TNO POLICY DOCUMENT ON LABORATORY ANIMALS AND ANIMAL EXPERIMENTS

TNO innovation for life

Commencement date: 1 January 2018

PREFACE

This TNO Policy Document ‘Laboratory Animals and Animal Experiments’ 2018 is the seventh since 1985. Contrary to the previous policy document, the present version only applies to TNO. As a result of a further unbundling of TNO and Triskelion BV, both parties have decided to pursue their own policy as from 2018.
The policy document is part of TNO’s Corporate Social Responsibility (CSR) policy. In line with this, TNO will take the greatest possible care in the decision making about animal experiments as well as in the performance of these experiments.

This policy document serves as a concrete guideline for TNO’s management and employees in:
- the design and implementation of high-quality animal experiments for the purpose of improving human health;
- the ethical treatment of laboratory animals before, during and after experiments;
- the continuous professionalisation of the personnel involved;
- contributing to the development, acceptance and implementation of Refinement, Reduction and Replacement (3Rs) of animal experiments, and
- communicating about animal experiments and alternatives within and outside TNO.

This policy document runs in parallel with the TNO strategy period 2018-2021. The Animal Experiments and Alternatives working group will draw up an annual plan with concrete objectives and actions and will assess whether the implementation of this policy is proceeding according to plan and whether adjustments need to be made.

POLICY DEVELOPMENT PROCEDURE

This document was drawn up under the direction of the internal official 13f3a in accordance with the Animal Experiments Act (Wod), who is also the chairman of the Animal Welfare Body (IvD) of TNO, with input from experts in the field of animal experiments and alternatives for animal experiments from the departments Metabolic Health Research (Leiden) and CBRN Protection (Rijswijk). The draft version of this document was submitted to the Managing Director of Defence, Safety & Security, Director of Food & Nutrition, the Directors of Research (Life and OWPS), the Integrity Officer of TNO and all members of the IvD as reviewers, and then presented to the TNO Executive Board, including the licence holder.

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1 VISION AND AMBITION

1.1 VISION

The use of laboratory animals poses a moral dilemma since animals can be given their own (or intrinsic) value, in addition to their usefulness to man. TNO therefore takes the greatest possible care with regard to decision-making on animal experiments and the performance thereof.

To answer important research questions in a number of TNO research areas - such as the efficacy and safety of medicines - the use of laboratory animals is currently unavoidable. This is partly a consequence of requirements imposed by the legislator and partly because there are no alternatives to these animal experiments yet. TNO considers answering these questions to be of such social importance that it considers the use of laboratory animals acceptable and even necessary in such cases. In doing so, we realise that the researcher responsible, who designs the experiment, the performer of animal experiments, and the official body that is ultimately accountable (TNO Executive Board), are responsible for the welfare of animals used in experiments in the broadest sense. In their actions and considerations, they must take the intrinsic value of the animal into account.

The tension between the two responsibilities (responsibility for effective research into human health and responsibility for the welfare of laboratory animals), in which TNO carries out its tasks, requires a continuous evaluation of the actions taken in this area. It is essential that the interests of humans and animals are carefully weighed against each other and that the intended results of the research actually benefit society.

TNO states, in line with the Animal Experiments Act, that the use of laboratory animals is only acceptable if there is no suitable alternative to the animal research available and if the social objective outweighs the discomfort to the animals. In doing so, TNO always makes an effort to conduct animal research with as few animals as possible and as little distress as possible while maintaining scientific integrity. The 3Rs, as described in the Principles of Human Experimental Technique (Russell & Burch 1959, see box), apply.

The trade-off between the social objective and the distress of the laboratory animals takes place in a society in which the interests of the animal receive increasing attention. In this society, scientific and technological developments create new opportunities, which also create new ethical dilemmas. TNO expressly takes this into account and, in this context, makes choices and considerations in dialogue with society, both at the level of the individual research proposal and on the basis of research programmes.

TNO sees the legal requirements with regard to animal experiments as a minimum that must be met. In addition to these legal obligations - described in the Experiments on Animals Act (2014) - TNO is actively developing innovations in the field of refinement, reduction and replacement of animal experiments. This is discussed in more detail in the following chapters.

Refinement:
Any method, addition or adaptation in an experiment that reduces pain, stress and/or distress to animals before, during or after the experiment.

Reduction:
Any approach that reduces the number of animals needed to obtain statistically and scientifically relevant results.

Replacement:
Any approach that replaces a method that uses live vertebrates or cephalopods.

1.2 AMBITIONS

TNO has the intention to conduct excellent biomedical research, with the aim of improving human health. To this end, various technologies are being developed and applied, both clinically and pre-clinically. Pre-clinical techniques (laboratory animals, in vitro, in silico) focus on the predictive value for humans. A number of examples of translational animal research are explained in the following box.

There are many actors who determine whether a new technology has added value: first of all the primary users (including drug developers), but also government agencies (frameworks in the field of ethics, costs, regulatory pressure), academia (offering new technological possibilities) and technology providers (techno start-ups, CROs, etc.). TNO's ambition is to look beyond the hype and to make a concrete contribution to the scientific substantiation of research models and - through contacts with the actors - to the implementation in practice. This also applies explicitly to methods that refine, reduce and replace animal experiments (3Rs).

TNO also has the ambition to pursue an active and balanced communication policy in the field of animal research and alternatives. This policy is aimed at professionals in biomedical research, but also at the general public.

Vaccination against Atherosclerosis
TNO has actively contributed to the preclinical phase of the development of a vaccination against atherosclerosis by using special mice (APOE*3 leiden.CETP mice) developed by TNO and the LUMC. These mice show a comparable disease development to that in humans, thereby enabling translations from mice to man. Currently, the research is advanced in such a way that a clinical study with the vaccine is ongoing.

Early recognition of NASH/fibrosis
Diagnosis of NASH (non-alcoholic steatohepatitis)/ Fibrosis is currently only possible by taking a (highly invasive) biopsy or by using MRI (only possible in advanced disease stages). Through TNO's participation in a multidisciplinary consortium in which various organs from mice have been collected and analysed using advanced -omics methods, an early predictive signature for the disease has now been found. Currently, a second consortium has started to translate this signature into a biomarker in the blood, enabling early non-invasive recognition of the disease and thereby allowing the start of treatment in time.

Intervention in case of organophosphate contamination
Most organophosphates, including nerve agents such as VX, are liquids. Incidents or Intentional misuse may lead to human exposure with potentially fatal outcomes. Rapid diagnosis of exposure is needed to enable and optimise timely interventions consisting of skin decontamination and medical countermeasures. Experimental findings are used to develop computer models in which effects of poisoning are related to levels of exposure. This approach is aimed at improving the extrapolation of effects of interventions to the human situation.

TNO has formulated an innovative multi-year programme proposal within the top sector Life Sciences and Health for the period 2018-2021, of which 3R innovations form an important part. Within the Early Research programme 'Organ-on-a-chip' TNO contributes to the ambitions of the Dutch government, as formulated in the recommendations of NCad to the Secretary of State for Economic Affairs 'Transition to animal-free research' (December 2016). TNO was involved in writing this advisory report and also actively participated in follow-up discussions and parliamentary question rounds.

Investment in animal-free innovation does not mean that TNO will not carry out animal tests in the coming years. It does mean that TNO will focus its own research resources on replacement and reduction, but certainly also on refinement. This includes both the development and implementation of these alternatives, so that they can be used as widely as possible.

Inspirational message
(Berthold Auerbach, 1812 – 1882)

The most reliable measure of the degree of civilization of a people and an individual is how they consider and treat the animals.

1.2.1 Excellent biomedical research

Over the next 4 years TNO will focus on helping companies to develop (personalised) interventions to prevent or cure diseases. The focus will be on metabolic diseases and immune health. TNO chooses - together with other knowledge institutions and companies - to develop new models that are more translatable to humans than current approaches. This concerns both animal models and non-animal models. This approach is a continuation of the policy of the past few years, in which the choice was made to carry out this research even more with partners in the field, in order to achieve a broader implementation of innovations.

1.2.2 Acceptance and implementation of innovations

In order to achieve (inter)national scientific and social impact, broad application outside TNO is essential. For this reason, the acceptance and implementation of innovations by industry, society and regulatory authorities will be actively stimulated by seeking cooperation with the relevant parties. TNO does this by setting up public-private partnerships with industry, governments and interest groups (including ProefdierVrij and patient associations). In addition, TNO actively contributes to expert groups on specific issues in the field of biomedical effectiveness and safety research.

1.2.3 Refinement of animal experiments

Refinement means that the discomfort (pain, suffering, distress or lasting harm) to the animals is kept as low as reasonably achievable in relation to the purpose of the experiment. In doing so, account will be taken of the views of experts with regard to, among other things, housing, care and control of experimental techniques such as administration, sampling, surgery and anaesthesia techniques. TNO applies the most recent insights and techniques in its animal experiments.

In addition, TNO actively contributes to the development of innovations in the field of refinement, for example by developing extremely sensitive measuring methods that reduce the need to take blood samples for biochemical analyses. Experiences are exchanged with colleagues inside and outside the organisation, including through the Biotechnical Association.

1.2.4 Reduction of animal experiments

TNO strives to ensure that every study is carried out with the minimum number of animals required to arrive at scientifically sound answers. This places high demands on:

- the definition of the question
- the design of the experiment (the experimental set-up)
- the professional competence of those performing the experiments
- the choice of the species and the quality of the animals
- the conditions under which the test is carried out
- statistical assessment

The assessment of the design and proposed execution of the test in relation to the question will be carried out by the researcher in collaboration with external experts and the Animal Welfare Authority. TNO actively contributes to innovations in the field of reduction, for example by developing non-invasive measurement methods – such as Retinal Imaging - that enable longitudinal studies to be carried out.

1.2.5 Animal-free innovations

Before considering an animal test, TNO will investigate whether the question can also be answered without the use of animals. The necessary knowledge and infrastructure is amply available for this purpose. In addition, TNO is actively researching the development of new animal-free methodology, such as the long-term research programme Organ on a Chip. By making use of its extensive knowledge of the (patho)physiology of humans and animals, coupled with knowledge of technological innovations (such as optics, materials, chemical analysis), TNO is ideally placed to accelerate animal-free innovations for research into complex biological mechanisms and diseases. TNO does this together with companies, university medical centres and NGOs.

1.3 DIALOGUE

TNO opts for active and diligent dialogue with stakeholders in the field of animal experiments, in line with its general communication policy and strategy. TNO's vision is that animal research is at present an essential part of research into the prevention and cure of human diseases. From an ethical and scientific point of view, TNO invests heavily in high-quality animal experiments with innovative translational models and, at the same time, in the development of animal-free innovations such as organ on a chip and computer models.

The aim of the dialogue is to share TNO's vision and practical approach with the professional and public environment and to implement the latest insights in the field of animal research and non-animal innovations in the organisation. Specific target groups are the general public, relevant ministries and implementing organisations, business organisations, patient organisations and NGOs.

In conducting this dialogue, information from the research groups involved is essential, and both management and employees have an active role to play. A balance will be sought between the desirability of the dialogue, on the one hand, and the safety of TNO employees, cooperating organisations and clients, on the other.

1.4 EXTERNAL ASSESSMENT

In accordance with the national Code of Openness among licence holders drafted in 2008, TNO reports annually on the animal tests carried out under its responsibility. This report includes a trend analysis of the registration of animal experiments and laboratory animals made available to the Netherlands Food and Consumer Product Safety Authority (NVWA) on an annual basis. TNO communicates about this via the TNO website, among other things, and as part of the CSR component of the TNO annual report. TNO also enables external stakeholders to ascertain its verifiability.

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2 STANDARDS

2.1 LEGAL FRAMEWORK

As far as the performance of animal tests is concerned, TNO has to deal with:

- The Animal Experiments Act ('Wod', based on European directive 2010/63/EU and last revised on 18 December 2014) as illustrated in Appendix 1
- National and international legislation in the field of consumer safety (including pharmaceutical legislation), the health and safety of employees and the protection of the environment and other legislation relating to animals (including the Animals Act).

TNO operates within the confines of these laws. This means, among other things, that TNO actively uses the 3Rs. Where an alternative method is available that uses fewer/no animals, this will be employed. Of course, in accordance with the law, no cosmetics will be tested on animals.

2.2 CODES OF CONDUCT AND QUALITY STANDARDS

In addition to the above laws, TNO operates in accordance with the following internal and external codes of conduct that are relevant to this policy area.

- The Dutch Code of Conduct on Scientific Practice
- The Dutch Code of Openness on Animal Experiments
- TNO's internal policy (TNO code, Regulations in the event of suspected misconduct)

TNO works in accordance with the requirements of ISO 9001. In addition, TNO's largest research group where animal tests are carried out is fully accredited by AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care). AAALAC is a globally accepted organisation that, through a voluntary accreditation and assessment programme, aims to optimise animal welfare and personnel safety beyond the minimum legal requirements for animal experiments.

The smaller TNO research groups where animal tests are carried out also strive to comply with the standards set by AAALAC for animal welfare and personnel safety internally. However, obtaining AAALAC accreditation is not feasible for these groups, given the small scale on which animal experiments are performed.

2.3 CORE VALUES

TNO has an organisational code in which integrity, independence, professionalism and social commitment are promoted as the most important core values.
In addition, TNO is characterised by its strategic values of market and customer focus, innovation and connection, and inspiration/human focus. The way in which TNO implements this animal experiments policy is based on its vision, ambition and core values.

3 ORGANISATION STRUCTURE

3.1 RESPONSIBILITIES

3.1.1 Management

Through the annual planning and control cycle, the management of the departments directly involved in the performance of animal experiments will ensure the effective facilitation of all aspects necessary for the optimal design and performance of animal experiments. Every year, objectives for improvements in the field of replacement, reduction and refinement of animal experiments are included in the quality plan in the broadest sense. Management monitors the implementation of and compliance with action points included in the quality plan.

3.1.2 Project managers, analysts, bio-engineers and animal care providers

The project managers, research technicians, biotechnicians and animal care providers take care of the quality of animal experiments and the welfare of the animals on a daily basis. To this end, they have the necessary powers and competencies, and work closely with each other as well as with the other expert persons and committees involved in animal experiments in order to maximise the success rate of the animal experiments. The concept of 'lifelong learning' is actively shaped by attending internal and external training courses. Improvement points are communicated in advance, usually via members of the Animal Welfare Body (IvD), and implemented actively where possible by means of welfare evaluations after the end of each experiment.

The department responsible for most animal experiments within TNO has a cooperation agreement with InnoSer Laboratories BV about the use of the animal facility. The agreements in this respect are stipulated in a cooperation agreement. There is a regular meeting between the research manager of TNO and the operational manager of InnoSer Laboratories BV, as well as between the Chair of the IvD and the operational manager of InnoSer Laboratories BV.

3.1.3 Animal experiments expert and designated veterinarian

On behalf of the TNO licence holder, the 13f3a official (animal experiments expert/internal supervisor) supervises and advises on the welfare and health of the laboratory animals and the quality of the work with laboratory animals in close cooperation with the designated veterinarian. The animal experiments expert and designated veterinarian are authorised to intervene or suspend an animal test in the event of an unauthorised act or unexpected serious discomfort.

The following four core values are central to exercising the role of animal experiments expert: transparency, independence, expertise and professionalism.
The animal experiments expert makes an active contribution to the further professionalisation of the Animal Welfare Body in general (see 3.2.2) and the associated roles and tasks in particular.
During the period of repositioning and redistribution of tasks, authorities and responsibilities arising from the unbundling between TNO and Triskelion BV, the four core values will continue to guide how the role of the animal experiments experts is interpreted. In this way TNO ensures that the welfare of laboratory animals is safeguarded in a transparent, independent, expert and professional manner. The role has been assigned to the staff department Operational Excellence & Auditing, which ensures the independent assessment of the activities.

Structured consultation with the licence holder and managers of the parts of the organisation where animal experiments are carried out takes place in order to promote the development and implementation of the animal experiments policy. Direct communication lines within the organisation with researchers, biotechnicians and animal care providers, as well as outside the organisation with fellow animal experiments experts facilitates optimal information transfer with regard to animal experiments and alternatives. Where necessary, the animal experiments expert will also give advice, solicited or unsolicited, to all parties directly or indirectly involved in the performing the experiments.

3.2 BALANCING INTERESTS

3.2.1 AEC-TNO

The Animal Ethics Committee TNO (AEC-TNO) assesses the importance and feasibility of the objective of the project, balancing this against the expected discomfort in laboratory animals and advises the competent authority, the Central Authority for Scientific Procedures on Animals (CCD) . If necessary, it could also apply this recommendation to project proposals from other institutional licensees.

In accordance with the Wod, the AEC-TNO includes experts in the fields of science in which TNO operates, including the 3Rs in those fields, design of animal experiments, veterinary practice, the keeping and care of laboratory animals, ethics, and laboratory animals and their protection. At least half of the committee (including the chair) consists of external members who have not had an employment relationship with TNO for at least the past five years. If necessary, the IvD will provide the AEC with a recommendation on certain projects.

Following the revision of the Wod on 18 December 2014, the mission of the AEC and its relationship to the licence holders has changed substantially. AEC-TNO, in close consultation with other AECs in the Netherlands, organised in the public AEC umbrella organisation (NVDEC), has redefined its position and working method and will continue to evaluate them and adjust them if necessary. In view of the licences granted by the CCD and the prospects for new licences, the continued existence of AEC-TNO is being carefully monitored in order to continue to guarantee the quality of the advice provided in the future. AEC-TNO is active in working groups of the public AEC umbrella organisation.

3.2.2 Animal Welfare Body

Following the revision of the Wod on 18 December 2014, the Animal Welfare Body (IvD) was established. The IvD has a fixed structure, consisting of the animal experiments expert (chairman) and at least one scientist.
In addition, the IvD has a number of permanent and ad hoc advisors, including the designated veterinarian, a number of scientists and various biotechnicians.

The statutory tasks of the IvD are to advise and guide researchers in the submission of project proposals, to check compliance with the Wod in the performance of animal experiments under approved project proposals, to supervise animal welfare and care, to facilitate the necessary information, to advise on the 3Rs, to register animal experiments and laboratory animals, and to coordinate the training and retraining of personnel involved in animal experiments. The tasks, powers and responsibilities of the IvD have been defined and in the meantime its working method is evaluated internally on a regular basis.

In addition to the internal evaluation of the IvD's working method, TNO's IvD is also a member of the national IvD platform and has direct contact via this route with other IvDs, the competent authority (CCD), the National Committee for Advice on Animal experiments Policy (NCad) and the NVWA. It is up to date with the latest news regarding the interpretation, change and content of the Wod and other IvD or animal-related matters. For example, there is a number of working groups in which TNO actively participates.

3.3 PERFORMING ANIMAL EXPERIMENTS

3.3.1 Experimental set-up

The experimental set-up of animal experiments will be determined by the relevant authorised and competent researchers. The quality of individual animal experiments carried out under approved projects, as well as the assessment of whether these studies fall within the scope of the approved projects, is guaranteed internally by the Animal Welfare Body. Together with the researchers, she tries to maximise the quality of the proposed animal experiments by optimally applying possibilities for replacement, reduction and refinement. The quality of research on laboratory animals is also safeguarded in TNO's integrated quality assurance system.

3.3.2 Selection, housing and care of animals

When selecting animal species to be used, TNO will focus on the development and application of (animal) models that are scientifically relevant to the research. This will be based on developing a strategy to efficiently identify the most relevant animal species in relation to predictability for humans or animals.

Housing and care of laboratory animals will be provided within state-of-the-art facilities that meet legal standards for the physiological and ethological needs of the animals. The care and treatment of the animals is carried out by the respective authorised and competent staff. TNO does not perform in-life experiments with non-human primates.

3.3.3 Surplus animals

Where animal experiments are carried out, a surplus of animals that are not usable may arise in various ways. Examples of this are the birth of animals in specific breeds that are not suitable for research, or the purchase of animals, which unexpectedly cannot be used in research. In order to avoid the sacrifice of animals without their use in animal experiments as much as possible, TNO has drawn up and laid down a number of specific procedures in SOPs. TNO uses the Jackson breeding strategy for this, which makes use of a core, expansion and production colony. These procedures ensure an optimal match between the supply and demand of self-bred animals, whereby the ordering of animals is subject to conditions, and which stimulates the use of surplus animals for the training of operations and the collection of tissue. In internal breeding, for example, market demand is taken into account and this is also communicated to the customer, and animals that can be used until later in life will remain in stock in order to increase their utilisation. To keep the internal breeding policy as tight as possible, TNO is also affiliated to the national network of breeding coordinators.

3.3.4 Dissemination of results

TNO aims to publish the results of its animal research in scientific journals as much as possible. In doing so TNO follows the international ARRIVE Guidelines to provide maximum insight into the approach and techniques followed by TNO and thus contribute to minimising unnecessary repetition of animal experiments.
In addition to scientific publications and presentations at scientific congresses, TNO also plays an active role in publicising its use of laboratory animals for methodical research, for example in the form of collaborating on television programmes in which the usefulness and necessity of using animals are explained.

4 TRAINING, AWARENESS AND EMBEDDING: CULTURE OF CARE

4.1 TRAINING AND REFRESHER COURSES

Through education, training and coaching, the level of expertise of qualified employees and the organisation is maintained at such a high level that the research results have the greatest possible utilisation. To this end, members of the Animal Ethics Committee and members and advisors of the Animal Welfare Body, researchers, biotechnicians and animal care providers participate in external and internal in-service training (research-related, animal-related, ethical and in the field of the 3Rs). Keeping a training record contributes to the transparency in this respect.

TNO also wants to contribute to the training of new researchers, biotechnicians and animal care providers, among other things by actively offering internships.

4.2 CHAIN RESPONSIBILITY

The responsibility that TNO takes for its animal experiments is not limited to that which takes place under its direct supervision, but extends throughout the entire chain. TNO charts this chain in order to set requirements for quality and animal welfare where necessary and possible.

4.2.1 Critical suppliers

Animals are generally obtained from approved establishments specialising in the breeding of laboratory animals or from its own breeding (see 3.3.4). In a limited number of cases and under strict conditions, animals are sourced from elsewhere, e.g. universities or farms.
Analysis of the quality of animal suppliers by means of questionnaires and audits aimed at quality in general and animal welfare in particular is an integral part of the chain responsibility that TNO takes. Suppliers of materials that are critical for the quality of animal experiments or the welfare of laboratory animals, such as suppliers of animal feed, are also quality controlled.

At the initiative of TNO, the national collaboration ASAP (Animal Supplier Audit Partners) has started with seven partners to jointly audit suppliers of laboratory animals, in order to increase audit quality and share resources. This initiative has taken shape in recent years (audits have been carried out at several suppliers) and may be extended to other critical suppliers of, for example, feed or bedding, but also other parties responsible in the chain.

4.2.2 Other parties in the chain

In addition, TNO may analyse animal tissues from animal experiments carried out elsewhere under the responsibility of TNO, or where laboratory animals that have undergone an animal test under the responsibility of TNO are transferred to another party. Examples include animals that are transferred to a quality control laboratory for health monitoring purposes, animals that undergo operations for which a party's own infrastructure is lacking for specific research questions (e.g. MRI scan), specific transgenic animals for biomedical research at other research institutions and animals that are not sacrificed after the animal test but are adopted or returned to their place of origin.

In these cases TNO will ensure that the laboratory animals originate from an external party or are transferred to an external party that complies with the minimum quality and animal welfare standards set by TNO. This policy component will be further defined and shaped in the coming period.

5 POLICY AUDIT

5.1 POLICY AUDIT

The implementation and execution of the animal experiments policy is in line with the TNO strategy period 2018-2021. The objectives described are put into practice annually and are included in the quality plans of the respective staff bodies and research departments. The policy objectives are reviewed annually by the Working Group on Animal Experiments and Alternatives, consisting of the animal experiments expert and the managers of the departments under whose responsibility animal experiments is performed. The working group reports its findings to the relevant unit directors and the licence holder.

Each year, the working group will assess whether the implementation of the policy is proceeding according to plan, on the basis of the action plan approved by management. The findings of the working group will be reported to the TNO Executive Board and communicated internally. The working group can advise management, solicited or unsolicited, with regard to the desired developments in the field of animal experiments and alternatives.

5.2 COMPLIANCE

5.2.1 Non-compliance with agreements and abuses

Non-compliance with agreements as stipulated in this policy and in laws and regulations are discussed with the management and the Animal Welfare Body, stating reasons for non-compliance whenever this is not in line with the values that are important to TNO.

There are several actors who can signal when non-compliance with agreements and procedures or malpractices occur.

1. Employees who see that policy is not being implemented or have questions concerning the content of the policy.
2. The management responsible for overseeing the implementation of the policy.
3. The animal experiments expert who is responsible for supervising the implementation of the policy and who is involved in the evaluation of incidents via the Animal Welfare Body.

Confidential counsellors are available to discuss issues of scientific and business integrity, behavioural interaction and conscientious objections. This route allows anonymous notification of non-compliance or other sensitive issues.

If non-compliance with policy is deliberate for reasons that are not based on integrity, the organisation will take action. The incident will be investigated. Management will decide on sanctions, taking advice from HR or other experts.

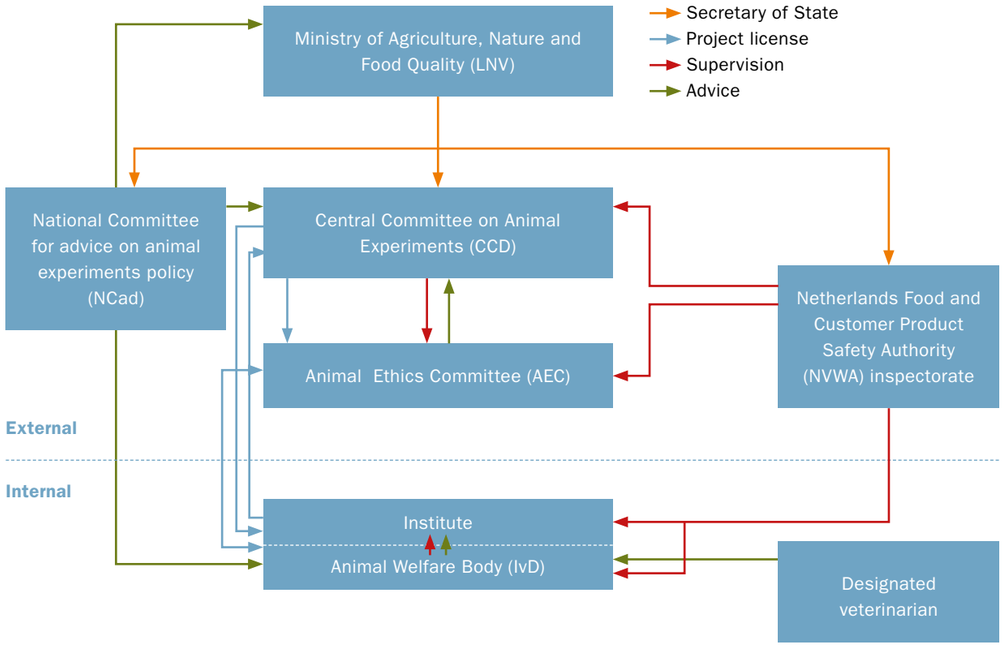
As far as is known, there have been no malpractices in the recent past.

5.2.2 Process and incident management

The recording and follow-up of incidents and gaps in the assurance of quality and animal welfare discovered by means of process audits are stored centrally and monitored/analysed annually. Where necessary, processes are adjusted and policy tightened up. This provides assurance that animal experiments are continuously carried out at TNO in accordance with best practices.

APPENDIX 1

Schematic representation of the relationship between the government and TNO with the associated roles.



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