Guidelines for Proper Conduct of Animal Experiments

June 1, 2006

Science Council of Japan

Preface

The necessity of basic considerations for the handling of laboratory animals in Japan had been based on the
Law for the Humane Treatment and Management of Animals (Law No. 105, 1973) and Standards Relating to the
Care and Management of Experimental Animals (Notice No. 6 of the Prime Minister’s Office 1980).

Under these conditions, the rationalization of animal experimentation was based on administrative
guidance rather than laws and regulations because of its importance in the advancement of scientific research. The
Science Council of Japan submitted a recommendation to the government in 1980 entitled “Establishment of Animal
Experimentation Guidelines.” In response to this recommendation, the Ministry of Education issued a notification
to related institutions entitled “Animal Experimentation in Universities, etc.” (Director General, Science and
International Affairs Bureau, 1987). Based on this notification, research institutions established policies for more
appropriate conduct of animal experiments and Institutional Animal Care and Use Committees, and applied them in
detail. As a result, it became possible to conduct highly creative scientific research in a free and open manner and
Japanese medicine and life sciences made remarkable progress on an international level.

For progress in life science, it is recommended to have a voluntary system of animal experimentation under
the responsibility of researchers who best understand the necessity of such experimentation. There are also calls for
the exercise of government authority in animal experimentation. Therefore, establishment of guidelines on animal
experimentation became an urgent necessity and Subcommittee 7 of the Science Council of Japan issued a proposal
entitled “Promotion of public understanding of animal experimentation” in 2004.

On receipt of this proposal, the Ministry of Education, Culture, Sports, Science and Technology and
Ministry of Health, Labor and Welfare compiled “Fundamental guidelines for proper conduct of animal experiment
and related activities in academic research institutions under the jurisdiction of the Ministry of Education, Culture,
Sports, Science and Technology” and “Basic policies for the conduct of animal experimentation in the Ministry of
Health, Labor and Welfare.” The two ministries requested the Science Council of Japan to prepare detailed
guidelines to serve as a reference material or a model when research institutions compile their own specifications for
animal experimentation in accordance with the above fundamental guidelines and basic policies.

Handling of laboratory animals is influenced by the religion and culture of each country. The so-called
North American model specifies voluntary management of animal experimentation without relying on legal
restrictions on scientific procedures, while Japan favors the establishment of a system based on Japanese customs.
With such a system, it is always hoped that animal experimentation will be promoted appropriately with the
understanding of the people and will contribute to advances in life science research.

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Basis and objectives

Animal experiments are indispensable in medical and life science education, research and testing. They should be managed and conducted voluntarily under the responsibility of each research institution. The researcher must draft the animal experiment protocol based on scientific rationale and also should consider the welfare of the animal. The researcher must have the Institutional Animal Care and Use Committee review the suitability of the proposed animal experimentation protocol when conducting an animal experiment.

These Guidelines were prepared with the objective of appropriate implementation of animal experiments from a scientific standpoint in accordance with policies on the conduct of animal experiments formulated by government organizations with jurisdiction over institutions conducting animal experiments (Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labor and Welfare, etc.) (“Fundamental guidelines for proper conduct of animal experiment and related activities in academic research institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology” Notice of the Ministry of Education, Culture, Sports, Science and Technology dated June 1, 2006 and “Basic policies for the conduct of animal experiments in research institutions under the jurisdiction of the Ministry of Health, Labor and Welfare,” Notification of the Ministry of Health, Labor and Welfare dated June 1, 2006). The handling of laboratory animals is specified in “Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain” (Notice No.88 of the Ministry of Environment dated April 28, 2006).

These Guidelines consist of chapters on the responsibility of institutions concerning voluntary management and the Institutional Animal Care and Use Committee at the beginning followed by chapters on animal experiment protocol; drafting and experimental procedures and selection of laboratory animals. These are followed by care and management of laboratory animals, laboratory animal health management, facilities and safety management, education and training of personnel and others including in-house inspections and assessment and information disclosure.

Each institution should formulate voluntary in-house regulations for proper scientific conduct of animal experiments based on these Guidelines.

Note: These Guidelines are not intended for application in education, research or testing aimed at improvements in care and management of livestock or in breeding in the agricultural sector, but should be used in such fields as required.
No. 1 Definitions

In these Guidelines, the terms are defined as follows.

1) Animal experiment
   Utilization of animals for education, testing, research, manufacture of biological products or other scientific purposes

2) Facilities
   Facilities and equipment used to perform animal experiments

3) Laboratory animal
   Animal of mammalian, avian or reptilian species used in animal experiments

4) Institution
   Organization (university, institute, independent administrative body, company, etc.) where animal experiments are performed

5) Director of institution
   Person with overall responsibility in the institution for proper and safe conduct of the animal experiments, (dean, director of an institution, principal of a school, chairperson of the board of directors, president, head of an institute, etc.)

6) Animal experiment protocol
   Protocol drafted beforehand for the conduct of an animal experiment

7) Researcher(s)
   Person(s) performing the animal experiment

8) Principal investigator
   The researcher who is in charge of all duties related to the animal experiment protocol

9) Manager
   Person in charge of the laboratory animals and facilities under the director of the institution (head of the animal experimentation facilities, department head, etc.)

10) Laboratory animal manager
    The laboratory animal manager assists the manager and is in charge of management of the laboratory animals

11) Animal technician
    Person in charge of care and management of laboratory animals under the laboratory animal manager or researcher

12) Manager, etc.
    Director of the institution, manager, laboratory animal manager, researchers and animal technicians

13) Policies
    Fundamental guidelines and basic policies specified by government agencies related to animal experiments and “Guidelines for Proper Conduct of Animal Experiments” (these Guidelines) specified by the Science Council of Japan.

14) Regulations, etc.
    In-house regulations of research institutions specified for the proper conduct of animal experiments and the proper care and management of laboratory animals based on related laws and ordinances and the policies

No. 2 Responsibilities of the director of the institution

The director of the institution bears the final responsibility for all experiments conducted in his or her institution. The director of the institution prepares the facilities considered necessary for proper care and management of the laboratory animals and proper and safe conduct of the animal experiments, appoints the manager and appoints a person with knowledge and experience related to laboratory animals as the laboratory animal manager. The director of the institution also provides education for related persons including the researchers and animal technicians with the cooperation of the manager and laboratory animal manager to inform them of the related laws and policies.

In each institution, in-house regulations including the authority and responsibilities of the director of the institution, standard operating procedures (SOP) for the conduct of animal experiments, proper care and management of laboratory animals and methods of maintenance and management of facilities should be established based on the policies.

An Institutional Animal Care and Use Committee should be established in each institution. The director of the institution requests the Institutional Animal Care and Use Committee to review the animal experiment protocols submitted by principal investigators based on scientific rationale and in consideration of animal welfare. The director of the institution then approves or does not approve the protocol based on the report of the Institutional Animal Care and Use Committee. After completion of the animal experiment, the director of the institution examines the results obtained and instructs the principle investigator and manager to make improvements based on advice of the Institutional Animal Care and Use Committee.
The director of the institution retains the animal experiment protocols, results obtained from the animal experiments and the minutes, etc. of the meetings of the Institutional Animal Care and Use Committee; assures transparency of the animal experiments and publishes the results within a range that does not interfere with research or corporate activities in consideration of protecting private information and research information. The director of the institution should take the necessary measures to provide education and training to improve the quality of laboratory animal managers, researchers and animal technicians.

No. 3 Institutional Animal Care and Use Committee

The Institutional Animal Care and Use Committee objectively reviews and inspects animal experiments at an institution to assure that they are planned and conducted properly. To achieve this, the Institutional Animal Care and Use Committee should be established independently from any organizations involved in administration of the facilities. The role and organization of an Institutional Animal Care and Use Committee are indicated below.

1) Roles of the Institutional Animal Care and Use Committee

Following consultation with the director of the institution, the Institutional Animal Care and Use Committee reviews from the standpoint of scientific rationale the animal experiment protocol submitted by the principal investigator in consideration of the “Law for the Humane Treatment and Management of Animals”, “Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain” and policies, and reports the results of the review to the director of the institution. The Institutional Animal Care and Use Committee also receives the results of implementation of the animal experiment protocol from the director of the institution, and examines the actual conditions at the facilities, etc., as required before reporting back to the director of the institution and providing advice.

The Institutional Animal Care and Use Committee obtains details of the situation regarding the education and training of laboratory animal managers, researcher(s) and animal technicians, and offers the director of the institution advice. The Institutional Animal Care and Use Committee may also participate in education and training as required. Items discussed by the Institutional Animal Care and Use Committee are recorded as the meeting minutes that must be maintained and retained. Institutional Animal Care and Use Committee meeting minutes include the items below.

(1) Day, time and location of meeting
(2) Names of members who participated in the meeting
(3) Details of items discussed at the meeting (details of questions from committee members and answers from principal investigators, etc.), and the results of discussions.

2) Institutional Animal Care and Use Committee organization

The Institutional Animal Care and Use Committee is composed of members appointed by the director of the institution. To assure that committee members possess the knowledge required to fulfill the role of the Institutional Animal Care and Use Committee, those appointed are researchers conducting animal experiments, laboratory animal specialists and other persons of knowledge and experience.

The number of committee members is decided taking into consideration factors such as the size of the institution, the scope of the research, and the number of animal experiment protocols to be submitted. A committee member should not participate in the review of an animal experiment protocol for an experiment for which he or she is principal investigator.

No. 4 Animal experiment protocol drafting and experimental procedures

When conducting animal experiments, the significance of the research and the reasons why animal experiments are required must be explained. Animal experiments must be conducted based on scientific rationale. At the same time, they should be conducted in compliance with the internationally accepted 3R principles of animal experimentation as clarified in amendments of the “Law for the Humane Treatment and Management of Animals” (Law No.105, 1973; the latest amendment on June 22, 2005), namely Replacement: the application of alternative methods that do not require the use of animals within limits that allow scientific objectives to be achieved, Reduction: the use of as few animals as possible within limits that allow scientific objectives to be achieved, and Refinement: the application of methods that do not distress the animals or subject them to pain within limits required for use. These 3R principles are the ideology behind both animal experimentation and the handling of laboratory animals. Consequently, within the limits required to achieve the objectives of research, they should be taken into consideration and applied appropriately when conducting animal experiments.

1. Drafting of the animal experiment protocol

In accordance with the above principles, the principal investigator should prepare an animal experiment protocol recording the necessary items in the form (2 below), and submit it to the director of the institution for
approval. The director of the institution requests the Institutional Animal Care and Use Committee to review the protocol content from a specialized standpoint. The Institutional Animal Care and Use Committee promptly reviews the protocol and immediately reports the results of the review to the director of the institution. The animal experiment can begin only after the principal investigator has received approval from the director of the institution.

The principal investigator conducts the animal experiment in compliance with the protocol approved by the director of the institution. If changes to the protocol are required that go beyond the approved scope of the experiment, procedures stipulated in the in-house regulations should be followed. After completion of the experiment, a report to that effect should be submitted to the director of the institution in compliance with the in-house regulations. If improvements indicated by the director of the institution are to be implemented, the principal investigator should confer sufficiently with the laboratory animal manager as required.

Below are examples of items that the principal investigator should consider when preparing a protocol, together with details of the animal experiment protocol form.

1) Items requiring consideration when drafting an animal experiment protocol
   * The objective and necessity of the animal experiment
   * Whether or not the animal experiment is unnecessary repetition
   * Whether an in vitro experiment could be conducted or the animal could be replaced by a phylogenetically lower species (use of alternative methods)
   * Whether a change could be made to a less invasive animal experimentation method.
   * The species of laboratory animals used and the genetic and microbiologic quality
   * The number of laboratory animals used
   * Educational and training experience of the researcher(s) and animal technicians.
   * Reasons why special cages and rearing environment are required
   * The anticipated disorders, symptoms and severity of pain resulting from experimental procedures
   * Measures to alleviate pain when it is anticipated that the laboratory animal will suffer severe pain
   * The use of sedatives, analgesics and anesthetics
   * Whether major surgical procedures should be repeated
   * Postoperative management methods
   * Terminal treatment of laboratory animals (method of euthanasia, etc.)
   * Whether the animal experiment could possibly affect people or the environment. If so, required measures and procedures
   * Issues concerning the occupational health and safety of the researcher(s) and animal technicians.

Concerning new animal experiments on as yet unrecognized research subjects, determining the experimental method and number of animals to use may pose problems. In such cases, attempts should be made to prepare a final protocol after conducting preliminary experiments to ascertain possible appropriate methods and number of animals. For protocols that entail unavoidable, severe pain for the animals, the principal investigator should conduct literature searches to determine whether alternative methods are available. If there are no alternative methods, in cases where the relief of pain through the use of measures such as anesthetics and analgesics is thought to be difficult, it is desirable that advice be obtained from a laboratory animal specialist as required. When this is necessary, it should be clearly noted in the protocol.

2) Animal experiment protocol form
   It is advisable to prepare the animal experiment protocol form referring to the examples below.
   (1) Principal investigator
       Name
       Affiliation and position
       Contact address
       Animal experiment experience and education and training
   (2) Name(s) of the researcher(s) [name(s) of subinvestigators]
   (3) Research subject
   (4) Research objective
   (5) Detailed experimental procedure to be used on the laboratory animals
   (6) Term of animal experiment
   (7) Type of animal experiment (details of specific content)
       Testing, research
       Education and training
       Other (enter specific details)
   (8) Laboratory animal species, strain, sex, age, etc, and number of animals used
   (9) Location where the animal experiment be performed
   (10) Rearing methods (rearing location, group or individual rearing, number of animals per cage in the case of group rearing, food)
   (11) Reasons why an animal experiment is necessary (specific details)
No alternative method
Sensitivity and precision of alternative methods are insufficient
Other (reasons:)

(12) Severity of pain in animals to suffer due to each of the procedures (refer to pain classification indicated in the Consensus Recommendation on Effective Institutional Animal Care and Use Committees drawn up by the Scientists Center for Animal Welfare (SCAW), (Laboratory Animal Science. Special Issue: 11-13, 1987)

(13) Pain alleviation methods for laboratory animals (specific details)
No measures implemented since pain is mild
No particular problems are thought to exist because restraint and constraint are short term
Anesthetics and analgesic will be used (drug name:)
No pain alleviation method exists that does not prevent the scientific objective being achieved (reasons:)
Long-term restraint and constraint are unavoidable (reasons:)
A humane endpoint will be applied (endpoint determination:)
Other ()

(14) Euthanasia procedures
Overdose of anesthetic
Inhalation of carbon dioxide
Cervical dislocation
Other ()

(15) Disposal of laboratory animal carcasses

(16) Physical, chemical and biological risk factors, use of genetically engineered animals

2 Experimental procedures

When conducting animal experiments, pain suffered by the laboratory animals should be reduced as much as possible within limits that allow the scientific objective to be achieved. Since scientific requirements differ for each animal experiment, the principal investigator should describe specific experimental procedures and the anticipated severity of pain in the animal experiment protocol and receive approval from the director of the institution after review by the Institutional Animal Care and Use Committee.

The principal investigator should retain test reagents, drugs and laboratory equipment appropriately. In particular, the laws and ordinances concerning the storage of controlled substances such as narcotics, poisons and deleterious substances must be observed.

When conducting experimental procedures researchers should bear in mind the following points.
* Acquisition of skills in restraining laboratory animals, administering drugs, obtaining samples and other techniques.
* Acquisition of skills relating to surgical procedures (prolonged operative procedures such laparotomy, thoracotomy, craniotomy, orthopedic surgery and other procedures should be conducted under the guidance of a specialist with sufficient knowledge and experience of those procedures.)
* Pain relief procedures for laboratory animals.
* Observation of experiment discontinuation and completion criteria (humane endpoint).
* Acquisition of knowledge and skills related to euthanasia procedures.

1) Laboratory and laboratory equipment

Laboratories designed for performing experimental procedures on animals and also for analyzing physiological functions should be constructed to prevent animals escaping and to enable easy cleaning and disinfection to prevent contamination by excrement and blood. Clean, hygienic conditions should be maintained at all times, and every effort made to organize the laboratory to assure that even if a laboratory animal escapes, it can be easily recaptured.

Laboratories for surgical procedures (operating rooms) differ in equipment requirements depending on the physical attributes of the study animal, the number of animals, complexity of the surgical procedure, the number and size of devices used and other factors. Experiments using rodents can be conducted in an ordinary laboratory if it is possible to use aseptic techniques to prevent microbial contamination in the surgical field. With large laboratory animals, surgical procedures are often complex, surgery is prolonged and it is conducted by a surgical team. This requires a correspondingly large operating table, inhalation anesthesia devices, surgical lighting, life monitoring devices and other equipment. Support areas such as examination rooms, X-ray rooms and changing rooms in close proximity to operating rooms should also be provided. In particular, when the objective is to conduct an animal experiment in which the animal lives for a long period after surgery, preventive measures against contamination should be implemented, the laboratory should be designed to enable easy cleaning after use and an air conditioning system to supply clean air should also be taken into consideration.

When it is necessary to conduct experimental procedures on laboratory animals in an animal rearing room, the influence on other laboratory animals being reared in the same room should be minimized as much as possible. For dogs, cats, monkeys and other animals exhibiting a high degree of emotional behavior, it is particularly important to assure that they do not feel any anxiety from sharing the same room.
2) Animal restraint

Physical restraint refers to localized or general restriction of the normal movements of laboratory animals manually or with devices for examinations, sample collection, dosing and treatment. Restraining devices (restrainers, etc.) should be an appropriate size and easy to use, and should cause laboratory animals as little discomfort and injury as possible. When using restraining devices, training of laboratory animals is required to enable them to become accustomed to the devices and researchers. With dogs, cats and monkeys, if they are conditioned for aggressive restraint, their limbs extend outwards and they assume an immobile posture for short experimental procedures in many cases.

Restraint for a prolonged period in a monkey chair or other device should be avoided unless it is essential for achieving the research objective. Light restraint such as a leash for restraining monkeys or other devices that do not interfere with the natural posture of the animal is applicable within the range of experimental purposes. Items that should be considered concerning restraining devices are indicated below.

* A restraint period only as long as that required to achieve the research objective.
* Frequent observation of the condition of laboratory animals.
* Release from the restraining device of laboratory animals suffering from trauma or poor physical condition due to restraint.
* Restraining devices should not be considered as rearing devices.
* Restraining devices should not be used as convenient tools for rearing management.

3) Food and drinking water restrictions

Achieving the objective of some research requires food and water restrictions for laboratory animals. Even if it is indispensable to improve reliability and reproducibility of data from animal experiments, the following items should be carefully considered.

* Even when food and water restrictions are required for experimental reasons, plans should be made so that the animals ingest the minimum amount of food and water required.
* A scientific rationale is required for the restriction of food and water for research purposes.
* To monitor the state of dehydration, physiological and behavioral indices should be observed, and body weight and other parameters measured.

4) Surgical procedures

When subjecting laboratory animals to invasive surgical procedures, particular attention should be paid to the following points to alleviate pain as much as possible to within the limits that do not prevent the objective of the research being achieved.

* As well as aseptic techniques for the surgery itself, postoperative aseptic techniques and postoperative management are important.
* Antibiotics should be administered in cases where the alimentary tract or other non-sterile site is surgically exposed or where there is the possibility of reduced immune function due to the surgical procedure. However, administration of antibiotics is not an alternative for aseptic techniques.
* For major surgery (laparotomy, thoracotomy, craniotomy, etc.), aseptic techniques, anesthetic and analgesic procedures, fluid infusion and keeping the animals warm are essential since body cavities are invaded and exposed resulting in substantial physical and physiological injury.
* For minor surgery (wound suturing, cannulation of a peripheral blood vessel, etc.), the conditions are not as strict as those for major surgery since body cavities are not exposed and there is virtually no physical injury or it rarely occurs. However, equipment must be sterilized and anesthetics should be used appropriately.
* Highly invasive, major surgery should be conducted under the guidance of a specialist with sufficient knowledge and experience of the techniques involved.

5) Analgesic procedures, anesthetics and postoperative management

The alleviation of pain in laboratory animals is important not only from the standpoint of animal welfare but also to assure the reliability and reproducibility of animal experiments.

* Analgesic procedures should be initiated when symptoms of pain are perceived in a laboratory animal. When an animal feels pain, species-specific behavior includes vocalization, depressed behavior, abnormal expressions or posture and lack of movement.
* To be able to perceive an abnormality, it is important to understand the behavioral, physiological and biochemical characteristics of that species (or individual) when at rest and at ease.
* To select analgesic and anesthetic methods that do not interfere with the objective of the research, advice should be obtained from a physician, veterinarian surgeon, pharmacist or other specialist as required.

The degree of observation of animals required during the postoperative recovery period depends on the animal species and the contents of the surgery. Attention should be focused on environmental temperature control, monitoring of cardiovascular and respiratory function and postoperative pain, with particular attention paid to symptoms of recovery from anesthesia.
6) Humane endpoint

The humane endpoint refers to the timing of termination of an experiment (in other words, the timing of the application of euthanasia procedures) to release a laboratory animal from severe pain and suffering. It is a term used in contrast to “death” as an endpoint that is used in protocols of animal experiments where the experiment continues until the animal’s death.

* As a rule, euthanasia procedures should be available for termination of animal experiments.
* At the final stage of an animal experiment or when analgesics, sedatives or other agents do not provide relief, euthanasia procedures should be performed to release the laboratory animal from pain and suffering (one pain relief method).
* Indications of when humane endpoint is applicable include food and water intake difficulties, moribund symptoms (self-injurious behavior, abnormal posture, respiratory disorders, vocalization, etc.), abnormal appearance over a prolonged period with no visible indications of recovery (diarrhea, bleeding, soiled genital area, etc.), weight loss (20% or more over several days), and marked increase in tumor size (10% or more of body weight).
* Reference should be made to pertinent international guidelines for details concerning determination of the humane endpoint.
* When conducting animal experiments in which the degree of pain and suffering is high, such as lethal toxicity studies, infection experiments and radiation experiments, the principal investigator should examine setting of the humane point in the planning stage of the animal experiment.

7) Euthanasia procedures

When disposing of laboratory animals on completion of the experiment in accordance with the animal experiment protocol or due to the laboratory animals being subjected to severe pain and suffering during the course of the experiment when anesthetics and analgesics can not be used in the research, the researcher(s) should conduct euthanasia.

Selection of the agent and method used for the euthanasia procedure depends on the animal species and the objective of the experiment. In general, a chemical method (overdose of a barbiturate anesthetic, administration of a non-explosive inhalation of anesthetic or carbon dioxide gas) or a physical method (cervical dislocation, decapitation, exsanguination under anesthesia, etc.) is used. However, from the standpoint of animal welfare, the principal investigator should seek the advice and guidance of a laboratory animal specialist as required since there are slight international differences on what are judged to be appropriate methods of euthanasia for laboratory animals.

* Euthanasia procedures refer to procedures resulting in the rapid loss of consciousness and then death of a laboratory animal not associated with pain or suffering. In addition to Guidelines on Methods of Sacrificing Animals (Notice No.40 of the Prime Minister's Office, July 4, 1995), international guidelines should be taken into consideration.
* Euthanasia should be performed by methods that do not cause distress to other animals in the laboratory. This requires careful attention because until animals lose consciousness they can vocalize and release pheromones.
* A person who has acquired the skills required for handling a particular animal species should conduct euthanasia procedures, and the death of the animal should always be verified.

8) Safety management considerations

Genetic engineering experiments, animal experiments using radioactive materials or radiation, experiments using poisons, deleterious substances or psychotropic drugs, and animal experiments using pathogenic agents or hazardous chemicals must be conducted in strict compliance with related laws and ordinances. Animal carcasses and laboratory waste must be disposed of appropriately using the methods stipulated in in-house regulations. In particular, laws and ordinances related to waste material regulated by law must be respected.

9) Reports of animal experiment results

In compliance with in-house regulations after conducting an approved animal experiment, the principal investigator must report the number of laboratory animals used, whether any changes were made to the protocol and
the results of the experiment to the director of the institution. The director of the institution should consult the Institutional Animal Care and Use Committee on the appropriateness of the experiment as required.

**No. 5  Laboratory animal selection and receipt**

Microbiologic control of the rearing environment is particularly important, the same as genetic control of laboratory animals. It can easily influence scientific reliability of animal experiments including accuracy and reproducibility of data. Consequently, when selecting animals for experiments, sufficient attention should be paid to both genetic and microbiologic quality. Health management and safe rearing of introduced laboratory animals should be based on “Standards Relating to the Care and Management of Laboratory Animals and Relief of Pain” and the “Standards Relating to the Care and Management of Domestic Animals.”

1) Introduction of laboratory animals

The following points shall be taken into consideration when introducing laboratory animals.

* The animals must be procured legally. The laws relating to the delivery and receipt of genetically modified animals and designated alien species, and the laws relating to the importing of rodents and primates must be observed (Note).
* The use of purpose-bred laboratory animals with accompanying microbiologic monitoring records or infectious disease test records is desirable. This animal production site data is useful for determining whether to accept the laboratory animals or not.
* Each time a laboratory animal is introduced, the order requirements and abnormalities in external appearance should be checked, and quarantine and acclimatization performed according to the animal species and conditions of the facilities.

Note: To prevent the occurrence of infectious diseases in humans due to animals when importing living mammals and birds and the carcasses of rodents and lagomorphs, the import of animals is controlled by the “Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases,” the “Enforcement Regulations of the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infectious Diseases” and other regulations. The system of notification of import also applies to rodents to be used as laboratory animals. In addition, when introducing laboratory animals that fall under the category of invasive alien species (cynomolgus monkeys, rhesus monkeys, Taiwan monkeys, etc.), procedures must be completed in compliance with the “Invasive Alien Species Law” and related laws; for laboratory animals that fall under the category of designated animals (Japanese macaques and other monkeys, poisonous snakes, etc.), the “Standards for Designated Animals” based on the “Law for the Humane Treatment and Management of Animals” apply; for laboratory animals that fall under the category of genetically modified animals, the “Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms” and related laws apply; for laboratory animals that fall under the category of domestic animals (pigs, sheep, goats, etc.), the “Domestic Animal Infectious Disease Control Law” and related laws apply; for dogs, the Rabies Prevention Law and related laws apply.

2) Quarantine and acclimatization

To prevent the spread of infectious diseases in facilities, newly introduced laboratory animals should be kept away from animals already present until their health condition has been verified. If symptoms are observed or when deemed necessary, microbiologic examinations should be performed. The following items regarding quarantine and acclimatization must be taken into consideration.

* Depending on the construction and sanitary conditions of the facilities, animal species and the objective of the animal experiment, the manager should respect the opinions of the laboratory animal manager and comprehensively determine the infectious diseases to be eliminated in the facilities.
* The principal investigator and laboratory animal manager should discuss necessary microbiologic control for individual animal experiments.
* Reports of microbiologic monitoring at the supply source can be used as quarantine reference materials. Obtaining information from the producer is important when considering quarantine procedures.
* The laboratory animal manager should determine the required quarantine period, risk to personnel and other animals, and whether treatment is required during the quarantine period.
* For mice, whether or not microbiologic cleaning by in vitro fertilization, embryon transfer or Caesarian section is required should be determined.
* Before use in animal experiments, it is necessary to set up an acclimatization period from the physiological, psychological and nutritional viewpoints for the laboratory animal. The acclimatization period differs depending on the method of transport and the required period of time, the animal species and intended purpose of the laboratory animal used.
* Primates should be given sufficient time to become acclimatized to the environment with respect to both personnel and laboratory equipment.
3) Transport

Transporting laboratory animals refers to moving laboratory animals between facilities. The following items should be taken into consideration during transport.

* Personnel involved in the transport of laboratory animals should endeavor to take care of the health and safety of the laboratory animals and to prevent any hazard, etc., for humans occurring due to the animals.
* In addition to causing laboratory animals fatigue and distress, transport influences data from animal experiments. To conduct scientifically correct animal experiments, transport should be completed in as short a time as possible.
* During transport, laboratory animals should be supplied with food and water as required while maintaining an appropriate temperature using air conditioning, ventilation, etc.
* To prevent environmental contamination by laboratory animals during transportation, care and management should be undertaken in essentially the same way as at the institution. Since transport involves the use of public transportation or highways, every effort should be made to prevent environmental contamination in the event of unforeseen circumstances. To do this, containers that not only prevent laboratory animals from escaping, but also from which it is difficult for microorganisms, waste material, etc., to reach the exterior should be used.
* Containers used for transport should have the structure and strength to prevent laboratory animals escaping. They should also be lightweight and compact, designed so they do not easily fall over, have lids that do not open due to vibrations, etc., and be well ventilated. In case laboratory animals show abnormal symptoms, escape, etc., containers should display a contact address (address, telephone number, etc.).
* When transporting across borders, the “International Air Transportation Association (IATA) Live Animal Regulations” concerning the transportation of live laboratory animals require careful consideration.

4) Provision of information on delivery and receipt of laboratory animals

Persons who supply or sell laboratory animals should provide information and explanations concerning the animals’ physiology, ecology, behavior and the correct care and management methods for the animals, microbiologic quality, infectious diseases, etc. At facilities receiving animals, in addition to quarantine, appropriate microbiologic cleaning when required (in vitro fertilization, embryo transfer, Caesarian section, foster nursing, etc.) or administration of drugs, vaccinations should be provided as required.

On delivery and receipt of genetically modified laboratory animals, the “Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms,” “Ministerial Ordinance providing Containment Measures to be taken in Type 2 Use of Living Modified Organisms for Research and Development” and other regulations must be observed.

No. 6  Care and management of laboratory animals

At facilities, laboratory animals must be correctly cared for and managed to increase the scientific reliability of animal experiments in consideration of animal welfare while also assuring the safety of the researcher(s) and animal technicians. In this respect, the following items should be taken into consideration.

* The objective of care and management (testing, research, education, etc.).
* Individual characteristics such as species, strain, sex, age, physical attributes, behavior, history and health condition.
* Whether authorization is required for care based on related laws (when caring for and managing animals that fall under the category of designated animals according to the Law for the Humane Treatment and Management of Animals or invasive alien species according to the Invasive Alien Species Law, authorization is required from the government or local authorities).
* Individual or group housing
* Rearing period
* Details of procedures in animal experiments (physical invasiveness, degree of invasiveness, items for daily observation, etc.)
* Genetic engineering procedures, immunosuppression procedures, infectious agents or administration of carcinogens.

1) Fundamentals of care and management

Laboratory animal managers and animal technicians should care for and manage laboratory animals with the aim of maintaining the inherent physiology, ecology and behavior of the animals and minimizing stress as much as possible. The manager, etc. should independently decide on the ideal rearing environment for laboratory animals taking into consideration the scientific objectives. When caring for and managing different animal species or numerous laboratory animals in the same facilities, the animals should be accommodated taking into consideration this combination within the limits to assure it does not prevent the objective of animal experiments, etc., being achieved. Animal technicians should supply the animals with food and water appropriately within the limits to assure that it does not interfere with the objective of animal experiments, etc., being achieved. In the event of
facilities, etc., being closed, transfer to other facilities of the animals present should be considered for the effective use of laboratory animals.

2) Cage environment and animal room environment

The environments inside cages and in the animal room are connected by ventilation but differences in temperature, humidity, etc., may occur. In general the temperature, humidity and concentration of gaseous and particulate substances reach higher levels inside cages than in the animal room. If attention is not paid to this point, it may unexpectedly influence the metabolism, physiological function, etc., of the laboratory animals being reared, or alter their susceptibility to disease.

The following items concerning cages and other rearing equipment should be taken into consideration.

* Cages with the structure and strength to prevent escape of the animals
* Easy access to food and water for individual laboratory animals
* Maintenance of normal body temperature
* Urination, defecation and preservation of natural posture
* Depending on the behavior inherent to the animal species, the cage and laboratory animals must be kept clean and dry.
* Depending on typical behavior of the animal species, social contact between animals and the formation of hierarchies
* Cages safe for laboratory animals (no sharp edges or protrusions, no gaps in which an animal’s body or limbs can become wedged)
* As far as possible, observation without interfering with the animal behavior
* Easy supply of food and water and easy changing of feeding and watering devices
* Cage structure permitting easy cleaning, disinfection, sterilization etc., and cage materials able to withstand these procedures
* Necessity and frequency of replacement of bedding, etc.

1) Housing space

Since determining whether housing space is appropriate involves various factors, only taking into consideration an animal’s weight and cage size alone is not sufficient. Rather than simply a larger floor area, increased cage height or increased cage wall area, a sheltered area, or complex cage structures are required for some animal species. Whether housing space is appropriate can be determined taking animal traits and behavior as indices. In addition to referring to literature references such as the “ILAR Guide for the Care and Use of Laboratory Animals”, the opinions of specialists and the necessity of conducting the research should be taken into consideration.

2) Environmental temperature and humidity

To assure that homeothermal animals are comfortable, their body temperature should be maintained within a normal range. Scientifically based recommendations for the appropriate range of temperature and humidity required by different animal species are specified in textbooks and other sources. For laboratory animals not completely awake after being anesthetized for a surgical procedure, laboratory animals without hair, newborn animals separated from their mother, chicks within a few days after hatching, the room temperature setting should be raised or topical warming is required.

3) Ventilation

The objective of ventilation is to supply the proper degree of oxygen by creating a static pressure difference between adjacent spaces. Ventilation also eliminates the heat load generated by animals, lighting equipment and other devices and equipment, reduces the concentration of gaseous and particulate substances, and regulates room air temperature and humidity. Ventilation inside cages does not necessarily reflect ventilation in the animal room. An air conditioning system is extremely effective to maintain the proper laboratory animal rearing environment. Consequently, as well as understanding the operating condition of the air conditioning equipment, measurement of animal room temperature, humidity, air change rate is required together with periodic inspection and maintenance of equipment.

4) Lighting

Lighting has physiological and morphological effects on various animals and can alter behavior. Inappropriate lighting periods, lighting intensity and light spectrum cause laboratory animals stress. The fact that many laboratory animals frequently used are nocturnal must be taken into consideration. In addition, it should be remembered that albino rats are more susceptible to retinopathy due to phototoxicity than non-albino animals, and even a small amount of light entering the room during the dark period when the lights are off can influence the estrus cycle of rodents.

5) Food

Unless instructed otherwise by the principal investigator, the animal technician should correctly provide laboratory animals with suitable nutritional, uncontaminated food every day. Attention should be paid to pathogens, vectors that transmit them (insects, etc.) and chemical contaminants that may be in the food so that they are not introduced into the facilities. The area where food or its ingredients are processed and stored should be kept clean and measures to prevent infestation by insects should be taken. Based on the storage temperature, food quality and other factors, the storage life of each kind of food should be determined by the laboratory animal manager. Feeding
devices that enable easy food intake should be used and care is required to assure they do not become contaminated with feces and urine.

(6) Water
The animal technician should check water bottles and automatic watering systems every day to verify that they are functioning correctly and kept clean. Animals unaccustomed to automatic watering systems may fall into a state of dehydration if observation is neglected. In such cases, the animals should be carefully trained to use the system. To prevent the transmission of microorganisms, rather than refilling water bottles it is preferable that the bottles themselves be changed.

3) Retention of records
The manager, etc. should keep record books and ledgers related to laboratory animal sources, rearing history, history of disease, etc., and strive to manage laboratory animal records properly to aid in laboratory animal care and management in facilities. This kind of documentation is also useful for assessing data reliability of animal experiments.

No. 7 Laboratory animal health management

Laboratory animal health management should be conducted scientifically. To prevent laboratory animals suffering injuries unrelated to the objective of the animal experiment or contracting a disease, the laboratory animal manager and researcher(s) should conduct necessary health management. In the event of injury or disease unrelated to the objective of the animal experiment, appropriate treatment should be provided within the limits that do not interfere with achieving the objective of the animal experiment. For this purpose, there should be exchange of information related to laboratory animal health conditions between the laboratory animal manager, the researcher(s) and the animal technician, and necessary measures should be implemented as quickly as possible.

Since laboratory animal health management requires understanding of animal species ecology, behavior and physiological and anatomical characteristics, the ability to distinguish when they are normal or abnormal and the ability to distinguish whether abnormalities are due to experimental procedures or other factors, the cooperation of all those involved as well as the laboratory animal manager is essential. If required, the advice of specialists on individual animal species, diseases, etc. should be sought.

When conducting laboratory animal health management, preventing infectious diseases influencing animals and humans as well as the experimental results is particularly important. Depending on the animal species and the objective of the animal experiment, the need to conduct quarantine, isolation and microbiologic monitoring must be conducted. When examining these points, the following items must be into consideration.

* Reported cases of infection of humans by laboratory animals include lymphocytic choriomeningitis originating from mice and hamsters, hemorrhagic fever with renal syndrome from rats and herpes B virus infection and bacillary dysentery from primates.
* When using bird species in animal experiments, infections by Chlamydia psittaci and salmonella require special attention.
* With regard to turtles, salmonella infection from green turtles has been reported.
* When rearing imported primates, advanced notification of the facilities and notification if there is an outbreak of bacillary dysentery are required in compliance with the regulations stipulated in the “Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infectious Diseases” and related laws.
* When conducting laboratory animal health management using domestic animals, consideration must be given to infectious diseases (domestic animal infectious diseases, notifiable infectious diseases) pursuant to the provisions of the “Domestic Animal Infectious Disease Control Law” and related laws and ordinances, and diagnosis and advice from a veterinarian must be sought if any abnormalities are observed.
* One important issue concerning quarantine is the detection of inapparent infections. Prevention of the provocation of an inapparent infection due to stress caused by experimental procedures assures the reliability of experimental results as well as preventing the spread of infections diseases in facilities. Items to be considered regarding quarantine are detailed in part 5.
* With some animal species, even if the pathogenicity of the pathogen is low resulting in an inapparent infection, there are cases where other animal species become infected and develop a disease, so isolated rearing should be provided for each animal species as a general rule.
* After an animal experiment has started, in addition to early detection and treatment of abnormalities by observation of laboratory animal symptoms, periodic microbiologic monitoring is effective for verifying health conditions in small animals such as mice, rats, guinea pigs and rabbits. The results of microbiologic monitoring are also useful for preventing infectious diseases in facilities.
* When providing another institution with laboratory animals, the provision of a health certificate issued by a veterinarian may be required. When facilities cannot conduct their own examinations or issue a health certificate, a laboratory animal checking organization can be requested to do so.
No. 8 Facilities

Respecting the opinions of the laboratory animal manager, the manager should provide the conditions necessary to meet the requirements for conduct of the research, for animal physiology, ecology and behavior, and sanitary management while establishing and administering the facilities. Cleaning and disinfecting floors, inside walls, ceilings, auxiliary equipment in the facilities should be easy, and the structure should facilitate maintenance of sanitary conditions to eliminate the possibility of laboratory animals being injured by projections, holes, depressions, inclined planes, etc. Inspections and maintenance of cages should be conducted to prevent laboratory animals escaping, to keep laboratory animals physically comfortable, and to make hygiene management and daily operations easy. The following items should be considered when setting up facilities.

* Equipment for care and management of laboratory animals, sanitation equipment for cleaning and disinfecting materials and devices, and experimentation equipment
* Assurance of structures and strength to prevent entry of wild animals
* Assurance of structures and strength to prevent laboratory animals escaping
* In facilities where animal experiments on infection with pathogens or using radioactive materials are conducted, effective equipment to prevent escape of infected animals, laboratory animals administered chemicals and laboratory animals treated with radioactive materials
* Facilities with the structure necessary to reduce odor and noise and storage facilities required for waste material.
* Within the limits that do not interfere with achieving the objective of the animal experiment, proper space, temperature, humidity, ventilation, lighting, etc., to assure laboratory animals are not subjected to excessive stress
* Depending on the animal species and the objective of the experiment, air conditioning equipment necessary to maintain a constant environment in the facilities
* In facilities for rearing laboratory animals extremely susceptible to infectious diseases, sanitation and air conditioning equipment necessary to control microorganisms
* Assurance of structures that enable researcher(s) and animal technicians to work without risk.
* Facilities and equipment such as safety cabinets, draft chambers and localized air exhaust equipment to prevent work related accidents as required. Also education and training of researcher(s) and animal technicians to familiarize them with safe operating procedures.
* When conducting gas sterilization of rearing equipment such as vinyl isolators, gas masks should be worn as required.
* For autoclaves and ethylene oxide gas sterilizers, periodic inspections as indicated by laws and ordinances, as well as daily checks before starting work.

No. 9 Safety management

The director of the institution should endeavor to assure health and safety during operation of the facilities based on related laws and ordinances. Necessary facilities should be provided and health management to prevent laboratory animal managers, researcher(s) and animal technicians from contracting diseases from laboratory animals should also be conducted. For animal experiments that involve materials posing a physical or chemical risk or that involve pathogens (“risk factors” hereinafter), and animal experiments using living modified organisms, it must be assured that they do not have any influence on human or laboratory animal safety and health or the ecosystem, and that disturbance of laboratory animals does not reduce the reliability of experimental results. Measures required to prevent disruption of public health, living environment and the ecosystem must also be implemented.

1) Understanding and dealing with risk factors

The director of the institution and the manager should have an understanding of the risk factors related to occupational safety and health. When assessing risk factors, the opinion of a specialist should be sought if necessary. At the planning stage of an experiment, the principal investigator should explain to the laboratory animal manager the types of risk factors and degree of risk involved, and request cooperation in care and management locations and the use of safety equipment for laboratory animals with risk factors. The principal investigator should also provide the researcher(s) and animal technicians with necessary information concerning risk factors, the degree of risk, methods of dealing with risk factors and accident prevention.

* To assess the degrees of risk posed by pathogens and chemical agents, reference should be made to related guidelines and databases.
* In areas or rooms where risk factors are present, the risk factors should be displayed. For genetic engineering experiments and animal experiments that use ionizing radiation, labeling is required as specified by law.

2) Prevention of injury by laboratory animals

Typical risk factors concerning animal experiments include infection of humans by a laboratory animal naturally infected with a pathogen, allergies caused by laboratory animal hair, etc., and bites and scratches by laboratory animals. The laboratory animal manager, researcher(s) and animal technicians should exchange information concerning the handling of animals posing such risks to prevent injury.
* To prevent being bitten by a laboratory animal when conducting an animal experiment, researcher(s) and animal technicians should receive prior education and training.
* Emergency medical supplies should be available and a system enabling prompt emergency measures by a physician at the time of accidents involving bites by poisonous animals such as poisonous snakes, as well as primates, dogs should be established.
* Measures required to prevent people not involved in the care and management of laboratory animals or in the animal experiment from touching laboratory animals should be taken.

3) Measures when laboratory animals escape

   The manager, etc., should implement measures necessary to prevent laboratory animals escaping from a facility where they are being kept. Outside of working hours, cage lids should be properly closed and cage doors should be locked.
   * The animal room door should be closed at all times and locked when necessary.
   * The number of laboratory animals should be checked when starting and when finishing work.
   * In-house regulations as a safeguard in anticipation of a laboratory animal escaping from the facility should be established.
   * If a laboratory animal that might injure or cause harm to humans escapes from a facility, the relevant authorities should be contacted at once.

4) Dealing with emergencies

   In coordination with the government agencies concerned, the manager should take measures to comply with anti-disaster measures, and draw up plans beforehand related to measures to be implemented in the event of an emergency such as an earthquake or fire.
   * In an emergency situation, measures should be taken to protect laboratory animals and prevent injury or harm to humans or problems related to environmental protection arising due to escape of laboratory animals.
   * A network for communication on holidays, at night and at times of emergency should be established, together with an emergency communication system.

5) Maintenance of the living environment

   The manager, etc. should treat laboratory animal waste material appropriately, keep the facilities, clean at all times, and prevent contamination of the environment by microorganisms, spread of odors, and infestation by insects. Also noise-proofing should be provided.
   * Carcasses of laboratory animals and laboratory waste must be treated appropriately in compliance with waste material classification of the local authorities concerned. When carcasses and animal waste are temporarily stored, measures to prevent spread of odors and entry of insects and to assure sanitation should be taken.
   * Syringes and needles used in animal experiments should be treated as infectious medical waste, collected in biohazardous material containers, stored carefully to prevent the contents of the containers from escaping, and disposed of in accordance with the regulations of the local authorities concerned.

No. 10 Education and training

   The director of the institution should endeavor to provide separate education and training of the laboratory animal manager, researcher(s) and animal technicians as required. Education and training should be provided prior to engaging in animal experiments and should also be provided later as required.
   Education and training should be conducted in accordance with in-house regulations, and the dates of instruction, educational content and the names of the instructor and those receiving instruction should be recorded and retained.
   Education and training content should be specified in the in-house regulations taking into account activities undertaken in the institution. From the viewpoint of proper conduct of animal experiments, the following items should be included in education and training.
   * Items related to pertinent laws and ordinances, bylaws, guidelines, in-house regulations
   * Items related to animal experiments, etc., and the handling of laboratory animals
   * Items related to the care and management of laboratory animals
   * Items related to safety assurance
   * Items related to the use of facilities

No. 11 Others

   With the aim of implementing scientific animal experiments, taking into consideration animal welfare, the director of the institution should conduct periodic in-house inspections and assessments to determine whether the experiments comply with policies and in-house regulations. Consideration should be given to receiving verification
by a person or persons not connected with the institution. Records of in-house inspections and assessment records should be retained for a fixed period of time.

Information related to animal experiments conducted at the institution based on in-house regulations should be disclosed by the director of the institution by a method determined appropriate in accordance with effects on the protection of personal and research information and proper corporate activities. Efforts should be made to improve the social transparency of information related animal experiments in the institution.

Additional provisions

Revision of these guidelines

These guidelines should be revised in accordance with developments in related areas of research and changes in society, as well as amendments of related laws and ordinances as required.
References

1. Related laws and ordinances, policies, etc.
   1) Law for the Humane Treatment and Management of Animals
   2) Standards relating to the Care and Management of Laboratory Animals and Relief of Pain
   3) Guidelines on Methods of Sacrificing Laboratory Animals
   4) Ministry of Education, Culture, Sports, Science and Technology: Fundamental
guidelines for Proper Conduct of Animal Experiment in Academic Research Institutions
   5) Ministry of Health, Labor and Welfare: Basic Policies for the Conduct of Animal Experimentation
      http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html
   6) Law concerning the Conservation and Sustained Use of Biological Diversity through Regulations on the
      Use of Living Modified Organisms
   7) Invasive Alien Species Law
      http://www.env.go.jp/nature/intro/
   8) Law concerning Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases
      http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=hourei&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD&EFSNO=361
   9) Domestic Animal Infectious Disease Control Law
   10) Rabies Prevention Law
      http://www.hourei.mhlw.go.jp/cgi-bin/t_docframe.cgi?MODE=hourei&DMODE=CONTENTS&SMODE=NORMAL&KEYWORD&EFSNO=403
   11) Director General, Science and International Affairs Bureau, Ministry of Education, Culture, Sports,
       Science and Technology : Animal Experimentation in Universities, etc. (Notification) 1987
   12) Research Promotion Bureau, Ministry of Education, Culture, Sports, Science and Technology:
       Introduction of Laboratory Animals in Universities, etc. (Notification) 2001
   13) Science Council of Japan: Establishment of Animal Experimentation Guidelines (Recommendation)
       1980. To refer to the data, contact the Science Council of Japan (03-3403-1091).
   14) Science Council of Japan: Report of the Special Committee on a Social Consensus on Promotion of Life
       Science Handling of Animals in Education and Research, 1997
       To refer to the data, contact the Science Council of Japan (03-3403-1091).
   15) Report of Subcommittee 7, Science Council of Japan : Promotion of public understanding of animal
       experimentation (Proposal) 2004
   16) Science Council, Ministry of Education, Culture, Sports, Science and Technology, Special Research
       Field Promotion Committee, Biosciences, Subcommittee: Manual of Safety management of
       Microorganisms for Research in Universities, etc. (Draft) 1998

2. Commentaries on related laws and ordinances and textbooks, etc.
   Ten commentaries and textbooks written in Japanese (omitted)

3. International policies and textbooks
   1) Russell W & Burch R. The Principles of Humane Experimental Technique. Chapter 4. The source,
      (http://altweb.jhsph.edu)
   2) ICLAS (International Council for Laboratory Animals). Guidelines for the regulation of animal
   3) CIOMS involving animals. 1985. (Council for International Organizations of Medical Sciences)/WHO.
      International guiding principles for biomedical research
   4) ILAR (Institute for Laboratory Animal Research)-NRC (National Research Council). Guide for the care
   6) SCAW (Scientists Center for Animal Welfare). Categories of biomedical experiments based on increasing
7) CCAC (Canadian Council on Animal Care). Guidelines on choosing an appropriate endpoint in experiments using animals for research, teaching and testing. 1997.
8) ILAR-NRC. Humane endpoints for animals used in biomedical research and testing. ILAR Journal 41 (2) Special edition. 2000.
12) EFPIA (European Federation of Pharmaceutical Industries Associations) & ECVAM (European Centre for the Validation of Alternative Methods). A good practice guide to the administration of substances and removal of blood, including routes and volumes. 1999.
17) U.S. National Research Council, Occupational Health and Safety in the Care and Use of Research Animals, 1997

Appendix

Members of No. 2 Expanded Committee on Establishment of Guidelines for Proper Conduct of Animal Experiments

Chairman: Ichiro Kanazawa (President, National Center of Neurology and Psychiatry)
Vice-chairman: Hideaki Karaki (Professor Emeritus of The University of Tokyo)
Secretary: Setsuo Hirohashi (Director, National Cancer Center Research Institute)
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Yoshikazu Shinoda (Professor, Tokyo Medical and Dental University, School of Medicine)
Norikazu Tamaoki (Deputy Director, Central Institute for Experimental Animals)
Ken-ichi Yagami (Director, Laboratory Animal Resource Center, University of Tsukuba)

Observers
Hiroki Matsuo (Director, Life Sciences Division, Research and Promotion Bureau, Ministry of Education, Culture, Sports, Science and Technology)
Noriyo Yoshikawa (Deputy Director, Health Sciences Division, Minister's Secretariat, Ministry of Health, Labor and Welfare)
Katsuhiko Shoji (Director, Office of Animal Companionship Policy and Coordination Division, Nature Conservation Bureau, Ministry of the Environment)