

UNIVERSITY OF HAIFA

Guide: Institutional Procedures for the Care and Use of Laboratory Animals Updated: January 2022

This guide must be updated at least once every three years

Table of Contents

Introduction

- 1.1 Principles for working with animals and program implementation
- 1.2 Institutional bodies: Composition and areas of responsibility
- 1.3 The Institutional Veterinarian
- 1.4 Members of the Institutional Committee
- 1.5 General principles for animal care
- 1.6 Reporting to the Animal Testing Council
- 1.7 Researchers' responsibilities
- 1.8 Training for workers involved with animal experiments
- 1.9 Authorization for working with animals
- 1.10 Veterinary assistance and training for ongoing activities

2. Operating procedures

- 2.1 Safety procedures
 - 2.1.1 Fire safety measures and first aid kits
 - 2.1.2 Worker safety in the animal facilities
 - 2.1.3 Health checks and vaccinations
 - 2.1.4 Health conditions
 - 2.1.5 Personal hygiene
 - 2.1.6 Operating procedures for animal experiments using biohazards
 - 2.1.7 Pest control
 - 2.1.8 Surgery
 - 2.1.8.1 Training
 - 2.1.8.2 Location: Operating rooms
 - 2.1.8.3 Planning
 - 2.1.8.4 Performing surgery
 - 2.1.8.5 Post-surgical follow-up

2.1.9 Blood collection

- 2.1.10 Euthanasia
 - 2.1.10.1 Euthanasia methods
 - 2.1.10.1.1 Euthanasia using CO₂
 - 2.1.20.1.2 Euthanasia using barbiturates
- 2.1.11 Medication and drugs
- 2.1.12 Environmental enrichment
- 2.1.13 Social environment
- 2.2 Operating procedures in a rodent facility
 - 2.2.1 Record-keeping for research conducted in the animal facilities
 - 2.2.2 Ongoing care regime
 - 2.2.2.1 Daily care
 - 2.2.2.2 Weekly and bi-weekly care
 - 2.2.2.3 Changing cages
 - 2.2.2.4 Changing water bottles

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Verify the numbering of the sections

Commented [ALE2]: I changed the title of this, since the section only consists of members of the committee It seems like that list should be part of Appendix A, not a separate section, but I left it as is to avoid changing the numbering at this point

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It seems like 1.3 should be Personnel Roles with Institutional Veterinarian under that

Commented [ALE4]: Name in English from:

https://www.gov.il/en/departments/units/animal_testing_unit/govil-landing-page

In another place I saw Council for Experiments on Animals https://research.technion.ac.ii/files/2014/11/EXPERIMENTS-ON-ANIMALS Israel-Law.pdf

which is preferred?

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https://in.bgu.ac.il/fohs/AnimalFacility/Pages/default.aspx https://shnaton.huji.ac.il/index.php/NewSyl/71168/1/2020/ pdf/

I also saw the term "behavioral enrichment" Which is preferred?

			2.2.2.5 I focess for cleaning and distinceting eages and covers
			2.2.2.6 Bottle-cleaning process
			2.2.2.7 Cleaning the animal rooms and corridors
			2.2.2.8 Storing food and sawdust for regular use
			2.2.2.9 Waste disposal
		2.2.3	Monitoring animals' condition
		2.2.4	Monitoring and care of animals in studies with severity levels 4 and 5
		2.2.5	Testing for pathogens
		2.2.6	Improper cage conditions
		2.2.7	Weekends and holidays
	2.3	Emerg	gency procedures
		2.3.1	General
		2.3.2	Preparation for emergencies
		2.3.3	Implementing emergency procedures
		2.3.4	Work plan during emergency situations
			2.3.4.1 Order of operations
		2.3.5	Emergency evacuation
		2.3.6	Evacuation plan
		2.3.7	2 3
		2.3.8	8
		2.3.9	End of the emergency situation
3.	Proce	dures fo	r procuring, housing, and transporting animals
	3.1		al procurement
	3.2		ring young/newborn animals
		3.2.1	Procuring young/newborn animals from outside the university
		3.2.3	Procuring animals from a local source
	3.3		aining animals
		3.3.1	Transporting animals to the animal facilities
		3.3.2	Bringing in new animals
		3.3.3	
		3.3.4	č
		3.3.5	Agreements for exceptions in animal housing arrangements
	3.4		procedure for quarantine
		3.4.1	Entry of employees and researchers into the quarantine unit
		3.4.2	Receiving imported animals into the quarantine unit
		3.4.3	Documentation for receiving animals into the quarantine unit
		3.4.4	Special care for animals in the quarantine unit
		3.4.5	Routine care for animals in the quarantine unit
		3.4.6	Introducing Sentinel Diagnostics into the quarantine unit
		3.4.7	Detection of contamination in a received shipment

Process for cleaning and disinfecting cages and covers

2.2.2.5

3.4.8

Transporting animals

3.5

Release from quarantine

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3.5.1	Procedure for	transporting	animals	from	Haifa	University	to other	research
instituti	ons in Israel							

- 3.5.2 Air transport
- 3.5.3 Moving animals within the university premises
- 3.5.4 Procedure for disposal of animals after an experiment
- 3.6 Ordering equipment and materials
 - 3.6.1 Bringing equipment and materials into the animal facilities
 - 3.6.2 Receiving shipments of food, disinfectants, and sawdust
- 3.7 Entry of workers/researchers into the animal facilities
 - 3.7.1 Behavior and safety procedures
- 3.8 Malfunctions
- 4. Procedures for working with wild animals
 - 4.1 Guidelines
 - 4.2 Ordering/procurement
 - 4.2.1 Collecting animals from and returning animals to natural areas
 - 4.3 Maintenance
 - 4.4 Sanitation activities: cleaning the animal facility rooms
- 5. Procedures for working with aquatic animals
 - 5.1 Structures and controls
 - 5.2 Drainage
 - 5.3 Control of climate, temperature, and ventilation
 - 5.4 Environmental inspection
 - 5.5 Water quality
 - 5.5.1 Removal and neutralization of chlorine and reactive chemicals and biological products
 - 5.6 Life support systems
 - 5.6.1 Water source based on proper supervision and research requirements
 - 5.6.2 Appropriately-sized biological filter for the biomass
 - 5.6.3 Noise and vibration control
 - 5.6.4 Lighting
 - 5.6.5 Adapting the area to physiological, behavioral, and social requirements
 - 5.6.6 Social environment
 - 5.6.7 Limiting escape opportunities; re-capture
 - 5.6.8 Environment enabling access to food and waste removal
 - 5.6.9 Environment is made of nontoxic materials
 - 5.6.10 Environmental, behavioral, and social enrichment
 - 5.6.11 Procedures for contact
 - 5.6.12 Isolation due to disease
 - 5.6.13 Food
 - 5.6.14 Substrate materials
 - 5.6.15 Sanitation, cleaning, and disinfection
 - 5.6.16 Waste disposal
 - 5.6.17 Pest control

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Is the meaning of this sanitation or ongoing?

- 5.6.18 Collecting animals from and returning animals to natural areas
- 5.7 Weekends, holidays, and emergency situations
- 6. Facilities
 - 6.1 Structures and controls
 - 6.1.1 Passageways
 - 6.1.2 Doors in animal facility rooms
 - 6.1.3 Windows
 - 6.1.4 Flooring
 - 6.1.5 Walls
 - 6.1.6 Drainage
 - 6.1.7 Climate and temperature control, ventilation
 - 6.1.8 Lighting
 - 6.1.9 Noise and vibration control
 - 6.1.10 Environmental control

7. Appendices

- A. Organizational chart
- B. Instructions for submitting and responding to research requests
- C. Prevention of Cruelty to Animals Law (Experiments on Animals), 1994
- D. Permit to harm animals in natural areas
- E. Summary of report submissions
- F. Rodent Import Request Form
- G. Table of conditions for housing animals in cages

 Cages: Animals will be kept in cages in accordance with international standards
- H. Guidelines for analgesics and anesthesia for rodents
- I. Schedule templates for activities in the animal facilities
- J. Identification tags
- K. Activity-tracking forms
- L. Blood collection report form
- M. Contact details for emergency on-call personnel
- N. Form for permitting/refusing vaccination

Commented [ALE10]: https://research.technion.ac.il/files/ 2014/11/EXPERIMENTS-ON-ANIMALS_Israel-Law.pdf Corrected name of law (there are two from 1994, I had mistakenly put the Animal Welfare Law title here

Commented [ALE11]: Verify numbering of appendices – in the original there is no appendix 'I

This is the title in the appendix – is it only for rodents or all animals?

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1. Introduction

General Statement

We, at the University of Haifa, are legally, scientifically, and morally responsible for all the living creatures that are dependent on us, including animals used for research purposes.

Therefore, every individual who works with these animals must ensure that the animals always receive the best care possible, and that their suffering is kept to a minimum.

Providing laboratory animals with humane treatment and appropriate care that causes minimal pain requires professional and scientific judgment based on knowledge of animals' needs in general, those of each species, and the needs specific to the research project.

We will not perform any experiment on laboratory animals without considering the value of the information that the experiment may yield. Animal experiments will not be conducted if similar results can be achieved in other ways. If this is not possible, we will use the smallest number of animals, on the lowest rank on the phylogenetic scale, which will enable the experiment to be conducted. We assume responsibility for ensuring that the facilities are suitable and the necessary equipment is appropriate for proper maintenance of laboratory animals. We will exercise discretion and sincere concern for all people who come into contact with the animals.

In order to ensure that the rules given here are followed, and to comply with all legal requirements, everyone who comes into direct or indirect contact with the animals is required to read the procedures and instructions in this guide, and to confirm in writing that they have done so by signing the pledge that they will act in accordance with them.

Responsibility for compliance with the conditions and guidelines derived from the Prevention of Cruelty to Animals Law (Experiments on Animals), 1994 (included in Appendix

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C) is delegated to the institution's administration, specifically the Vice President for Research (hereinafter the "Institutional Director"), the Institutional Animal Care and Use Committee (hereinafter "the Institutional Committee") and the Institutional Veterinarian.

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- 1.1 Principles for working with animals and program implementation

 There are three branches of the animal care and use program at the university:
 - Institutional Director: Vice President of the University and Dean for Research and Development, Prof. Ado Itzhaki
 - Institutional Veterinarian: Dr. Barak Carmi
 - Institutional Committee for the Care and Use of Laboratory Animals: according to the
 requirements of the Animal Testing Council, every institution that receives approval for
 animal experimentation must establish an Institutional Committee for the Care and Use of
 Animals (IACUC). For this purpose, the Institutional Director appoints members of the
 Institutional Committee for a period of three years.
- 1.2 Institutional bodies: Composition and areas of responsibility
 As detailed below, responsibilities pertaining to the care and use of animals at the
 university are divided among three branches: the administration (Institutional Director), the
 Institutional Committee, and the Institutional Veterinarian.
- 1.2.1 The Institutional Director appoints the members of the Institutional Committee and is responsible for allocating the resources necessary for ongoing program implementation.
 Resources include funding for the Institutional Committee's operation and the financial resources and facilities necessary for the maintenance and care of the animals.
- 1.2.2 The Institutional Director's duties include:
 - Allocating resources for carrying out the research program according to the Institutional Committee's recommendations
 - Ensuring that the experiments are conducted in adherence with and according to the Institutional Veterinarian's instructions

Commented [ALE17]: This acronym is introduced, but not used in the guide

• Providing guidance and delegating authority to enable efficient program implementation

The two other branches are under the Institutional Director's authority: the Institutional Animal Care and Use Committee and the Institutional Veterinarian. The Institutional Committee's role is to oversee the program's daily operations and supervise program implementation. The Institutional Veterinarian is responsible for ensuring compliance with standards and requirements regarding the animals' welfare.

1.2.2. The roles of the Institutional Animal Care and Use Committee

As established by the Animal Testing Council, the Institutional Animal Care and Use Committee (IACUC or Institutional Committee) is responsible for implementing the legal provisions and rules in the amended Prevention of Cruelty to Animals Law (Experiments on Animals), 2001. Additionally, the Committee will act according to instructions received from the Council and in accordance with accepted guidelines, even if they are not explicitly stated in the law or rules. The Institutional Committee's role of overseeing the program's daily operations and supervising program implementation includes the responsibility for regularly monitoring and evaluating the plan for the care and use of animals. The university assumes responsibility for providing guidance, background materials, access to the necessary resources, and appropriate training, as needed, to help committee members understand their role and responsibilities and to evaluate the issues brought before them. The Institutional Committee will establish policies and procedural rules for conducting experiments on animals.

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https://research.technion.ac.il/files/2014/11/EXPERIMENTS-ON-ANIMALS_Israel-Law.pdf

which is preferred?

Commented [ALE19]: I added the word 'amended' because above the 1994 law is cited English name of 2001 law from

https://research.technion.ac.il/files/2014/11/EXPERIMENTS-ON-ANIMALS Israel-Law.pdf

The Institutional Committee's duties include:

- Biannual examination of the program for the care and use of laboratory animals
- Formulating guidelines for conducting research and the care and use of animals
- Discussion and approval of requests to perform experiments on animals
- Planning training and certification programs for researchers, students, and employees
- Supervising the experiments being conducted
- Biannual monitoring of animal experiments, in accordance with legal requirements and the Council's guidelines
- Routine inspections (at least semi-annually) of animal breeding and housing facilities
- Addressing various requests to use animals at the university
- Reviewing the report received from the Institutional Veterinarian and making recommendations for improvement
- Submitting an annual report to the Institutional Director on the care and use of animals at the university
- Recording minutes of all Committee meetings, which will be kept for three years

Reports to the Council for Animal Testing:

Reports will be submitted at times determined according to the Council's request (Appendix E):

- Annual Report
 - Details of experiments that were approved and carried out during the previous period, including the actual usage data. In the annual report, the University of Haifa will report on the use of animals at the institution during the previous year,

Commented [ALE20]: The numbering of the appendices was changed in the Hebrew so this is ה' not 'I – it should be changed here in the Hebrew guide as well.

including active approval permits, an institutional summary, the Institutional Committee's permitting activity, and new approval permits.

- o Current membership of the Institutional Committee
- Veterinary reports: The University of Haifa will issue a quarterly veterinary report in the
 first week of April, July, and October, and an annual veterinary report in the first week of
 January. The reports will indicate:
 - Changes in staff at the animal facilities: scope of employment, numbers of employees, and positions;
 - Changes in the scope of activity in the animal facilities: number of active cages;
 types of animals in discontinued experiments; animal rooms in which work was discontinued, etc.;
 - Discontinuation of any type of activity at the facility in the previous quarter or expected for the next quarter;
 - Cases of diseases or epidemics in the animal facilities and the type of treatment provided; any outbreak of diseases or epidemics at the animal facilities must also be reported to the attending veterinarians, on behalf of the Council, as close as possible to the date of the event.
- Reports on changes: The University of Haifa will immediately report to the Council
 regarding any change of the Institutional Committee chairperson or the Institutional
 Veterinarian. Any problem or malfunction that arises will be reported to the Council, as
 close as possible to the date of the event.

1.2.3 Committee Composition

• Two scientists from the faculty who are involved in animal experiments

Commented [ALE21]: ריכוז מוסדי s this an accurate translation? What does it entail exactly?

Commented [ALE22]: I put these as a bulleted list as above, rather than phrases separated with semicolons

 $\begin{tabular}{ll} \textbf{Commented [ALE23]:} Does this mean the Animal Testing Council? \end{tabular}$

- The Institutional Veterinarian
- A faculty member not involved in animal experiments
- A university employee from a non-scientific background

1.3 The Institutional Veterinarian

The Institutional Veterinarian is responsible for the health and wellbeing of all animals at the university. The university must provide the Institutional Veterinarian with sufficient authority, access to all animals, and the resources necessary to administer an appropriate care plan. The Institutional Veterinarian must supervise all aspects of animal care in order to comply with the procedures.

The university must employ a veterinarian to oversee the health and wellbeing of the animals, provide them with medical care, supervise disease prevention measures, minimize the suffering of animals before, during, and after the experiments, euthanize them if necessary, and instruct the staff regarding all these matters (Section 12, The Veterinary Doctor's Law, 1991).

The Council's decision pertaining to the expertise and scope of duties of the Institutional Veterinarian must also be taken into account.

The veterinarian must be a "veterinary doctor" holding a degree with a specialization in laboratory animal medicine or one who has been authorized by the Director of Veterinary Services for the purposes of this law (Section 5 of the Veterinary Doctor's Law, 1991) as qualified to work with laboratory animals, and must have experience working with animals. The university will employ another veterinarian with the appropriate educational qualifications to provide backup for the Institutional Veterinarian when necessary.

 "The institution must employ a veterinarian to oversee the health and wellbeing of the animals, provide them with medical care, supervise disease prevention measures, Commented [ALE24]: Is this the public representative mentioned in the chart below (with the emails etc.)?

Commented [ALE25]: https://leap.unep.org/countries/il/national-legislation/veterinarian-doctors-law-1991

Commented [ALE26]: this is given above; does it need to be repeated?

minimize the suffering of animals before, during, and after the experiments, euthanize them if necessary, and instruct the staff in all these matters." (Section 12, The Veterinary Doctor's Law, 1991).

- The Institutional Veterinarian has the authority to order the termination of any
 experiment and/or to prohibit the conducting of any experiment and/or to ask the
 researcher for clarification and/or to order immediate measures to be undertaken in order
 to ensure the animals' welfare.
- The Institutional Veterinarian supervises the safety, health, and wellbeing of all animals
 within the university's area of responsibility. The Institutional Veterinarian is responsible
 for preventing diseases, minimizing the animals' suffering before, during, and after
 experiments, and euthanizing them when necessary.
- The Institutional Veterinarian is responsible for training researchers and the research
 team, briefing them in the relevant contexts, and assisting with their certification to work
 with laboratory animals.
- The Institutional Veterinarian is responsible for updating the rules and procedures, and
 for transferring and distributing the relevant information in an effective manner to the
 target audiences.
- At any time, the Institutional Veterinarian may enter any animal breeding or
 experimentation facilities, provided that the necessary steps have been taken to prevent
 harm to the experiments or the animals. The Institutional Veterinarian may read any
 document to verify whether it complies with legal provisions.
- The Institutional Veterinarian monitors and supervises all experiments using animals.
- 1.3.1 Requests for conducting experiments on animals

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- A researcher must submit an application for any experiment using animals by completing
 the Ministry of Agriculture's online form. This must be done for any experiment
 beginning in mid-2021 or retroactively from when it began.
- Committee members will receive applications to review at least one week prior to the
 meeting. The Institutional Committee will discuss each request, and may approve, reject,
 or request corrections and/or clarifications. Any amendments to applications will be
 submitted to the Institutional Committee for further review.
- Approval of requests by the Institutional Committee is granted by a majority vote from
 meeting participants, with each participant having one vote, provided that the
 Institutional Veterinarian has approved the request.
- The minimum quorum for a committee meeting is five committee members.
- No discussion will take place without the presence of the Institutional Veterinarian.
- In the event that a request is made by a member of the Institutional Committee, or if there
 is any conflict of interest with a committee member's research, that member will be
 excluded from participating in the discussion.
- When an experiment is approved, the Institutional Committee will determine the duration
 of the permit's validity, which shall not exceed four years.
- Approval permits must be in Hebrew (with an abstract in English) and must include the following details: researcher's name, experiment title, time period of the experiment, approval permit number, license numbers to work with laboratory animals for all researchers involved in the experiment, and clear conditions for ending the experiment.
- Approval permits will be sent to the animal facilities to be used by the researchers in procuring the animals. The researcher must keep all approval permits and protocols

Commented [ALE29]: Is this the head researcher only?

relevant to that experiment in an accessible place. The Institutional Veterinarian must also have a copy of the approval permits. The approval permits must be available in the animal facility rooms for immediate review and use.

The Institutional Committee will not approve any experiment that is identical or similar
to an existing experiment, in accordance with guidelines regarding the submission and
processing of research requests from third-party bodies within the institution.

1.3.1.1 Permits for exceptions

The Institutional Director may authorize an experiment in exceptional situations that pose an imminent danger to public health or to the animals' health if an experiment is not conducted, and when it is not possible to convene the Institutional Committee.

1.3.2 Requests to perform experiments on animals: Special considerations

1.3.2.1 Experiment endpoints and development of humane experiment endpoints

Another way to significantly minimize pain and suffering is to refine an experiment by striving to end it as soon as possible. Measures taken to end experiments early in order to prevent or end intractable pain and/or severe suffering are referred to as humane endpoints. It is essential that humane endpoints ensure that the goals of the experiment will be achieved, despite its early termination. Ideally, an experiment will be designed in such a way that the endpoint will occur before the onset of suffering and pain, to the extent that this is possible. Additionally, conditions for ending an experiment or removing animals from an experiment even if its goals were not achieved will include general health indicators and criteria specific to the experiment model.

1.3.2.2 Requests for pilot trials

These requests are submitted according to the same procedure as any other request for animal experimentation, and are reviewed by the Institutional Committee.

Commented [ALE30]: What kind of use?

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Commented [ALE32]: https://www.research.psu.edu/anim alresourceprogram/experimental-guidelines/humaneendpoints

Commented [ALE33]: I took out a redundant phrase, verify the shortened version is accurate.

1.3.2.3 Genetically modified animals

For any genetically modified animals, the Institutional Committee must be informed if it is expected that the genetic modification will negatively affect the animal's behavior.

1.3.2.4 Pain-relieving medications

Experiments should be designed to avoid pain or suffering. If this is not possible, the researcher will prepare an appropriate plan for the use of analgesics, anesthesia, or other pain-relieving measures such as anti-inflammatory drugs, antibiotics, or sedatives. The Institutional Veterinarian will be consulted as necessary. In addition to using pain-relieving medications, modern medical techniques that significantly reduce the need to use invasive procedures to collect data for the experiment should be used whenever possible. The University of Haifa should constantly upgrade the animal facilities with leading technologies to ensure they are equipped with every available means to prevent unnecessary suffering of the animals.

A list of analgesic drugs and anesthetics, including dosages and methods for administration, appears in Appendix H.

1.3.2.5 Use of restraint devices

Approving the use of restraint devices will take into consideration that "restraint devices should be suitable in size, design, and operation to minimize discomfort, pain, distress, and potential injury to the animal" (National Research Council, 2011, p. 29) The Institutional Committee will only approve use of restraint devices if there is no alternative and if they are used for the shortest possible time to achieve the experimental results. The animals will undergo a process of becoming accustomed to the device. If an animal does not become accustomed to the device, making it impossible to obtain data from it, that animal will be removed from the experiment. The researcher will conduct daily monitoring and documentation, and the

Commented [ALE34]: Should the term analgesic drugs be used here? Or is that too specific?

Commented [ALE35]: Verify the numbering of the appendices – some are not labelled or mislabeled in the original

Commented [ALE36]: I see both terms restraint device and restraining device used in the literature – is there a preference?

Commented [ALE37]: This is a direct quote from the NRC manual; I added the citation information The quote actually ends: "... injury to the animal and the research staff."

Institutional Veterinarian will conduct regular inspections to examine whether the restraint devices are causing any diseases, behavioral changes, or other problems.

1.3.2.6 Watering and feeding regimen

Certain studies (behavioral studies, brain sciences, etc.) require a specific watering and/or feeding regimen. Effort must be made to protect the animals' welfare by imposing the minimal restrictions that will allow the researcher to obtain experimental results.

- The approval permit granted by the Institutional Committee includes the requirement that
 the researcher must monitor the animals and keep written documentation of their daily
 food and water consumption.
- The animals must be weighed at least once a week. In experiments with a severe feeding
 restriction, the Institutional Committee can require weighing at more frequent intervals
 (more than once a week). If there is a significant weight loss (10%), the Institutional
 Veterinarian will give instructions, which must be followed.

1.3.2.7 Procedures involving multiple surgeries

Surgery should be avoided whenever possible, especially multiple surgeries on one animal. However, the Institutional Committee will approve this under several conditions:

- The animal's health must be protected.
- The procedure is a significant and necessary aspect of obtaining experimental results.

The Institutional Committee will not approve surgeries on a single animal for multiple experiments. If the Institutional Committee approves more than one surgery on an animal, it will be closely monitored by the attending veterinarian.

1.3.2.8 Prior knowledge needed for field studies

Commented [ALE38]: I think there is a spelling mistake in the Hebrew לנתר linstead of

Commented [ALE39]: This is the term used in Guide for the Care and Use of Laboratory Animals: Eighth Edition (2011).

(rather than the more literal 'responsible veterinarian')

Commented [ALE40]: What is meant by field studies in this context?

Researchers conducting research must be familiar with zoonotic diseases, safety, procedures, and laws pertaining to their research area.

1.4 Members of the Institutional Committee:

Name	Telephone	Email
Prof. Ado Itzhaki, Vice President and Dean for Research and Development, member by virtue of his position	04-8240622	izhaki@research.haifa.ac.il
Prof. Inna Gaisler, Committee Chair	04-8249674	igsalomon@psy.haifa.ac.il
Dr. Shai Gabay, member	04-8249747	sgabay@psy.haifa.ac.il
Dr. Estee Kurant, member	04-6647982	ekurant@univ.haifa.ac.il
Dr. Barak Carmi, Institutional Veterinarian	04-8249761	bcarmi@univ.haifa.ac.il
Mr. Salman Abu-Rochan, public	04-8391173	eco.salman@gmail.com
representative		
Ms. Shoshi Zalka, committee coordinator	04-8249278	szalka@univ.haifa.ac.il

For an organizational chart, see Appendix A.

1.5. General principles of animal care

This procedural guide for the use and care of animals highlights the fact that everyone involved in using or breeding animals for research or teaching purposes must take responsibility to protect the animals' wellbeing. This guide is based on the American National Research Council guide (NRC, 2011), with adjustments made according to Israeli laws and regulations. Scientists and veterinarians cooperatively wrote this guide, with the goal of maintaining scientific rigor and the integrity of biological research that uses laboratory animals, so that it will meet the expectations held by their colleagues and society at large.

1.5.1 The 3Rs principle

A practical approach to the decision-making process pertaining to the care and use of animals in scientific research is known as the 3Rs principle: replacement, reduction, and

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But I left it for now, to avoid renumbering all the sections.

Commented [ALE42]: https://carmelltd.haifa.ac.il/index.php/explore-tech-

inn/huresearchers/177-gaisler-salomon-inna
This is how she is listed on her website, should Salomon be added?

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Commented [ALE44]: https://sciences.haifa.ac.il/faculty_pages/estee-kurant/

Commented [ALE45]: https://sciences.haifa.ac.il/adminstaff/carmi-barak-carmi/

Commented [ALE46]: Some of the items under the Institutional Veterinarian section seem like they should go here (genetic modification, restraint devices, multiple surgeries, etc.)

Commented [ALE47]: https://ec.europa.eu/health/scientificcommittees/opinionslayman/en/non-human-primates/glossary/tuv/three-rs-principle.htm

Commented [ALE48]: I combined some redundant sentences; verify nothing essential was inadvertently left

refinement. The University of Haifa has adopted this approach, and this guide provides a basis for developing a comprehensive program for the care and use of animals at the university according to this principle, and to continuously strive to improve the program.

Russell and Bartz (1959) published a practical approach for researchers to use when considering the use of animals in research, which they termed the 3Rs principle. Over the years, the 3Rs principle has evolved into an internationally accepted approach to the design of humane studies using animals. The 3Rs have a hierarchical order. Replacement refers to using a method that does not require the use of animals whenever possible. Reduction involves a qualitative aspect, which refers to using the animals that are lowest on the phylogenetic scale in order to meet the research objectives; and a quantitative aspect, which refers to using the minimum number of animals that will yield the experimental results. Refinement refers to using a variety of tools and methods in order to eliminate or minimize animals' pain and suffering.

Reduction and refinement are assessed on a case-by-case basis. It is not acceptable for a researcher to justify doing additional experiments using the same animal by invoking the reduction argument. Using animals in multiple experiments should be minimized. Any proposed experiment should be weighed against experiments that have already been conducted.

The following are principles for ethical and acceptable use of animals for research purposes:

- Permits for experiments on animals will not be granted if the research goals can be achieved through reasonable alternative methods.
- The smallest possible number of animals needed to conduct the experiment will be used.
- When conducting experiments on animals, effort will be made to minimize the pain and suffering they are caused.

Commented [ALE49]: The full reference should be given at the end in the sources section (or in footnotes).

Commented [ALE50]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6826930/

It is written this way in the literature

The University of Haifa adheres to these principles, and they guide the Institutional Committee's work.

The University's procedures were established in accordance with the Prevention of Cruelty to Animals Law (Experiments on Animals), 1994:

- Experiments that cause pain or suffering will not be performed without using general or local anesthesia or analgesia.
- Experiments that involve relaxing peripheral muscles without using general anesthesia
 are prohibited, unless using anesthesia invalidates the fundamental goal of the
 experiment, or if anesthesia is expected to cause greater suffering during the experiment.
 In such cases, alternative measures must be taken to minimize pain and suffering.
- Experiments will use animal species that are the lowest possible on the phylogenetic scale that enables the experiment to be conducted without inhibiting its goals.
- When animals are to be euthanized after an experiment, this shall be done before it
 regains consciousness, whenever this is possible. Animals that experience, or are
 expected to experience, intense pain or prolonged suffering as a result of the experiment
 will be euthanized even if the goals of the experiment were not achieved.

If there are doubts regarding the degree of pain or suffering, the Institutional Committee will make a decision that protects the animal and prevents any unnecessary pain and suffering.

Commented [ALE51]: Should the 2001 version be cited here as well?

Commented [ALE52]: Verify this is the accurate term

1.6 Reporting to the Animal Testing Council

The Institutional Committee for the Care and Use of Animals will report to the Animal Testing Council in accordance with the schedule received from the Council, as detailed in Appendix E.

1.7 Researchers' responsibilities

Researchers are responsible for ensuring that the experiments they conduct are in accordance with the Prevention of Cruelty to Animals Law (Experiments on Animals), 1994 (see Appendix C) and any amendments to its rules and regulations, Animal Testing Council regulations, and University of Haifa guidelines. It is the researchers' responsibility to be familiar with the law, regulations, rules, and guidelines and to act in accordance with the sections that are relevant to their work. Researchers' additional duties include:

- Submitting a request to conduct an experiment using animals by completing an online form on the Animal Testing Council website.
- Providing detailed documentation of their activities in the relevant area. This
 documentation must be saved and available for review for two years from the end of the
 research project in the framework of which the experiment was conducted.
- Reporting any malfunction, abnormality, or problem that arises during their work to the
 Institutional Veterinarian, as soon as possible. The Institutional Veterinarian will then
 report this to the Institutional Committee.
- Tracking genetically modified animals and reporting any unusual issues related to these animals to the Institutional Committee and the Institutional Veterinarian.

Commented [ALE53]: Can this short section be combined with another?

Commented [ALE54]: Verify numbering of appendices

Commented [ALE55]: Should the term "head researcher" be used here?

- Ensuring that all members of their laboratory accurately and completely follow the
 procedures approved in the permits as well as the Institutional Veterinarian's instructions
 and guidelines.
- 1.8 Training workers involved with animal experiments

All employees involved in animal experiments must receive appropriate training. They must pass a course for working with animals recognized by the Animal Testing Council that is offered through the research institution or another similar institution. The course will provide a certificate upon completion. A digital copy of the certificate must be available on file with the research institution.

The training course must be completed prior to any work with animals. In exceptional cases in which it is not possible to complete the course (for example a student who arrives at the institution towards the end of the academic year), the student must receive basic training from the Institutional Veterinarian and will be granted a temporary permit to work with animals for up to six months, after which they will be required to complete the course.

The training course consists of a theoretical part and a practical part.

The theoretical part includes: explanation of the Prevention of Cruelty to Animals

(Experiments on Animals) Law; the 3Rs principle; methods for pain relief and minimizing suffering including anesthesia, analgesia, aseptic surgery, monitoring post-surgery recovery, and euthanasia; the responsibilities of the institution, the Institutional Committee, and the researchers; forms and reporting procedures related to the work; safety measures for working with animals (including zoonotic diseases); procuring animals, and transporting animals.

The practical application part includes: animal care and maintenance, moving animals in and out of cages, recognizing emergencies and providing treatment during emergencies,

Commented [ALE56]: Should these be bullet points?

administering anesthesia, preparing animals for surgery, post-surgery recovery treatment, and euthanizing animals.

At the end of the course, participants will take a test and receive a numbered completion certificate, signed by the Institutional Veterinarian.

1.9 Authorization for working with animals

For research staff members to receive authorization to work in the university's animal facilities, they must meet each of the following conditions:

- a) Passing a course on working with laboratory animals at an institution authorized for this purpose by the Israel Animal Testing Council
- b) Being listed in the experiment protocols
- c) Receiving training at the University of Haifa animal facilities
- d) Reading this procedural guide and confirming, in writing, a commitment to work according to its rules
- e) Receiving permission from the Institutional Director
- f) Receiving safety training in accordance with university procedures

Animal handlers are exempt from the first two conditions, but are bound by the others.

The Institutional Committee's secretary will keep a file of all authorization certificates for working with animals. Employees who do not present such a certificate will not be granted a permit for working with animals. The Institutional Veterinarian is responsible for enforcing these regulations.

1.10 Veterinary assistance and training for ongoing activities

 $\label{lem:commented} \begin{tabular}{ll} Commented & [ALE57]: The Hebrew says 5 conditions but 6 are listed \end{tabular}$

I put letters instead of numbers to avoid confusion with the section numbers; they could be bullet points

Researchers and other employees require assistance and support in the framework of their ongoing activities working with animals:

- During regular operating hours, an attending veterinarian with knowledge and experience in working with rodents will be present in the animal facilities.
- The attending veterinarian will provide guidance to the workers.
- The veterinarian will be available to provide explanations and training regarding animal care and maintenance, and any procedures necessary for working with the animals.

2. Operating Procedures

2.1 Safety procedures

Safety procedures in the animal facilities will be followed in accordance with general safety procedures as they appear on the university's online portal.

Information about employees will be stored in a place that is not accessible to unauthorized people.

2.1.1 Fire safety measures and first aid kits

Each room in the animal facilities must have access to each of the following:

- Fire detection systems and fire extinguishers
- First aid kits and bite kits
- Eyewash stations
- Emergency showers
- Medical care providers

2.1.2 Worker safety in the animal facilities

- Animal facility employees must have access to areas that are separate from the animal rooms, such as office workspaces with computers, places to rest, a dining hall, and meeting rooms for staff meetings and training sessions.
- All individuals who come into contact with animals must receive appropriate training.
 They must take the maximum preventative measures to protect themselves from contracting diseases.
- As part of their certification, researchers and other animal facility employees will
 undergo zoonosis training provided by the Institutional Veterinarian, as well as safety
 training provided by the safety department regarding chemical, microbiological and
 physical hazards, handling of waste materials, and other potentially dangerous aspects of
 the work.
- Every individual employed in the animal facilities must receive annual training on workplace safety.

2.1.2.1 Safety and security

Every individual working in the animal facilities must ensure that they work in a safe and secure manner, without taking unnecessary risks.

- Uniforms are provided to animal facility workers to wear during work hours. Green
 gowns are for the rat rooms, blue gowns are for the mouse rooms. Uniforms must be sent
 to the laundry to be washed regularly.
- Safety equipment will be provided and available as needed. All employees will be issued permanent or disposable safety equipment and protective clothing including: head

Commented [ALE58]: This is discussed above.

Commented [ALE59]: And being injured in other ways?

coverings, gloves, smocks, masks, aprons and hearing protection headsets. Individuals entering the animal facilities who do not regularly work there will be given disposable safety equipment. Additional safety items will be provided as needed.

Only work shoes may be worn in the animal facilities.

2.1.3 Health checks and vaccinations

- Employees must present a health certificate before working with animals. This certificate
 will be kept on file in the archives.
- Tetanus: It is recommended that all employees working with animals receive a tetanus vaccine. Any employee who chooses not to receive a tetanus vaccine must sign a form confirming that they made this decision voluntarily. (Appendix N: Procedure 07-57)
- Zoonosis vaccines: zoonosis are animal diseases that can be transmitted to humans
 through normal contact or animal bites or scratches. In the event of an injury to an animal
 facility worker, the attending veterinarian will inform the health clinic of the possibility
 that there is zoonosis in the animal facility.

2.1.4 Health conditions

- Allergies: people working in the animal facilities may develop allergies to certain
 animals. Depending on the severity of the allergy, workers will be provided with
 appropriate protective clothing, or may be assigned to work with different species or
 animal populations. Latex-free gloves are provided for workers who are sensitive to latex.
- Pregnancy: if any animal facility worker becomes pregnant, the Institutional Veterinarian
 must be notified in sufficient time to minimize that employee's exposure to diseases that
 may cause complications during pregnancy, in case such a disease occurs in the animal
 facilities.

Commented [ALE60]: I added hearing protection into this list, rather than in the first sentence

Commented [ALE61]: This seems to repeat the first sentence; is it needed?

Commented [ALE62]: This section doesn't mention requirements for vaccines.

2.1.5 Personal hygiene

- Hygienic supplies necessary for showering, such as soap, shampoo, and towels, will be provided.
- Regular showers: all staff members are required to shower after finishing work or any
 time they have become unclean to an extent that they may present a danger to themselves,
 others, or the animals.
- Quarantine areas: workers must wear special uniforms in the quarantine areas that are not worn in other areas.
- 2.1.6 Procedures for animal experiments that involve biohazard substances

Biological substances may be used only after receiving approval from the Institutional

Biosafety Committee, under the authority of Prof. Fuad Fares, and the approval of the University

Safety Officer, Ayelet Anati.

- Researchers with special requirements will be given permission to use separate work
 rooms, for a limited and predefined time period, after prior coordination with the
 Institutional Veterinarian. If necessary, entry into these rooms will be restricted to
 authorized individuals only.
- Virus injections will be carried out in designated areas and only after receiving practical instruction from a laboratory manager experienced in working with viruses.

2.1.7 Pest control

- The Institutional Veterinarian will prepare a pest control program against various types of pests.
- The animal facilities will be regularly disinfected according to the pest control plan.

Commented [ALE63]: It seems the order of these should be reversed (first requirement to shower, then provision of supplies)

Commented [ALE64]: This seems like a more general term than biohazard substances. Is it accurate? בחומרים ביולוגיים

 $\label{lem:commented} \textbf{[ALE65]:} \ \mathsf{I} \ \mathsf{found} \ \mathsf{this} \ \mathsf{name} \ \mathsf{of} \ \mathsf{the} \ \mathsf{committee} \\ \mathsf{here:}$

https://resau.haifa.ac.il/2017/03/30/facility-safety-plan/and similarly named committees at other universities

Commented [ALE66]: https://www.linkedin.com/in/fuadfares-a5b51019a/?originalSubdomain=il English spelling of name

Commented [ALE67]: https://www.linkedin.com/in/ayeletanati-86637342/?originalSubdomain=il

2.1.8 Surgeries

Some research requires surgeries on animals. The surgeries must be approved by the Institutional Committee and must be planned so that there will be as little damage as possible to the animal.

2.1.8.1 Training

Researchers who perform surgeries must undergo training for aseptic surgeries. This training may be given by a veterinarian or a researcher who has received appropriate training and has experience in this field.

2.1.8.2 Location: Operating rooms

Operating rooms will be used for this purpose only. Operating rooms will be cleaned and disinfected so as to maintain conditions that are as sterile as possible. The room will contain the necessary equipment and supplies. Regular inspections will be conducted to verify all materials' expiration dates and the dates on which equipment and devices were disinfected. There must be appropriate lighting in the room. Bins will be provided for the disposal of needles, scalpels, and biological waste.

2.1.8.3 Planning surgery

All aspects of the surgery should be prearranged, planned, and documented in advance, including: consultations with the attending veterinarian, the anesthetics and analgesics to be used, the course of the surgery, and post-surgical follow-up. There must be a treatment plan in case the surgery is not successful and the animal is harmed during or after the surgery. Before the surgery, it must be ascertained that the sterilization period for the operating room has not expired.

2.1.8.4 Performing surgery

Commented [ALE68]: It seems like some of the issues discussed above regarding surgeries should be in this section (multiple surgeries, pain relief measures, etc.)

 $\label{lem:commented} \textbf{[ALE69]:} \ \ \text{There was a note here in the original that says}$

<u>להמשיך מכאן</u>

Is that relevant to the translation?

The surgery should be performed under suitable conditions in a room that has been designated for this use and approved by the Institutional Veterinarian. Sterilized surgical instruments must be used. The surgeon must wear gloves and a mask and observe all rules of aseptic surgery.

2.1.8.5 Post-surgical follow-up

The animal's recovery must be monitored after the surgery. This includes checking its temperature and doing a general behavior check. The researcher and animal facility team, including the attending veterinarian, will conduct tests and document the results for approximately one week following the surgery. After that, the animal may be returned to its cage provided that it has resumed normal behavior.

Even if it is known beforehand that the animal will not survive the surgery, it must be performed in a designated operating room under sterile conditions, in order to prevent unnecessary injury to the animal. Every surgical activity must be recorded on the follow-up forms that are kept in the animal facility rooms with the research ethics protocols.

2.1.9 Blood collection

Blood sampling is one of the most common procedures performed on laboratory animals. The volume of blood collected, the frequency, and the method used are dictated by scientific considerations, such as the physiological effect of significant blood loss on the analysis and the reliability of the experimental results, as well as the animal's welfare. See Appendix L.

It is important to minimize the number of puncture sites and not to repeat the procedure at the same site multiple times. Guidance and training are necessary for successful blood collection and for minimizing harm to the animals. Samples taken from different blood vessels (e.g., central and peripheral) may yield different values.

Commented [ALE70]: And other vital signs?

Commented [ALE71]: The NRC guide uses the term nonsurvival surgery; should that be used here?

2.1.10 Euthanasia

Euthanasia is a humane act, conducted using methods that lead to unconsciousness and quick death, without causing the animal pain or distress. Euthanasia methods should be conducted in accordance with American Veterinary Medical Association guidelines, unless there is a justified scientific or medical reason for an exemption, and only if it has been approved by the Institutional Committee.

- When euthanizing an animal, every effort will be made to prevent, to the greatest extent
 possible, any physical, mental, or emotional harm to the animal. Euthanasia will be
 conducted in accordance with procedures determined by the Institutional Veterinarian.
- The time from the start of the euthanizing procedure until the animal's death should be as short as possible.
- The most appropriate euthanasia method for the experiment and for the animal species should be used.
- The individual performing the euthanasia must be qualified and skilled in the selected
 method. The procedure will usually be conducted by an animal facilities employee who
 has received appropriate training. If it is necessary for a researcher to euthanize animals,
 s/he should receive appropriate training from one of the animal facilities' veterinarians.
- Euthanasia should not be performed without proper training, as this harms the animals.
- Euthanasia procedures will be conducted according to the research protocols, as approved by the Institutional Committee.
- The attending veterinarian should examine any animal that appears to be suffering or in
 distress. The veterinarian has the authority to decide to euthanize the animal in order to
 prevent further suffering. In such cases, the veterinarian must inform the researcher.

2.1.10.1 Euthanasia methods

2.1.10.1.1 Euthanasia using CO₂ + isoflurane

- Euthanasia should be performed in cages designed for this purpose, and not in any other
 place in the facility.
- Animals should not be overcrowded in the euthanasia cage.
- The euthanasia process must be conducted immediately. If a delay is expected, the
 rodents must be provided with food and water and not be overcrowded in the cage, until
 the euthanasia can be carried out.
- The process will usually be performed by first administering a flow of isoflurane anesthetic gas at a concentration of 5%.
- During this procedure, the following safety regulations must be observed:
 - Signs must be posted clearly marking the room in order to restrict unauthorized entry during the euthanasia process.
 - After activating the isoflurane vaporizer, workers must wait outside the room. The
 door to the room must be kept closed.
 - When the isoflurane flow is finished and vaporizer activity ends, wait for the air pressure to drop, then turn off the vaporizer without opening the device's lid.
 - Regularly check the pipes that deliver the isoflurane for leaks by applying soapy foam and repair any leaks.
- Once it is confirmed that the animals have been deeply anesthetized, a flow of CO₂ gas will be directed into the euthanasia chamber, at a pressure of 20-30 bar.
- After opening the CO₂ gas balloon tap, wait outside the room for approximately 10 minutes, with the outer door closed.

Commented [ALE72]: In the Hebrew here it says ההרדמה Which means anesthesia, but the section is on euthanasia, correct?

Commented [ALE73]: Here the word ההקרבה Is used, but I used euthanasia in all cases in English. Are there other terms that should be used? The only other term I am aware of in English is "humane killing" or "mercy killing" but those seem less scientific.

Commented [ALE74]: Only rodents? Are other animals ever euthanized?

Commented [ALE75]: The issue of the dedicated facility is already given above.

Commented [ALE76]: https://www.kentscientific.com/products/vetflo/

Commented [ALE77]: this site suggests soapy water, is that more accurate?

Commented [ALE78]: This phrase seems more relevant to this statement than the next one, where it appears in the original.

- Stop the flow of CO₂ by closing the balloon tap. Verify that the animals have been fully euthanized. Open the vacuum tap for 7 minutes so that excess gases will be removed directed from the euthanizing device and directed outside the building. The lid of the device should not be opened during this time.
- Ensure there is proper ventilation in the area. Do not keep doors closed during holidays, weekends, or vacations.
- In euthanasia using only CO₂, first administer the gas slowly (10%-20% of the chamber volume per minute). The flow rate should be increased only after the rodents are deeply anesthetized. Verify the rodents have been fully euthanized before stopping the gas flow.
- After removing the carcasses, the euthanasia chamber should be washed in the sink with soap and water and left to dry. Alternatively, the chamber may be disinfected with aerosol and dried.
- Young rodents under the age of 14 weeks are resistant to the effects of CO₂, so an
 alternate euthanasia method must be used, for example anesthetizing them with CO₂ then
 injecting an anesthetic such as 0.1 ml of pentothal into the abdominal cavity.
- Researchers who have rodents to be euthanized by animal handlers should leave the
 animals in their original cages, clearly designate which animals are intended to be
 euthanized, authorize this with their signature, and notify the animal handlers. The
 researcher must ensure that the cage has food and water and that the rodents are not
 overcrowded.
- Dry ice is not an acceptable method of euthanasia due to the inability to control the amount of gas released.

2.1.10.1.2 Euthanasia with barbiturates

Commented [ALE79]: This seems like it should go under safety guidelines. Perhaps all the safety rules should be put separately after the procedure.

- Inject Pentobarbital Na at a dose of more than 100 mg per kg IP.
- Wait several minutes.
- Check the animal's breathing and color to verify it was fully euthanized.

2.1.10.1.3 Euthanasia via terminal phlebotomy (rodents only - mainly mice)

- Anesthetize the animal with isoflurane (See Appendix F).
- Lay the animal on its back.
- Stretch the left front limb to reveal the chest area.
- Insert a 27G needle between the fourth and third ribs.
- Gently aspirate blood.
- After finishing the procedure, verify that the animal is not breathing and its heart is not beating.

2.1.11 Medications and drugs

All medications and drugs (including, for example, cannabis) must be purchased in accordance with the laws, regulations, and university procurement procedures. Medications and drugs are defined according to the university's safety department. The required drugs must be reported to the university safety department and may only be purchased with their approval.

Drug procurement is under the responsibility of the Institutional Veterinarian.

- All medicine and drug purchases must be reported.
- Follow-up reporting must be conducted, including administration of the drugs and disposal of drugs that have passed their expiration date.
- Records must be available at all times and provided in response to any request.

Commented [ALE80]: This was a bullet point, but since it is a different method, it seems it should have its own number. Verify.

Also verify the term phlebotomy

It could be terminal bleeding or terminal blood collection

- At least once per year, the Institutional Veterinarian will review the list of drugs being used in order to substitute drugs according to new knowledge in the field.
- Medications and drugs will be stored according to the laws and procedural guidelines. If necessary, they will be kept in a safe or a dual lock safe.
- Drugs will be administered according to the university's procedures and the safety department's instructions regarding use of dangerous substances.

2.1.12 Environmental enrichment

The main goal of environmental enrichment is to improve animals' psychological wellbeing by providing sensory and motor stimulation using structures and resources that allow for the expression of the various species' typical behaviors.

- Rodent cages will have a substrate material that allows them to dig and nest.
- All animal cages will include enrichment structures and resources.
- If it is not possible to add enrichment resources to certain animal cages, this must be
 reported to the Institutional Veterinarian and the Institutional Committee in order to
 receive approval for this exemption.
- Change, diversification, and renewal of the enrichment resources should be considered once a year.
- The Institutional Committee will conduct annual examinations on the use and effectiveness of the enrichment resources.

2.1.13 Social environment

Animals need social interaction and activity as an essential part of their development and wellbeing.

Commented [ALE81]: This is the phrase used in the NRC guide

- Animals will not be isolated in separate cages.
- If an experiment necessitates keeping an animal isolated, this will only be done with the approval of the Institutional Committee.
- The isolation time will be the shortest possible for the purpose of the experiment.
- Any animal kept in isolation will be provided with additional enrichment resources.
- 2.2 Operating procedures in the rodent facility

All routine care activities and examinations will be recorded by the animal facility employees who perform these activities as part of their regular duties. These routine activities will be recorded daily in an activity-tracking form posted at the door of each animal room (see Appendix I). All permits will be kept in the relevant animal rooms. Along with each permit will be a form tracking all the special treatments or surgeries performed on the animals (Appendix K).

- 2.2.1 Record-keeping for research conducted in the animal facilities
 - A daily report will be made by the person in charge of each room, which includes contact information (name and phone number), room temperature and humidity, and the dates on which the room was cleaned, the cages were cleaned and the substrate material changed, and the carts for transporting cages were cleaned. This documentation is done digitally and sent directly to the veterinarian's email and mobile phone.
 - Each room must have a current copy of the experiment approval permits. For follow-up
 activities that are part of ongoing studies, the permit for the original experiment must also
 be attached and available on computers near the animal rooms.
 - If the permit specifies a tracking regimen, or if multiple procedures are being performed at different times, a computerized progress report will be made on the procedures and

Commented [ALE82]: Should this be animal facility?

monitoring the health of the animals in the room. This report will include: the date of the visit to the room and/or performance of the procedure (injections, weighing, surgery, measurements, etc.).

- Each cage will have an identification card indicating the required information: the current permit (experiment approval) number, the name of the responsible researcher or responsible student and their mobile phone numbers, the animals' species, sex, age, the number of animals, the date they were placed in the cage, and the severity level of the pain and suffering expected for the experiment (levels 4, 5 in bold).
- An online monitoring chart will be maintained and updated weekly, tracing the use of animals in experiments under the supervision of the Institutional Committee.

2.2.2 Ongoing care regime

2.2.2.1 Daily care

Animal facility employees will visit every room at the beginning and end of each work day and perform various checks to verify that the rooms and animals are in good condition. The checks should cover the following issues:

- Animals' general condition
- That no cages are open
- That water bottles have not spilled
- Excessive urine or feces, which may necessitate changing the sawdust sooner than the scheduled day
- Status of water and food in the cages (ad libitum)
- Condition of sawdust; dry sawdust must be provided
- Inspecting all equipment

Commented [ALE83]: I made the wording in this section and the parallel one on page 54 the same, although the original varies slightly in phrasing

- In rooms with an automatic watering system, nozzles should be checked
- Temperature and humidity in the room; minimum and maximum values should be recorded, and the thermometer reset
- Cleanliness of the room
- Any unusual procedures should be noted, such as: water deprivation regime, isolation, surgery, etc.

Any observed problems must be recorded in the activity-tracking form and reported to the director of the animal facilities.

2.2.2.2 Weekly or bi-weekly care

- Mouse cages will be changed weekly, on fixed days. If cages are crowded or if it is noted
 that the sawdust is soiled, the cage will be changed even if it not the scheduled day.
- Rat cages will be changed weekly, on fixed days. If cages are crowded or if it is noted
 that the sawdust is soiled, the cage will be changed even if it is not the scheduled day.
- Equipment will be cleaned weekly.
- All climbing nets and other enrichment resources will be changed bi-weekly (each week, they will be changed in half the room). Food will be transferred from one net to another.
- An external pest control company will carry out the pest control program, according to the veterinarian's requirements.
- The Shabbat clock (automatic timer) should be checked weekly.
- An attending veterinarian will check the condition of the cages weekly.
- Work clothes will be exchanged twice each week.

2.2.2.3 Cage changes

Commented [ALE84]: Can this be called the activity log?

Commented [ALE85]: Is it possible to combine these as "rodent cages"?

Commented [ALE86]: Shouldn't this be in the section on pest control?

During the scheduled weekly cage change, employees will only use equipment (brushes, spatulas, etc.) from that room. No equipment will be moved from room to room, except for the cage-transporting carts. Cages (whether clean or dirty) must not be placed on the floor, but only on carts or shelves. Employees will examine the animals' condition during the cage change. Employees will report any abnormality they observe in the animal's condition to the attending veterinarian.

2.2.2.4 Changing water bottles

Water bottles in the rodent cages will be refilled on the days of the cage change and again on Thursdays, as well as during the week as needed.

2.2.2.5 Washing and disinfecting cages and covers

The cages from each animal room will be stacked on the carts and taken to the washing room, which must be adequately spacious and convenient for this work. Soiled sawdust will be emptied from the cages into a sawdust collection receptacle (hood) in the washing room. Any cages that are not clean after the normal washing procedure will be soaked in water until the dirt softens, and then will undergo through another washing procedure. Cages from Specific Pathogen Free (SPF) rooms will be autoclaved.

2.2.2.6 Bottle-cleaning procedure

Bottles will be cleaned with a bottle brush that has been dipped in a disinfectant solution and then cleaned in a mechanical bottle-washing machine. Any bottles that are still not clean following the normal washing procedure will be soaked in a tank/sink and then cleaned again.

The stoppers will be cleaned with an antiseptic and then washed in the bottle-washing machine.

Commented [ALE87]: Are the bottles changed? Or just refilled?

At the end of each work day, the water in the bottle-washing machine will be emptied and the next day it will be replaced with fresh water.

2.2.2.7 Cleaning the animal rooms and corridors

- The corridors in the animal facilities will be cleaned every day with water and detergents (bleach). The interiors of the animal rooms will be cleaned once a week.
- Twice a year, all animal rooms and corridors will be thoroughly cleaned and disinfected.
 This includes washing the walls with a large brush dipped in a bucket filled with disinfectant and water. See Appendix I.

2.2.2.8 Storing food and sawdust

Food and sawdust will be stored in a warehouse designed for this purpose, and controlled for temperature, humidity, and cleanliness.

2.2.2.9 Waste disposal

Waste will be separated according to type and disposed of accordingly. Bins for storing waste will be located in designated areas.

Biological and chemical waste will be disposed of according to the university safety department's instructions.

2.2.3 Monitoring animals' condition

Researchers and animal facility workers will conduct clinical monitoring, according to the guidelines in the ethical protocol for the experiment. This includes observing the animals in their cages so as to cause them minimal disturbance and stress. Attention should be paid to the following signs:

- Activity: apathy, restlessness, weakness, sleepiness
- Eating: Not eating or reduced eating
- Drinking: dehydration, decreased or increased water consumption
- Breathing: rate, difficulties
- Discharge from eyes or nose, sneezing, coughing
- Mouth: condition of teeth, tongue, excessive salivation
- Diarrhea: signs of diarrhea in the cage, feces around the anus or base of the tail, rectal prolapse
- · Lack of feces in the cage or signs of constipation, reduced eating, fasting
- Condition of the fur: loss, scruffy, damp
- Skin wounds: itchy patches, redness, sores, scabs, secretions
- Tumors or swellings
- · Limbs: abnormal standing position, limping
- Persistently turning to one side or tilting the head to one side
- Blood in the cage

If any of these signs, or any other deviation from the animals' normal condition, are noticed, the attending veterinarian must be informed and it must be recorded in the activity-tracking form.

2.2.4 Monitoring and care for animals in studies with severity levels 4 and 5

Experiments with severity level 4 cause moderate to severe pain or stress that is treated with pain-relieving drugs. Experiments with severity level 5 cause significant, persistent pain or distress and the animals are not given pain-relieving drugs, or the experiment may cause cancerous tumors or lead to the animal's death (such as the use of poisons).

Commented [ALE88]: Should increased eating be noted as

Commented [ALE89]: This was under eating, but it seems to belong here

Commented [ALE90]: This was in the next point with lack of feces, but seems to belong here

Commented [ALE91]: This is the term used here:

https://your.yale.edu/policies-procedures/guides/4446clinical-signs-pain-and-disease-laboratory-animals

- The weight of animals used in the experiment will be monitored daily and recorded in the
 experiment activity-tracking form.
- Signs of dehydration will be monitored by testing the skin elasticity on the back of the neck, and any abnormality will be recorded in the experiment activity-tracking form.
- Nasal dryness or itching will be monitored and any abnormality will be recorded in the experiment activity-tracking form.
- Animals will be observed for signs of pain, tremors, and/or scruffy fur and any abnormality will be recorded in the experiment log activity-tracking form.
- The animal's movement will be monitored, for example lack of voluntary movement or depression that manifests as inactivity.
- The animal will be monitored for signs such as drooping eyelids, abdominal swelling, development or spreading of skin sores, necrosis and/or inflammatory necrosis, nasal or rectal bleeding; any of these signs will be recorded in the experiment activity-tracking form.

Supportive care will be provided as necessary and according to the animal's condition, such as giving it soft food placed on the cage floor, administering water manually twice a day, and manually-assisted urination twice a day. Pain-relieving medication will be administered according to the protocol and/or as needed. All treatments will be conducted after discussion with and approval by the Institutional Veterinarian. All treatments will be recorded in the experiment activity-tracking form (start date, method, and end date).

All activities must be reported and coordinated with the attending veterinarian.

Commented [ALE92]: Can there be a general heading at the top of this list saying each of these issues will be monitored and the information recorded in the activitytracking form (rather than writing it each time) If any of the following parameters is detected, the animal's involvement in the experiment will be terminated, and this will be documented and reported to the attending veterinarian and the research director:

- A decrease of over 20% in the animal's weight
- · Complete cessation of the animal's voluntary movements
- Abdominal swelling
- Bleeding from the nose or rectum
- Development of a generalized inflammatory wound or necrosis

2.2.5 Testing for pathogens

Animals will be tested quarterly for pathogens including: bacteria, viruses, and parasites. Sentential Diagnostics Laboratory will be contracted to do this work. At the appropriate time, the data from Sentential Diagnostics will be sent to a company specializing in this work, in order to carry out the appropriate tests. The Sentential Diagnostics tests are performed according to FELASA recommendations: one full panel and three short panels.

- A rat and a mouse between 3 and 5 weeks old will be included in the tests.
- For every 50-80 cages, one cage containing two animals is needed for Sentential
 Diagnostics testing
- After 12 weeks, they will be sent for tests: pathology, parasitology, serology and histopathology. The test results are useful indicators of the general health status of all the animals.
- If any pathogens are detected, the attending veterinarian will determine the appropriate medical treatment, based on the nature of the disease.

Commented [ALE93]: Is this accurate?

Commented [ALE94]: Please verify this section – I am not sure of the intention.

2.2.6. Improper cage conditions

Any abnormalities in cage conditions must be reported to the attending veterinarian and the researcher. If any unusual conditions are observed in the animals or the cages, the animal must be removed from the cage and examined more thoroughly.

- An employee who identifies a sick or injured animal must immediately inform the attending veterinarian.
- The attending veterinarian will make regular visits to the animal facilities to examine the condition of the animals and the cages.
- The attending veterinarian will decide the appropriate course of action regarding this
 animal, including medical treatment, terminating the experiment, or euthanasia.

2.2.7 Weekends and holidays

Routine care activity continues in the animal facilities on weekends and holidays. Inevitably, animals may require veterinary care during these times.

- Technological devices will be used to send alerts regarding failure of any utility system in the animal rooms (air conditioning, Individually Ventilated Cage transport carts, etc.).
- An animal facility employee will be on call and available during all non-work hours:
 weekends, holidays, and nights.
- A veterinarian will be on call and available to come to the university animal facility if urgent veterinary care is needed.
- The list of on-call employees will be made available via the university's emergency preparedness system.

2.3 Emergency procedures

2.3.1 General

There should be an emergency preparedness plan to safeguard the health of employees and animals during general safety problems and natural disasters. An integral part of emergency preparedness is training that provides employees with the knowledge, skills, and capabilities to respond appropriately and effectively manage a disaster event. In emergency situations, when the facility must be evacuated for a significant time, or during any abnormal situation, procedures must be followed to ensure that the animals receive appropriate care. These procedures must include predefined information and actions to enable response to emergency situations, since they may arise without warning.

2.3.2 Preparation for emergencies

Emergency preparedness plans are designed to prevent unanticipated shortages or malfunctions at the time of need.

- The Institutional Veterinarian will tour the animal facilities twice a year to assess
 preparedness for emergency situations, inspect equipment, test employees regarding
 emergency procedures, etc.
- A food reserve sufficient for at least two weeks must be kept in the animal facility warehouses, in case an emergency makes it impossible to receive food supplies.

2.3.3 Implementing emergency procedures

Emergency procedures will be implementing in response to the following situations:

- Fire
- A major medical emergency
- Risk of exposure to hazardous chemicals or biological materials

 A general state of emergency resulting in suspension of the university's activities (wildfire, war, etc.).

For internal emergencies at the animal facilities (for example, an employee being bitten by an animal), the on-call employee and the Institutional Veterinarian must be notified immediately (See phone list in Appendix M). If it is necessary to evacuate the animal facility, the evacuation plan must be followed.

In a general emergency (fire, major medical emergency, etc.) the animal facilities' on-call employee must be immediately notified (Appendix M), and it must be reported to the 24-hour emergency center (7000) and the security and safety hotlines (internal: 57000 external: 04-828-0700). The evacuation plan will be implemented.

2.3.4 Work plan during emergency situations

In the event that the administration decides to suspend activity at the university, minimal care procedures will continue to be carried out, provided this does not pose an immediate danger to employees' lives. Minimal care includes:

- Providing and changing water and food supplies
- Regular inspections

2.3.4.1 Order of operations:

- The work will begin in the SPF complex and continue in the Science Building II and the Rabin complex.
- Minimal care will be provided once every two days, starting the day following the university's closure.

Commented [ALE95]: Two different terms are used in Hebrew

שריפה Both would normally be translated as 'fire' – is there a difference? I put wildfire here to indicate something larger.

Commented [ALE96]: Does this need a separate numbering? It seems it could be bullet points under 2.3.4

Commented [ALE97]: I found the English name Rabin complex on a university map, but nothing similar to Science II Building – verify this is the accepted name of the building

These activities will be carried out according to the schedule of on-call employees
 (Appendix M), which will be made available to all employees at all times. The schedule
 will have a list of on-call employees and their roles. A veterinarian will come to the
 animal facilities once every four days.

Activity during an emergency will be carried out according to the following schedule:

Day 1 of the emergency situation: no activity

Day 2 of the emergency situation: on-call employee 1

Day 3 of the emergency situation: no activity

Day 4 of the emergency situation: Institutional Veterinarian as on-call employee

Day 5 of the emergency situation: no activity

Day 6 of the emergency situation: on-call employee 2

Day 7 of the emergency situation: no activity

Day 8 of the emergency situation: attending veterinarian as on-call employee

Day 9 of the emergency situation: no activity

Day 10 of the emergency situation: on-call employee 3

If it is not possible to care for the animals for more than three consecutive days, the Institutional Veterinarian must come to the animal facility and make a decision regarding what to do with the animals: to continue care according to the emergency procedures, euthanize the animals, or any other decision based on the veterinarian's professional judgment.

2.3.5. Emergency evacuation

Commented [ALE98]: Does "of the emergency situation" need to be repeated each time?

Commented [ALE99]: Here the word יוסול is used; is this the accurate translation (rather than extermination)?

If an emergency alarm sounds, or if the premises must be immediately evacuated for any reason, all employees must immediately cease their work. If employees are working with animals, and there is no time to act according to the evacuation plan, steps must be taken to secure the animals in their cages and to protect the animals' lives, as long as this does not pose a danger to the employees. In any case, animals must not be taken outside the animal facilities. If any animals are outside their rooms at the time of the emergency event, employees assume the responsibility for returning the animals to their rooms, provided this does not pose a danger to their lives. If the emergency situation is localized and not all the animal rooms are affected, the Institutional Veterinarian will implement the partial evacuation plan.

2.3.6 Evacuation plan

Full evacuation: if the entire university must be evacuated, a general emergency plan will be implemented, in which everyone in the animal facilities will be evacuated, in accordance with section 2.3.3 of this guide.

Partial evacuation: if the emergency situation is localized and does not necessitate a full evacuation, but only evacuation of some animal rooms, this will be carried out according to the following outline:

- Rabin complex: the animals will be transferred to the conference room in Science
 Building II, which will be closed to anyone not involved in caring for the animals.
- Science Building II: the animals will be transferred to the conference room in the Rabin complex, which will be closed to anyone not involved in caring for the animals.
- Institute of Evolution: the animals will be transferred to the conference room in Science
 Building II, which will be closed to anyone not involved in caring for the animals.

SPF: the animals will be transferred to the conference room in the Rabin complex. These
animals will be returned to SPF only after quarantine.

2.3.7 Emergency closure of the university

In the event of a fire, war, or any other situation that causes the university administration to decide to suspend university activity, minimal maintenance and care procedures will be carried out in the animal facilities by the on-call employees according to the schedule, provided that this does not pose an immediate danger to their lives. Every animal facility employee will receive a copy of this schedule. Activity will be carried out according to a work plan established by the Institutional Veterinarian. If possible, the researchers will be consulted, in order to give priority to specific animals (for example, preserving a breeding nucleus). The on-call employee will be accompanied by a security officer. At the end of this work shift, the on-call employee will submit an updated report to the Institutional Veterinarian. If it is impossible to come to the university for more than three consecutive days, the Institutional Veterinarian will make a decision regarding what to do with the animals: to continue care according to the emergency procedures, euthanize the animals, or any other decision based on the veterinarian's professional judgment.

No activity will take place if it poses a danger to employees' lives, or if university administration decides that even emergency personnel cannot enter the university grounds.

2.3.8 Training

Animal facility employees will be given briefings and refresher training on emergency
procedures once every six months, in the framework of regular meetings and training
sessions carried out by the Institutional Veterinarian.

 Emergency procedures will also be covered in the annual training provided to all animal facility employees by the university safety department.

2.3.9 End of the emergency situation

At the end of the emergency situation, the Institutional Veterinarian will conduct an investigation and inspect all the rooms that were affected.

- If evacuated rooms were not damaged and the veterinarian approves re-occupancy, the rooms will first be cleaned and disinfected.
- Animals that were temporarily housed in rooms that are not usually animal rooms will be returned to the cleaned and disinfected animal rooms. They will be tested for pathogens, via Sentinel Diagnostics Laboratories.
- Additional tests may be ordered with Sentinel Diagnostics, according to the Institutional Veterinarian's decision.
- The emergency event will be reported to the Institutional Committee.
- 3. Procedures for procuring, housing, and transporting animals

3.1 Procuring animals

- The researcher will transmit orders for animals to the animal facility. Procuring animals
 will be done through a computerized internet system. Each researcher who is authorized
 to engage in animal research will have a unique username and password for the
 computerized system.
- All orders for procuring animals and all receipt of animals must be approved by the attending veterinarian and reported to the Institutional Veterinarian.

- The computerized system has a database of experiment approval permits granted by the Institutional Committee, which includes the number of animals that can be used in each experiment.
- Each researcher will be able to procure animals only using his/her permit approval number. Once the quota of animals approved for a certain experiment has been reached, the researcher cannot procure more animals using the same permit approval number.
- All receipts must be saved in the "Delivery Receipts" folder together with a copy of the order from the website.
- A researcher who wants to procure laboratory animals from sources other than those
 generally used by the university's animal facilities must first submit an ethics application,
 receive approval from the Institutional Committee, and consult with the Institutional
 Veterinarian. Prior authorization is required for any procurement or import of animals
 from within Israel or abroad.
- Procuring animals from abroad, whether they are imported personally or through the animal facilities, may only be done through the animal facilities' procurement department and by filling out the appropriate forms. Before submitting an order to the overseas procurement department, an import permit must be obtained from the Ministry of Agriculture. The import permit will be transmitted to the Institutional Veterinarian.
- Animal suppliers, within Israel and abroad, must be approved by the Institutional
 Veterinarian, who will examine the suppliers' work methods, including their animal
 maintenance, care, and transport.
- 3.2 Procuring young/newborn animals
- 3.2.1 Procuring young/newborn animals from outside the university

Commented [ALE100]: The full name of the committee is given in the original, but the shortened name is generally used throughout so I used it here too.

Commented [ALE101]: What is meant by being imported personally?

The animal facility must verify that there is a valid permit for the experiment.

- Animals between one day and one week old will be accompanied by a lactating female (preferably the biological mother).
- For mice between one to three weeks old, there may be up to eight young per lactating female in homozygous strains (outbreed) and up to 21 young per lactating female in heterozygous strains (inbreed).
- There may be up to 15 rats from one week old through weaning age per lactating female.
- When the animals are intended for immediate and intensive use upon arrival, young over seven days old may be procured without a lactating female, if the attending researcher commits in writing to euthanize the animals immediately upon their arrival.
- A researcher may bring animals to the university from sources other than the approved ones only after receiving approval from the Institutional Committee. A current health report must be obtained from the supplier and transmitted to the Institutional Veterinarian before the animals arrive at the university. The researcher may begin the procurement process only after receiving approval.

3.2.2 Procuring animals from a local source

Researchers who work with their own transgenic lines of mice and rats can procure them after weaning age. Researchers procure these animals through the website using the ethics number for the experiment.

3.3 Maintaining animals

3.3.1 Transporting animals to the animal facilities

Commented [ALE102]: They are euthanized before use in the experiment?

Commented [ALE103]: Is this different from the similar point above about approved sources?

Commented [ALE104]: Verify this, I'm not sure I understand it correctly.

Commented [ALE105]: The Guide for the Care and Use of Laboratory Animals: uses both terms maintaining animals and housing animals

- A valid health report must be obtained from the supplier and transmitted to the
 Institutional Veterinarian Prior before the animals arrive at the university. The
 procurement process may begin only after approval is granted.
- Orders for animals must be submitted in accordance with accepted NRC rules. A
 purchase requisition form must be completed.

3.3.2 Receiving new animals

- The attending veterinarian is in charge of receiving animals. If the animals are not from a licensed supplier, they will be put in the quarantine unit (see, section 3.4).
- Before work with new animals begins, they must be given time to acclimatize. For animals procured from within Israel, wait at least 3 days; for animals imported from abroad, wait at least a week.
- Immediately upon arrival, animal facility employees will transfer the animals from the cardboard shipping boxes into clean cages with food and water.
- Animals must be housed in cages that meet accepted conditions; see Appendix G.
- Each cage will have a computer-generated label that matches the label on the corresponding animals' shipping containers. Cages will be placed in the appropriate rooms. Each cage must have an identification card indicating the following information: current permit (experiment approval) number; name of the responsible researcher or responsible student and his/her mobile phone number; the number of animals and their species, sex, and age; the date the animals were put in the cage; the severity level of pain and suffering expected for the experiment (levels 4, 5 in bold); and genotype information, if necessary, Appendix J.

Commented [ALE106]: This is said above; is it intentionally repeated?

- Animals will be put into cages according to the usual density tables, unless otherwise instructed.
- It must be ascertained that the animals arrived in good condition, i.e.: no wounds, signs of
 illness or appearance of being unwell for any reason.
- When putting animals into cages, their sex must be determined. Males and females must not be caged together. Animals of different breeds must not be caged together.
- Employees who notice anything unusual regarding the animals must report it to the
 attending veterinarian and record it on the shipping defects form. This includes: dead
 animals, injured animals, animals that look ill or unwell, stale food or unclean sawdust in
 the shipping crate, a hole in the shipping crate, excessive dampness, etc.
- Animals will be brought into the facilities only after receiving approval. There is no need
 to contact the Institutional Veterinarian for the arrival of animal shipments from
 regularly-used suppliers (such as Envigo), but orders from non-standard suppliers must
 coordinated and approved.
- If the documents are not approved, the animals must be quarantined upon arrival, before being received into the animal facilities.

3.3.3 General

- During experiments, animals must be kept in the animal facility or other approved areas.
- If it is necessary to take animals out of the animal facility, this may be done only with the approval of the attending veterinarian.
- At the end of the experimental treatment, researchers must ensure that there is water and food in the cage, unless other procedural instructions have been approved by the Institutional Committee.

Commented [ALE107]: https://www.envigo.com/ourwork-with-animals

• Animals younger than weaning age must be kept with lactating females.

3.3.4 Breeding colonies

- Breeding to increase the number of animals may only be done if it has been approved in
 the permit for the relevant experiment. The size of the colony and the breeding regime
 will be determined according to the approved target need, and not beyond that. Breeding
 will be conducted in accordance with the approval permit.
- The need for breeding colonies will be examined. Colonies will be kept at the minimum number required for ongoing activity.
- Animal facility employees will maintain breeding colonies in accordance with the agreement between the researchers and the attending veterinarian.
- Mating will be done according to an outbreeding method of "mixing" according to an ABCD rotation, or inbreeding (mating among siblings).
- All actions will be recorded on the cage cards and the breeding tracking form. For all
 litters, this includes the dates they were born and the number of offspring. When they are
 weaned, the number of weaned animals (males and females) must be recorded. The name
 of the breeding colony must be indicated on the form.
- Any hybridization conducted at the university must be approved by the Institutional Committee, with a separate permit.

3.3.5 Agreements for exceptions in animal housing arrangements

Researchers who need separate animal rooms due to special requirements (such as: biological risk, special lighting hours, use of particular equipment, etc.) may receive them after prior coordination with the attending veterinarian. Even in these cases, the animal density cannot exceed what is accepted in other animal facility rooms. Use of these rooms will be granted for a

limited and predetermined period. Researchers who want to provide the care and treatments for their animals themselves (due to special techniques, special animals, or use of pathogens) may do so only after coordination with the attending veterinarian. In any case of unusual maintenance conditions or treatment (such as food or water deprivation, or researchers caring for the animals), a written agreement will be drawn up between the animal facility and the researcher, and the cages will be marked with an appropriate label (as indicated in section 3.3.2).

3.4 Work procedures for the quarantine unit

The quarantine unit is a closed unit designed to receive rodents (mice and rats) from unknown sources before they are taken into the animal rooms. Operational procedures in the quarantine unit must be followed carefully because lack of vigilance could lead to an outbreak of diseases and damage the research. Animals from different sources should be separated.

- Animals received from an authorized supplier do not need to be placed in quarantine.
- Animals from an unauthorized supplier will be quarantined for about seven weeks after arrival.
- The quarantine unit is for all animals intended for eventual placement anywhere in the
 animal facility, regardless of their final destination unit. Animals will be released from
 quarantine only after receiving a clean report of health.
- 3.4.1 Entry of employees and researchers into the quarantine unit
 - Only animal facility employees who are authorized to work in the quarantine unit are permitted to enter.
 - Researchers and students are not allowed to enter the quarantine unit, except in special cases and only after receiving permission from the Institutional Veterinarian.
 - It is forbidden to conduct any research or rehabilitation activity in the quarantine unit.

Commented [ALE108]: Is this what is meant by טיפול עצמי in this context?

Commented [ALE109]: The responsible veterinarian? The committee?

Commented [ALE110]: Or other animals?

- Anyone who enters the quarantine unit may not enter other animal facilities for 24 hours, unless special permission to deviate from this rule is granted by the Institutional Veterinarian.
- When entering the quarantine unit, it is mandatory to wear a disposable gown, apron, gloves, and a head covering.

3.4.2 Receiving imported animals into the quarantine unit

- Prior approval must be obtained from the Institutional Veterinarian.
- The precise date and time that the animals will be received must be coordinated with the attending veterinarian. Effort should be made to receive animals during normal work
- During normal work hours, animals will be received by an animal facility employee
 authorized to work in quarantine. The employee will label the cage with the experiment
 ethics number, as received from the researcher.
- Animals received outside of normal work hours will be kept in their shipping cartons in
 the animal reception room. The next morning, they will be immediately taken into the
 quarantine unit by an authorized animal facility employee.

3.4.3 Documentation for receiving animals into the quarantine unit

- All animals being received must have a health report from their place of origin.
- The Rodent Import Request Forms must be filled out; see Appendix F.

3.4.4. Special care for animals in quarantine

The following preventative treatments will be given to each cage, according to need, from the time they are brought into the quarantine unit:

- For the entire time in the quarantine unit (usually seven weeks), the animals will be given food that contains 18% protein and fenbendazole at a concentration of 150 mg/kg, as a treatment against parasitic intestinal worms.
- Animals will be given Baytril 10% in the drinking water, at a dilution of 0.5 ml in 200 ml water or 50 mg in 200 ml water for 4 weeks. The water with Baytril will be changed every week.
- During the weekly cage change, the cages will be sprayed with Ivermectin against ectoparasites for 4 weeks. Ivermectin at 0.1 mg concentration will be put into sterilized, cooled tap water at a 1:10 ratio (5 ml Ivermectin in 54 ml water). A new solution will be made each week. After transferring the mice to a different, clean cage, employees will spray the animals and the cages they are in 4-5 times.
- Note: If the animals arrive after work hours, this procedure will be done first thing the next morning.
- 3.4.5 Routine care for animals in the quarantine unit
 - Cages will be changed before each weekend, on Thursdays, to prevent infections and to maintain cleanliness.
 - Employees must wear gloves during cage changes.
 - Everything in the cage will be changed every time: substrate, nets, filter cover, and water bottle.
 - Material from the dirty cage on the equipment cart will be emptied into a separate garbage receptacle, which should be taken out immediately after the changing process is finished.

Commented [ALE111]: This is a brand name – should it have the TM symbol?

Commented [ALE112]: This is a brand name – should it have the TM symbol? https://allbirdproducts.com/products/baytril-10

Commented [ALE113]: in the original it is written 01 without a decimal Is this accurate, with the decimal?

It seems if it was meant to be 1 there would not be a 0 first

Commented [ALE114]: The Hebrew says בכל סוף שבוע וימי חמישי But it doesn't make sense that they would be exchanged every Thursday and every weekend – is this correct?

- While washing the cages, there must not be any unrelated equipment in the cage-washing machine.
- Dirty cages must not be left open to the air in the room. The drying equipment must remain in the quarantine unit only. All equipment for the quarantine unit must remain in the room!
- Under no circumstances shall a bottle that has been used in an animal cage be refilled.
 Only new, clean bottles may be filled!
- During the cage change, only the cage label (which is outside the cage and does not come
 into contact with the animals) will be transferred from the used cage to the new one.
- Re-filling water used bottles is strictly forbidden! Providing a new clean bottle is the only
 possible option.
- All work surfaces must be disinfected with Virusolve spray before the weekly cage changes, between cleaning batches of cages, or during any other work with the cages.
- The food and sawdust for the quarantine room must be stored separately.
- 3.4.6 Introducing Sentinel Diagnostics in the quarantine unit
 - The general requirements will be as stated in section 2.2.5.
 - Tests from the quarantine unit will be sent after seven weeks.
 - All documentation will be recorded in the quarantine follow-up form.
- 3.4.7. Detection of contamination in a shipment

If monitoring detects the presence of a pathogen in a certain group of mice, the following steps must be taken:

Commented [ALE115]: Does this need to be repeated? Why not combine it with the previous item on the same topic?

Commented [ALE116]: All these sections on Sentinel Diagnostics need to be carefully verified

- The head researcher in whose animal population the infection was discovered must be informed. If the researcher states an intention to continue working with the diseased animal (provided that the disease does not cause suffering) the veterinarian will oversee treatment, including administration of medication. Following this, several rounds of Sentinel Diagnostics will be conducted, until negative test results are achieved.
- Depending on the type of pathogen and the treatment regime, the quarantine unit may be closed, so that no animals may be taken out and no new shipments may be accepted.
- The Institutional Veterinarian will decide what actions should be taken regarding the other animals in the quarantine unit.
- The room and its equipment will be thoroughly disinfected and the air intake unit filters
 will be replaced. The need for disinfection, the disinfectant used and the time of
 disinfection will be determined according to the type of pathogen

3.4.8 Release from quarantine

Only after all tests have been completed and the Institutional Veterinarian has reviewed the results and granted approval may animals be released from quarantine.

3.5 Transporting animals

When transporting animals, maximum care will be taken to ensure their welfare and they will be transported in the shortest time possible.

Any researcher who wishes to transport laboratory animals to this research institution or any other institution must coordinate the shipment with the Institutional Veterinarian and receive approval for it. The Institutional Veterinarian will inspect the receiving institution.

Commented [ALE117]: Should these be bullet points too?

Commented [ALE118]: Should this specify the vet only needs to inspect receiving institutions other than the university animal facilities?

- An attending veterinarian will give approval, with his signature, for the following shipment details: the sending entity/researcher; the receiving entity/researcher; the animals' sex, breed, and age; number of animals being shipped; shipping conditions such as: packaging, sawdust, food, and transport method.
- It is essential to fill out the research institute's Rodent Import Request Form; see
 Appendix F.
- The Institutional Veterinarian will approve, with his signature, the health status of the shipped animals.
- Completing this form does not nullify requirements for filling out additional forms as required by regulations or law.
- 3.5.1 Procedure for transporting animals from Haifa University to other research institutions in Israel
 - Animals may only be transported in a vehicle driven by a driver trained for this purpose.
 Both the vehicle and driver must be approved by the attending veterinarian. If no approved driver is available, a university employee who has been authorized by the veterinarian for this purpose may accompany the transport, and all regulations must be followed.
 - Animals must be transported under appropriate conditions (for example, air temperature between 20-22 degrees Celsius) and in compliance with the time schedule.
 - The shipping and receiving sites will coordinate the animal transport in advance, to avoid delays.
 - The animals will be transported in filtertop transportation cages in which there is sawdust and food.

Commented [ALE119]: https://www.carfil.eu/en/housing-cages-filtertop-cages/

- Cages will be placed on a clean surface, and will be secured properly within the transport vehicle.
- The transport vehicle should take the shortest possible route to the destination, and effort should be made to avoid traveling during times when the travel is likely to take longer.
- Animals must not be overcrowded during transport. The number of animals should be appropriate for the size of the transport cage. Unrelated males should not be caged together.
- Animals must not be left in the vehicle unattended.
- Loud music should not be played in the vehicle.
- Smoking in the vehicle while transporting animals is strictly prohibited.
- The vehicle driver must be in possession of a transport document describing the number of animals and their species, age, and health certificates.
- The attendant (or driver) will receive instructions from the veterinarian regarding the
 transport (travel time, air temperature). A form with departure time and arrival time must
 be filled out and signed by the person receiving the animals.
- Once animals have left the animal facilities, they should not be returned to it; if this
 occurs, they must be quarantined.

3.5.2 Air transport

Air transport of animals will be conducted in accordance with the rules accepted by the transporting airline and those of the International Air Transport Association.

3.5.3 Moving animals within the university premises

Commented [ALE120]: or unfamiliar males?

Commented [ALE121]: Note that in the Hebrew a sentence is repeated verbatim.

Animals may be moved within the university premises in cages or disposable cardboard boxes intended for this purpose, which are kept in the warehouse.

In public areas, cages should be covered with opaque cloth or paper to prevent exposing the public to allergens and to prevent exposing the animals to bright light, extreme weather conditions, etc. Animals, their cages, or their water bottles may only be moved from their unit in the animal facility with the explicit permission of the attending veterinarian.

3.5.4. Procedure for disposal of animals after an experiment

To minimize the danger of spreading infections in the animal facilities that may harm animals or employees, it is essential to observe all relevant hygiene and care regulations as stated in the NRC guide as well as any legal provisions pertaining to the removal of animals and cages after an experiment. In specific, the following rules must be observed:

- Euthanasia will be conducted by a team of animal facility employees or researchers who
 have received the appropriate training.
- Euthanasia cages must be clearly and prominently marked. There must be food and water in the cages.
- Euthanized animal carcasses will be placed in plastic bags and stored under suitable refrigeration conditions to prevent decay before they are disposed of outside the university.
- The cages, with the sawdust still in them, will be taken to a designated evacuation area.

 Identification tags should not be removed from the cages.

 Animals that were treated with any biological materials must be placed in a special compartment in the freezer marked "treated animals" to be disposed of by the company that removes biological materials.

3.6 Ordering equipment and materials

- Equipment and materials may be ordered from the university's warehouses by the
 administrative staff. Orders are based on a current consolidated list. Requests must be
 submitted by animal facility employees for approval.
- Disinfectants will be ordered by the responsible employee.
- Special equipment and materials such as medicines, medical equipment, etc. must be ordered by the attending veterinarian.

3.6.1 Bringing equipment and materials into the animal facilities

- Nondurable materials (such as: cleaning and disinfecting products and implements, paper products, sawdust, food, etc.) will be brought into the animal facilities in coordination with one of the employees.
- Small equipment used for regular work with the animals (writing implements, notebooks, tweezers, scissors, ear tagging tools, etc.) will be cleaned and disinfected before being brought into the animal facilities. These items will be kept permanently in the same room, in order to reduce the chances of spreading infections throughout the facility.
- Large and heavy equipment such as gas tanks and other various apparatus may be
 brought into the animal facilities only with the Institutional Veterinarian's approval.

 Equipment must first be disinfected and cleaned in accordance with animal facility
 procedures. The equipment will be installed by professionals authorized to transport
 and/or assemble it.

- 3.6.2 Receiving shipments of food, cleaning products, and sawdust
- Food and sawdust will be procured from authorized and well-known suppliers (such as Envigo).
- When inventory supplies run low, an animal facilities employee will submit an order in coordination with an attending veterinarian.
- The room will be closed and locked. Entry will not be permitted until the following day.
- Food will be stored on shelves or pallets in a warehouse designated for food and sawdust.
- Prior to unloading bags of food into the warehouse, expiration dates should be checked. It should be verified that expiration dates are three to four months from the date of receipt.
- If the expiration date is less than two-and-a-half months from the date of receipt,
 approval must be obtained from the attending veterinarian before the food shipment is
 accepted.
- 3.7. Entry of workers/researchers into the animal facilities
- Only animal facility employees, researchers, and laboratory staff members who have animals in a specific animal facility unit are permitted to enter that unit.
- Only authorized personnel may enter or work in animal facility units. Unauthorized
 individuals who are accompanied by an authorized employee or researcher may be
 granted permission to enter the animal facility, provided they are given on-the-spot
 training and sign a form agreeing to follow all procedures and safety regulations.
- Animal facility employees must show their ID tag at the entrance before entering the animal rooms.

Commented [ALE122]: https://www.envigo.com/our-work-with-animals

- Work in the animal facilities units will be conducted between the hours of 07:00 and
 19:00. This includes rooms with different lighting hour regimes. Work outside these hours will only be allowed after receiving permission from the attending veterinarian.
- Employees entering the animal rooms will wear specially-colored robes according to the animals housed in that room (blue for mouse rooms and green for rat rooms).
- Entry is permitted for agricultural workers or maintenance personnel who were called in
 to address a problem on the animal facility premises, members of the university's ethics
 committee, or any other person who received prior approval from the attending
 veterinarian.
- Conducting experiments in the animal facilities without obtaining prior approval from the Institutional Veterinarian is absolutely prohibited.

3.7.1 Behavior and safety procedures

- Everyone entering the animal facilities must wear clean protective clothing including animal facility robes, shoe covers, and disposable gloves.
- Do not eat, drink, smoke, apply make-up, or touch contact lenses inside the animal rooms and corridors.
- Do not create unnecessary noise (including cell phone use).
- All surfaces and equipment such as scales, carts, etc. must be cleaned with a disinfectant
 solution before and after use. Disinfectants will be kept in the animal room or in the
 corridor. After all work, employees must wash their hands with soap and water or Septol
 (antiseptic hand cleanser).

- Researchers working in the conventional animal units must wait 48 hours before being
 permitted to work with SFP animals or to come into contact with equipment or work
 surfaces that were used with SPF animals.
- If necessary, the Institutional Veterinarian or attending veterinarian will be permitted to
 enter the SPF rooms 12 hours after working in conventional animal rooms, provided that
 they thoroughly wash their entire bodies and completely change their clothes.
- In emergency cases, the Institutional Veterinarian or attending veterinarian may grant permission to individuals to enter the SPF room less than 48 hours after working in conventional units, but not in less than 12 hours.
- Ensure that all unit doors are closed. Do not leave any door open after passing through it.
- Plastic cages and water bottles may not be taken out of the animal facilities except with
 the explicit permission of the attending veterinarian. No equipment may be taken without
 permission from an animal facility employee.

3.8 Malfunctions

- If there is a malfunction in any animal facility system such as: electricity, air
 conditioning, heating-cooling, water, etc., the appropriate maintenance worker must be
 called to make the repair, and the attending veterinarian must be informed.
- Any repair or installation that requires financing from the budget must be coordinated with and approved by the laboratory director.
- If a malfunction occurs during non-work hours, the attending veterinarian will personally
 assess the urgency of the situation and take the necessary appropriate steps to address it.
- 4. Procedures for working with wild animals

4.1 Guidelines

Commented [ALE123]: is this second sentence needed?

Commented [ALE124]: Only plastic cages?

Some researchers may work with wild animals that the Institutional Veterinarian is not familiar with. In such situations, the responsible researcher who has the most knowledge and experience in the relevant area will provide information and guidance to the animal facility employees regarding appropriate work procedures, maintenance, and health issues.

- Employees must pass the ethics course for working with rodents before working with wild animals.
- A researcher who is not authorized to work with these animals can work under the supervision of an authorized researcher for a maximum of six months.
- The Institutional Veterinarian will oversee activities in the animal facilities, with the
 assistance of a responsible researcher with relevant experience, who will ensure that
 conduct with the animals is appropriate.

4.2 Procuring wild animals

- Wild animals that are trapped in the field will kept in quarantine for about a month after the day they arrive at the university facilities.
- No capture permit is required for animals designated as pests (for example: moles).
- Animals not designated as pests must be acquired in accordance with the procedures for procuring animals, section 3.1.
- 4.2.1 Collecting animals from and returning animals to natural areas

Any activity involving the collection, maintenance, or sampling of wild animals may be carried out only after receiving the appropriate permits from the Israel Nature and Parks Authority, see Appendix D.

4.3 Maintenance

Commented [ALE125]: Should these be in the order they are mentioned in the text?

- Each animal facility employee will take care of the animals one day out of every four.
 This involves changing the animal cages, putting clean sawdust in them, and providing sufficient amounts of the appropriate food types, without excessive waste.
- All care activities will be documented on a weekly form; see Appendix K.
- Twice each day, the temperature and humidity will be checked to verify that conditions
 meet accepted standards, and this information will be documented.
- Employees will ensure that all windows or other openings through which pests could
 enter are closed. All doors must be locked at the end of the work day.
- Keys to animal rooms should be kept in a place that is accessible to all employees and researchers.
- Workers from the contracted pest control company will conduct periodic inspections according to a schedule determined by the veterinarian
- The cages or rooms (depending on the type of animal) will have a sign indicating all the relevant details regarding the animals.
- Note: For rodents, it is recommended to use red-tinted enrichment devices that provide
 them with shade.

4.4. Ongoing activities: Cleaning the animal rooms

- It is mandatory to wear a gown and gloves when entering any animal room.
- The cages will be cleaned with soap and chlorine once a week. All equipment must be
 dried after it is taken out of the cage-washing machine. Manual washing will be done
 only in designated sinks within the animal facility.
- Cages must not be placed on the floor, whether they are cleaned or not.

Commented [ALE126]: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5073063/

- The animal facility must be in a general state of orderliness, including arrangement of cages, nets, springs, cleaning products, equipment, tables, and vents.
- Floors will be cleaned three times a week. Only cleaning materials and tools specific to
 the animal facilities may be used.
- Animals must be moved gently and carefully so as not to cause them injuries or unnecessary stress.
- Cage lids must be closed tightly to prevent animals from escaping or falling, particularly from cages on high shelves, which could cause death or paralysis.
- Food will be allocated to animal cages in accordance with the instructions of the responsible researcher.

5. Procedures for working with aquatic animals

Various species of aquatic animals are kept in tanks in separate rooms in the university's animal facility, which are designated for this purpose.

The following guidelines must be adhered to, unless a change is approved by the Institutional Committee for the purpose of specific research:

- Various species of ornamental fish are kept in the same room.
- Xenopus frogs, newts, and Spanish salamanders are kept in the same room.
- The edible fish barramundi and tilapia are kept in the same unit, in separate tanks.
- Since every species of fish and other aquatic animals has specific maintenance conditions, there is no uniform procedure for their maintenance and care.
- The animal tanks should be labeled with the relevant information, including genotype details if necessary.

Commented [ALE127]: When I looked up the terms סופופו צפרדעי קסנופוס It is defined as Xenopus frogs

But this seems very specific.

Should this simply say frogs, newts and salamanders? Or is it even more general for amphibians?

Commented [ALE128]: Only these two?

5.1 Structures and controls

All the appropriate conditions for regular rooms in the animal facility, as described in previous chapters of this guide, must also be met in the rooms where aquatic animals are kept.

All safety procedures for working with animals apply to the aquatic animals; this is particularly crucial regarding safety procedures for working with electrical devices in the aquatic environment.

5.2 Drainage

All rooms and areas for aquatic animals must have a floor drain that is at least 60 centimeters wide. All tanks for amphibians must have upper and lower drains to prevent flooding, and at a height that will prevent the tank from drying out if the drain is left open.

5.3 Climate and temperature control, ventilation

- Animal facility rooms for aquatic animals must have ventilation rate of at least six changes of fresh air per hour.
- Tanks for tropical fish need heating elements and a thermostat to maintain the desired water temperature. If the temperature is too high, take out some water and add cold water.
- In the amphibian rooms, the water and air temperature must remain between 12 and 18
 degrees Celsius. The water must stand for about two days before it is used to fill the
 tanks. The aquatic animal rooms must be equipped with electronic temperature control
 systems that have fresh air alerts and filters.

5.4 Environmental inspection

The air and water quality systems must be able to send malfunction alerts. An employee must feed the animals and check the rooms at least once a day.

5.5 Water quality

- The water quality must be suitable to each aquatic animal species in terms of temperature, acidity, salinity and oxygen level.
- The water quality must be documented.
- 5.5.1 Removal and neutralization of chlorine and reactive chemical and biological products Before water is provided to aquatic animals, it must be filtered through biological and chemical filters to remove all contaminating or dangerous substances such as chlorine and nitrogenous waste. All tanks must have particle and charcoal filters. The water used in most tanks is treated by reverse osmosis, after which salts and bicarbonate are added. Water quality must be checked regularly and adjustments made as needed.

5.6 Life support systems

5.6.1 Water source based on proper supervision and research requirements

In studies that examine quality (salinity or biological load), the condition of the fish in response to the water quality is strictly monitored.

5.6.2 Appropriately sized biological filter for the biomass

Each system must be populated gradually. The filters in each system must be appropriate for the number of fish and tank size, based on minimum ammonia nitrite levels. If the filter malfunctions, the water should be partially replaced frequently (every day) until the filter stabilizes.

5.6.3 Noise and vibration control

Noise and vibrations from devices in the water should be minimized. Air compressors and pumps should preferably be placed outside the water so their noise and vibrations do not

Commented [ALE129]: Should this say "Preferably every day"?

If not, should it simply say "replaced every day" without frequently?

penetrate the tanks; due to the phenomenon of acoustic reflection, noises from the surrounding environment are virtually inaudible in the aquatic medium.

5.6.4 Lighting

Lighting must be suitable for each animal species, and according to the needs of the experiment.

- 5.6.5 Adapting the area to the physiological, behavioral and social requirements
 - Enrichment structures and resources for fish and amphibians include plants, floating or submerged vessels in which they can hide, a gravel bed, and tanks that allow for social interaction. Enrichment resources are provided according to the type of research and its needs. Every change pertaining to the environmental or socialization means in the tanks must be tested for its effectiveness and potential harm to the aquatic animals.
 - Any equipment that is moved between tanks must be first thoroughly disinfected to prevent the transfer of contaminants or pathogens.
 - Throughout the year, the aquatic environment must be kept stable and uniform according
 to the needs of each species. If there is any change, intervention must be undertaken
 immediately to restore the desired stable state.

5.6.6 Social environment

Social aquatic animals interact with other members of their species. If the needs of the experiment require separating them, additional environmental enrichment resources must be provided.

5.6.7 Limiting escape opportunities; re-capture

Triniaria (ALE130): זיהומים Could mean either of these Is it appropriate to include both? All tanks containing aquatic animals that tend to jump must be covered with nets that have appropriately-sized holes to prevent escape. However, it should be possible to observe what is happening in the tank without disturbing the animals' activity.

5.6.8 Environment enabling access to food and waste removal

Feeding should be done in such a way that all individuals have access to the food. Waste is removed through biological filters, particle filters, and maintaining the water quality.

5.6.9 Environment made of nontoxic materials

All materials that the aquatic animals come into contact with must be made of nontoxic materials. Materials should be clean and chemical-free.

5.6.10. Environmental, behavioral and social enrichment

- Amphibious reptiles should have access to dry land.
- Amphibians in the aquatic phase should have easy access to floating surfaces so that tadpoles close to metamorphosis do not drown.
- Amphibians after metamorphosis should be provided with a suitable terrestrial environment that has relatively high humidity and access to appropriate food sources.

5.6.11 Procedures for contact

Contact with aquatic animals should be minimal. When necessary, it must be done using appropriate methods as described in the protocols. Treatment of aquatic animals usually done under anesthesia (TricaineSMS) and with powder-free nitrile gloves.

5.6.12 Isolation due to disease

In studies that examine morbidity in fish or amphibians, healthy individuals are kept in a separate room from the diseased ones. Work must be done in the room with healthy animals

Commented [ALE131]: בשיטות מתאימות קיים במתקן/פרוטוקול before it is done in the rooms with diseased animals; this work order must be strictly maintained. Fish and amphibians that spontaneously contract diseases must be separated from the healthy ones and treated until they recover or die.

5.6.13 Food

- The animals' food must be stored at the temperature recommended by the manufacturer.
 The food must be free of contamination. Food should not be given to the animals if there is any suspicion, based on appearance or smell, that it has become spoiled or infested.
- Each aquatic animal species must be given appropriate food that meets its nutritional
 needs. In most cases, dry commercial food should be used. If necessary, provide live food
 such as artemia (brine shrimp) and rotifers or canned food such as bloodworms, beetles,
 or other insects.

5.6.14 Substrate materials

The amount and type of substrate materials used are based on the animal species and the conditions in which they are being kept, in accordance with the recommendation of the responsible researcher. Substrate materials must undergo periodic sterilization.

5.6.15 Sanitation, cleaning, and disinfection

The frequency for cleaning and disinfecting the tanks is determined by the water quality.

The minimal condition is that the animals can be observed and inspected.

Containers for frogs and newts must be cleaned and disinfected once every six months.

Fish tanks are cleaned and disinfected between groups. If any animals in a tank become ill, all
the items with which the diseased animals came into contact must be removed and replaced. The
contaminated items must be disinfected with vaporized hydrogen peroxide. The macro-

environment of the rooms in which the tanks are located must be routinely cleaned and disinfected with products that are safe for aquatic animals.

5.6.16 Waste disposal

- The primary waste product from aquatic systems is used water. The water may be
 recycled through the filters or directed into the sewage system treated by the local
 authority. Dry waste collected and disposed of according to the same procedures that are
 described in the relevant section pertaining to waste removal from other animal rooms.
- Water that has been exposed to polluting elements undergoes a treatment of chlorination or chemical disinfection before disposal.
- Aquatic animal carcasses are disposed of in the same way as terrestrial animals.

5.6.17 Pest control

Pesticides are highly dangerous to aquatic animals. In general, pest control operations are conducted between cycles of animals, according to the "all-in-all-out" method. Therefore, there is no regular schedule for pest control. All pest control activity must be documented.

5.6.18 Collecting aquatic animals from and returning animals to natural areas

Any activity involving the collection, maintenance, or sampling of amphibians in the field may be carried out only after receiving the appropriate permits from the Israel Nature and Parks Authority.

5.7 Emergencies, weekends, and holidays

This procedure is similar to the corresponding procedures for terrestrial animals: during emergencies (section 2.3) and weekends and holidays (section 2.2.7).

Commented [ALE132]: Only amphibians? Not fish?

6. The Animal Facilities

The animal facilities at the University of Haifa keep the following types of animals: rats, mice, moles, and aquatic animals.

The animals are kept in facilities designed for this purpose, which have received approval from the Animal Testing Council.

The facilities are maintained so that they meet all requirements for animal facilities, including:

- A safe and secure environment that does not endanger the animals.
- Animals are housed in conditions that enable them to rest, sleep, and breed.
- Animals are able to freely move in their cages, including staying away from other aggressive animals.
- Animals have free access to food and water.
- Animals are able to keep distance from urine and feces.

The animal facilities associated with the Psychobiology Laboratories are located in the Rabin Building, 5th floor, where approximately 1,000 cages of mice and rats are kept. This animal facility consists of five rooms for rats and three rooms for mice, plus a quarantine unit.

The animal facility has two operating rooms equipped for surgical procedures, which are separate from the rooms where the animals are housed.

There is a separate room for euthanizing animals, a waste-disposal room with a refrigerated unit, storage rooms, and a washing room with machines for washing equipment.

Researchers' laboratories may include rooms for additional procedures.

Commented [ALE133]: I substituted aquatic animals for fish because above other types of aquatic animals are discussed

Commented [ALE134]: I do not see anything with a name similar to this on the university's English website

Commented [ALE135]: Dishwasher seems too specific and washing machine implies clothes – is this ok?

Animal Facility in the Science II Building, Terrace Building, 2nd floor, where a total of about 160 cages of mice and rats are kept. This animal facility includes three holding rooms, an operating room, a washing room, a warehouse, and a waste-disposal area with a refrigerator.

The SPF animal facility is located in the Science II Building, Terrace Building, 1st floor. It includes two holding rooms, where a total of 230 cages are kept, a washing room with machines for washing equipment, an autoclave, a biological fume hood, and a services room.

Beit Sala houses about 100 cages of mice in open caging and in IVC.

Room 25 houses about 100 cages of mice in open caging and reverse regime.

Institutional Veterinarian: Dr. Barak Carmi

Attending veterinarian: Dr. Corina Dollinger

The animal facility of the Institute of Evolution: a multi-purpose building in which a total of about 100 cages of rats are housed, with five holding rooms, an operating room, a washing room, a waste-disposal room with a refrigerator, and a storage room.

Animal Facility Director: Dr. Imad Shams.

Oranim College: There is no research activity at this location. The animals are only for observation and teaching purposes and are kept in a live-animal area. There are plans to carry out various studies at this location; if this is done, a written report will be sent to the Council for Animal Testing.

Faculty member responsible for the animals: Ms. Nina Dinov.

Commented [ALE136]: I found the name Terrace Building on a university map

Commented [ALE137]: What is reversed?

All animals are under the supervision of the Institutional Veterinarian according to accepted NRC rules. Each new animal facility will be approved by the Council for Animal Testing before it is populated with animals to be used for research.

6.1. Structures and supervision

6.1.1. Corridors

The corridors must be no less than 1.8 meters wide, in compliance with the university's safety regulations, in order to allow free passage of equipment and carts.

6.1.2. Animal room doors

The doors must be at least one meter wide to allow the free passage of equipment and carts. Doors must be made of a material that can be cleaned and disinfected.

6.1.3. Windows

Rodent rooms may not have external windows. If a window exists, it must be closed so that no light penetrates from outside and nobody can look into the room from the outside. Only small windows facing an interior room within the animal facility are permitted.

6.1.4. Floors

Floors in the animal rooms must be appropriate for work with hazardous materials, and therefore should be sealed, preferably with PVC.

6.1.5. Walls

The walls must be painted with washable paint so they can be cleaned and disinfected.

6.1.6. Drains

It is preferable that animal rooms do not have drains, to prevent entry of unwanted pests.

Any drains must remain closed, and only opened when it is necessary to drain liquids.

6.1.7. Climate control, ventilation, temperature control

- The animal rooms must have ventilation systems that allow for 20 changes of fresh air per hour and have HEPA filters.
- Each room must have climate-control systems that allow for full control of temperature and humidity. In some rooms, dehumidifiers and humidifiers have been installed.
- The ventilation systems in the animal facilities are backed up by an emergency generator.

6.1.8. Lighting

Lighting systems in the animal rooms are connected to an electric timer so that an artificial daily regime of light and darkness may be created.

6.1.9. Noise and vibration control

For the animals' comfort and safety, it is important to avoid noise and vibrations. Devices that create loud noises or vibrations are not permitted in the animal rooms. The use of mobile phones or anything else that may disturb the animals is prohibited.

6.1.10. Environmental control

An alert system in the animal facilities sends notifications regarding any malfunction in the electricity or climate control systems to the on-call employees in the general university system and the on-call employees for the animal facilities.

