Distribution of airborne mouse allergen in a major mouse breeding facility

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Background: *Occupational allergy to mice is a major cause of disability among workers in mouse breeding and research facilities. Efforts to prevent and treat allergy require a detailed knowledge of exposure levels to allergen.*
Objective: *This study was designed to quantitate the level of major mouse allergen (*Mus m *I) in central room air and immediate breathing zones under a variety of working conditions.*
Methods: *An Andersen sampler (Groseby Andersen, Spirotech Div., Atlanta, Ga.) was used to collect allergen in each room. A Gillian Personal sampler (Gillian Instrument Corp., West Caldwell, N.J.) collected particles in the worker breathing zone. ELISA was used to quantitate the concentration of* Mus m *I collected on the two collection devices.*
Results: *Total* Mus m *I recovered from Andersen samplers ranged from 0.2 to 1.5 ng/m³ in rooms without mice and 0.5 to 15.1 ng/m³ in rooms with mice. Allergen recovered from the zone of worker activity ranged from 1.2 to 2.7 ng/m³ in rooms without mice and from 16.6 to 563.0 ng/m³ in rooms with mice. Direct mouse contact was associated with the highest levels of exposure to* Mus m *I. Analysis revealed the bulk of allergen to be in mid-particle size ranges (3.3 to 10 μm) for mouse-containing rooms and in small particle size range (0.43 to 3.3 μm) for non-mouse–containing rooms, suggesting that small particles were carried along corridors from rooms with mice into non-mouse–containing rooms. Ventilation characteristics of rooms and mouse population density were evaluated with a "mouse loading" index (number of mice per cubic meter of ventilated air per hour). Mouse loading correlated strongly with small particles (< 3.3 μm) in ambient air.*
Conclusions: Mus m *I is widely distributed within mouse breeding facilities. Direct worker contact with mice seems to be the major factor in high level exposure. (J ALLERGY CLIN IMMUNOL 1994;94:810-17.)*

Key words: *ELISA,* Mus m *I, ventilation, particulate distribution, air sampling*

Respiratory allergy in mouse-containing laboratories and mouse breeding facilities represents a major occupational hazard for workers. Previously reported prevalence of respiratory allergy ranged from 20% to 30%, with asthma being a prominent complaint.[1-4] Airborne levels of allergen in laboratory animal facilities have been measured in several previous studies with a variety of assay and air sampling techniques; concentrations of allergen in the range of 1 to 300 ng/m³ have been measured and presumed to be of clinical significance.[5-10] Most of these studies had limited scope and failed to take into account characteristics of ventilation and the role of worker activity.

The reported particle size of airborne mammalian allergens has varied in previous studies from

Abbreviations used
PBS: Phosphate-buffered saline
PIV: Pressurized, individually ventilated

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large particles of greater than 10 μm to small particles of less than 5 μm.[6, 8, 11, 12] The rate of particle settling in undisturbed air is highly dependent on particle size. Particles of 10 μm or greater, containing the cat allergen *Fel d* I, settled almost completely in still air over several hours, but smaller particles remained airborne for much longer.[11] The relationship of particle size to the expression of clinical allergy is poorly understood. Particle sizes greater than 10 μm do not penetrate the lung with a high degree of frequency, but, presumably, will deposit in the nose and on the conjunctiva with the resulting symptoms of rhinoconjunctivitis. Particles in the range of 1 to 4 μm would be expected to deposit directly on the bronchial mucosae and potentially produce the symptoms of asthma.

We studied airborne mouse urinary allergen, *Mus m* I,[13] in a mouse breeding facility (The Jackson Laboratory, Bar Harbor, Maine). We were primarily concerned with the aerobiology of the facility under normal working conditions, so that actual worker exposure could be evaluated in various locations and with different types of activity. Variations of allergen concentration in the ambient room air and in the proximity of worker activity were compared with other characteristics, such as mouse population density and ventilation. Areas without mice were also studied. Workers who never have direct contact with mice might be exposed secondarily through mouse handlers who frequent these areas and through patterns of ventilation in corridors connecting mouse-containing and non-mouse–containing areas.

METHODS

Rooms tested

A total of 13 rooms at the Jackson Laboratory were studied: five rooms (rooms 1 to 5) did not contain mice or any other animals. (These rooms were administrative offices and a lunch room.) Rooms 1 to 4 were connected to mouse-containing rooms by corridors. Room 5 (lunch room) was in a separate building containing no mice but was frequented by workers from mouse production rooms. This room had some equilibration with outside air through open windows and frequently opened doors. Of the eight mouse-containing rooms, four (rooms 6 to 9) were used primarily for research purposes, and the remaining four (rooms 10 to 13) were production rooms used to breed mice in large quantity. Approximately one fourth of a production room's total cages are changed on each of 4 workdays, and the fifth day is spent cleaning the room. Mouse rooms are swept or vacuumed at the end of each workday and cleaned thoroughly (i.e., floors swept and mopped, walls and racks wiped) on Fridays. Clean cages with fresh pine shavings replace soiled cages, and soiled cages with soiled bedding are transferred to a washing facility.

Six mouse rooms contained conventional cage types with loose-fitting paper filter bonnets to protect animal health. Production mouse rooms 10 and 11 contained pressurized, individually ventilated (PIV) caging systems. In the PIV system each mouse cage has its own air supply and exhaust, and the air is changed at a rate of about 60 air changes per hour inside the cages. PIV caging permits an increase in the population density of mice in a room and minimizes pathogen transfer between mouse cages. The air pressure inside PIV cages is slightly higher than room pressure. Mouse room air exchange rates varied from approximately 5 to 11 air changes per hour. Mouse room air exchange rates were determined by the Technical Services Group at the Jackson Laboratory within 8 months of monitoring. Ceiling supply diffusers are in a high-aspirating configuration to maximize air mixing and minimize thermal stratification. Typically, exhaust louvers are located close to floor level along adjoining side walls between mouse cage racks.

For each room, mouse density (number of mice per cubic meter of room volume) was related to the air exchange in m^3/hr, by calculating a "mouse loading factor." This is (no. mice/m^3)/[(m^3/hr of air supplied to room)/room volume in m^3] and can be algebraically reduced to mice/m^3 of air/hr.

Recovery of *Mus m* I from wall surfaces

For each day, 1 m^2 of wall surface was wiped completely with a 2 × 2 inch gauze square wetted with distilled water. A section of the central area of four walls for each room was wiped. The gauze square was then eluted with 20 ml of 2.5% Tween-20 in phosphate-buffered saline (PBS), in a Petri dish overnight with constant agitation. The eluate was expressed from the gauze, freeze-dried, suspended with distilled water, and assayed for *Mus m* I as described below.

Andersen sampler measurements

Measurements were made as described previously[14] with a modified Andersen air sampler (Graseby Andersen, Spirotech Div., Atlanta, Ga.).[15] The sampler consists of a pre-separator stage and eight removable aluminum stages (0 through 7) containing stainless steel collector plates for a total of nine stages. A vacuum pump, which is attached to the sampler, draws room air through the sampler at a constant flow rate of 28 L/min. The pre-separator retains particles of 10 μm or greater in size. The other stages are constructed so that progressively smaller ranges of airborne particles are trapped. The last stage (stage 7) traps particles as small as 0.4 μm in aerodynamic diameter. At the end of a sampling period, the sampler is disassembled. Each removable stage is eluted with 10 ml of distilled water. The eluate is promptly frozen and freeze-dried; and each stage is resuspended in 1 ml of 2.5% Tween-20 in

TABLE I. The Jackson Laboratory room characteristics

Room No.	No. of mice*	Air changes/hr	Mouse loading†	*Mus m* I in ambient air [ng/m³ (SEM)]‡		N (no. of samples tested)
				Total	Particles <3.3 μm	
1	0	–	0	0.6 (0.3)	0.3 (0.2)	7
2	0	–	0	0.7 (0.2)	0.3 (0.2)	5
3	0	–	0	1.5 (1.2)	0.2 (0.1)	3
4	0	–	0	0.2	0.1	1
5	0	–	0	0.6 (0.4)	0.1 (0.02)	3
6	1,658	9.8	0.8	1.2 (0.5)	0.1 (0.1)	3
7	1,371	11.0	0.9	0.5 (0.1)	0.1 (0.03)	3
8	9,894	5.1	2.7	2.2 (0.8)	0.2 (0.05)	3
9	4,863	10.5	3.3	3.4 (0.9)	0.2 (0.04)	3
10	62,540	10.5	11.0	2.7	0.4	2
11	68,363	5.4	15.8	8.1 (1.2)	0.9 (0.2)	4
12	27,900	7.0	10.0	3.5 (0.8)	0.5 (0.1)	3
13	55,860	10.5	10.8	15.1 (8.6)	1.0 (0.2)	3

*Average number of mice per room for the time period that measurements were made.
†Mice per cubic meters of air per hour.
‡*Mus m* I recovered from all stages of the Andersen sampler including the pre-separator were added for each 8-hour day for the calculation of total levels. *Mus m* I recovered from the last four stages of the Andersen sampler were added for the calculation of levels less than 3.3 μm. Multiple runs in a given room were averaged. Detection limit was less than 0.02 for each stage. For the calculation of means, a value of 0.01 was assigned when the measurement fell below the detection limit.

PBS. Before reassembly, the entire sampler is carefully cleaned with detergent, rinsed with distilled water, and dried.

All Andersen sampler measurements were made during daytime working hours at a standardized monitoring location. The sampler was placed in the center of the mouse room at a height of 5 feet between mouse racks in front of a side-wall air exhaust grill.

Several separate 8-hour collections were made over a 10-day period for each room. Average room values of *Mus m* I recovery in nanograms per cubic meter were calculated with a detection limit level of greater than or equal to 0.02 ng/m³ for the assay. Levels below the detection limit were assigned a value of 0.01 ng/m³ for the purpose of averaging data and statistical analysis.

Personal sampler measurements

Personal breathing zone air was sampled with pumps worn on the belt and set at 4 L/min (Gillian Instrument Corp., West Caldwell, N.J.). Samples were taken with an inhalable particulate "cut plate" (a metal dish that sits on the top of the collecting apparatus and takes all particles larger than 10 μm) (Air Diagnostics, Inc., Naples, Maine) and 25 mm Teflon filter that collect particles larger than 10 μm and smaller than 10 μm, respectively. The collecting device was attached to an employee's lapel and worn during the workday from 8:00 AM to 4:00 PM. The filter and cut plate were eluted with constant agitation overnight in 2.5% Tween-20 in PBS. The allergen content in nanograms per cubic meter was calculated, taking into account the total amount of allergen recovered, the length of the collection period, and the flow rate of the device.

ELISA for measurement of *Mus m* I

A sandwich ELISA technique was used to determine the *Mus m* I and mouse albumin content in samples. The ELISA plates were coated (50 μl per well) with an affinity-purified monospecific anti-*Mus m* I sheep antibody (AP-SH407) (purified from polyclonal native serum) in 0.05 mol/L borate buffer with pH of 8.6; plates were then incubated overnight at 4° C and washed four times with PBS containing 0.05% Tween-20. A previously quantitated sample of *Mus m* I was used to generate a standard curve and plated along with samples in triplicate and incubated overnight at 4° C. The plates were washed four times with PBS containing 0.05% Tween-20 and biotinylated AP-SH407 (BAP-SH407) was incubated for 1 hour at room temperature. After four washes, the plates were incubated with horseradish peroxidase–conjugated streptavidin (TAGO Immunologicals, Burlingame, Calif.) for 30 minutes at room temperature and 5 minutes at 37° C. The plates were washed three times with PBS containing 0.05% Tween-20 and once with PBS and incubated with the color developing reagent, containing 0.5 mg/ml orthophenylenediamine and 0.006% hydrogen peroxide in 0.2 mol/L potassium phosphate buffer, pH 7.0, in the dark for 20 minutes at room temperature. The optical densities of the wells were read at 495 nm on a Dynatech MR 5000 microplate reader (Dynatech,

TABLE II. Recovery of *Mus m* I from wall wipes and personal samplers

Room no.	*Mus m* I on walls [ng/m² (SEM)]*	N	*Mus m* I from personal samplers [ng/m³ (SEM)]†	N (no. of samples tested)
1	4.4 (1.2)	4	2.3 (0.8)	14
2	–	–	1.2 (0.5)	4
4	–	–	2.7	2
6	22 (8)	5	17 (9)	3
7	25 (14)	5	17 (7)	6
8	86 (22)	5	143 (38)	8
11	–	–	421 (136)	10
12	–	–	90 (24)	10
13	–	–	563 (151)	10

*For each day, 1 m² was wiped on four different walls, and the result is averaged to give a value per square meter. For each room, separate sections of four walls were wiped on a number of days, and the result listed is an average *Mus m* I recovered in nanograms per square meter. Standard error of the mean is shown in parentheses.

†*Mus m* I recovered from personal filters and cut plates was added. All of the 8-hour measurements were averaged. The detection limit was 0.4 for each assay, and a value of 0.2 was assigned to samples below the detection limit. Standard error of the mean is shown in parentheses.

Chantily, Va.) equipped with a statistical data analysis package. Optical densities of the wells containing the standards were converted into a standard curve of concentrations by means of semilogarithmic regression analysis. Average total recovery of *Mus m* I from central room air (recovery from all of the Andersen sampler stages) and from personal samplers (recovery from the cut plate and filter) are given in nanograms per cubic meter.

RESULTS

General room characteristics

The ventilation rates and number of mice in the tested rooms varied widely as summarized in Table I. Mouse loading (mice/m³/hr) varied over a 20-fold range. *Mus m* I recovered from Andersen samplers ranged from 0.2 to 1.5 ng/m³ in rooms without mice and from 0.5 to 15.1 ng/m³ in rooms with mice. The production rooms with PIV cages (rooms 10 and 11) did not differ significantly in central air *Mus m* I from the production rooms (rooms 12 and 13) with conventional cages. Smaller particles recovered from the last four Andersen sampler stages (particle size, 0.43 to 3.3 μm) are also compared in Table I. These small particles did not differ in non-mouse–containing rooms compared with mouse-containing rooms used for research purposes. However, the levels of these particles were two to three times higher in mouse production rooms.

Allergen levels from the personal sampler varied from 1.2 to 2.7 ng/m³ in rooms without mice and from 17 to 563 ng/m³ in rooms with mice (Table II). Measurements made in one room, with PIV cages (room 11) were not significantly different from measurements obtained in the two rooms with conventional caging systems (rooms 12 and 13).

In one room without mice and three rooms with mice, we measured the accumulation of *Mus m* I on vertical wall surfaces. In the room without mice, an average of 4.4 ng/m² was recovered. In the three rooms with mice, the average recovery ranged from 21.5 to 85.9 ng/m².

To determine whether contamination might occur from airborne particles during the elution process, a sampler set up in a non-mouse–containing room for 8 hours without the pump running was disassembled, and the stages were eluted. No *Mus m* I was detectable.

Particle size characteristics of ambient *Mus m* I

The analysis of Andersen sampler recovery of *Mus m* I is summarized in Fig. 1 for three categories of rooms: five non-mouse–containing rooms (rooms 1 to 5), four rooms with low mouse loading (rooms 6 to 9), and four rooms with very high mouse loading (rooms 9 to 13). Among the non-mouse–containing rooms, three (rooms 1, 2, and 4) showed a pattern of increased concentration of *Mus m* I in the mid (3.3 to 10 μm) and low (0.43 to 3.3 μm) particle size categories. This suggests that ventilation over great distances preferentially conducts low particle size allergen from mouse-containing to non-mouse–containing rooms. A

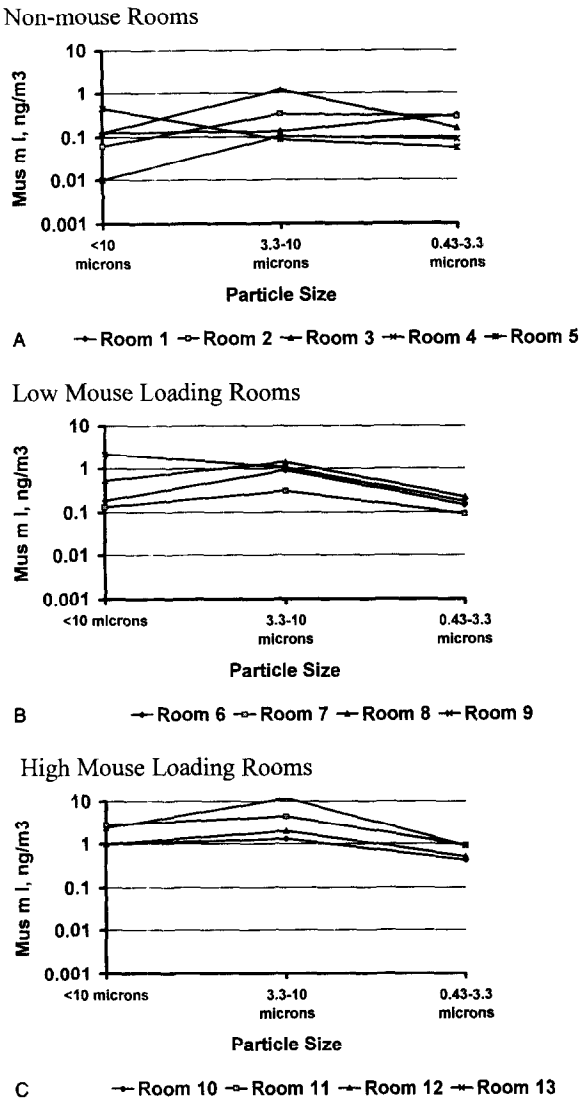

FIG. 1. Particle size distribution of airborne *Mus m* I. Airborne *Mus m* I deposited in the Andersen sampler pre-separator (>10 μm), stages 0 to 3 (3.3 to 10 μm), stages 4 to 7 (0.43 to 3.3 μm) are illustrated. Airborne levels are calculated as nanograms per cubic meter. Results from non-mouse–containing rooms (1 to 5) **(A)**, from rooms with low mouse loading (6 to 9) **(B)**, and rooms with high mouse loading (10 to 13) **(C)** are illustrated in *top, middle,* and *bottom panels,* respectively. A number of 8-hour collections in each room are averaged (see Table I). A Kruskal-Wallis analysis of variance was carried out for individual measurements made in the three categories of room; for all three particle size categories, the *p* value was less than 0.0001, indicating significant differences between the rooms.

strikingly different pattern was observed in room 5 in which large particle size allergen predominated. This room is not connected to mouse rooms by corridors, and the allergen present is presumably carried in by workers. The results for

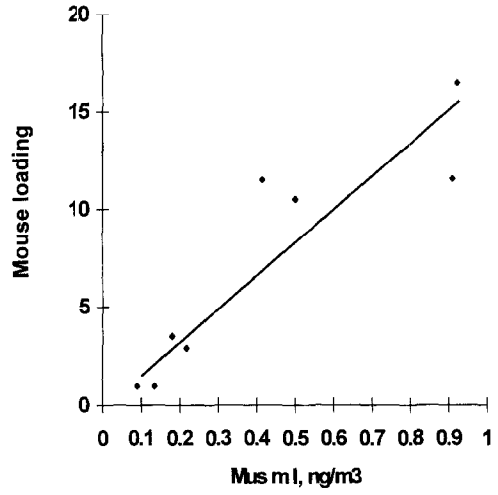

FIG. 2. Correlation of central room *Mus m* I carried on small particles (<3.3 μm) with mouse loading (number of mice per cubic meter per hour) in rooms 6 to 13. A significant correlation coefficient was obtained ($r = 0.909$, $p = 0.0017$).

the mouse rooms (Fig. 1, *middle and bottom panels*) show a fairly consistent pattern with the bulk of *Mus m* I carried on mid-range particles. The rooms with PIV cages (rooms 10 and 11) do not differ markedly in pattern from the production rooms with conventional caging (rooms 12 and 13).

Worker exposure

In general, individuals with moderate to heavy direct mouse contact (categories 2 and 3) had much higher amounts of *Mus m* I for both particle size categories. Workers involved with jobs such as room cleaning had much lower exposure levels, especially in the large particle size category.

Factors correlated with central room content of *Mus m* I

The relationship between *Mus m* I levels and mouse loading is highly significant for allergen carried on small particles 3.3 μm or less ($r = 0.909$, $p = 0.0017$) (illustrated in Fig. 2). The correlations for larger particles (>10 μm) ($r = 0.698$, $p = 0.054$) and medium-sized particles (3.3 to 10 μm) ($r = 0.528$, $p = 0.178$) were much less significant (not illustrated). Mouse loading, which is a composite of mouse density and ventilation characteristics, seems to primarily affect small particle levels of allergen in the central room air. Larger particles may tend to settle out before they reach the location of the sampler.

The levels of *Mus m* I in the worker's breathing

TABLE III. Worker exposure levels and personal sampler measurements of *Mus m* I

Worker exposure score*	Number of worker shift days averaged	Pre-separator (particles >10 μm)†	Filter (particles <10 μm)‡
0	20	1.4 (0.4)	0.7 (0.4)
1	7	86 (51)	19 (10)
2	8	322 (194)	28 (19)
3	32	187 (42)	80 (18)

Mean *Mus m* I values are given in nanograms per cubic meter. Standard error of the mean is shown in parentheses.

*0, Non-mouse room worker; *1*, working within the mouse room without direct mouse contact; usually tasks involving agitation of room dust such as room cleaning; *2*, working directly with only small numbers of mice during a work shift; usually doing procedures related to research (i.e., injections, autopsy, euthanasia, surgery); *3*, constant direct exposure to large numbers of mice during cage changing.

†Kruskal-Wallis analysis of variance. For all four categories of worker exposure: chi square = 38.10, $p \leq 0.0001$. For three categories of workers exposed to mice: chi square = 3.29, $p = 0.193$.

‡Kruskal-Wallis analysis of variance. For all four categories of worker exposure: chi square = 37.62, $p \leq 0.0001$. For three categories of workers exposed to mice: chi square = 8.80, $p = 0.0123$.

zone correlated with the levels of allergen in ambient air. For this evaluation particle sizes studied were grouped into those more than 10 μm and those less than 10 μm because the personal sampler could distinguish only those ranges of particle size. The eluate of the Andersen sampler preseparator (>10 μm particles) and the combined eluates of stages 0 through 7 (<10 μm particles) were compared with eluates from the personal sampler. The correlation was better for large particles (>10 μm) ($r = 0.553$, $p = 0.0036$) than for small particles (<10 μm) ($r = 0.411$, $p = 0.035$).

DISCUSSION

This study demonstrates that *Mus m* I is widely distributed in the air in a mouse breeding facility, even in rooms that do not contain mice. Four of the rooms without mice were connected to mouse rooms by corridors (rooms 1 to 4). Although the average *Mus m* I level in rooms with mice was higher than that in rooms without mice, some rooms without mice had levels as high or higher than those of rooms with mice. For example, room 3 (a non-mouse–containing room) had total *Mus m* I levels of 1.5 ng/m^3, higher than rooms 6 and 7, which contained mice. Smaller allergen particles (i.e., <3.3 μm) showed an even more striking overlap between rooms with and without mice (Table I). In rooms without mice but connected to mouse rooms by corridors, *Mus m* I was carried predominantly on mid-sized and small particles. It seems likely that small, slowly settling particles are carried by air through corridors from the mouse rooms, which are all under positive pressure with respect to connecting corridors. In contrast, room 5, which was in a separate building and frequented by mouse workers, had *Mus m* I levels primarily in the large (>10 μm size) (Fig. 1). We suggest that allergen in this room entered primarily as large particles on the clothing and hair of animal workers.

Within mouse rooms, the level of *Mus m* I in ambient air was correlated to mouse loading. *Mus m* I carried on particle sizes 0.4 to 3.3 μm showed a highly significant correlation to mouse loading ($r = 0.9$), but *Mus m* I carried on larger particles, greater than 3.3 μm, showed much less correlation. The clinical relevance of ambient air levels is somewhat questionable because no worker remains stationary in the central part of the room.

The primary purpose in this study was the evaluation of airborne *Mus m* I under working conditions, so that worker exposure could be directly assessed. A breathing zone personal sampler was attached to workers for an 8-hour work shift and amount of allergen was calculated in nanograms per cubic meter. Mean worker exposure was significantly higher than central room air levels, with workers directly handling mice having the highest levels. In this latter category, mean levels of up to 317 ng/m^3 were observed for particles larger than 10 μm and up to 78 ng/m^3 for particles smaller than 10 μm (Table III). This strongly suggests that there may be significant opportunity for reduction of worker exposure through local vents for caretakers changing cages.

The clinical significance of specific levels of airborne *Mus m* I, or any measured allergen, is difficult to evaluate, but levels in the nanograms per cubic meter range would likely be significant,

especially in light of the fact that low nanogram amounts of another allergen, *Fel d* I, have been shown to produce substantial drops in lung function in sensitized subjects in experimental systems.[16] Worker exposure was assessed in this study by cumulative measurements of *Mus m* I collected on a lapel sampler during the work shift. This cumulative level seems to be dependent on the amount of direct mouse contact (Table III) and probably represents an average of very large, minute-to-minute, changes in airborne levels generated by specific worker tasks. The fact that worker exposure to *Mus m* I correlated to some extent with central room levels of *Mus m* I suggests that worker activity and central room levels of allergen may be related in some way.

We know from previous studies[17] that person-to-person variation in lung sensitivity to an allergen varies more than 100-fold. Therefore the susceptibility of workers to airborne allergen would be expected to vary greatly. Tidal ventilation of workers could be estimated at about 600 L/hr for sedentary activity with higher levels during heavy work. Assuming 600 L/hr of inhaled air, average worker exposure to *Mus m* I ranged from 1.7 ng/hr, in non-mouse–containing areas, to 333.0 ng/hr in room 13. This is clearly significant, even taking into account the fact that only a percentage of the particles would be small enough to penetrate the lungs. Reliable information regarding the level of large particles of allergen that would be adequate to produce symptoms as a result of deposition on the conjunctiva and in the nose is not available.

It is therefore probable that for the most sensitive individuals, even the non-mouse–containing areas of The Jackson Laboratory would have enough airborne allergen to produce symptoms. This is confirmed by clinical observations over the last 10 years. Some office workers at The Jackson Laboratory, who have never had any direct contact with mice, unexpectedly experienced clinical symptoms when exposed to mice. It has been noted by the Jackson Laboratory Health Office that workers, who cannot tolerate working in mouse-containing areas, because of respiratory symptoms, either leave the facility or are moved to areas where their symptoms are absent or tolerable. The airborne level of allergen probably determines this segregation of workers.

Another factor of importance is the role of airborne allergen concentration in primary and ongoing sensitization. In the case of pollen allergy, sensitive individuals can be shown to have seasonal variations in the level of IgE antibody and in the degree of end-organ sensitivity.[18-20] We have no information regarding the dose of allergen that is necessary to sensitize an individual and how it compares to the dose that subsequently produces symptoms. This question could only be answered by monitoring large numbers of workers who are exposed for the first time to various levels of allergen and by evaluating sensitization and clinical symptoms over time. A prospective study at The Jackson Laboratory is underway to further define some of these issues.

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