


# Details of the HKUST Health Monitoring, Disease Surveillance and Adverse Event Investigations



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# Why Define Health Status of Research Animals?

***FELASA Guidelines for the Accreditation of Health Monitoring Programmes and Testing Laboratories involved in Health Monitoring***  
[Lab Anim \(NY\)](#). 2010 Feb;39(2):43-8. doi: 10.1038/labnan0210-43. [Nicklas W<sup>1</sup>](#), [Deeny A](#), [Diercks P](#), [Gobbi A](#), [Illgen-Wilcke B](#), [Seidelin M](#).

- *Preamble: Defining the health status of animals used in research is key to the reliable interpretation of results obtained from experiments involving the use of animals, and in obtaining reproducible experimental results. Microbiological standardisation has reduced the numbers of animals used by reducing the variation within and between test groups. It has also improved the overall health of laboratory animals, thus improving their welfare, and has reduced human health risks due to zoonotic disease.*



# The Federation of European Laboratory Animal Science Associations

*FELASA has a long tradition of publishing recommendations on health monitoring of breeding and experimental colonies of rodents and rabbits*

- ▶ FELASA guidelines for the accreditation of health monitoring programs and testing laboratories involved in health monitoring  
Werner Nicklas, Adrian Deeny, Piet Diercks, Alberto Gobbi, Brunhilde Illgen-Wilcke & Michel Seidelin *Journal: Lab Animal* 39, 43–48 (2010), doi:10.1038/lablan0210-43

AALAS - FELASA working group on health monitoring of rodents

(URL: <http://www.felasa.eu/working-groups/working-groups-past/aalas-felasa-working-group-on-health-monitoring-of-rodents/> )

# Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units.

[Nicklas W<sup>1</sup>](#), [Baneux P](#), [Boot R](#), [Decelle T](#), [Deeny AA](#), [Fumanelli M](#), [Illgen-Wilcke B](#); [FELASA \(Federation of European Laboratory Animal Science Associations Working Group on Health Monitoring of Rodent and Rabbit Colonies\)](#). [Lab Anim.](#) 2002 Jan;36(1):20-42.

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# 1 Preamble

Monitoring of laboratory animal breeding and experimental colonies, with the intention of harmonizing procedures primarily among countries associated with FELASA, but also worldwide.

**The use of the recommendations will be facilitated by a basic knowledge of microbiological standardization and diseases of laboratory animals**

## 2 General considerations

- ▶ These recommendations constitute a common approach for health monitoring of laboratory animals and the reporting of results. **Actual practice may differ from these recommendations in various ways depending on local circumstances, such as research objectives and local prevalence of specific agents,**
- ▶ **Health monitoring schemes must be tailored to individual and local needs.** However, quality aims must be clearly defined and an appropriate system of preventive hygienic measures (e.g. barrier systems) developed to meet those aims.
- ▶ Finally, a **health monitoring programme should be established in every facility** to demonstrate whether the quality aims have been met by monitoring the effectiveness of the preventive measures



## 3 Risk of introducing unwanted microorganisms

The risk of inadvertently introducing microorganisms (viruses, bacteria, fungi and parasites) into breeding units is generally lower than for experimental units. Introduction of unwanted microorganisms is mainly due to one or more of the following factors:

- **animals,**
- **biological materials,**
- **equipment and**
- **staff**



## 4 Frequency of monitoring and sample size

- Colonies should be monitored at least quarterly.
- Depending on **local circumstances and needs, more frequent monitoring may be carried out for a selection of some frequently occurring agents that have a serious impact on research.**
- Sick and dead animals should be submitted for necropsy. These animals should be examined...
- ...in addition to those already scheduled for routine monitoring.
- The out-come of the necropsy may prompt an increase in the sample size and frequency of monitoring.



**Table 1 Calculation of the number of animals to be monitored**

Diseases with an infection rate of 50% or more (Sendai, MHV) require far fewer animals to detect their presence than diseases with low infection rates.

**Assumptions**

1. Both sexes are infected at the same rate
2. Population size > 100 animals
3. Random sampling
4. Random distribution of infection

The sample size is calculated from the following formula:

$$\frac{\log 0.05}{\log N} = \text{Sample size}$$

$N$  = percentage of non-infected animals

0.05 = 95% confidence level

**Relation of sample size to prevalence rate**

Suspected prevalence rate (%)	Sample sizes at different confidence levels		
	95%	99%	99.9%
10	29	44	66
20	14	21	31
30	10	13	20
40	6	10	14
50	5	7	10

Example: 10 animals should be monitored to detect at least one positive animal if the suspected prevalence rate of an infection is 30% (confidence level: 95%)

# FELASA Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units.

- ▶ These recommendations are now widely used and breeders or users commonly report on health monitoring of their animal colonies, using the phrase “in accordance with FELASA recommendations”.

Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units. [Nicklas W<sup>1</sup>](#), [Baneux P](#), [Boot R](#), [Decelle T](#), [Deeny AA](#), [Fumanelli M](#), [Illgen-Wilcke B](#); [FELASA \(Federation of European Laboratory Animal Science Associations Working Group on Health Monitoring of Rodent and Rabbit Colonies\)](#). [Lab Anim.](#) 2002 Jan;36(1):20-42.



# Herd Health Management

- ▶ defined as 'a method to optimise health, welfare and production in a population of ... [animals] ... through the systematic analysis of relevant data and through regular objective observations of the ... [animals] ... and their environment, such that informed, timely decisions are made to adjust and improve ... [colony] ... management over time'.
  - ▶ <https://www.nottingham.ac.uk/research/groups/dairy-herd-health-group/herd-health.aspx>



# Conceptual foundations for infectious disease surveillance

- ▶ The purpose of this report is to offer concepts for consideration in developing infectious disease surveillance systems, defined here as active, formal, and systematic processes intentionally directed to rapidly seek out and identify infectious disease agents or disease.
- ▶ Mark C. Thurmond J Vet Diagn Invest 15:501–514 (2003)
  - ▶ <http://journals.sagepub.com/doi/pdf/10.1177/104063870301500601>



# Adverse events at research facilities

- ▶ Identifying the various events that can endanger animal and human lives and lead to loss and damage of property is essential in planning efficient measures for prevention and mitigation. Categorizing the possible events into groups based on their effects can help in coordinating and managing efforts to prevent and/or reduce the impact of such events.

- ▶ **Swapna Mohan, Lori L Hampton & Susan Brust Silk**

- [https://grants.nih.gov/grants/olaw/references/lab46\\_06\\_0617.pdf](https://grants.nih.gov/grants/olaw/references/lab46_06_0617.pdf)

**TABLE 5 | Inadvertent contained adverse events**

<b>Adverse event</b>	<b>Secondary effects</b>
<b>Biological</b>	
Adverse reaction to biologics, drugs, chemicals	Reactions in other animals Interference with study results
Veterinary care issues; surgical, treatment, analgesia	
Disease/infestation	
Failed euthanasia	
<b>Mechanical</b>	
Electrical issues	Fire and related damage
Water supply	Flooding
HVAC	Potential for infections due to contaminated air
Lighting	Disruption of light/dark cycle
Construction/maintenance	Damage due to wear and tear
<b>Husbandry-related</b>	
Inadequate, inaccessible or spoiled food/water	Odors Aggression
Sanitation issues	Stereotypies
Overcrowding	Interference with study results
Insufficient enrichment	Morbidity and mortality
Accidents like cage flooding	
<b>Human error</b>	
Escapes	Negative publicity
Improper care during transportation	Interference with study results
Inadequate care/attention	Injury to people, animals
Mishandling due to inadequate training	
<b>Animal nature</b>	
Aggression toward other animals	Risk and injury to animals and people
Getting trapped, injured (e.g., chewing wires)	
Escapes	
Aggression toward people	



# HKUST – The Questions

It is not just the organisms but the objectives of the programme.

- What are you trying to exclude and why?
- What will you do if you get a positive?
- What are our resources and how best to employ them.
- What are our risks - imports and/or closed colonies?
- What are your colony units - IVC cages or open cage rooms?
- Are we going using sentinels or EA dust?
- Are we going to use sentinels or live sampling?



# Risk-Analysis Programme

- ▶ How are our room(s) HVACs configured:
  - ▶ Pressure differentials?
- ▶ Wild rodents
- ▶ User compliance
- ▶ Institutional support





# The key is...

...These things determine our frequency of sampling and how I sample?

**NO COOK-BOOK RECIPES**



# HKUST Circumstances

- ▶ we import animals almost monthly from a range of the sources and so the approved supplier concept is flawed.
  - ▶ (Should I treat the 4 main commercial suppliers the same way as universities and other sources?)
- ▶ We determine a colony as low risk or high risk.
  - ▶ Based on our assessment of the health report and the quality of the laboratory



# ICLAS - Performance Evaluation Program for Diagnostic Laboratories (PEP)

- ▶ PEP was established in 2007 to enable research animal diagnostic laboratories to monitor and improve their diagnostic performance through a process of self-assessment.
- ▶ The Program is open to any diagnostic laboratory worldwide. There are no specific eligibility requirements. There are currently have 20 participants
- ▶ <http://iclas.org/animal-quality-network/performance-evaluation-program-for-diagnostic-laboratories-pep>



# Overview of Program

- ▶ Participating laboratories are sent standardised rodent specimens produced by the Network laboratories.
- ▶ Following analysis, participating laboratories request an 'Expected Results' report containing details of the actual biological contents of the specimens.
- ▶ A comparison of results enables the participating lab to monitor and evaluate the sensitivity and specificity of its health monitoring assays.




# Benefits of participating in PEP

- **Improved Diagnostic Performance:** use of a scientifically robust program to help you monitor the sensitivity and specificity of your lab's health monitoring assays.
- **Support and advice:** access to expert help and advice from the Network Laboratories.
- **Verification of participation:** official Participation Certificate plus a web link from the Network's PEP web page to your laboratory's website.

# We do sampling of all imports

- ▶ If over a 100 animals we sample on an assumption of 30% prevalence for the 6 most prevalent organisms,
  - ▶ on the assumption of common things commonly.
- ▶ We do live testing:
  - ▶ 5 animals per swab of the fur and 5 faecal pellets 4 days after arrival.
- ▶ Once the results are back (usually 10 to 14 days) the animals that are low risk go to the PI.
- ▶ For those sources we consider high risk, we keep the animals isolated for a further 4 weeks
  - ▶ repeat testing using a comprehensive panel of serology looking for seroconversion using the blood spot model (2 animals per filter paper)



# Finally the programme is meaningless unless...

- ▶ You monitor your facilities' sanitation programme,
- ▶ You monitor your facilities' autoclave,
- ▶ Your users' compliance with SOPs
- ▶ Your users' use of biologicals
- ▶ You have disease surveillance of colonies
- ▶ You have Adverse Event Reporting (and PAM)
  - ▶ We have a gross pathology programme with City U's vet school's path labs

# Weaknesses at HKUST:

- Biologicals
  - No users are having their cell lines tested
- Environmental monitoring
  - Just getting started
- User compliance and cooperation
  - Efforts to accept results from sources and laboratories of uncertain/unreported quality standards
- Bacteriology – really nothing meaningful to date
  - Cost of bacteriology to test for the FELASA list of organisms
  - Problematic shipping of bacto samples overseas
  - I don't know what is important because researchers don't involve APCF in research design



# Report of the FELASA Working Group on evaluation of quality systems for animal units.

[Lab Anim.](#) 2004 Apr;38(2):103-18.

[Howard B<sup>1</sup>](#), [van Herck H](#), [Guillen J](#), [Bacon B](#), [Joffe R](#), [Ritskes-Hoitinga M](#).

## Abstract

This report compares and considers the merits of existing, internationally available quality management systems

- the Good Laboratory Practice Guidelines,
- ISO 9000:2015 (International Organization for Standardization) and
- AAALAC International (Association for Assessment and Accreditation of Laboratory Animal Care International).
- Management needs to determine, on the basis of a facility's specific goals, whether benefits would arise from the introduction of a quality system and, if so, which system is most appropriate.
- The successful introduction of a quality system confers 3rd-recognition against an defined standard, thereby providing assurance of standards of animal care and use, improving the quality of animal studies, and contributing to the three Rs- reduction, refinement and replacement.

	AAALAC	GLP	ISO 9000:2000
Subject	Strengths		
Principal focus	The animal care and use programme	The consistency of studies	The customer
Applicability	An animal facility alone can be accredited. Peer review of animal units	Details of studies for which GLP compliance is claimed are documented	Customer focused—i.e. business friendly. ISO standards are available for a wide range of businesses so the philosophy is transferable
Animal welfare and law	Heightens awareness of laboratory animal welfare globally. Where there is no existing law, the ILAR Guide is the minimum standard	GLP requires compliance with National law—animal welfare is assured to this extent	Meets regulatory requirements concerning animal welfare
External consideration	Well respected in institutions conducting experiments on live animals, including US agencies	Assures sponsors and regulatory bodies that work is rigorously carried out and documented	Gives customer confidence that quality is provided
Internal quality assurance	A facility manager can introduce it without seeking specialist assistance	Quality assurance unit is obligatory and leads to better consistency	Obliges internal review of the management system
Working processes	Support processes are reviewed	All steps in the process are described in SOPs and legal documents	Principally a management tool to ensure processes are coordinated and effective
Inspection	Site inspections are carried out by external visitors	External independent (government-appointed) inspectors	External inspectors
Direct costs	No costs except for the annual fee	Inspections are free of charge	Cost of certification is relatively low
Ongoing costs	Annual report, annual fee. Ongoing quality assurance reports and SOPs are not obligatory, so relatively inexpensive	Costs are associated with the QA unit and setting-up and maintaining SOPs; there is a continuing need for documentation (expensive)	No major expenditure required. Maintenance of an established accreditation is relatively cheap
Flexibility (1)	Flexibility towards local situation—if local legislation is more stringent than the ILAR-Guide, then that becomes the standard	Mandatory government requirement for certain studies. SOPs are prepared by the establishment and so can reflect its needs	Facility specifies its own procedures providing these raise overall performance
Flexibility (2)	Working standards can be changed whenever you wish, providing they meet the minimum defined standard	High-quality working standards may positively influence other, 'non-GLP' studies in the same unit	The need to retain and adhere to policy documents assures consistency of management. Facilities are encouraged to continually innovate and improve

(Continued)

Table 1 (continued)

	AAALAC	GLP	ISO 9000:2000
Subject	Weaknesses		
Bureaucracy	It is necessary to describe and adhere to a detailed, programme description	Slowness of procedures due to the bureaucratic nature of the process. Needs for paperwork and confidentiality may make procedures appear rigid	There may be a large amount of paperwork at the beginning of the process, depending on the 'starting position'
Resources	High initial demands on time and resources, even if a different QA system is already in place. Less to maintain the system	High ongoing costs in terms of personnel and time. Animal care staff, analytical staff and directors are subordinated to the QA process	Once the system is in place, ongoing maintenance needs are minimal and principally address improvements
Standards and applicability	In some respects ILAR Guide standards differ from EU standards. Standards also differ between European countries. In all cases, the requirements of national legislation have to be met, although if the AAALAC standards exceed other requirements, the highest standard is applicable	A study-based system, not primarily directed at the animal facility. Animal facility can only be accredited as part of a larger establishment conducting regulatory work (e.g. pre-clinical safety studies) or as a CRO for in-life parts of studies	The customer and final product count, rather than the way the process works. The management framework is less rigidly defined, so operational standards are less critical than production settings
Subjectivity	Subjectivity may be introduced by individual site visitors; review by 32-Member Council minimizes inconsistencies	Each facility determines its own working practices but needs to ensure that these are audited. Approval is by the inspectors; policies may vary between countries	Provides no detailed guidelines for implementation. Variability between business types, certifying bodies and auditors, means that subjective differences may lead to inconsistencies in quality

# Animal health and welfare: Veterinary care of laboratory animals

<http://www.felasa.eu/working-groups/working-groups-past/veterinary-care-of-laboratory-animals/>

- ▶ In general, animal health and welfare are the responsibilities of the veterinary profession but when dealing with laboratory animals the potential effects on research should also be considered.
  - ▶ When communication with the researcher is not possible, the veterinarian's decision on treatment or euthanasia of the animal, at her/his professional discretion, must be respected.
- ▶ Disease diagnosis should be performed by the veterinarian and appropriate analytical services should be available. Disease in individuals should be treated accordingly but, when a disease affects several animals and may become a hazard to the colony or the research veterinarian should have the authority or the institutional support to decide on the best method of control and treatment in accordance, whenever possible, with the researcher.
- ▶ The veterinarian should keep records of all scheduled animal health programmes under her/his direct supervision as well as all cases of control and treatment of diseases.
  - ▶ Recording of treatments, observations and assessments can also be delegated to other staff, such as animal care technicians.