



Session 3

Good animal welfare practice



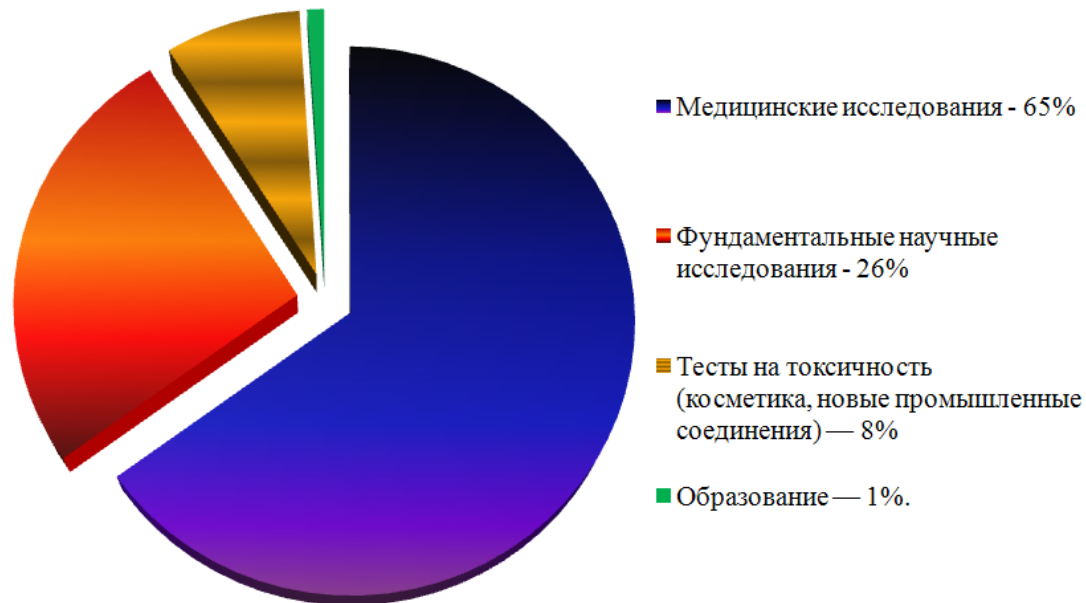
Monitoring animal health as the basis for proper preclinical studies

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The role of animals in studies.

- ▶ Experiments on animals are conducted in many areas of scientific research: medical, military, space, testing of new drugs, cosmetics, household chemicals, industrial compounds, in education. On the whole in the world more than 100 million laboratory animals per year are involved in experiments [Taylor K. et al., 2008].



Taylor K., Gordon N., Langley G., Higgins W. (2008) Estimates for Worldwide Laboratory Animal Use in 2005. *Alternatives to Laboratory Animals (ATLA)*, 36(3): 327 -342.

The role of animals in studies.

- ▶ In 2010, the American Association for Laboratory Animal Science AALAS published the poster "Animal Roles in Medical Discoveries", which lists the Nobel Prizes in medicine and physiology from 1901-2010, with the name of the scientist, the name of the discovery and the type of animals that were involved.
- ▶ "A look at the Nobel Prizes in Medicine and Physiology awarded from 1901 to the present shows that animal research has played a key role in these important discoveries. Animal research must continue for similar medical advances in the future".
- ▶ Animal research has played an important role in almost every medical breakthrough of the last century and the present. Since 1901, almost every Nobel Prize winner in physiology and medicine has relied on data from animal experiments.

Animal Roles in Medical Discoveries

Nobel Prizes for Medicine & Physiology from 1904 to present. Research with animals must continue for similar medical advances to continue.

Year	Scientist	Animal(s) Needed	Contribution to Modern Medicine
1904	Pavlov	Dog	Animal responses to various stimuli
1905	Koch	Cow, Sheep	Studies of pathogenesis of tuberculosis
1906	Golgi, Cajal	Dog, Horse	Characterization of the central nervous
1907	Laveran	Bird	Role of protozoa as cause of disease
1908	Mechanikoff, Ehrlich	Bird, Fish, Guinea pig	Immune reactions and functions of phagocytes
1910	Kossel	Bird	Knowledge of cell chemistry through work on proteins, including nuclear substances
1912	Carrel	Dog	Surgical advances in the suture and grafting of blood vessels
1913	Richet	Dog, Rabbit	Mechanisms of anaphylaxis
1919	Dondet	Guinea pig, Horse, Rabbit	Mechanisms of immunity
1920	Krogh	Frog	Discovery of capillary motor regulating mechanism
1922	Hill	Frog	Consumption of oxygen and lactic acid metabolism in muscle
1923	Banting, Macleod	Dog, Rabbit, Fish	Discovery of insulin and mechanism of diabetes
1924	Einthoven	Dog	Mechanism of the electrocardiogram
1928	Nicolle	Monkey, Guinea pig, Rat, Mouse	Pathogenesis of typhus
1929	Eljzman, Hopkins	Chickens	Discovery of antineuritic and growth stimulating
1932	Storrington, Adrian	Dog, Cat	Functions of neurons
1934	Whipple, Murphy, Minot	Dog	Liver therapy for anemia
1935	Spemann	Monkey, Frog	Embryonic effect in amphibian development

The International Organization for Standardization (ISO) has defined quality as:

"A complex set of characteristics of an entity that have the capacity to meet stated and implied needs" (ISO 8402, 1994).

In the case of animals, ideally a quality management system should benefit the animals and enhance/retain their welfare.

Quality assurance for working with laboratory animals is determined by 3 systems:

- ▶ Accreditation by the Association for Accreditation of Laboratory Animal Care (AAALAC International)
- ▶ Good Laboratory Practice (GLP)
- ▶ International Standardization Organization ISO 9000



ISO 9000:2000

*Howard B, van Herck H, Guillen J, Bacon B, Joffe R, Ritskes-Hoitinga M
Report of the FELASA Working Group on evaluation of quality systems for animal units//
Lab Anim. 2004 Apr;38(2):103-18.*

AAALAC International

▶ Founded in 1965

It is a voluntary, non-profit corporation whose activities are controlled by the Board of Trustees consisting of representatives of more than 60 scientific, professional, educational organizations and the organization of the animal welfare society: ICLAS and FELASA, etc.

Re-accreditation is carried out once in 3 years

The focus of attention:



Assessment of the quality of animal care, review and implementation of the principles of 3Rs.

Health and Safety Risks



Good Laboratory Practice (GLP)

- ▶ It was created in 1978.
- ▶ Reaccreditation is held once every 2 years.
 - ▶ It's in focus:
- ▶ The organizational process and the conditions under what the laboratory plans, conducts and controls the studies.
- ▶ All research data is recorded and reported.
- ▶ Resources are provided to maintain the quality and integrity of research data.
- ▶ It is guaranteed that these data can be retrospectively verified.

International Standardization Organization

ISO 9000

- ▶ It was founded in 1947.
 - ▶ Focus of attention:
 - ▶ Quality management system and customer satisfaction.
 - ▶ Permanent improvement
 - ▶ Efficient resource management

As part of the research, the ISO system includes: development and improvement of processes for animal care, service provision, personnel training, improvement of operational processes, etc.

Comparison of strengths and weaknesses of different quality systems for animals. Strengths

Topic	AAALAC	GLP	ISO 9000
Focus	Animal Care and Use Program	Study quality	Sponsor
Application area	Animal welfare conditions, animals themselves	Study Details and GLP Compliance Statement	Customer focus, i.e. business
Animal welfare and legislation	Raises awareness of laboratory animal welfare worldwide	Requires animal welfare to be consistent with national law	Complies with regulatory requirements for animal welfare
External approval	Reputable animal experimentation institutions	Guarantees sponsors and regulatory authorities that work is rigorously completed and documented	It gives customers confidence that quality is ensured.
Internal quality	Provided by the head of the institution	Quality Assurance System Required	Internal verification of management system support
Work processes	Are being considered	All processes are described in SOPs and legal documents.	Are a management tool
Inspections	External specialist	External independent (appointed by the government) inspectors	External inspectors

Comparison of strengths and weaknesses of different quality systems for animals. Strengths

Topic	AAALAC	GLP	ISO 9000
Primary costs	No expenses except annual fee	Inspections are free	Certification cost is relatively low.
Current expenses	Annual report, annual fee.	Quality control, maintenance of SOPs (expensive)	No major expenses are required.
Flexibility (1)	Flexibility regarding local law	Mandatory state requirement for certain studies. SOPs are prepared by the institution and may reflect its needs	The entity defines its own procedures for improving overall performance.
Flexibility (2)	Operating standards are subject to change at any time if they comply with minimum standards.	Quality work standards can positively influence other research, for example, non-GLP in the same unit.	The need to maintain and adhere to program documents, to ensure management consistency. It is recommended to constantly innovate and improve services.



Comparison of strengths and weaknesses of different quality systems for animals. Weaknesses

Topic	AAALAC	GLP	ISO 9000
Bureaucracy	It is necessary to describe and adhere to the detailed description of the program	The slowness of the procedures due to the bureaucratic nature of the process.	At the beginning of the process, there may be a large number of documents, depending on the “initial position”
Resources	High initial requirements for time and resources, even if another QMS is already implemented. Less to maintain the system	High running costs. Animal care staff, analytical staff and directors are subordinate to the quality assurance process.	Once the system is installed, current maintenance needs are minimal and mainly aimed at improving
Standards and Applicability	Standards vary between countries. In all cases, the requirements of national law must be observed, although if AAALAC standards exceed other requirements, the highest standard applies.	The research-based system is not primarily aimed at animals. Keeping animals can only be estimated as part of a study	The control framework is less rigidly defined, so operating standards are less critical than production parameters.
Subjectivity	Subjectivity can be manifested by individual specialists; Board review of 32 members minimizes non-compliance	Each object defines its own working methods, but must ensure that they are tested. Approval by Inspectors	Differences between types of businesses, certification bodies and auditors means that subjective differences can lead to inconsistencies in quality.

Quality control of laboratory animals

- ▶ 1. Welfare Control
- ▶ 2. Sanitary control
- ▶ 3. Health control (infectious diseases)
- ▶ 4. Health control (non-infectious diseases)
- ▶ 5. Genetic control

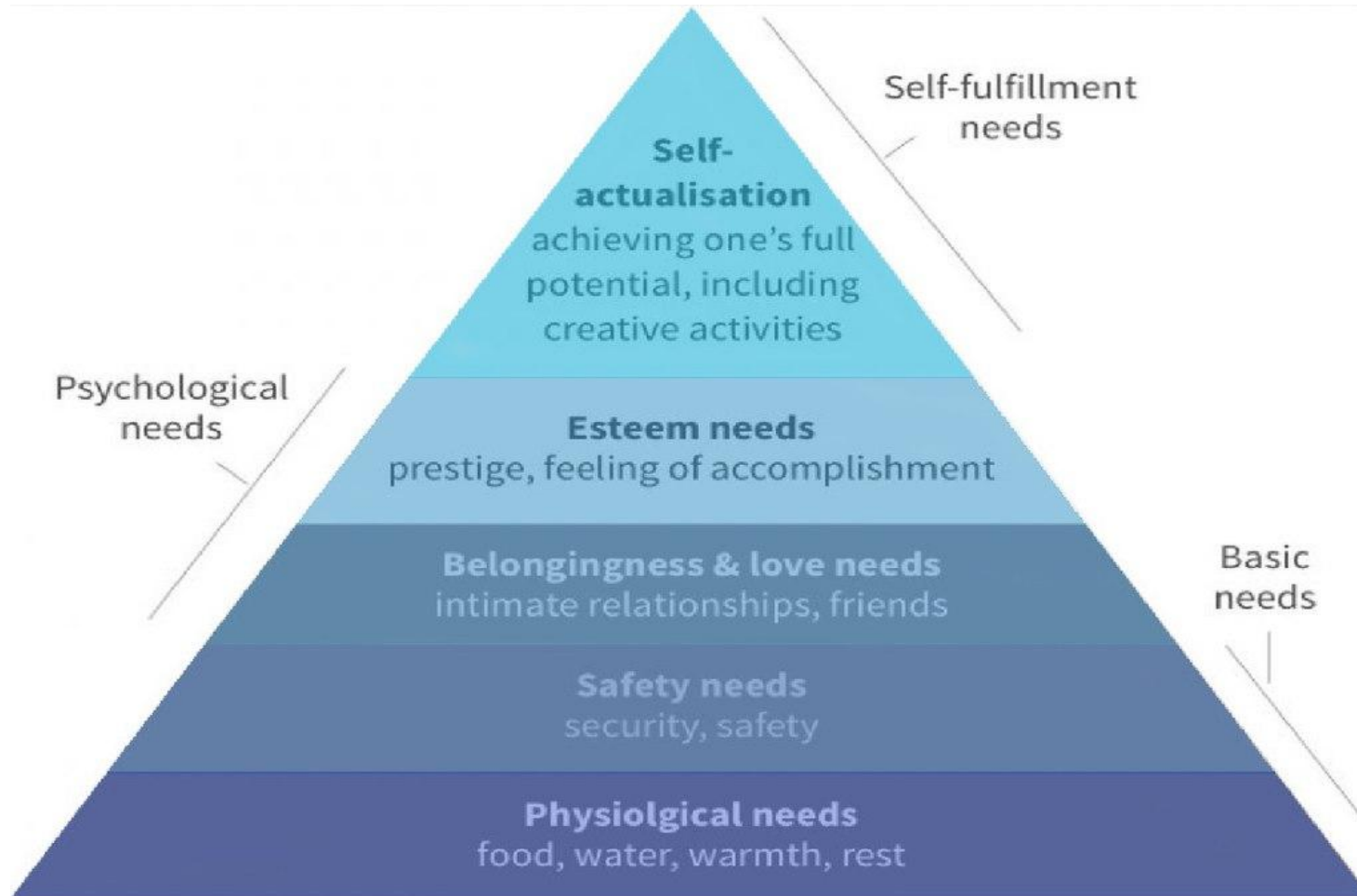
Experimental quality control

- ▶ 1. Control by BEC experts
- ▶ 2. Control and validity of the model
- ▶ 3. Control of pain, stress during the experiment.
- ▶ 4. Control of humane endpoints

Welfare Management

- ▶ Barrier systems appropriate to the animal species
- ▶ Adequacy of territory for living depending on body weight and life cycle
- ▶ Adequacy of food and water
- ▶ Quality and consistency of food and water
- ▶ Social interaction opportunity
- ▶ The ability to exercise natural behavior
- ▶ No fear (smell, sound, pose...)
- ▶ Positive reinforcement

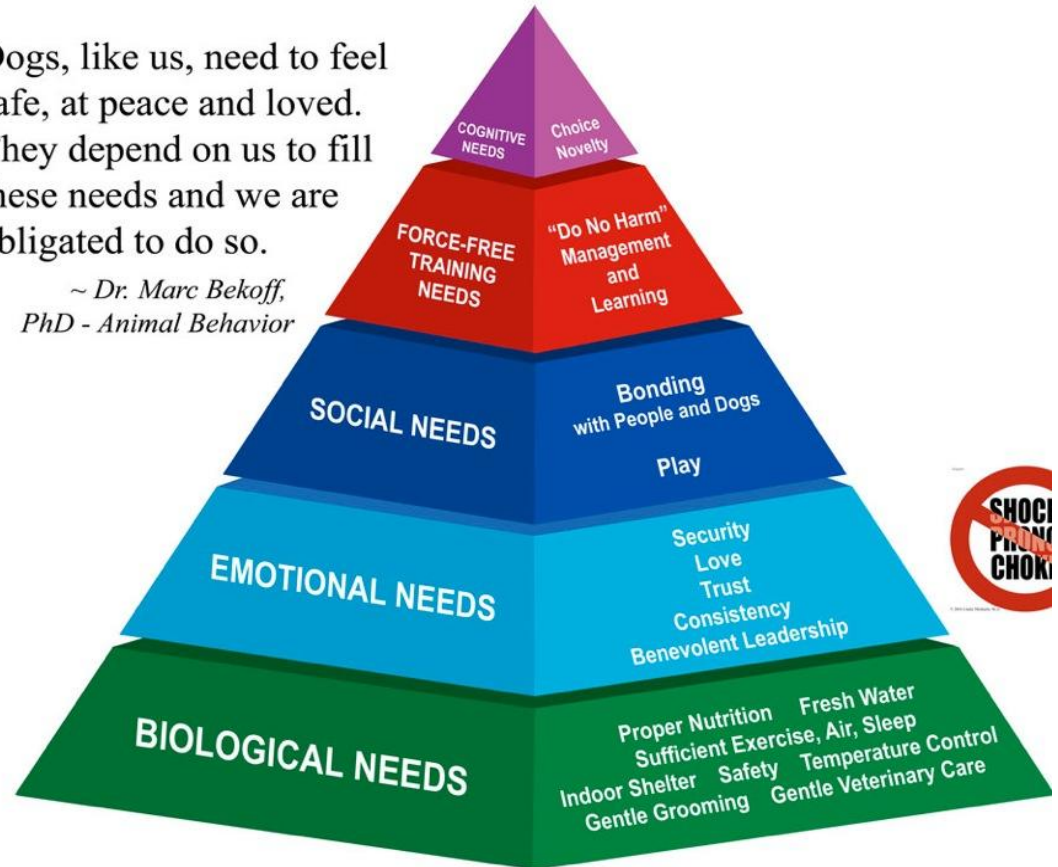
Hierarchy of needs (human)



Hierarchy of Dogs needs

Dogs, like us, need to feel safe, at peace and loved. They depend on us to fill these needs and we are obligated to do so.

~ Dr. Marc Bekoff,
PhD - Animal Behavior



Hierarchy of Dog Needs™



Barrier systems appropriate for animal species

Atraumatic,
Presence of recreation areas, shelters



Area adequacy for living according to body weight and life cycle

Life cycle	Weight	Min cell size (cm ² , m ²)	S cells per animal (cm ² , m ²)	Min height (cm ² , m ²)	Age	Min S for lying (m ²)	S shelves (m ²)
Adults - Group Content					For rabbits	For pigs	For cats
Adults - Single Use							
Pairing							
Mother and child							

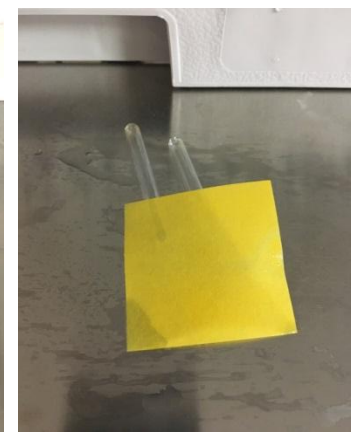
Neonatal care



Adequacy of food and water

Quality and continuity of food and water

- ▶ Compilation and analysis of life cycle dependent diets
- ▶ Frequency of viewing the fullness of the feeders, drinkers
- ▶ Feed and water desprivation
- ▶ Water Quality Control
- ▶ Reliability of the drinking system
 - ▶ non-contamination (ensuring continuity of water supply),
 - ▶ the hygiene of the drinkers,
 - ▶ disinfectant residues from drinkers and spouts



Opportunities for social interaction



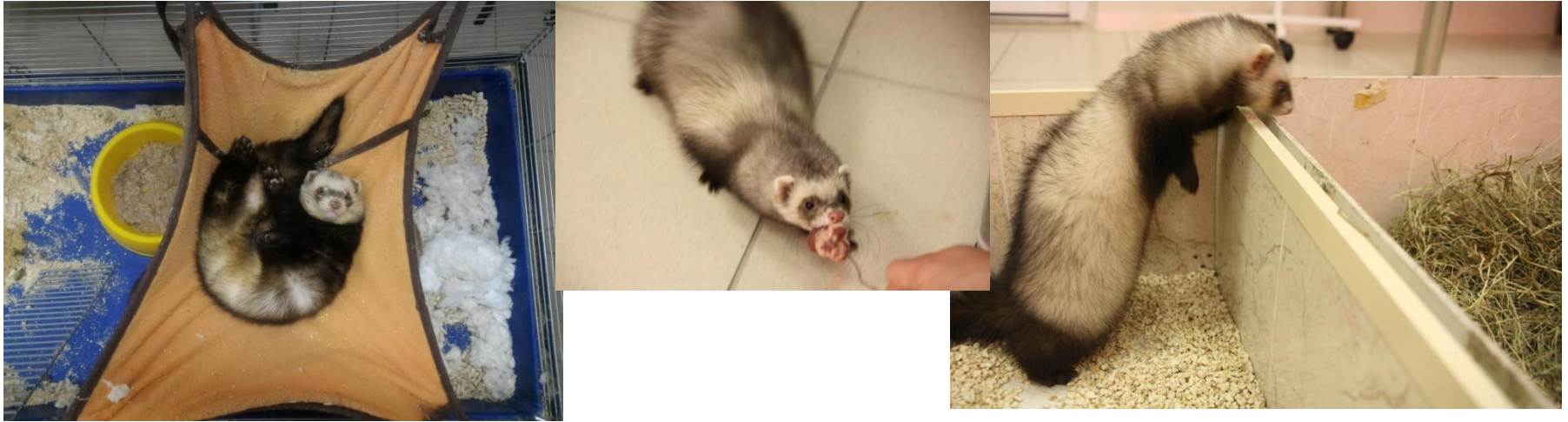
Opportunities for social interaction



The opportunity to realize natural behavior



The opportunity to realize natural behavior



Territory survey, search for shelter, female/male

Hunting, finding food

Hideout in a mink.

Climbing

Accommodation in hangers or on surfaces

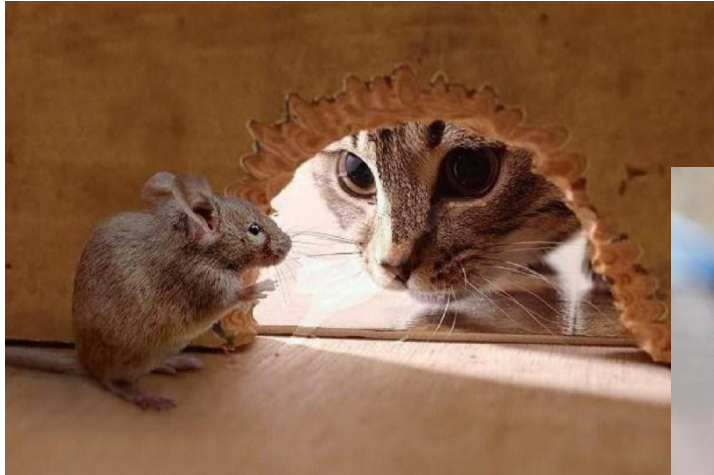
Implementation of motor activity in horizontal and vertical planes

Interaction with a person

Grooming opportunities



Absence of fear (smell, sound, posture...)



Positive reinforcement

- ▶ Dainty
- ▶ Pleasant tactile effect (caress)
- ▶ Game
- ▶ Walking and so on.



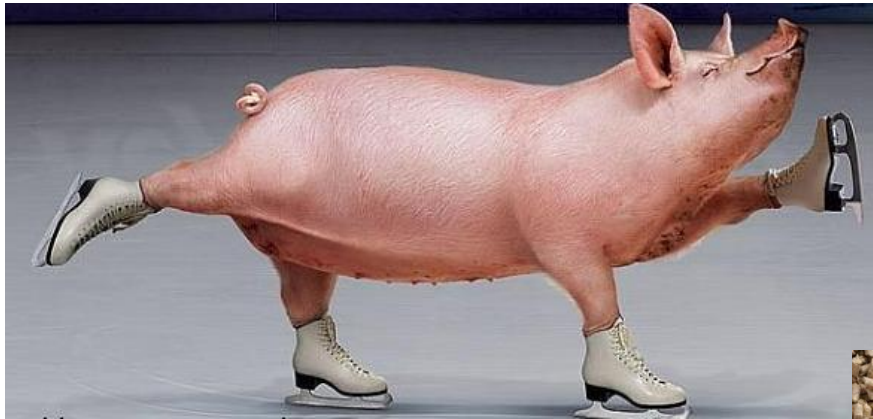
Sanitary monitoring

- ▶ Temperature and humidity
- ▶ Dust and gases in the air
- ▶ Noise and vibration
- ▶ Illuminance (possibility of individual self-regulation)
- ▶ Obtaining physiological doses of UV radiation
- ▶ No pathogenic microflora on surfaces, in the air
- ▶ Lack of contact with animals potentially affected by infectious diseases
- ▶ Hygienic care

Flooring and bedding as one of the factors of hygiene

Floor covering: ceramic tiles are unacceptable, animal paws slide on them. A non-slip material with satisfactory hygienic characteristics is required.

In addition, the animals should be able to dig through the bedding and build nests out of it, preference should be given to solid floors only where the pigs lie in the enclosure.



Temperature and humidity

Purpose of the room	Permissible air temperature		Relative humidity	Air exchange rate per hour (supply / exhaust)
Mini - pig room	depending on the weight of the animals*:		40-75%	10/8 (20/15 at high population density)
	Weight kg	T, °C		
	until 3	30-36		
	3-8	26-30		
	8-30	22-26		
30-100	18-22			
> 100	15-20			
Dog rooms	15-21 °C		not standardized *	10/8 (20/15 at high population density)
Premises for keeping rabbits	15-22 °C		more than 45%	10/8 (20/15 at high population density)
Ferret rooms	15-24 °C		not standardized *	
Facilities for keeping mice, rats, hamsters, degu	18-26 °C		45-65%	
Gerbil Rooms	20-26 °C		35-55%	
Guinea pig rooms	15-26 °C		45-65%	

РД-АПК 1.10.02.04-12;
РД-АПК 3.10.07.02-09;
SP 2.2.1.3218-14;
*GOST 33217-2014;
GOST 33216-2014.

Guidance on maintenance and use of laboratory animals (edited by I.V. Belozertseva), Moscow, 2017;
Appendix A of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes. Strasbourg. -2006;
Handbook of laboratory animal management and welfare/Sarah Wolfensohn, Maggie Lloyd.- 3rd ed.-2003;
Dogs as laboratory animals. I. Institute of Laboratory Animal Resources (U.S.). Committee on Dogs.-1994.

Dust and gases in the air

SP 2.2.1.3218-14 Sanitary and epidemiological requirements for the design, equipment and maintenance of experimental and biological clinics (vivariums)

$\text{NH}_3 \leq 10 \text{ mg/m}^3$,

$\text{CO}_2 \leq 0.15 \text{ vol.}\%$ (2773 mg/m³)

hazard class IV

DST 2.2.5.686-98 Maximum allowable concentrations (MPC) of harmful substances in the air of the working zone. Hygienic standards

NH_3 - up to 20 mg/m³

Dust of plant and animal origin (woolen, down) up to 2

hazard class IV

GOST 30494-2011 entitled "Residential and Public Buildings. Parameters of microclimate in premises".

CO_2 counts 1464 - 1830 mg/m³.

hazard class IV



Noise and vibration

- ▶ "Guide to the Care and Use of Laboratory Animals" noise exposure is higher than 85 dB and can affect both the hearing system and other organs and systems of animals.
- ▶ Annex A of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS No. 123) - recommendations are made to minimize extraneous sound signals in the ultrasonic range.
- ▶ Ultrasound (above 20 kHz) from laboratory equipment, including dripping taps, trolley wheels and computer monitors, can cause abnormal behavior and reproductive disorders in animals.

Sound Level, dBA	Impact	Literary source
73-100 dB	effect on the immune system: increased corticosterone , increased thymus mass.	Archana , Namasivayam , 2000
	causes vasoconstriction of the vessels of the tail in the rat.	Borg , 1978
	effect on the reproductive system: violation of the estrous cycle in females	Gamble , 1976
	effect on the blood system: a decrease in the number of eosinophils.	Geber et al ., 1966
	effect on the immune system: 24 hours after the cessation of exposure - increased levels of IgM and decreased phagocytic activity, on day 7 in the spleen: decreased proliferative activity of lymphocytes, increased activity of NK cells.	Van Raaij et al ., 1996

Noise and vibration

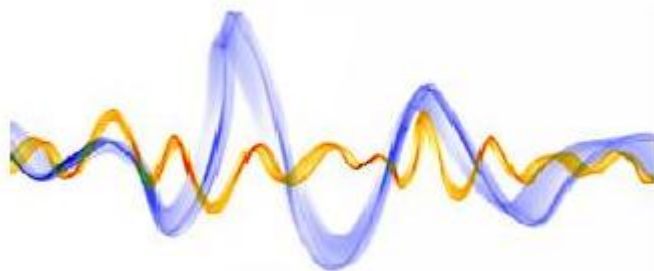
The sources of literature present the following ranges of vibration, which are considered acceptable (i.e. do not cause changes in biometric, physiological, biochemical and other parameters):

human - 41-100 Hz and up to 1.0 m/s²,

mouse - 31-70 Hz and up to 1.0 m/s²,

rat - 31-50 Hz and up to 1.0 m/s²

Rabey et al., 2014



changes with the central nervous system,
heart, hearing organs

Lighting

Purpose of the room	Light intensity, lx
Mini - pig room	50-250 (in the light period, not less than 8 hours) 2.4-4.0 (during rest, sleep)
Dog rooms	323 (light period 10-12 hours)
Premises for keeping rabbits	350 (maximum intensity)
Ferret rooms	* 100 (maximum intensity in the light period (8-16 hours))
Premises for keeping small laboratory rodents: mice, rats, hamsters, gerbils, degu	325-400 (maximum intensity) ** 25-40 (minimum intensity) 130-270 (for selected species) Light period not more than 16 hours

*ГОСТ 33217-2014;

**ГОСТ 33216-2014;

Руководство по содержанию и использованию лабораторных животных (под ред. И.В. Белозерцевой), Москва, 2017;

Code of practice for the housing and care of laboratory mice, rats, guinea pigs and rabbits, Australia, 2004. ГОСТ 33217-2014;

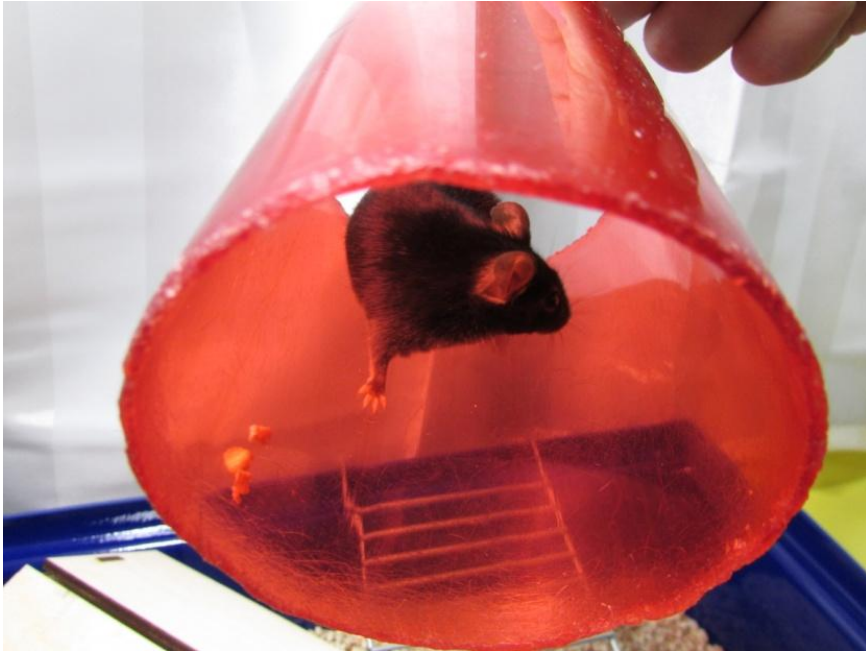
Dogs as laboratory animals. I. Institute of Laboratory Animal Resources (U.S.). Committee on Dogs.-1994;

Handbook of laboratory animal management and welfare/Sarah Wolfensohn, Maggie Lloyd.– 3rd ed.-2003;

Code of practice for the housing and care of laboratory mice, rats, guinea pigs and rabbits, Australia, 2004.

Makarova, M.N.; Rybakova, A.V.; Kildibekov, K.Yu. Lighting requirements for the laboratory animals vivarium and nursery premises (in Russian) // International bulletin of veterinary science. -2017, № 3. –С. 138-147.

Lighting (possibility of individual self-regulation)



- ▶ The most important processes in mammals that can change significantly under the influence of light are: visual orientation, photoperiodic regulation and metabolic regulation.

Providing animals an opportunity to control their own contact with light by means of environmental upgrades (e.g. sufficient bedding material for tunneling, use of environmental upgrades) can reduce excess exposure to light and improve animal welfare.

Receiving physiological doses of UV-radiation

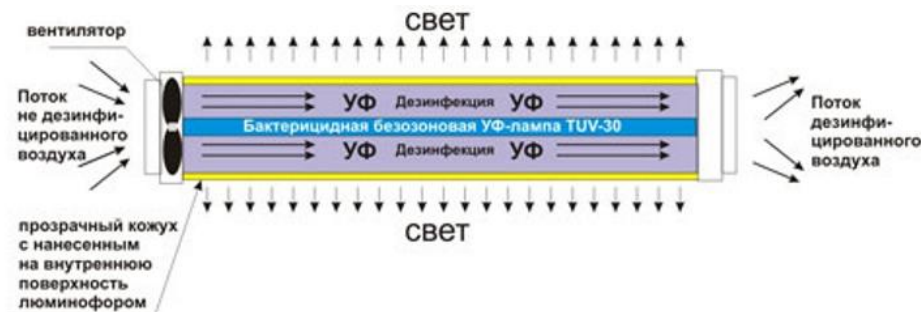
- ▶ Ultraviolet radiation of the middle and near to visible parts of the spectrum (280-380 nm*) has a beneficial (tonic, erythema, antirahit) effect. It is for the sake of this property of ultraviolet radiation hygienic installations are arranged.

UV insufficiency violates the physiological functions of organs and systems of the body: general oppression occurs; decreases the immunobiological reactivity and resistance of the young, especially to colds and infectious diseases.

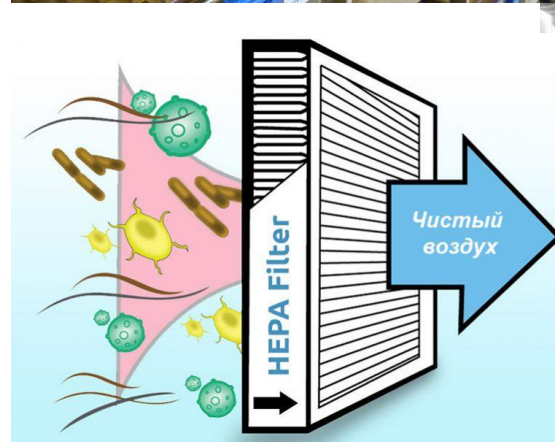


Absence of pathogenic microflora on surfaces, in the air

- ▶ Evaluation of the quality of disinfection of premises and equipment
- ▶ Evaluation of bacterial sowing of work surfaces, tools and equipment.
- ▶ Evaluation of bacterial contamination of air
- ▶ Evaluation of bacterial contamination of cells, content aviaries, environmental fortification elements



Absence of contact with animals potentially affected by infectious diseases



Health control (infectious diseases)

- ▶ FELASA recommendations for the health monitoring of breeding colonies and experimental units of **cats, dogs and pigs**// Laboratory Animals. **1998**. Vol. 32,1-17.
- ▶ Health monitoring of non-human primate colonies. Recommendations of the Federation of European Laboratory Animal Science Associations (FELASA) Working Group on **non-human primate** health accepted by the FELASA Board of Management//Laboratory Animals. **1999**, Vol. 33 Suppl 1:S1-18.
- ▶ Revised recommendations for health monitoring of **non-human primate** colonies (2018): FELASA Working Group Report// Laboratory Animals. **2019**. Vol. 53(5): 429–446.
- ▶ FELASA recommendations for the health monitoring of **mouse, rat, hamster, guinea pig and rabbit** colonies in breeding and experimental units// Laboratory Animals. **2014**, Vol. 48(3) 178–192.

Classifying animals by status

Category	Name	Characteristic	Barrier
1	Conventional (CV)	Carriers of various unknown microorganisms	None (open system)
2	Improved Conventional (MD or Minimal Diseases)	Carriers of various unknown microorganisms	Incomplete barrier system
3	Pathogenic Flood Free (SPF)	C are free of one or more specific pathogenic microorganisms	Barrier system
4	Maximum free from opportunistic flora (SPF)	C are free of several specific pathogens	High Security Barrier System
5a	Microbial (axenic GF)	Hysterectomy Free from any or known life form of microorganisms	isolator
5b	Gnotobiota (GFX categories)	All life forms of microorganisms are known.	Special control isolator

Vaccination, on the example of mini-pigs.

Diseases	Vaccination age
Colibacillosis	1-5 days
Salmonellosis	From 20 days
Pasteurellosis	From 20 days
Swine fever	1.5 months
Leptospirosis	1.5 months
Foot and mouth disease	2-2.5 months
Encephalitis	2 months
Aujeszky 's disease	From 2 days (2 weeks)
Erysipelas	2-2.5 months



Health control (noninfectious diseases)

- ▶ Blood test
 - ▶ Biochemical
 - ▶ Hematological
- ▶ Urine test, feces.
- ▶ Clinical examination
- ▶ Instrumental research methods:
 - ▶ ULTRASOUND
 - ▶ ECG and others.



Non-infectious diseases in the nursery

- ▶ Metabolic diseases
- ▶ Tumor diseases
- ▶ Gastrointestinal diseases
- ▶ Conjunctivitis
- ▶ Diseases of the respiratory system
- ▶ Development anomalies
- ▶ Allergic diseases
- ▶ Pathological course of pregnancy
- ▶ Genital Diseases

Hygiene care

Skin care:

- cleanup
- washing up
- ectoparasite examination



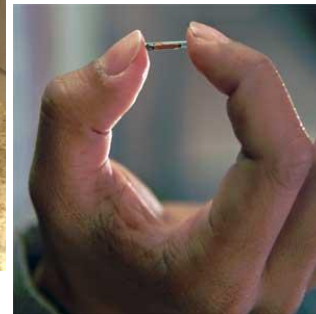
Eyes and ears care:

- cleaning

Hoof care:

- pruning

Identification: chipping



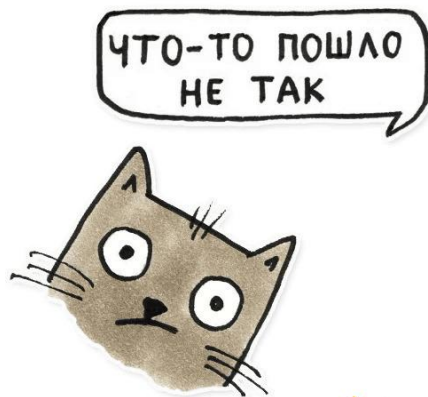
Genetic control

- ▶ Inbred or linear animals: Artificially obtained through sibling crosses for > 20 generations. 100% homogeneity, maximum data homogeneity
- ▶ Outbred or non-linear. Breeding requires a large breeding nucleus (250-350 heads), the percentage of inbreeding is no more than 1%. Characterized by the concept of "runoff". Gives the maximum variety
- ▶ Genomodified (bio-models): Knockouts, transgenes, knockdowns, etc.

Quality control experiment

Control by BEC experts

- ▶ Preparing animals for the experiment - training, adaptation, trust building.
- ▶ Determining the degree of severity of procedures
- ▶ Conformity of performed manipulations to the study plan and SOP
- ▶ The Risk Assessment at the BEC Study Approval Stage Design and take action if "something went wrong" as planned.



 diets.ru

- Selezneva,A.I.; Rybakova,A.V.; Makarova, M.N.; Kovalyova, M.A.; Khodko, S.V.; Makarov, V.G. *Psycho-emotional condition and preparation of the laboratory rats for diagnostic and treatment procedures (in Russian) // International Veterinary Journal. -2013, № 3. –C. 72-78.*
- Selezneva,A.I.; Makarova, M.N.; Rybakova,A.V. *Randomization methods of animals in experiment (in Russian) // International bulletin of veterinary medicine. -2014, №2. –C. 84-89.*
- Rybakova,A.V.; Makarova, M.N. *Marking and identification of the laboratory animals for carrying out of the research works (in Russian) // International bulletin of veterinary science. -2014, №4. –C. 81-90.*

Experimental methods

▶ The injection of investigational substances

Turner P.V., et al. Administration of substances to laboratory animals: routes of administration and factors to consider // J. Am. Assoc. Lab. Anim. Sci. – 2011. – Vol.50. – No.5. – P.600-613.

Rybakova AV, Makarova MN, Kukharenko AE, Vichare AS, Rueffer F-R. Current requirements for and approaches to dosing in animal studies

*//Vedomosti Nauchnogo tsentra ekspertizy sredstv meditsinskogo primeneniya
2018;8(4):207-217.*

▶ Application of correct anesthesia protocols

Cicero L. et al. Anesthesia protocols in laboratory animals used for scientific purposes

// Acta Biomed 2018; Vol. 89, N. 3: 337-342

▶ The use of finger or ear clipping for marking animals

Wever K.E. et al. A systematic review of discomfort due to toe or ear clipping in laboratory rodents

//Laboratory Animals 2017, Vol. 51(6) 583–600

▶ And others.

Model control and validation

- ▶ **Prospective validation**
- ▶ **Accompanying validation**
- ▶ **Retrospective Validation**
- ▶ **Revalidation**

Rat female locomotor activity in the Open Field test, $M \pm SEM$, $n=20$

Test location	Animal sex	Number of squares visited	The number of wall racks
RMC «HOME OF PHARMACY» JSC	males	24,3 \pm 2,5 ($C_V=47\%$)	10,4 \pm 0,8 ($C_V=36\%$)
	females	32,3 \pm 2,1 ($C_V=47\%$)	13,9 \pm 1,1 ($C_V=47\%$)
FGBU IN SPHU	males	39,0 \pm 2,4 ($C_V=28\%$)	11,4 \pm 0,6 ($C_V=25\%$)
	females	23,6 \pm 2,5 ($C_V=47\%$)	10,7 \pm 1,0 ($C_V=41\%$)

Control of pain, stress during the experiment (control of humane endpoints)

- ▶ There must be a documented procedure (SOP)
- ▶ Implementation of the procedure at all key points of the study (the most vulnerable)
- ▶ Making a decision on:
 - ▶ Carry out additional diagnostics
 - ▶ Opportunities for pain relief, drug therapy application
 - ▶ Need for individual accommodation
 - ▶ Euthanasia

The decision to euthanasia is made jointly by study director and the veterinarian!

The journal aims to improve the quality of experimental research by disseminating advanced knowledge about laboratory animals and their use for scientific purposes. Of particular interest are those studies that examine the conditions of laboratory animals in terms of their welfare, reducing the level of stress and pain in the experiment, as well as replacing models on animals by alternative methods. The journal discusses aspects related to the development and validation of new experimental models and the use of new species as laboratory animals in experiments in the pharmacology and toxicology of drugs and medical products.

<https://labanimalsjournal.ru/>

Thank you for your attention!

