Purchase and breeding of laboratory animals

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Introduction

At Utrecht University (UU) and the University Medical Centre Utrecht (UMC) Utrecht, laboratory animals are purchased and bred for use in animal experiments. By optimising the purchase and breeding of laboratory animals, we can guarantee the welfare of the animals, minimise the number of surplus animals and maximise the quality of studies. In this policy document, we outline the framework for this. The policy is based, among other things, on the advice 'Genetically modified animals killed in stock' part 1[1] and 2[2] of the Netherlands National Committee for the Protection of Animals Used for Scientific Purposes (NCad) and the revised guidelines 'The generation, breeding, genotyping, monitoring and keeping of genetically modified animals'[3] of the Central Authority for Scientific

Procedures on Animals (CCD) . However, this document is expressly not limited to genetically modified animals alone.

1 Purpose

This policy is intended to:

- establish frameworks for the procurement of laboratory animals;
- establish frameworks for the in-house breeding of laboratory animals;
- establish frameworks for outsourcing breeding to preferred suppliers;
- establish frameworks for monitoring and breeding new genetically modified lines;
- ensure optimal coordination between supply and demand for animals bred in-house;
- ensure the welfare of animals involved in breeding is guaranteed;
- ensure that unique breeding lines are preserved for science and society;
- align with national policy.

2 For whom is this policy?

The policy and the implementation guide Breeding of laboratory animals (hereinafter referred to as the implementation guide) for the purchase and breeding of laboratory animals are binding for employees of Utrecht University and UMC Utrecht. We expect external parties that depend on Utrecht University and/or UMC Utrecht for the purchase and breeding of laboratory animals to comply with this policy. Deviations from this policy are only possible in consultation with the Utrecht Animal Welfare Body (AWB).

Regarding the purchase of laboratory animals, the policy applies to all laboratory animals, and with regard to breeding, it applies to mice, rats and zebrafish. For the breeding of other animal species, we make specific agreements with users for each animal species or line.

3 General guidelines

3.1 Purchase or breeding of laboratory animals

When choosing between purchasing, outsourced breeding or breeding themselves, Utrecht University and UMC Utrecht apply the *'no, unless*' principle. If an animal species is available elsewhere, the animals are in principle purchased from this supplier and not bred ourselves. Deviation is only in exceptional cases possible, after approval by the Animal Welfare Body (AWB)*. The above restriction does not apply if breeding is part of a study, for example because the study is conducted with embryos or animals that have not yet been weaned.

*Where the document refers to consultation with and approval by the AWB, external parties must consult with and obtain approval from the responsible AWB.

The facility where the animals are housed may impose additional requirements on the animals to be purchased. See the implementation guide Ch.9 for details of these additional requirements.

3.2 Project licence and work protocol

3.2.1 Purchase of animals

The purchase of animals is only permitted on the basis of a work protocol approved by the AWB for the use of the animals in an experiment. Deviations from this rule are only possible with the approval of the AWB.

Exceptions to this are:

- Animals purchased for health monitoring purposes where animals cannot be replaced by using Environmental Health Monitoring options.
- Animals purchased for the purpose of establishing or renewing a breeding line. A department-specific breeding protocol (see 4.3), hereinafter referred to as the breeding protocol, must be in place for this purpose.

3.2.2 Starting breeding lines

Starting a line through breeding is only permitted if there is demonstrable prospect of continuation or progress of a project, for example on the basis of a CCD project licence. Deviations from this are only possible in consultation with the AWB. Information about this is included in the breeding protocol (see 4.3). If breeding involves discomfort or the creation of genetically modified lines, a project licence must always be obtained for breeding the animals (see 3.3). Within Utrecht, a genetically modified (GM) line database has been created containing all the details of the mouse, rat, and zebrafish lines present. This overview can be requested from the breeding coordinators. When aligning the breeding protocol for the purchase of a new line, this database is consulted by the AWB to prevent the presence of the GM line at another location in Utrecht.

3.2.3 Maintenance breeding

As with starting a line, maintaining lines requires demonstrable evidence of a project's progress or continuation. The implementation guide Ch.3 describe *best practices* for maintenance breeding. During breeding evaluation meetings (see 4.2), coordination takes place regarding the progress of the breeding program (see 4.6).

3.2.4 Production breeding

Upscaling breeding to the level of production breeding is only permitted on the basis of a valid project licence and a work protocol for the use of the animals approved by the AWB. Deviations from this rule are only possible after approval by the AWB, for example when adult animals are needed in research, resulting in a long period of time between the start of breeding and the execution of the experiment. When the approval of a work protocol has expired, the line in question is scaled down to maintenance breeding by the breeding manager.

3.2.5 Situations in which breeding is part of the study

Breeding animals as part of a study, for example when pregnant animals are exposed to test substances, or when the study is conducted with embryos or animals that have not yet been weaned, is only permitted based on a valid project licence and a work protocol for the use of the animals approved by the AWB.

3.3 Implementation EU framework genetically modified animals

As of 1 January 2023, the revised CCD guidance document 'The generation, breeding, genotyping, monitoring and keeping of genetically modified animals'[3] came into effect. This guidance document was drafted to implement the requirements set out in the Implementing Decision (2020/569/EU)[4]. The guidance document takes into account the recommendations from the European Commission's 2021 consensus document 'Working document on genetically altered animals'[5].

According to this guidance document, authorisation is required for:

1. the creation of genetically modified lines or the crossing of two or more existing lines;
2. invasive genotyping without identification;
3. the recovery (cleaning) and cryopreservation (freezing) for scientific purposes.

The implementation guide Ch.10 describe how we implement the above points in Utrecht.

4 Specific guidelines for breeding mice, rats and fish

4.1 Breeding coordinators

In accordance with the advice of the NCad[1], Utrecht University and UMC Utrecht have appointed breeding coordinators at all facilities where animals are bred. They have thorough knowledge of the breeding of the animal species in question. The breeding coordinators inform the AWB about the status of breeding management for all lines within Utrecht University and UMC Utrecht. The researcher (owner of the line) coordinates the details of each breeding programme (including age, breeding strategy, transport) with the breeding coordinator. The researcher must follow the advice of the breeding coordinator that results from this. The basic principle is that each breeding programme is managed by the breeding coordinator and/or breeding manager.

4.2 Targeted communication and co-ordination

Communication between the researcher, breeding coordinator and the AWB takes place at regular intervals, at least at the following times:

- New researchers follow the intake procedure of the relevant animal facility before starting with the breeding. If the researcher carries out breeding activities himself, he must be assessed for competence before starting (see Lifelong Learning policy)
- Before breeding commences, agreements relating to breeding are laid down in the breeding protocol. Breeding animals is only possible on the basis of a breeding protocol approved by the AWB.
- At least once a year, the breeding coordinator checks breeding results, animal stocks and other matters that may affect the breeding results. The breeding coordinator communicates with the

researcher about this when necessary. The researcher must follow the advice of the breeding coordinator that results from this.

- Throughout the year, the AWB conducts random audits of the breeding programme.
- At least once a year, breeding is evaluated in consultation with the researcher, the breeding coordinator, the breeding manager (if applicable) and the AWB. The breeding coordinator is responsible for initiating the evaluation meeting.

4.3 Breeding efficiency and animal welfare

In the breeding protocol, details are laid down to optimally guarantee breeding efficiency and the welfare of the parents and offspring involved. Insofar as not specified in the breeding protocol and in this document, breeding is carried out in line with other (policy) documents (Policy on the prevention of individual housing of laboratory animals, Policy on surplus laboratory animals, reuse and rehoming, and the department-specific breeding manual agreed with the AWB).

4.4 Surplus animals

The breeding of laboratory animals always results in surplus animals. Breeding is organised in such a way that the number of surplus animals is as low as possible. Agreements on this are laid down in the breeding protocol. Based on the periodic evaluation of the breeding programme, adjustments can be made to reduce the number of surplus animals. During this evaluation, the destination of these surplus animals is also discussed. Where possible, surplus animals are used in ongoing projects. They can serve as teaching animals or as suppliers of tissues and organs. Where possible, the supply and demand of surplus animals are matched via ATEX (see Policy on surplus laboratory animals, reuse and rehoming).

4.5 Outsourcing breeding to external parties

If breeding is outsourced to an external party, this can only be done with a preferred supplier in accordance with the microbiological quality control of the university's own animal facilities. The (mouse) lines remain the property of the licence holder. This policy therefore also applies to these breedings regarding delivery to third parties and backup of unique lines. In consultation with the AWB and breeding coordinator, the researcher decides whether breeding can be carried out within an animal facility of the UU/UMC or whether it must be outsourced to an external party. During this consultation, the AWB lays down agreements regarding the breeder's openness to audits. The welfare requirements must also comply with the AWB policy documents regarding animal welfare. Each year, the researcher requests data on the number of animals bred, delivered, and killed for use in breeding or experimentation, which is discussed in the annual registration meeting. For the sake of openness and transparency, UU/UMC Utrecht publishes this data in the annual report Animal Experiments in Utrecht. Each year, the researcher and the AWB hold an evaluation meeting on breeding results, experimental plans, and communication with the external party. A breeding audit is conducted every three years, during which a representative of the breeder is invited to the evaluation meeting. If the AWB deems it necessary, it conducts an audit at the external party.

4.6 Maintenance or cryopreservation

When the offspring of a line are not used in studies for a definite or indefinite period of time, the AWB, in consultation with the breeding coordinator and breeding manager and after consultation with the researcher, will decide whether the breeding line will be maintained or cryopreserved. The decision must consider: 1. the uniqueness of the line in question, 2. the expected duration for which the line will not be used, and 3. the balance between the number of surplus animals produced by maintenance breeding and the number of animals that will be needed to cryopreserve the line and restart breeding from cryopreservation. The breeding coordinator advises the researcher and AWB on cryopreservation.

4.7 Backup of unique lines

A unique line is a line that is not available elsewhere (commercially or non-commercially), either on the shelf or in the freezer, and that has scientific value. The UU and UMC Utrecht make every effort to ensure that the continued existence of a unique line is guaranteed at all times and that this line remains available for future use within or outside their own institution even after breeding has ceased. Therefore, researchers who breed a unique line are obliged to create a backup of this line at an early stage of breeding, for example through cryopreservation (rats and mice) or glycerol DNA stock (zebrafish).

4.8 Delivery to third parties

The UU and UMC Utrecht are not commercial breeding companies. The delivery of animals from breeding to third parties is therefore only permitted under the following conditions:

- it is a one-off request, for example to bridge the gap until the third party has its own breeding programme; or
- there is a collaboration in which UU or UMC Utrecht is actively involved as a partner, but the research is conducted by third parties.

Structural delivery to third parties outside the facility where the animals are bred, without collaboration or for profit, is not permitted.

When delivery to third parties takes place, the researcher must ensure in advance that the receiving party has the correct permits, that the animals (with their health status) are accepted by the receiving party, and that the transport of animals complies with the legal requirements.

5 Future prospects

This policy describes how UU and UMC Utrecht currently deal with the purchase and breeding of laboratory animals. However, both institutions are aware that developments are ongoing. They therefore pay continuous attention to developments that can contribute to the quality of research and the 3Rs. This policy will therefore be evaluated regularly, at least every three years, and updated where necessary.

In relation to this policy, the AWB is currently working on the implementation of the following topics:

- expanding the database of genetically modified mouse and rat lines at national level in collaboration with the breeding coordinators;
- optimising ATEX as a national and international database that facilitates tissue exchange;
- investigate the possibility of jointly placing genetically modified lines bred at multiple national and international facilities with a commercial *preferred supplier*.

6 Literature

1 Genetically modified animals killed in stock, NCad, 2016

2 Genetically modified animals, Dead or killed for use in breeding or animal testing, part 2, quality criteria, NCad, 2018

3 Revised guidance document 'Het generen, fokken, genotyperen, monitoren en houden van genetisch gewijzigde dieren', 2023 (Dutch only)

4 Implementing Decision (2020/569/EU)

5 European Commission, Directorate-General for Environment, *Framework for genetically altered animals under Directive 2010/63/EU on the protection of animals used for scientific purposes* , Publications Office of the European Union, 2022

7 Glossary

Cryopreservation	In order to keep (unique) lines available or to ensure a stable baseline, semen or embryos (rats and mice) from the line in question can be frozen.
Breeding coordinator	This person ensures that the breeding of (genetically modified) animals is carried out professionally and in accordance with legislation and regulations. In doing so, this person advises the AWB and the researcher.
Breeding manager	This person's task is to maintain the breeding line as agreed by the breeding coordinator, AWB and researcher and laid down in the breeding protocol.
Glycerol DNA stock	In order to keep (unique) lines available or to ensure a stable base line, the DNA construct (zebrafish) of the line in question can be frozen in glycerol.
Rederive	Also known as sanitation. A laboratory animal facility has a controlled microbiological status. If the animals do not meet this status, rederivation can be used to achieve the desired microbiological status.

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