system to dilute and remove aeroallergens (Reed et al. 1999; Swanson et al. 1990). Animal density can be a major factor in ambient aeroallergen concentrations, and maintaining the number of animals in a room at an acceptable, predetermined density can be an effective means to help control aeroallergen levels. In Figure 6, the direct relation between animal density and aeroallergen levels described by Gordon et al. (1992) is shown. At the least, a maximum occupancy should be established and observed for animals and workers based on heat load calculations. However, depending on ventilation efficiency, the effect of ventilation on room heat load may not be proportional to its effect on aeroallergen levels.

Job Rotation

Total exposure is a function of the time one is exposed (duration) to a given concentration of aeroallergen and the frequency of the exposure event. Based on these factors, exposure is typically reported as a time-weighted average, which can express a short-term exposure (e.g., 15 min) including typical activities or exposure averaged over a full workshift (usually 8 or 10 hr). Any one of these factors—concentration, duration, and frequency—can reduce the time-weighted average. Reducing the concentration of exposure has been the subject of considerable discussion. Reducing

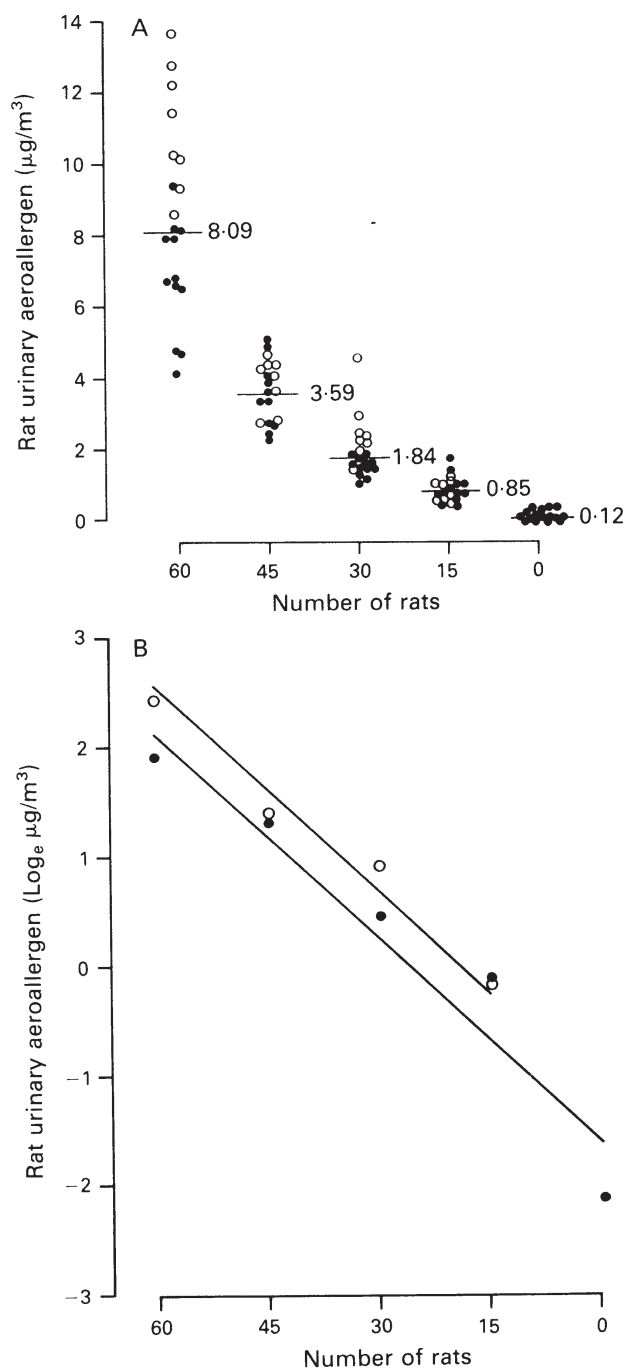


Figure 6 Effect of reducing stock density. A: Rat urinary aeroallergen concentrations measured when the stock density was reduced from 3.1 to no rats m³ (60 to no rats). The measurements made on cleaning out days are shown as open circles. The geometric mean (GM) is indicated. B: Relation between log allergen and number of rats on cleaning out (○) and non-cleaning out (●) days. Allergen concentration = $\exp(-1.2158 + 0.0621 \times N - 0.4210 \times D)$, where N = number of rats and $D = 1$ on non-cleaning out days and 0 on cleaning out days. Reprinted with permission from Gordon S, Tee RD, Lowson D, Wallace J, Newman Taylor AJ. 1992. Reduction of airborne allergenic urinary proteins from laboratory rats. *Br J Ind Med* 49:416-422.

the duration and/or frequency of exposure through job rotation, specifically for higher exposure activities, is yet another method to reduce worker exposure. The disadvantage of this approach is that the total number of employees exposed may be greater, which is inconsistent with the traditional safety philosophy to reduce exposures as much as possible for as many as possible.

Proper Use and Maintenance of Equipment

As noted by Gordon et al. (1997b), the improper use of safety equipment can compromise the effectiveness of engineering controls. Thus, ensuring the proper use and operation of ventilation and safety equipment is paramount. Ventilation systems require regular preventive maintenance (including proper maintenance and testing of HEPA filters) and performance monitoring (e.g., temperature, relative humidity, supply- and exhaust-air volumes, system balance, static pressure differentials). Automated controls and remote sensors should be monitored and calibrated periodically to ensure adequate system performance, and alarm set points should warn of degraded performance in advance of unsatisfactory environmental conditions.

Good Housekeeping

Animal rooms should be frequently cleaned using wet methods. The fate of aeroallergens in the room environment depends on the effectiveness of ventilation controls either to contain or capture aeroallergens at the source or to dilute and remove aeroallergens from the air. Left in the room environment, aeroallergens will eventually either (1) settle out onto horizontal surfaces (particulates approximately 10 µm and larger), or (2) adhere to hard surfaces (especially true of particles less than 10 µm) (Hinds 1999). These settled and adhered particles can become secondary sources of exposure, especially in the presence of poor cleaning habits or inappropriate cleaning methods. Dry sweeping, for example, can be a significant source of exposure because resuspended aeroallergens are introduced into the worker's breathing zone only feet away from the point of emission. Compliance with accreditation agencies and concerns for animal health usually promote satisfactory cleanliness within the animal facility.

Personal Hygiene

In concert with PPE, personal hygiene is an important factor in exposure control. There should be no eating, drinking, tobacco use, or application of cosmetics in the animal room. Before workers leave the animal room, in addition to removing contaminated clothing, they should always wash their hands and any exposed skin. They should also wash their hands immediately after handling animals with bare hands. Shower facilities should be available for workers to use after exiting the animal room, specifically at the end of the workday before they go home. If shower facilities are not available, workers should be encouraged to shower at the earliest

opportunity after leaving work and definitely before they go to bed, where aeroallergens in the hair could contaminate bedding and pillows and be the source for subsequent exposure.

Proper Handling of Waste and Contaminated Clothing

Consideration should be given to the storage and fate of animal waste and used bedding, as well as the handling of contaminated reusable clothing. Animal carcasses, tissue, and serum all have allergen components, and used rodent bedding is often heavily contaminated with allergenic urinary proteins (by some definitions, these could be considered biologically hazardous waste). Handling and disposal processes should be evaluated and modified as necessary to mitigate exposure. Likewise, the handling and laundering of contaminated clothing should be evaluated and modified to ensure the health and safety of personnel involved in the process. Special labeling and off-site training and education may be appropriate to deal with this potential source of exposure and liability.

Training and Education

Effective employee education and training are important components for successful management of LAA (Botham et al. 1995; Fisher et al. 1998; NRC 1997; Olfert 1993; USDDS 1998). Workers should be aware of the hazards and risks of LAA and trained in the proper use of equipment, personal hygiene, personal protection, and housekeeping techniques. Perhaps the most important elements of such training are proper work practices, specifically the use of safety equipment, intended to control exposure. Personnel should be well aware of the measures they can take to minimize their exposure to allergens and the relative risks of particular activities (Lukas and Charron 1993). LAA education efforts should convey the following information:

- hazards and risks of working with laboratory animals;
- importance of good personal hygiene (e.g., washing hands frequently and showering after work);
- proper use of PPE to protect the respiratory system, skin, and eyes;
- prescribed work practices and proper use of equipment; and
- importance of participating in medical surveillance programs, awareness of allergy symptoms, and benefits of seeking medical advice and assistance at the onset of symptoms.

Personal Protective Equipment

Consistent with recommendations from the *Guide for the Care and Use of Laboratory Animals* (NRC 1996), personnel at risk for exposure to hazardous agents or contaminated airborne particulates should be provided with suitable PPE, including respiratory protection (Richmond et al. 1993). Such PPE includes long-sleeved laboratory coats or scrubs,

hair bonnets, shoes or shoe covers, and gloves and eye protection, all of which can help reduce personal exposure and risk of sensitization as well as reduce the spread of allergens throughout the facility and into the home (NRC 1997). Gloves less prone to puncture (e.g., nitrile) along with proper animal handling and restraining techniques can reduce the risk of bites. Although traditionally considered a last resort for exposure control when engineering and administrative controls are not possible or effective, PPE, specifically protective clothing and gloves, is often appropriate regardless of other controls due to the nature of animal care and use. Wearing such clothing is not unusual in many animal facilities; however, the impetus for use is more often to protect animal health rather than human health. Considerations for human health dictate donning all protective equipment before entering the animal room and removing it when exiting. Personal clothing worn into the animal room should be kept to a minimum and stored in lockers (under positive pressure, if possible) (Lindqvist et al. 1996).

Respiratory Protection

Respiratory protective equipment (RPE¹) can help reduce personal exposure and, in the case of sensitized personnel, may be the only alternative for those working directly with animals or entering an animal facility. The two basic types of respirators include (1) supplied air systems, which provide clean air to the wearer, and (2) air purifying respirators, which clean the air as it is drawn through filter material or a canister by negative pressure caused by inhalation. Supplied air systems provide superior protection but are generally impractical in the animal room. Air-purifying respirators are available in half-face and full-face designs, and they include powered air-purifying respirators that provide filtered air with a battery-powered fan. In the United States, certified air-purifying respirators must demonstrate a minimum filter efficiency of 95% for the most penetrating aerosol size (0.3 μm), and models with 99 and 99.97% efficiency are also available. Air-purifying respirators have been tested to filter up to 98% of aeroallergens (Sakaguchi et al. 1989), which is consistent with manufacturer performance data; however, actual performance varies depending most significantly on proper fit (leakage around the face seal) (Olfert 1993). Nonetheless, respiratory protection can effectively reduce exposure to aeroallergens, and mandatory use of RPE has been an integral component of successful LAA management programs (Botham et al. 1995; Fisher et al. 1998).

The half-face air-purifying particulate respirator, shown in Figure 7, is available in various styles and is perhaps the most common type of respirator worn in the animal room. This type of respirator can significantly reduce inhalation exposure, but it leaves the eyes unprotected. Full-face air purifying respirators fitted with HEPA filters can be effective for reducing exposure; however, they are more appropriate for specific high-exposure tasks as opposed to full-shift work due to comfort (Hunnskaar and Fosse 1993; Seward 1999).

Laminar flow powered air-purifying respirator ("PAPR")

devices, marketed as the air helmet and air hat and shown in Figure 8, provide 100% HEPA-filtered air to control exposure and relieve symptoms for sensitized workers (Slovak et al. 1985). Experience has shown that initial fit and proper maintenance of the air hat are important to avert aeroallergen re-entrainment and provide consistent protection.

Workers who wear respirators for protection from aeroallergens should participate in a formal respiratory protection program with medical clearance and surveillance, respirator fit testing, and respirator use training. An important consideration for all respiratory devices is that facial hair at the sealing surface (where mask contacts skin) will compromise performance. Schaefer (2000) provides a good overview of the options and considerations regarding respiratory protection in the animal facility, including recent changes to RPE regulations and standards in the United States (Schaefer 2000).

Surgical Masks

Disposable surgical masks and single-strap "nuisance" dust masks do not provide effective respiratory protection. Surgical masks generally provide a limited aerosol barrier, intended to prevent patient exposure to viable microorganisms in large droplets from the wearer's exhaled breath. They are basically nonsealing air-purifying devices with highly variable aerosol filtration efficiency; they do not afford the fit, filter efficiency, or protection factor of approved respiratory protection (Belkin 1997; Kournikakis et al. 2000; McCullough et al. 1997; Richmond et al. 1993). Surgical masks are rated in



Figure 7 Half-face air-purifying particulate filter respirator (N95). This disposable respirator provides at least 95% filter efficiency for protection from particulate, including aeroallergens (Kimberly-Clark Corporation, Roswell, Georgia²).

²Reference to products and manufacturers in this issue of *ILAR Journal* does not constitute endorsement by the author, by ILAR, or by the National Research Council.



Figure 8 Worker wearing a belt-mounted powered air-purifying respirator ("PAPR") system to control aeroallergen exposure during cage cleaning operations (3M Corporation, St Paul, MN).

terms of percentage of bacterial filtration efficiency; however, there is no standard test method. A standardized study of 42 commercially available surgical masks revealed that bacterial filtration efficiency varied from 13 to 98% (Heinsohn et al. 1995).

Perhaps of greater significance is that surgical masks are not designed to seal to the face, and considerable leakage can occur at the perimeter of the mask. This characteristic allows aeroallergens (and other airborne biosafety hazards) to leak directly into the wearer's breathing zone. Consequently, the wearer experiences reduced breathing resistance and a more comfortable fit due to reduced temperature and humidity buildup. These performance deficiencies render surgical masks more comfortable to wear than fitted respiratory protection, and they continue to be favored in many animal environments where RPE is not mandatory. These same deficiencies are reflected in regulations that require US health care workers to wear fitted and approved RPE for protection from biohazards such as tuberculosis (USDHHS 1999). Where contamination from expired breath is a concern and

aeroallergens and biohazards may be in the worker's breathing zone, approved and properly fitted RPE provides superior protection for both animal and human health. The recent marketing of some manufacturers' mask products as both surgical masks and respirators is not an issue, provided the product has been properly approved (by the National Institute for Occupational Safety and Health in the United States) for use as a respirator.

Summary

LAA has been successfully managed using a comprehensive program including described exposure control methods and medical surveillance as well as treatment (Fisher et al. 1998; Lindqvist et al. 1996). The degree to which particular controls are appropriate and effective vary depending on a number of factors such as animal types and numbers, the physical facility, effectiveness of any existing controls, training and education, and worker motivation. The relative effectiveness of specific control measures is also a function of the exposed population (i.e., percentage of normal [no evidence of allergic disease], atopic, asymptomatic, and symptomatic individuals). Although a mathematically significant reduction in allergen exposure may reduce the incidence of sensitization, the same reduction may not be biologically significant to relieve symptoms among sensitive individuals. Because there is no clearly established threshold for allergen exposure that supports a minimum safe exposure level, and because any exposure to animal allergens may induce disease, all exposures should be reduced to the extent feasible.

All potential control measures should be evaluated in light of the total impact from laboratory animal allergy and implemented considering compliance requirements, feasibility, cost, and ethics. To be successful, controls must be protective, reliable, measurable, accepted by workers, compatible with the work process, cost effective, and financially feasible.

Additional information is provided in Appendixes A and B. Appendix A contains a summary of recommendations from the National Institute for Occupational Safety and Health to reduce exposures to animal allergens in the workplace and prevent animal-induced asthma and allergies (USDHHS 1998). Appendix B is an outline of suggested components for a comprehensive program to manage LAA.

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Appendix A

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.
- Decrease animal density (number of animals per cubic meter of room volume).
- 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 such 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.

Appendix B

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

[†]Abbreviations: ASHRAE, American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc.; HEPA, high-efficiency particulate air; LAA, laboratory animal allergy.

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) Environmental 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
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