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Noise Produced by Vacuuming Exceeds the Hearing Thresholds of C57Bl/6 and CD1 Mice

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Daily vacuuming of floors and flat-shelf racks is a standard procedure in our rodent housing rooms. To determine whether the noise produced by this activity is a potential stressor to animals used for transgenic and knockout mouse production, we measured the sound levels in our genetically engineered mouse facility under ambient conditions and at the in-cage and room levels during vacuuming. Spectral analysis showed that vacuuming produces a multitonal, low-frequency noise that is not attenuated by microisolation caging with bedding material. Comparison of cage-level spectral analysis results with age-specific audiograms of C57Bl/6 and CD1 mice showed that vacuuming produces frequencies audible to C57Bl/6 mice at 3 and 6 mo of age and to CD1 mice at 1 mo of age. These findings suggest that vacuuming in animal rooms could be a source of stress to animals with these genetic backgrounds.

Abbreviations: ABR, auditory brainstem response; CAP, compound action potential; dB, decibel; GEMF, genetically engineered mouse facility; Hz, hertz; kHz, kilohertz; SPL, sound pressure level

Audiogenic stress can be defined as a stress response invoked by a noise stimulus that the listener perceives as noxious. The neuroendocrine cascade initiated by unwanted sound results in diverse extra-auditory effects,[1] and these effects may vary with the intensity, frequency, bandwidth, and duration of the sound;[6,10,20,44] between species;[3,22] and among individuals.[4,39] Much of the work on audiogenic stress has been conducted in rodent models, and the results of these studies indicate a variety of adverse effects, including teratogenesis,[30,48] embryotoxicity,[23,32,33,52] resorption,[48,52] abortion,[7] and intrauterine growth retardation[17] in mice. Furthermore, acute, unpredictable noise decreases splenic lymphocyte counts and increases plasma corticosterone levels in adult mice,[25] results in reduced weight gain in weanling mice,[21] and alters estrus cycles in adult rats.[15] In addition, rat pups exposed to low-frequency, high-amplitude noise exhibit decreased bone length and mass.[12] Because of the potential detrimental effects of noise, both the *Guide for the Care and Use of Laboratory Animals*[31] and the Code of Practice for the Housing of Animals in Designated Breeding and Supplying Establishments (Scientific Procedures Act)[9] advocate the elimination of unnecessary noise in animal housing areas.

Studies of audiogenic stress in laboratory rodents necessarily occur in laboratory conditions, often with noise stimuli that exceed 90 dB and are chronic or cyclical in nature.[8,34,36] However, even moderate, short-term noise can induce changes in physiology and behavior. For example, exposure to an 80-dB noise for a few minutes caused behavioral sensitization in rats,[11] and rats exposed to 90 dB of white noise for 5 min daily exhibited increased grooming and rearing behaviors and had morphologic changes in their intestinal epithelium. [2] Furthermore, the bandwidth, amplitude, and duration of the noise stimulus in the latter study are similar to those generated during routine workdays in animal facilities.[29,37,42] The inference can thus be made that some animal husbandry procedures produce noise levels sufficient to alter the behavior and physiology of experimental animals, and it is therefore important to identify and ameliorate those noises wherever possible.

Vacuuming of floors and flat-shelf racks is an integral part of animal husbandry standard operating procedures in our vivarium, and we hypothesized that the noise associated with vacuuming is a potential stressor to mice housed in our genetically engineered mouse facility (GEMF). We therefore measured sound levels at the room level (outside of the mouse cage) and at the cage level (with the microphone placed inside the cage) during vacuuming. We then compared curves from the spectral analysis of our sound measurements with the compound action potential (CAP) audiograms of young C57Bl/6 and CD1 mice, to determine whether these mice are capable of hearing the sounds associated with vacuuming. Both lines are known to exhibit early-onset hearing loss, and they are used extensively in our GEMF for transgenic and knockout mouse production.

Materials and Methods

The animal facilities of The University of Texas MD Anderson Cancer Center and The Jean Roche Institute at the Université de la Méditerranée are fully accredited by the Association for Assessment and Accreditation for Laboratory Animal Care International. All animals are cared for in accordance with standards set forth in the *Guide for the Care and Use of Laboratory Animals*.[31]

Facility. Sound measurements were performed in the GEMF, which consists of 2 rooms, A and B, connected by a solid-core door. Room B also is connected to a common hallway by a solid-core door. The 2 rooms are similar in dimensions, and each contains 3 flat-shelf racks and a class II, type A biological safety cabinet. Animals are housed in polycarbonate microisolation cages with contact bedding (Bed-o'cobs, The Andersons, Maumee, OH); surgical drapes are placed between the cages and shelves for thermal insulation and to reduce vibration.

Equipment. The vacuum cleaner used in our facility contains a high-efficiency particulate air filter (model UZ878, Nilfisk-Advance America, Malvern, PA). Sounds were measured and analyzed with a real-time sound level analyzer (model CEL-490.

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Table 1. Comparison of CAP audiograms and SPLs under ambient and test conditions

					CAP threshold (dB)/SD			
					CD1 (n = 20 per group)		C57Bl/6 (n = 7 per group)	
Frequency (Hz)	Aa/Ba	Av/Bv	AvB/BvA	Avcage/Bvcage	1 mo	3 mo	3 mo	6 mo
1000	55.8/52.1	79.2/77.2	67.7/62.9	79.9/77.7	103/0	103/0	103/0	103/0
2000	53.6/50.7	80.8/80.3	67.5/63.0	77.5/82.1	82/0	95/0	95/0	99/5
4000	48.4/46.2	78.1/77.4	59.9/62.4	75.1/83.3	82/0	105/0	76/3	80/3
8000	42.4/40/4	72.4/65.6	51.7/52.5	66.2/73.2	81/0	95/0	55/3	60/2
16000	nm	nm	nm	nm	64/0	92/0	50/3	60/2
32000	nm	nm	nm	nm	71/0	92/0	92/0	92/2

Aa, ambient noise, Room A; Ba, ambient noise, Room B; Av, room-level noise during same-room vacuuming, Room A; Bv, room-level noise during same-room vacuuming, Room B; AvB, room-level noise in room A during vacuuming of Room B; BvA; room-level noise in room B during vacuuming of Room A; Avcage, cage-level noise during vacuuming of Room A; Bvcage, cage-level noise during vacuuming of Room B; nm, not monitored; SD, standard deviation.

C2, Casella USA, Amherst, NH). The analyzer is equipped with a nondetachable combined electret microphone and preamplifier (model CEL-485, Casella) and an octave-band analyzer. This device can capture sound-pressure levels (SPLs) and frequency levels in real time. SPLs were measured in 20-µPa units and reported in decibels (A scale). Spectral data were analyzed by use of specialized computer software (Cel Soundtrack DB23 software, version 1.04, Casella USA, Amherst, NH).

Sound measurements and spectral analysis. SPLs and frequencies were measured in each of the 2 rooms for 4 conditions: ambient (no human activity in the rooms), at room and cage levels during vacuuming in the same room, and at room level during vacuuming in the adjoining room. Measurements were conducted with connecting and hallway doors closed. Biological safety cabinets were turned off, and no husbandry or research activities were performed during sound measurements. Ambient noise was measured in each room to determine the baseline noise levels. The vacuum then was switched on, and SPLs were measured while the floors and shelves were vacuumed in room A with the microphone held at a distance of 0.3 to 1.2 m from the vacuum. To measure sound at the cage level, an unoccupied microisolation cage with bedding material was placed on a rack to simulate standard housing conditions, and the analyzer was placed in the cage. The size of the analyzer prevented replacement of the wire bar lid; a small (0.5 cm) gap remained between the edges of the cage and cage top. SPLs were then measured from within the cage while the floor and shelf were vacuumed. Finally, noise levels in room A were measured during vacuuming in the adjoining room. Measurements then were repeated for room B. SPLs were measured for the duration of vacuuming (approximately 10 to 15 min) The range of frequencies measured was 16 to 8000 Hz. Noise measurements and spectral analysis were performed by personnel from MD Anderson's Department of Environmental Health and Safety.

Compound action potential (CAP) audiograms. CAP threshold data reported here for C57Bl/6 and CD1 mice is based on prior work by one author (CMR) and has been described previously.[41] The electrophysiologic system used in this study was similar to that described by Cazals and Huang.[5] Study groups are described in Table 1. Briefly, electrodes were implanted under stereotactic guidance near the auditory nerves of male CD1 and C57Bl/6 mice (Charles River Laboratories, France) according to methods described by Giraudet and colleagues.[16] After verification of an evoked potential in response to a broadband click, the electrode was fixed to the skull hole with acrylic cement (Dentalon Plus, Heraeus Kulzer, Weherheim, Germany).

Animals were placed in a double-walled cabin (Amplifon, Milan, Italy), and cochlear sensitivity was assessed by measuring the threshold of the auditory nerve CAP at frequencies of 0.5, 2, 4, 8, 6, and 32 kHz with tone pips (rise and fall, 2 ms; rate, 30 pips/s) delivered by means of an earphone maintained on the animal's head by the fixed connector, at a distance of 0.5 cm from the ipsilateral ear pinna. SPLs were measured in decibels with a condenser microphone (model 4191, Bruel and Kjaer, Naerum, Denmark) placed at the external auditory meatus; for each frequency, we recorded 200 auditory responses to obtain an average SPL for comparison.

Results

Spectral analysis. Results of the spectral analysis of ambient noise and noise during vacuuming are shown in Figure 1. Peak SPLs occurred at frequencies of 1000 to 4000 Hz, overlapping the lowest limits of the hearing range of *Mus musculus* and well below the reported range of greatest sensitivity for this species. Ambient noise levels in both rooms peaked between 50 and 60 dB and were slightly higher in room A, but by no more than 3.7 dB. Vacuuming increased same-room noise levels by more than 23 dB, to levels ranging from 77.2 to 80.3 dB. Microisolation caging provided only slight protection from the vacuuming noise in room A; and in room B, the noise levels at the cage level exceeded those at room level at frequencies greater than 500 Hz. Measurements made in adjoining rooms showed that closing the door between the 2 rooms reduced peak noise levels to the 60- to 70-dB range, or approximately midway between ambient and room levels.

Comparison of spectral analysis with audiograms of C57Bl/6 and CD1 mice. Hearing thresholds as determined by CAP audiograms and SPLs under ambient and test conditions are shown in Table 1. Ambient noise levels were below the hearing thresholds of C57Bl/6 and CD1 mice in all age groups studied. Figures 2 and 3 illustrate the overlap between cage-level noise produced during vacuuming and the CAP thresholds. At frequencies between 4000 and 8000 Hz, same-room vacuuming generated cage-level SPLs within the hearing range of 3- and 6-mo-old C57Bl/6 mice and 1-mo-old CD1 mice.

Discussion

We found that vacuuming produces cage-level noise that exceeds ambient levels by more than 23 dB, at frequencies and amplitudes that fall within the lower end of the hearing range of *Mus musculus.* The lower limit of hearing in *Mus musculus* is 1000 to 2300 Hz and extends as high as 80,000 to 100,000 Hz,[13,14,24,28,43] with peak sensitivity at about 14,000 to 16,000 Hz.[13,43] The peak SPLs produced by vacuuming clustered within the 1000 to 4000 Hz range, and frequencies between 2000 and 8000 Hz were

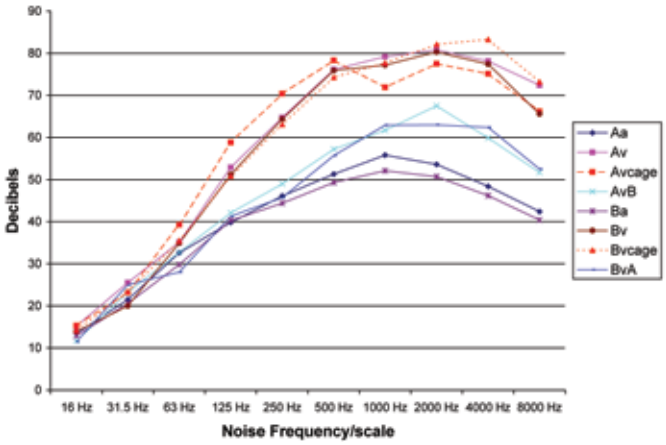

Figure 1. Comparison of noise curves measured under ambient conditions and during vacuuming. This figure shows the spectral analysis of room noise under ambient conditions and during vacuuming in Rooms A and B. Aa, ambient noise in Room A; Ba, ambient noise in Room B; Av, room-level noise during same-room vacuuming of Room A; Bv, room-level noise during same-room vacuuming of Room B; AvB, room-level noise in Room A during vacuuming of Room B; BvA; room-level noise in room B during vacuuming of Room A; Avcage, cage-level noise during vacuuming of Room A; Bvcage, cage-level noise during vacuuming of Room B.

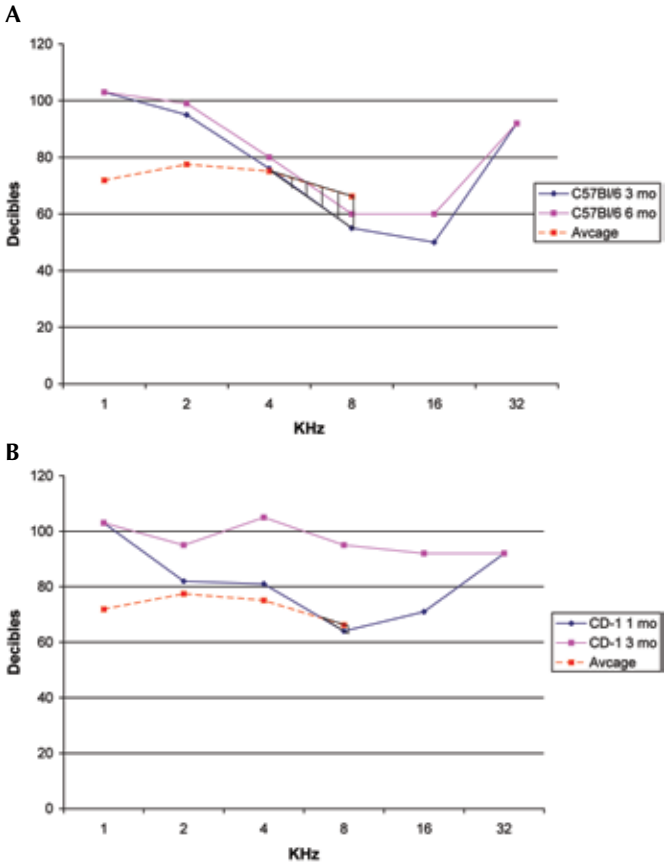

Figure 2. Comparison of cage-level noise during vacuuming with CAP audiograms of C57Bl/6 (A) and CD1 (B) mice: Room A. The hatched area represents the range of audible noise produced during vacuuming. Cage-level noise exceeds the hearing thresholds of both age groups of C57Bl/6 mice. Avcage, cage-level noise during vacuuming of Room A.

generated at amplitudes high enough to be detected by feral house mice under all conditions in the present study. Although we did not measure frequencies greater than 8000 Hz in these rooms, sound analysis performed in a third room outside the facility detected patterns similar to those reported here: SPLs measured at the room and cage levels in the third room tapered rapidly at frequencies higher than 5000 Hz, an effect that likely was due to the limitations of our microphone. SPLs approached ambient levels at 20,000 Hz, the maximum frequency detectable by our equipment (data not shown).

Our study has several important limitations. As mentioned earlier, our equipment was unable to measure sounds in the ultrasonic range. In addition, because of the tapering effect mentioned earlier, we did not measure frequencies higher than 8000 Hz. Therefore, we cannot draw conclusions about the total noise content of the rooms. Another limitation was the use of A scale for sound measurement, which approximates the sensitivity of the human, rather than the rodent, ear. Because of the restrictions on frequency detection and acoustic measurement, our findings are of limited applicability to mice with a broader range of hearing. Finally, intra-strain and stock variations in hearing ability may exist between mice acquired from different vendors. The mice used for collection of CAP audiometric data were from a different production facility than those we use in our GEMF. Therefore, the perception of vacuuming noise by our mouse population may be better, or worse, than that of the mice in the CAP study.

We chose to compare the results of vacuuming noise with audiograms from C57Bl/6 and CD1 mice because these lines are commonly used in our GEMF for rederivations and for production of transgenic and targeted mutant mice. Both lines exhibit sensorineural hearing loss of genetic origin, beginning with loss at higher frequencies and progressing to loss at lower frequencies with age.[27,38,41,45,49,51] Hearing loss progresses more rapidly and is more severe in CD1 mice than C57Bl/6 animals. Specifically, 1-mo-old CD1 mice can detect frequencies of 4000 to 6000 Hz at SPLs between 60 and 80 dB; by 3 mo of age, the mice are insensitive to frequencies higher than 4000 Hz unless SPLs approach or exceed 90 dB.[41] By contrast, the C57Bl/6 mice in the study we describe remained sensitive to frequencies of 4000 to 6000 Hz until 6 mo of age.

Notably, the auditory thresholds reported here are somewhat higher than those reported by some other researchers in mice of comparable age. For example, Willott and Turner[50] reported that 3-mo-old C57Bl/6 mice are sensitive to frequencies of 4000 to 24000 Hz at amplitudes of 20 to 30 dB and, at 6 mo, can detect frequencies of 4000 to 16000 Hz at amplitudes of 30 to 50 dB. We do not know why the auditory thresholds of the C57Bl/6 mice we studied were higher than those reported elsewhere, although substrain variations and differences in experimental methodologies may play a role.

When we compared the curves of cage-level noise from rooms A and B with the CAP thresholds we obtained, we found that SPLs produced at 4000 to 8000 Hz were high enough to fall within the hearing range of C57Bl/6 mice at 3 mo and 6 mo of age and of CD1 mice at 1 mo of age. The area of overlap was much greater for C57Bl/6 mice, reflecting the less-pronounced hearing loss in this strain. In room B, the vacuuming noise exceeded the hearing threshold of CD1 mice by only a narrow margin, and in room A, it was barely audible at only 1 of the frequencies measured. Although the degree of overlap between the vacuuming noise and the hearing ability of C57Bl/6 and CD1 mice may be small, mouse audiograms are based on mean responses and represent a range of sensitivities. Whereas some of the mice tested will have higher hearing thresholds than those indicated on an audiogram, others will have lower thresholds. CD1 mice, in particular, can exhibit a high degree of interindi-

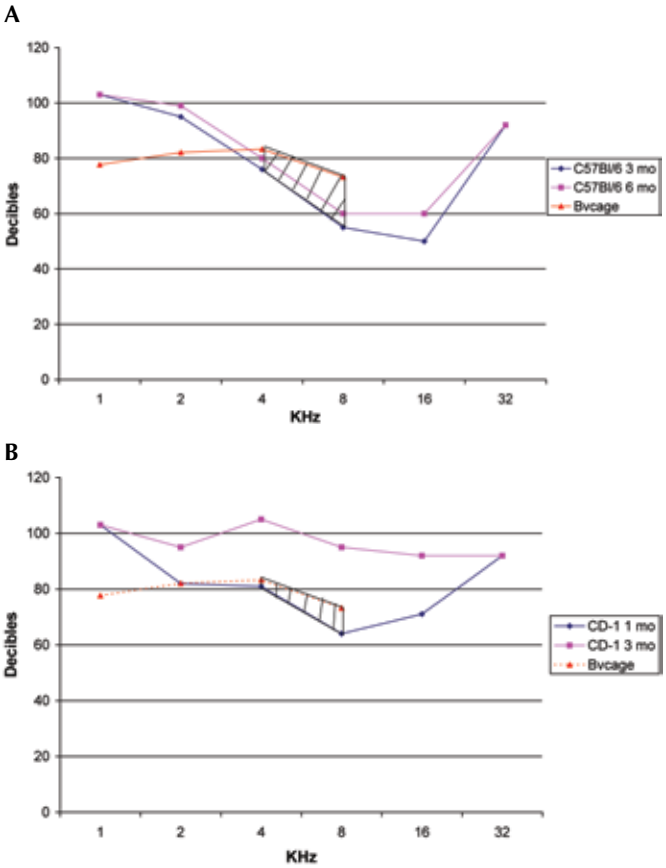

Figure 3. Comparison of cage-level noise during vacuuming with CAP audiograms of C57Bl/6 (A) and CD1 (B) mice: Room B. The hatched area represents the range of audible noise produced during vacuuming. Bvcage, cage-level noise during vacuuming of Room B.

vidual variation in hearing. Although the standard deviation in the CD1 test groups we used for comparison was never greater than 5 dB,[40] others reported a standard deviation of 23.7 dB in 6-mo-old CD1 mice at 8000 Hz compared with a standard deviation of 6.2 dB in C57Bl/6 mice of comparable age; this pattern of broad standard deviations persisted into higher frequencies and at all age groups tested.[45] In addition, CD1 mice show 2 distinct hearing profiles, with some test subjects exhibiting a uniform loss of sensitivity across all frequencies measured, while others retain normal auditory brainstem response thresholds at frequencies below 12,000 Hz.[27] This variability probably reflects the heterogeneous genetic background of CD1 mice;[51] unlike C57BL/6 mice, which are inbred to reduce genetic variation, CD1 mice are maintained as an outbred stock.

We wanted to measure the noise levels produced by vacuuming to determine whether this activity was audible and therefore possibly stressful to our mouse population. We have shown that, even within the limitations of our sound measuring equipment, vacuuming produces noise that falls within the hearing range of 2 mouse lines genetically predisposed to early-onset hearing loss. Determination of the audibility of a stimulus, however, does not predict behavioral or physiologic consequences.[18,35] CAPs and auditory brainstem responses, methods used to evaluate absolute hearing thresholds in animals, measure electrophysiologic responses to a range of pure tones. Divergence between these auditory thresholds and behavioral or physiologic responses are described in the literature. Behavioral sensitivity to sound declines less rapidly than auditory nerve responses,[19] and mice with hearing losses at higher frequencies show exaggerated startle responses at lower frequencies.[49] Other researchers have found associations between intermittent noise exposures below the optimum frequency range for mice (similar to those measured in our study) and physiological responses. In Swiss mice, intermittent pure-tone frequencies between 7000 and 10,000 Hz at 85 to 95 dB and lasting only 28 to 39 s increase plasma corticosterone levels,[47] whereas a 4000-Hz signal applied for 6 min each hour at a similar intensity is sufficient to decrease fertilization and implantation rates and reduce embryo sizes in naturally mated females.[52] Pregnant CF-1 mice exposed to random periods of narrow-band, 103-dB noise centered at 3000 Hz and lasting a maximum of 8 min suffered decreased pregnancy rates.[33] These studies suggest that even brief exposure to noise that falls outside the optimum hearing range still may induce a stress response in mice. Without a clear understanding of the relationship between auditory and behavioral or physiologic thresholds, we cannot assume that that there is a 'safe' level of noise exposure. Given that alternatives to vacuum cleaning are available and considering the known effects of audiogenic stress on implantation, embryogenesis, and postnatal development in rodents, we recommend that facilities using C57Bl/6 and CD1 mice for the production of genetically engineered mice re-evaluate the risks and benefits of vacuum cleaning.

Many questions remain about the effects of noise on commonly used stocks and strains of mice, and even less is known about its effects on genetically engineered animals. However, evidence suggests that altering the environment in other ways can produce phenotypic change. Housing in an enriched environment with running wheels reduced cerebral β-amyloid levels and plaque formation in a mouse model of Alzheimer disease;[26] and in R6/1 mice, a model of Huntington's disease, exposure to a variety of novel toys rescued protein deficits associated with the *HD* transgene. R6/1 mice with environmental enrichment also exhibited improved rotarod performance and maintenance of body weight compared to controls.[46] Noise, like enrichment, is an environmental variable, and it too may alter the behavioral and physiologic phenotypes of genetically engineered mice. Laboratory animal care staff and researchers working with transgenic and targeted mutant mice should be aware of the potential confounding effects of noise.

In conclusion, we have shown that routine vacuuming produces cage-level noise that exceeds ambient levels by at least 23 dB and is audible to C57Bl/6 mice at 3 and 6 mo of age and CD1 mice at 1 mo of age. Vacuuming therefore may be a source of audiogenic stress in these mouse lines. The specific biological and behavioral consequences of exposure to the low-frequency, recurrent, and unpredictable noise produced by vacuuming are unknown and deserve further study.

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