Evaluation of individually ventilated cage systems for laboratory rodents: cage environment and animal health aspects

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Summary

The use of individually ventilated cage (IVC) systems has become an attractive housing regime of laboratory rodents. The benefits of IVC systems are, reportedly, a high degree of containment combined with relative ease of handling, and a high degree of protection from allergenes.

In the present study we tested whether two IVC systems (BioZone VentiRack, IVC1 and Techniplast SealSafe, IVC2S), in which we held mature male NMRI mice, were constructed to maintain a constant differential pressure, positive or negative, during a prolonged period of time. We also measured ammonia (NH_3) concentrations after about 2 weeks of use, and CO_2 build-up during a 60 min simulated power failure situation. In addition, animal weight development and bite-wound frequency were recorded (Renström *et al.* 2000).

From the present study it is concluded that the IVC1 air handling system provides a more uniform and balanced differential pressure than the IVC2S. Both systems effectively scavenge NH_3 when bedding material is not soaked by urine. Although the IVCs are dependent on the continual function of the fans to work properly, it seems unlikely that CO_2 concentrations increase to hazardous levels, as a result of a one hour power failure, with the type of cages used in this study. Differences in weight development and bite-wound occurrence were noted between the two IVC systems. Causes for these differences could not be established and need more investigation.

Keywords Individual; ventilation; cage; carbon dioxide; ammonia; differential pressure; bite wounds; growth; mice

Rats and mice are used extensively in biomedical research. During recent decades vendors have improved the health status of animals they deliver to biomedical research facilities by use of barrier breeding and isolator techniques. The individual research facilities are faced with the problem of protecting the animals from pathogenic organisms while allowing a more open access to the animals when they are used in research projects. Different systems are in use to ensure that the high health standards of delivered animals are maintained. Such systems include filter-top cages, barriers, and isolators. During the recent decade much has been done to develop individually ventilated cage (IVC) racks as an alternative animal husbandry system. Several factors have been the driving force for such a development. One

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Accepted 5 June 2000

is the recognized protective value of the filter-top avoiding the negative consequences arising from the lack of effective ventilation (Corning & Lipman 1991,1992, Lipman *et al.* 1992,1993, Perkins & Lipman 1995). Another factor is the demand from researchers to have access to their animals, while keeping them isolated.

Several studies have shown that the IVC systems minimize spread of pathogens between cages (Lipman *et al.* 1993, Clough *et al.* 1995, Morrell 1997). Such results infer that the IVC systems can be used both to protect animals that are free from pathogens, and to quarantine animals of unknown health status. The latter possibility is an obvious advantage with the increasing global exchange of genetically modified animals between laboratories.

Besides the obvious benefit of a system that can increase the possibility of maintaining a high health standard, the IVC systems can be used to optimize the housing of laboratory rodents in several ways. If a new facility is constructed where the cage system is based on individual ventilation the general ventilation might be reduced with reduced heating and ventilation costs as a consequence. IVC systems can also be used in an old facility to increase the holding capacity, since more cages can be held in one room without endangering health quality. IVC systems might also be used to improve the working environment by a reduction of airborne allergens (Clough *et al.* 1995, Reeb-Whitaker *et al.* 1999).

Faced with the planning of a new facility for laboratory rodents we decided to evaluate two different IVC systems: Techniplast, SealSafe (1284L) and Biozone, VentiRack (VR-20049 AS). We investigated whether the IVC systems could control the production of NH_3 in cages in use, and if the systems were capable of maintaining a negative or positive pressure for a prolonged period of time. CO_2 levels within cages after a simulated power failure were also measured. Since reports have suggested that the work environment can be improved by the use of IVC systems, (Clough *et al.*1995, Reeb-Whitaker *et al.* 1999) we also investigated the content of mouse allergens in room air. Finally, an ergonomic evaluation was performed (Renström *et al.* 2000).

Methods

Individually ventilated cage systems from Biozone, Margate, UK, (VentiRackTM VR-20049AS) and Techniplast Gazzada, Buguggiate, Italy (SealSafe 1284L) were delivered from the vendors and validated on site by each company. The IVC systems were placed in two adjacent animal rooms which had a temperature of $22 \pm 1°C$ and a humidity of $55 \pm 5\%$. The room air, the fresh air source for the IVC systems, was changed 17 times per hour. Extracted air from the cages was scavenged by the room exhaust system. The photoperiods were from 07:00–19:00 h. The animals had free access to R36 (Lactamin, Vadstena, Sweden) rodent diet and water at all times.

The VentiRack (IVC1) was equipped with 49 MAKROLON type II (floor area $= 370\ cm^2$), and the SealSafe (IVC2S) rack was equipped with 42 MAKROLON type IIL (floor area $= 530\ cm^2$) cages. The cages had aspen wood shavings as bedding material (B&K Universal, Sollentuna, Sweden). NMRI male mice, 10 weeks of age, were purchased from B&K Universal, Sollentuna, Sweden. The mice were randomly placed three per cage, 114 (IVC1) and 116 (IVC2S) mice in total, and were allowed to adjust to the new environment for 2 weeks before the test period started. After the acclimatization period the animals were inspected and weighed. At the end of the test period the animals were again weighed to calculate growth. Throughout the test period the animals were inspected and bite wounds were noted. In some instances severely affected animals were put into separate cages or culled by cervical dislocation.

The differential pressure was measured with a Testo-model 512 instrument (Buhl & Bonsoe A/S, Denmark), with a range between ± 0–1.999 hPa, at the start of the test period and after 10 days of use when the IVC systems were set to operate under negative pressure. The differential pressures were also recorded after the IVC systems were set to operate under positive pressure and finally after 14 days of use under positive pressure.

At the end of each of the negative and positive pressure test periods the NH_3 content of the air was measured with a toxic gas monitor, model SC-9, (Riken Keiki, Tokyo, Japan). At the end of the positive pressure period the IVC fans were shut off to simulate a power failure situation and both the CO_2 (measured with a 2001VTC-mini CO_2 monitor, Telaire Europe AB, Delsbo, Sweden) and the NH_3 air content was measured once per 15 min for one hour. The probes were held 1–2 cm above the bedding material.

Results

Negative pressure

The evaluation of the IVC systems started with measurements of the relative air pressure in individual cages when the systems were set to operate under negative pressure. Tables 1 and 2 summarize pressure data obtained at the beginning of the test period and after 10 days of use.

IVC1 (Table 1) The relative pressure in the IVC1 cages was uniform between cages. The mean ± SD pressure was −1.3 ± 0.5 Pa at the beginning of the test and −0.8 ± 0.4 Pa after 10 days of use. No cages were found with positive pressure (statistical evaluation of pressure differences day 1 *vs* day 10, $t = -3.2$, $P < 0.002$, inter-cage variance at day 10 = 0.24).

Table 1 Relative pressure (Pa) in individual IVC1 cages at the beginning of the negative pressure test period and after 10 days of use

Cage position	1	2	3	4	5	6	7
Differential pressures (Pa) at beginning of test							
1	−0.5		−0.8	−1.0	−1.3		−1.4
2		−0.9		−0.8		−1.3	
3	−0.8		−1.6		−1.7		−1.4
4		−1.3		−1.4		−2.8	
5	−1.1		−1.1		−1.6		−1.2
6		−1.5		−1.4			
7							
Differential pressures (Pa) after 10 days of use							
1	−0.3		−0.1	−0.8	−1.0		−0.9
2		−1.1		−0.7		−1.4	
3	−0.4		−1.5		−0.8		−0.9
4		−0.9		−1.2		−1.3	
5	−0.8		−0.4		−0.5		−0.8
6		−0.1		−0.5			
7							

Cages in position 4:1 were reference cages that contained no animals

Table 2 Relative pressure (Pa) in individual IVC2S cages at the beginning of the negative pressure test period and after 10 days of use

Cage position	1	2	3	4	5	6
Differential pressures (Pa) at beginning of test						
1	−17.5		−6.5	−11.2	−8	
2		−12		−19.5		−4
3	−5		−11		−5.5	
4		−20.5		−9.5		−13
5	−22		−10		−3	
6		−16.5		−16		−9
7	−15.5		−13.5		−7.5	
Differential pressures (Pa) after 10 days of use						
1	−12	**+3**	−6.5	−14.3	−3.5	−7
2	−2	−8	**±0**	−4	−7	**+2.5**
3	**+2**	−9	**+7**	−2.5	−0.5	−4
4	−7	−16.5	**+11**	−3	−2	−7.5
5	−16.9	**±0**	**+1**	−1	−2	−3
6	−1.5	−2.5	−0.5	−11	−3	−1
7	−9	**±0**	−8	**+7**	−5.9	−0.5

Cages in position 4:1 were reference cages that contained no animals. Note that some cages (bold figures) were operating under positive pressure

IVC2S (Table 2) At the first test every other cage was measured and all were found to have relative negative pressures. The mean ± SD pressure of all cages was −11.6 ± 5.5 Pa. After 10 days of use some of the cages that were tested before were found to have a positive pressure (bold figures). At that point it was decided to measure all cages. After 10 days of use the mean ± SD pressure was −3.5 ± 5.9 Pa (statistical evaluation of pressure differences day 1 *vs* day 10, $t = -5.35$, $P < 0.001$, inter-cage variance at day 10 = 34.4).

Ammonia content (Table 3) After 10 days of use the NH_3 concentration in the caged air was measured. Since the air supply was taken from the room some NH_3 was detected in the reference cages. In some cages the animals had favoured one corner for urination. Although the ventilation rate was high in the

Table 3 Ammonia (ppm) values measured in IVC2S and IVC1

Cage position	1	2	3	4	5	6	7
IVC2S NH_3 (ppm)							
1	1* (3)		1.5 (3)	7.5	11* (3)		7 (3)
2		3.5 (3)		3 (3)		4.5 (1)	
3	0 (3)		3.5 (3)		2 (3)	15* (3)	6.5 (3)
4		2 (3)		2.5 (3)		3 (3)	
5	8* (3)		20* (3)		5.5* (3)		8.5* (3)
6		2.5 (3)		6* (3)			
7							
IVC2S NH_3 (ppm)							
1	8.5 (1)		9 (2)	12	5 (3)	20* (3)	
2		5 (3)	40* (3)	6.5 (3)		5 (3)	
3	4 (3)		10 (3)		5 (3)		
4		7 (1)		6 (3)		20 (3)	
5	7 (3)		6 (3)		4.5 (3)		
6		5.5 (3)		7 (3)		6 (3)	
7	5 (3)		6 (3)		8 (2)		

Figures within parentheses are number of animals in each cage. *Cages where wet corners were noted. Cages in position 4:1 were reference cages that contained no animals. IVC = individually ventilated cage

Table 5 Relative pressure (Pa) in individual IVC2S cages at the beginning of the positive pressure test period and after 14 days of use

Cage position	1	2	3	4	5	6
Relative pressures (Pa) at the beginning of the positive pressure test period						
1	8		9	8.5	9	
2		5		9.5		8
3	10.5		8		11	
4		7		14		10
5	10.5		12.5		7.5	
6		9		9		11
7	9		12.5		7	
Relative pressures (Pa) after 14 days of the positive pressure test period						
1	13.5		15	13	5.5	
2		6.7		22		9.5
3	15		23		17	
4		11.5		17		16
5	16		20		11.5	
6		15.5		18		19
7	15		21		11	

Cages in position 1:4 were reference cages that contained no animals

Table 4 Relative pressure (Pa) in individual IVC1 cages at the beginning of the positive pressure test period and after 14 days of use

Cage position	1	2	3	4	5	6	7
Relative pressures (Pa) at the beginning of the positive pressure test period							
1	0.9		0.7	0.8	0.7		0.8
2		0.7		0.6		0.6	
3	0.6		0.5		0.3		0.6
4		0.6		1.2		0.3	
5	1.3		1.4		1.3		1.1
6		1.8		1.5			
7							
Relative pressures (Pa) after 14 days of the positive pressure test period							
1	1		0.7	0.8	0.8		1.2
2		0.7		0.7		0.7	
3	1.3		0.6		0.7		1.2
4		0.9		0.8		0.5	
5	1.8		1.9		1.8		1.2
6		2.6		1.5			
7							

Cages in position 1:4 were reference cages that contained no animals

Table 6 Ammonia (ppm) values measured in IVC2S and IVC1 at the end of the positive pressure test period

Cage position	1	2	3	4	5	6	7
IVC1 NH_3 (ppm)							
1	0 (3)		1.5 (3)	4	5.5* (3)		1.5 (3)
2		6.5 (3)		1.0 (3)		1.0 (3)	
3	2.5 (3)		1.5 (3)		1.0 (3)		2.0 (3)
4		1.5 (3)		3.5 (3)		1.5 (3)	
5	6* (3)		7.5 (3)		3.5 (3)		3.5 (3)
6		1.5 (3)		5 (3)			
7							
IVC2S NH_3 (ppm)							
1	2 (1)		1.5 (3)	4.5	0.5 (3)		
2		0 (3)		1 (3)		1 (3)	
3	0.5 (3)		2.0* (3)		1 (3)		
4		4.5 (1)		4.0 (3)		5.5* (3)	
5	15* (3)		1 (3)		1.5 (3)		
6		1 (3)		0.5 (3)		6* (3)	
7	0 (3)		2 (3)		2 (2)		

Figures within parentheses are number of animals in each cage. *Cages where wet corners were noted. Cages in position 1:4 were reference cages that contained no animals. IVC = individually ventilated cage

Table 7 The effect of a power failure simulation on CO_2 and NH_3 concentrations in the cage air

	IVC1		IVC2S	
Time	CO_2 (ppm)	NH_3 (ppm)	CO_2 (ppm)	NH_3 (ppm)
0	1571	5.5	1100	20
15	>9999	1	3215	11
30	8074	4.5	2608	12.5
45	7677	6	2549	13
60	7313	9.5	3542	15.5

cages, the concentrated urination had soaked the bedding. In such cages significantly higher NH_3 concentrations were recorded.

Positive pressure

The tests continued, after cage cleaning, for another 14 days when the IVC systems were set to operate under a positive differential pressure. The results are summarized in Tables 4 and 5.

IVC1 (Table 4) The differential pressure in the IVC1 cages was uniform between cages. The mean±SD pressure was 0.9±0.4 Pa at the beginning of the test and 1.1±0.5 Pa after 14 days of use ($t=-1.6$, not significant [NS] inter-cage variance at day 10 = 0.3).

IVC2S (Table 5) The mean±SD pressure of all cages at the start of the positive pressure test period was 9.3±2.1 Pa. After 14 days of use the mean±SD pressure had increased to 15.1±4.6 Pa ($t=-5.3$, $P<0.001$, inter-cage variance at day 10 = 21.2).

Ammonia content (Table 6) After 14 days of use under positive pressure conditions the air NH_3 content was again measured. Also here some soaked corners were observed in the cages with correspondingly high NH_3 levels in caged air. Many cages with animals had lower NH_3 concentrations than the reference cages, as was also observed under the negative pressure conditions.

Power failure simulation

When the ventilating fans were shut off a rapid increase in CO_2 concentrations were observed in cages in both IVC systems (Table 7). The room air contained 684 ppm CO_2 and 9 ppm NH_3.

Animal weight and bite wounds

After 2 weeks of acclimatization, the mean±SD, weight of the animals placed in the IVC1 cages was 41.5±3.9 g ($n=114$). The IVC2S animals weighed 40.1±3.5 g ($n=116$) (NS). Four weeks later the weights were 44.0±5.4 g ($n=112$, $t=-3.9$, $P<0.001$) and 41.9±4.1 g ($n=113$, $t=-3.5$, $P<0.001$) respectively. The numbers of bite-wounded animals were counted throughout the study and differed significantly between IVCs. Cumulatively, seven mice in the IVC1 were found with bite wounds, whereas 30 were found in the IVC2S ($\chi^2=15.2$, $P<0.001$).

Discussion

The differential pressure in IVC1 cages was lower and more uniform between cages than in the IVC2S racks both at negative and positive pressure. The operating differential pressures in both systems are, however, small, so it must be considered unlikely that the animals are being affected. Of more concern is the finding that some IVC2S cages were changing from negative to positive pressure during the test period of 14 days. Such a malfunction might cause an unwanted spread of allergens and microorganisms in the animal quarters. Upon inspection it was found that dust particles had clogged the outlet air vent, preventing an effective exhaust. The manufacturer has been informed about the malfunction and a new construction of the air vent has been presented.

Both IVC racks are provided with a function that continually measures the differential air pressure in one cage. In the IVC1 the test cage gives a good indication of the differential air pressures within all cages since the between-cage variation is low. In the IVC2S, however, the value of the pressure indication might be questioned as the between-cage variation is high.

The NH_3 concentrations in static, filter-top cages may be very high. Lipman *et al.* (1992) reported 256 ppm NH_3 in cages with

five mice after 7 days. Such high NH_3 concentrations may well be harmful for the animals and might possibly affect results obtained from the use of animals housed under such conditions. Low concentrations of 10 ppm cause ciliostatis in rat trachea (Serrano 1971) but in humans a threshold limit is set at 25 ppm (Gamble & Clough 1976). In the view of this background it is interesting to note that the NH_3 concentrations in cages from both IVC systems under study were generally below 10 ppm after 2 weeks of use, with the exception of cages that had accumulated urine in 'soaked corners'. In many cages that contained animals the NH_3 content in the caged air was lower than in the reference cages. Possibly this reflects an uptake and metabolism of NH_3 by the animals.

It might be possible to reduce the NH_3 concentrations in cages even further by choosing another bedding material. Perkins and Lipman (1995) have shown that aspen bedding, as was used in the present study, is the worst choice. After 7 days with five mice per filter-top cage, 350 ppm NH_3 concentrations were found in cages with aspen bedding. No detectable levels of NH_3 were, on the contrary, detected from cages with corncob bedding material.

The power failure simulation is important because the ventilation of the cages is highly dependent on the fans. High concentrations of CO_2 and NH_3 might build up in a short period of time to concentrations hazardous to the animals. After a one hour shut down of the fans we could, however, not observe any overt behavioural signs indicating that the cage environment was unhealthy. Although the CO_2 concentrations increased rapidly in both systems the CO_2 levels were relatively stable between 30 and 60 min during the fan shut-off period. The stable CO_2 concentrations might indicate that the level reached after 60 min reflects the situation of a longer period of time. Since we did not measure the CO_2 concentrations for more than 60 min it is possible that CO_2 levels might be higher after a more prolonged power failure. This possible hazard needs further investigation.

The highest concentrations of CO_2 were measured in the IVC1 cages, probably reflecting the fact that these cages are more tightly sealed than the IVC2S cages are. Actually, the IVC2S cage top is equipped with a filter to prevent asphyxiation accidents in case of a power failure. The CO_2 concentration of 3542 ppm measured in the IVC2S cages after a 60 min fan shut off, corresponds well with what has been reported for static filter-top cages (Perkins & Lipman 1996). As it is well known that mice can live and reproduce in such cages it might be concluded that these concentrations are not problematic. Considerably higher concentrations have to be reached before any effects on animal behaviour can be detected. Nielsen *et al.* (1993) reported no effect on respiration or tidal volume of 2.7% CO_2. The LC_{50} of CO_2 is not reached until 8.8% (Harafuji & Uchiyama 1989).

Obvious differences between the two IVCs were found in weight and number of bite-wounded mice. This finding might indicate that some, by us not yet identified, factor such as ultrasound, draft, or light conditions stressed the animals, and needs to be studied more in detail. One possible reason for the difference in bite-wound occurrence could be the different cage sizes used in the present study. The IVC2S cages were 530 cm^2 and the IVC1 cages were 370 cm^2. It is well known from poultry keeping that a reduction in space decreases agonistic behaviour (Cunningham 1988). Recently, an investigation was presented that showed that this is also the case in mice (van Loo *et al.* 1999). In this particular study it was found that the numbers of wounds were significantly fewer in small cages (80 cm^2/mouse) than in larger cages (125 cm^2/mouse). Poole and Morgan (1973) reported that in colonies of different sizes in a uniform cage size the social structure changes depending on how large the group is. In a small group of three animals one male rapidly becomes dominant, and the others become subordinate. There was no change of this structure in a period of 21 days. In a larger group (9 and 12 animals) changes in dominance was observed and the social structure had the form of a partial hierarchy. Of great interest for the present results is the observation by Poole and Morgan (1973) that the average number of attacks by a domi-

nant male on a subordinate was significantly higher when the individual space was large. With this background, it might also be possible to account for the differences in weight between mice kept in the two IVCs under study.

Although our study considers the Biozone (Ventirack VR-20049 AS) and Techniplast (SealSafe 1284L) IVC racks, the criteria we considered can be applied to all the racks on the market. By using these methods, prospective customers can ask more informed questions when they are making purchasing decisions, and promote the development of future IVC systems.

Conclusion

The study shows that the IVC1 air handling system provides a more uniform and balanced differential pressure than the IVC2S. Both systems effectively scavenge NH_3 when bedding material is not soaked with urine. Although the IVCs are dependent on a continual function of the fans to work properly it seems unlikely that CO_2 concentrations build up to hazardous concentrations with the cage types used in the present study. The differences in weight increase and bite-wound frequency are matters that need more investigation but might depend on differences in cage size.

Acknowledgments The authors thank Scanbur and Biozone for their kind provision of IVCs for the present study, and Jan-Erik Dahlerus, Biomedical Center, Uppsala University for technical assistance. We also thank Bo Salling, Scanbur, for providing the relative pressure measuring equipment, and Lennart Lindberg, SVA for providing the NH_3 and CO_2 measuring devices.

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