Deutsche
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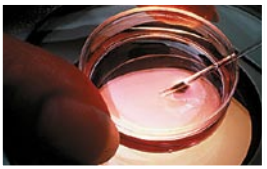
Animal Experiments in Research



DFG

Imprint

Publisher's address:
Lemmens Medien GmbH
Matthias-Grünewald-Str. 1-3
D-53175 Bonn
Telefon: +49 228/42137-0
Telefax: +49 228/42137-29
E-Mail: info@lemmens.de
Internet: www.lemmens.de

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Printed by:
Courir-Media GmbH, Bonn

ISBN 978-3-932306-87-7

The German Library – CIP Standard Cataloguing

Animal Experiments in Research
Eds. Senate Commission on Animal Protection and Experimentation,
Deutsche Forschungsgemeinschaft – Bonn: Lemmens Medien GmbH, 2007

ISBN 978-3-932306-87-7

Production: Lemmens Medien GmbH, Bonn

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Issued by the Senate Commission on Animal Protection and Experimentation

with the assistance of
Cornelia Exner (responsible),
Hans-Joachim Bode,
Karin Blumer
and Christian Giese

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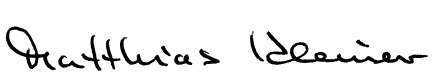
Preface

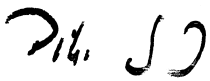
The Deutsche Forschungsgemeinschaft (German Research Foundation, DFG) and the Max Planck Society (MPG) recognise the enormous ethical responsibility which is linked to basic biological and medical research. When supporting and performing experimental research with animals, this is the aspect on which they concentrate particularly.

Animal protection is an important social issue in many European countries. A high degree of animal protection has been established in Germany. The DFG and MPG are aware that experimental animals must be kept appropriately to the species and be dealt with sensitively, and that this is not only an ethical necessity, but also a precondition for the quality of experimental research on animals. Accordingly, they have always made every effort to improve the conditions under which experimental animals are held and to ensure that they are treated as carefully as possible. Animal experiments and replacement and complementary methods for animal experiments are closely connected. The financial support for the latter approaches in basic research has long been greater than for actual animal experiments. Replacement and complementary methods are used to acquire detailed knowledge on cellular structures and processes, which are then validated in animal experiments. Only with this combination is it possibly to recognise and understand the processes which occur in nature in the living organism and finally - with the necessary modifications - in the human body. We consider that causal research is impossible without animal experiments.

This study is presented by the DFG Senate Committee for Animal Experiments in Research. It is intended to fulfil the wish for up-to-date and intelligible information on animal experiments in research, as expressed in an opinion survey among different social groups and experts. We hope that readers interested in research and animal protection will profit from reading it.



Professor Dr.-Ing. Matthias Kleiner
President of the German Research Foundation



Professor Dr. Peter Gruss
President of the Max Planck Society

Animal Experiments:

Definition and Numbers

Nematodes, fruit flies, mice

In 2000, a report caused a sensation throughout the world. Scientists had succeeded in largely decoding the human genome. The analysis of the hereditary information (DNA) of complex animals - such as humans, the fruit fly Drosophila melanogaster, the rat and the mouse – is one of the most important scientific achievements of recent years. However, major progress has been made in other areas of the biosciences, including new knowledge about the structure of the ribosomes - the protein factories in body cells - and the possibilities of using stem cells in treating diseases. New knowledge of this sort has often helped to improve our medical care and nutrition and has helped to ensure increases in life expectancy and improvements in the quality of life.

Progress in the biosciences would be inconceivable without the use of animal experiments. It has only been possible to understand processes in the organism with the help of animal experiments. This includes the function of the sense organs and of the nervous, hormonal and immune systems. Animal experiments will also be necessary in future, for example in understanding the functions of genes, as the significance of individual genes for the total organism can only be established in the intact living organism.

Animal experiments have been used for centuries to study physiological processes and to develop new medical methods. However, there have been opponents of these experiments for just as long. Then as now, they accuse scientists of giving humans priority over animals. Another point of criticism is that the results of animal experiments cannot be transferred to man and that animals are made to suffer just to satisfy scientific curiosity. Some of the original experiments on animals now really do appear cruel - but the same applies to surgery on man in the same period. The main reason is that the operative techniques and possibilities for anaesthesia were inadequate. The discovery of anaesthesia was a blessing for both animals and man and is now routine in animal experiments.

Even in the 19th century, criticism of animal experiments led to new laws for the use of animals in research. These have been continuously improved and all European countries now possess detailed legal regulations for the performance of animal experiments. The German Animal Welfare Act is one of the most restrictive in the world. This ensures that animal experiments are only performed to an extent which is accepted by society and is subject to official monitoring. Before an animal experiment for biomedical research is performed in Germany, there is a hearing in an Animal Protection Committee, with members including scientific experts and representatives of societies for animal protection. As part of a balanced consideration of legally protected values, this committee evaluates not only the scientific necessity of an animal experiment, but, in particular, its ethical defensibility. It is often difficult to reach this decision and there may be differences of opinion. Legally prescribed animal experiments include checking the safety and efficacy of drugs for man. In such cases, the necessity of

human protection is reason enough to make it unnecessary to justify each individual experiment separately. To ensure the high bioethical standard in animal experimental research throughout Europe, the European Science Foundation (ESF) – an association of organisations supporting research – has developed a position paper for dealing with experimental animals. This emphasises the significance of three important principles which must be considered in research. These are known as the three Rs and are aimed at *Reducing* and *Refining* animal experiments and their *Replacement* with alternative or complementary methods. These principles are also implicitly laid down in the German Animal Welfare Act, with the addition of the aspect of ethical evaluation. In spite of these legal regulations, may people retain their reservations about animal experiments and consider that the legal regulations are too weak.

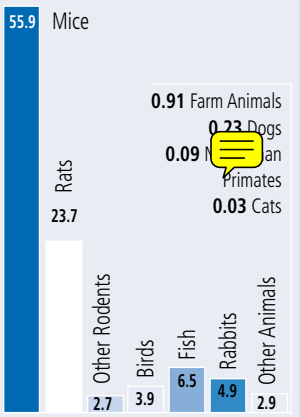
What is an animal experiment and which animals are used?

The 1998 version of the German Animal Welfare Act defines animal experiments as, "Experimental procedures or treatments of animals, if these may be linked to pain, suffering or damage to these animals, or on the hereditary material, if these may be linked to pain, suffering or damage to the animals with modified hereditary material or the animals which bear these "(§ 7). *Animal experiments are only permitted in Germany for the following four purposes:* research to maintain health in man or animals, detection of effects endangering the environment, checking the safety of drugs or chemicals and basic research.

The Animal Welfare Act distinguishes between animal experiments requiring approval and those requiring only notification. The legal regulations apply in principle to all animal species, including worms, insects and cold blooded and warm blooded vertebrates. Experiments on vertebrates are subject to especially strict conditions and require approval in principle, if there is the possibility that they could be linked to pain, suffering or damage. The conditions under which these animals are kept and cared for are also officially monitored.

Animal experiments requiring notification include legally prescribed animal experiments (for example, from the laws on drugs and chemicals), experiments to test vaccines during the approval procedures, the removal of organs and experiments for training or postgraduate training (e.g. of medical or biology students). In contrast, in public discussions, the term "animal experiment" is mostly used more broadly and includes every use of animals for scientific or medical purposes. The Council of Europe guideline defines animal experiments more broadly than the German Animal Welfare Act. This considers all areas in which animals are used for experiments or other scientific purposes. Animal experiments are mostly performed on rodents, particularly mice and rats. Somewhat fewer experiments are performed on guinea pigs. Large great apes – such as chimpanzees and

Proportion of Species 2004
(in per cent)



Source:
BMVEL Animal Protection Report 2005

bonobos – have not been used in animal experiments in Germany since 1992. The numbers of other types of primates (mandrills and new-world monkeys) and of lemurs (galagos, loris and others) is below 0.1% of all experimental animals and has remained about constant in recent years.

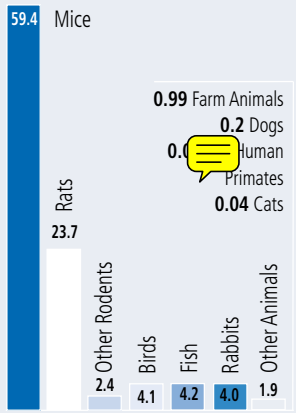
Animal experiments in numbers

In 2005, 2.41 million experimental animals were used in Germany. The number of experimental animals fell continuously from 1991 to 1997, with an overall reduction of up to 40%. The numbers have increased again since 1998; this is mainly due to the increased use of so-called transgenic mice. These animals are used in biomedical research to identify the genetic causes of diseases and to develop new therapeutic procedures. Although the number of animal experiments had declined in previous years, there has been an increase in the number of experimental animals since January 2000. This is mostly due to increases in the numbers of mice and rabbits and is linked to changes in the method of counting in the new order on reporting numbers of experimental animals. Whereas the old reporting order only counted animals which counted as experimental animals in accordance with § 7 of the Animal Welfare Act, the new order also includes those animals used for scientific training, the isolation of vaccines and sera for vaccination, for organ removal or for cell culture. About a third of the recorded animals were used for purposes which did not have to be reported according to the old legislation. Accordingly, the current numbers of experimental animals are not comparable with the figures from previous years. It was mainly the inclusion of animals killed painlessly for organ removal which caused this increase in the numbers of experimental animals.

Many of the experiments performed still serve consumer protection. Many of the experimental animals used in Germany in 2005 too were for safety testing, quality controls or toxicology testing. This includes testing of drug tolerability and testing of the environmental risk from substances (for example, testing of industrial waste water). Many of these animal experiments are legally prescribed and are the precondition for the approval of drugs or of other substances with which humans come into contact. Similar figures have been recorded in other European countries, for example Great Britain.

The number of experimental animals used in research makes up about 0.5% of all animals killed annually in Germany. 99.5% of the animals are killed for other purposes, particularly for human food. Thus more than 48 million pigs, more than 3.4 million cows, 2.1 million sheep and goats (Federal Statistical Office and Federal Ministry of Food, Agriculture and Consumer Protection). The number of chickens killed is about 476 million, which is much higher still. Aside from food, animals are also killed in large numbers during pest control and by hunters and anglers. The annual average is that about 250,000 wild pigs and one million roe deer are killed (German Association for the Protection of the Hunt).

Proportion of Species 2005
(in per cent)



Source:
BMVEL Animal Protection Report 2006

Animal Experiments
in Practice:

Areas in which experimental animals are used

Basic Research

The aim of basic research is to acquire new knowledge which can form the basis for applied research. Basic medical or biological research is not intended for any direct medical application, but develops the scientific foundation on which all subsequent research is based. Basic medical research uses laboratory animals to identify the preconditions for research which is directly related to the patient. The resulting knowledge facilitates the understanding of living processes and how they may be disturbed. Although the implementation of the results of basic research cannot be planned and its direct benefits cannot be predicted in the short term, biomedical research without it is totally inconceivable.

Many results in basic research are found by using cell cultures. In cancer research, these studies are intended to aid the understanding of the cell biological principles of the formation of cancerous cells. Parallel to this, the development of the tumour is studied in the living animal, in so-called animal models like the mouse. Once the mechanisms of tumour formation and growth are more closely understood, useful research on new therapeutic approaches will be possible.

Animal experiments are also necessary for research into infectious diseases. Here it is a question of identifying the infection routes and the mechanism of the immune response. Basic research has an established role in bacteriology, virology, parasitology,

Running for research

The times when a laboratory mouse climbs into a running wheel to get some exercise are not distributed randomly throughout the day, but follow a circadian rhythm, which is evidently genetically influenced. With the help of a computer, the running wheel activity is measured and evaluated.

Current examples of medical research

- Improved diagnosis and treatment of cancer
- Improved diagnosis and treatment of cardiovascular diseases
- Improved treatment of metabolic diseases, such as diabetes mellitus
- New treatments for autoimmune diseases, such as rheumatism and multiple sclerosis (MS)
- Improved allergy treatment
- Development of treatments and vaccines for AIDS
- Diagnosis and specific treatment of neurological diseases such as Parkinson's and Alzheimer's diseases
- Improvement of transplantation procedures
- Development of artificial organs to replace loss of organ function (biomaterials)
- Further development of neuroprostheses for paraplegic patients
- Improvement in non-invasive diagnosis (e.g. computer tomography, CT)
- Research on the potential of stem cells as new therapeutic approach
- Development of new approaches for somatic gene therapy for hereditary immune deficiencies

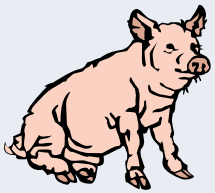
immunology and tropical medicine. Knowledge of the interaction between viruses and their host cells allows specific treatment of viral diseases, such as flu, herpes infections or smallpox, and preventive measures. For example, this knowledge has been implemented in the area of protective vaccination. Animal experiments are necessary, as the complex interrelationships in the disease process can only be investigated in live, intact organisms. This also applies to comparative studies of the function of the nervous system, the cardiovascular system and the mode of action of hormones.

There are also very dynamic developments in the areas of genomic and stem cell research. It is hoped that stem cell research may lead to new therapeutic approaches for the treatment of neurological diseases, such as Parkinson's disease, or of heart attacks.

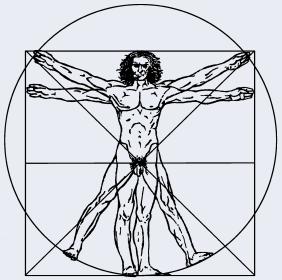
Examples of the use of animals is research

Rat, Mouse
- Cancer research
- Metabolic diseases
- Tests of drug activity
- Genome research

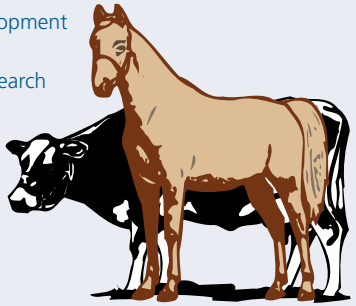
Rabbit
- Vaccine development
- Tests of drug activity

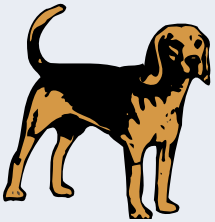


Pig
- Transplantation surgery
- Osteosynthesis
- Emergency surgery
- Diabetes research
- Cardiovascular diseases
- Osteoporosis research
- Veterinary research



Cow, Horse
- Vaccine development and isolation
- Veterinary research





Dog
- Cardiovascular research
- Heart surgery
- Bone marrow transplantation
- Osteosynthesis
- Diabetes research
- Veterinary research

Cat
- Heart surgery
- Neurophysiological studies
- Development of hearing aids
- Research on cat leukosis
- Veterinary research

Increase in medical knowledge

Medical progress is inseparably linked to basic research and the use of animal experiments. An excellent example of the medical application of knowledge from research with animal experiments is the development of methods for treating diabetes mellitus. In the 1920s, insulin was identified as a hormone which regulates blood sugar concentration. Studies on dogs and rabbits led to this discovery and helped to understand the action of insulin on blood sugar concentrations and to develop new therapies. In 1923, the Canadian scientists Frederick Banting and J.J.R. McLeod were awarded the Nobel Prize for the discovery of insulin. Dogs and rabbits were later replaced to a large extent in physiological research by rats and mice. The rapid reproduction of these species permitted specific breeding for individual clinical presentations. These include the so-called "diabetes mouse", with raised blood sugar values, and the "Zucker rat", which suffered from severe obesity.

Immunology is another important research area which could not dispense with the use of animals. Themes studied include protection from pathogens and rejection of transplants after an organ transplant. There are numerous examples of the usefulness of animal experiments in the development of vaccine sera and the study of the course of diseases. These include the development of antisera to diphtheria (guinea pigs), vaccines against yellow fever and polio (mouse and monkey) and studies on the pathogenesis of tuberculosis (sheep and cow), typhus (mouse, rat and monkey) and malaria (dove). This was pioneering progress in medicine. Animal models are still used today in medical research. For example, the 1996 Nobel Prize was awarded for the studies of Rolf Zinkernagel (Switzerland) and Peter Doherty (Australia) on the organism's immune response to virus-infected cells. Some of these advances were based on experiments with mice. The American Stanley Prusiner used experiments on hamsters and mice to identify prions as the trigger of diseases leading to neuronal degeneration. Prusiner was awarded the 1997 Nobel Prize for this work.

Animal experiments have led to the development of new surgical techniques and to the refinement of operating methods. The first experiments on tissue transplantation were performed in the mouse at the start of the 20th century. These days, animal models are used for kidney transplantation, bone marrow transfer and heart surgery, to develop new methods for the cure or alleviation of organic diseases in man. Pigs are usually used, but also dogs and sheep.

Learning and memory training

Cognitive processes – the processes of learning, memory and perception – are impaired in many psychic diseases. These disturbances serve to impair the patient's quality of life. Animal models are used to investigate new therapeutic approaches and their consequences for memory performance or learning behaviour

Animal experiments: **Increases in medical knowledge**

1900

- Treatment of vitamin deficiencies, such as rickets
- Electrocardiography in the *frog* (ECG) and heart catheter
- Passive immunisation against tetanus and diphtheria *(rabbit, mouse, horse as serum donor, guinea pig)*
- First transplantation experiments in the *mouse*

1920

- Discovery of thyroid hormones, leading to the possibility of treating poor thyroid function
- Discovery of blood sugar regulation by insulin (first experiments in *dogs*)

1930

- Therapeutic benefit of sulphonamides, a group of synthetically produced drugs used for syphilis
- Vaccination against tetanus
- Development of blood clotting factors, modern anaesthetics and neuromuscular inhibitors

1940

- Therapy of rheumatoid arthritis and whooping cough
- Discovery of the therapeutic benefit of various antibiotics, including penicillin and streptomycin
- Discovery of the rhesus factor (*rabbits* and rhesus *monkeys*)
- Treatment of leprosy
- Factors to evaluate the tissue tolerance of transplantations

1950

- Oral vaccination against polio
- Discovery of the first chemotherapies for cancer
- Cardiac pacemakers and open heart surgery

1960

- Vaccination against German measles
- Bypass operations on the heart
- Therapeutic benefit of cortisone
- Development of radioimmunoassays (RIA) for the detection of tiny quantities of antibodies, hormones and other substances in the body
- Discovery of antihypertensive drugs

Animal experiments: **Increases in medical knowledge**

1970

- Vaccination against measles, extinction of smallpox
- Treatment of disturbances in the perfusion of coronary arteries
- Heart transplantation
- Development of new non-addictive analgesics
- Discovery of oncogenesis (=origination and development of malignant tumours)
- Laser therapy for retinal detachment
- First antiviral drugs
- Development of monoclonal antibodies (=antibodies from the descendants of genetically identical cells) *(mouse)*
- Improvements in intensive medicine

1980

- Organ transplantation *(dog, pig)*
- Use of cyclosporine, an antibiotic to reduce transplant rejection
- Implantation of artificial hearts
- Vaccines against hepatitis B
- Azidothymidine (AZT) for the treatment of AIDS
- Treatment of deafness with cochlear implants (=inner ear implants) *(cats)*
- Drugs to lower cholesterol
- Discovery of genes to suppress tumours
- Studies on the formation of cancer metastases
- Treatment of leukaemia in children
- Disintegration of kidney stones by ultrasound
- Diagnosis and treatment of borelliosis, a bacterial disease transmitted by ticks

1990

- Improvements in operative techniques in minimally invasive surgery (endoscopy) to minimise stress on the patient and to accelerate recovery
- New diagnostic and therapeutic approaches in the treatment of breast cancer
- Separation of hereditary predisposition and environmental effects in the initiation of breast cancer

2000

- Decoding of the genome for the fruit fly, mouse, rat and man

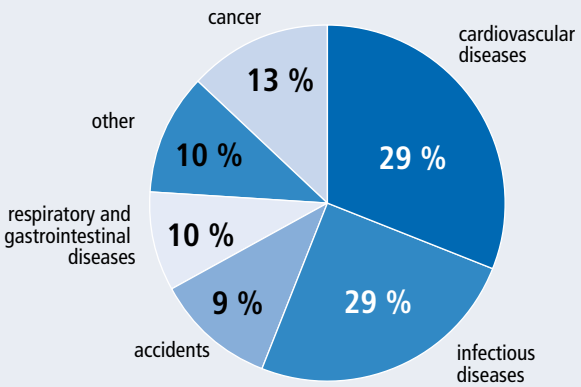
Focal points in biomedical research

As a consequence of improved medical care in western countries, human life expectancy has increased and neonatal mortality has decreased. In spite of medical progress, many diseases can only be treated symptomatically, as their origin has not yet been adequately researched. Society therefore still has great hopes of progress in medical care.

In many diseases, successful treatment depends on diagnosis in good time. This is why much medical research is concentrating on improving diagnostic methods. Non-invasive diagnostic techniques include positron emission tomography (PET) and computer tomography (CT) and do not require any sort of operation, so that they are less disturbing for the patient. Together with the development of new contrast media, these open up new diagnostic possibilities. The American Allan M. Cormack and the Englishman Godfrey N. Hounsfield were awarded the Nobel Prize in 1979 for the development of computer tomography, for which they used the pig and other animals as model organisms. These highly sensitive diagnostic procedures are also used to treat domestic animals in veterinary medicine. Experience gained in human medicine with ultrasound diagnosis, X-rays and computer tomography is also exploited in modern veterinary medicine.

In chronic diseases, such as diabetes mellitus, rheumatism and multiple sclerosis (MS), but also in allergies, the objective is to alleviate the stressful symptoms and to prolong life expectancy.

Causes of 58 million deaths in the world



Source:
WHO, 2001

Current focal points in basic research

- Cell biological and molecular genetic principles for the origin and growth of cancer cells
- Function of viruses and their interaction with host cells – specific treatment of viral infections
- Function of the nervous system and of the hormones
- Function of the heart and of the cardiovascular system, to increase knowledge of cardiovascular diseases
- Immunobiology and parasitology
- Research on stem cells to develop methods to treat neurological diseases (such as Parkinson's disease) or to replace tissues (for example, myocardial infarction)
- Research on tropical and subtropical diseases, such as malaria and haemorrhagic fever
- Gene transfer to treat hereditary diseases
- Neurobiologische Forschung zum besseren Verständnis der Gehirnfunktionen
- Neurobiological research to increase understanding of brain functions
- Function and interactions of genes (genome research)
- Origin and development of organs
- Control of gene expression to clarify the function and functional disturbances of the cardiovascular system, the reproductive organs, the hormone system and others
- Knockout mice and transgenic mice strains as animals models for human clinical presentations (e.g. deafness, metabolic disturbances)

Transplantation medicine

About 3,500 organ transplantations are performed each year in Germany. For the recipients of the organs, this procedure is either life saving, or leads to a great improvement in the quality of life. The operative techniques and all procedures to avoid rejection reactions were mostly developed in animal experiments. Future developments are also dependent on preclinical studies with animals. The aim of these experiments is to improve patient care and to prolong the period for which the donated organs function. Methods of suppressing immune reactions against donated organs must be developed which minimise the complications suffered by the recipient. Another objective is to improve the necessary surgical techniques and the conservation of the donated organs during transport.

The term xenotransplantation (from the Greek xenos = foreign) means the transplantation of organs from one animal species to another, or from an animal to man. This has a special role in transplantation research. The studies aim at finding species with organs which are suitable for transplantation, because of shared biomedical or physiological properties. For anatomical and physiological reasons, the domestic pig is currently regarded as the most promising organ donor for man. Animal experiments are therefore an important interface to research on farm animals.

The possibility of xenotransplantation is a currently controversial issue. Rather than a permanent transplantation, another possibility is to employ xenotransplantation as an emergency procedure, if no suitable human organ is available at once. Current research in this area is at a very early stage.

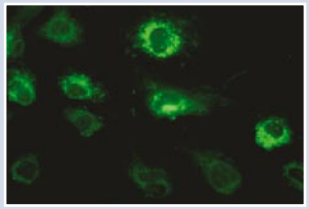
Man or animal?
Operations in animals and in man are about equally technically demanding

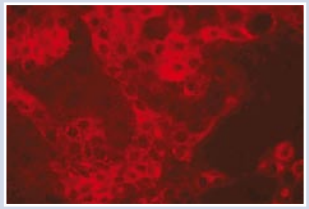
Cell and tissue replacement in man

Many of the diseases known today are due to the loss of cells or tissue, or loss of their function. In degenerative diseases, such as Parkinson's or Alzheimer's diseases, and also in accidents, myocardial infarction and arthrosis, there is loss of cells and tissue, with major consequences for the patient's quality of life. Drug treatment, surgical correction and implantation of tissue (skin or nerve cells) or of biomechanical systems (heart valves, artificial hearts, heart pacemakers, artificial joints) are procedures based on animal experiments. Artificial culture of replacement tissue from the patient's own body is known as "tissue engineering" and it is possible that this may be used in the future to replace lost cells or tissue from the patient's own body. Stem cells

have already been successfully applied to bone marrow transplantation. This approach offers the possibility of allowing some types of tissue to regrow. Moreover, in the so-called "biohybrid implants", the body cell structures and functions are combined with electronic or mechanical implants. New developments are also to be expected in the area of biosensors (implantable electronic aids for seeing and hearing).

Stem cell research





In vitro experiments with mouse stem cells
In culture media, embryonic mouse stem cells differentiate into structures resembling liver cells, which are capable of producing the proteins albumin (green) and alpha-1-antitrypsin (red).

The aim of stem cell research is to decipher the principles of cell differentiation and to establish the possibilities of influencing this. Stem cells are cells which are still largely capable of dividing and developing. The "totipotent" cells can do everything, from which complete living creatures can develop. The current view is that this no longer applies to "pluripotent" embryonic stem cells, although these still have a versatile potential for development. This also applies to the "adult" stem cells from fully developed organs, such as bone marrow, skin or the central nervous system, which can repair damage in the organism.

Animal experiments have a long tradition in developmental biology, which has studied this theme intensively. One objective of biomedical research is the development of new therapeutic approaches for diseases which are currently still incurable. Thus, the transfer of stem cells from the pancreas of adult mice can influence type I diabetes in mice.

Initial successes have also been achieved in the treatment of paraplegically paralysed rats. Embryonic stem cells from the brain were capable of forming a type of bridge between bone marrow stumps, re-endowing the animals with limited mobility. Animal experiments have also been used to win initial knowledge on the possible potential for differentiation of tissue stem cells. There is evidence that stem cells from the bone marrow develop in the brain into nerve cells, which resemble the other neurones in the central nervous system. One long term objective is to use human stem cells to culture complex cell structures or complete organs for transplantation. Progress in this area would greatly decrease the risk of intolerance and rejection reactions.

The potential for stem cells and their possible medical uses are immense. However, more studies in cell biology and animal experiments are needed to sound out the possibility of using embryonic and adult stem cells to heal tissue damage.

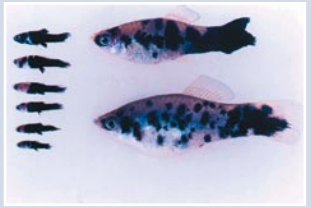
Genome research, mutagenised and transgenic animals

Genome research deals with the recording and decoding of the function of the hereditary material in living organisms. This concerns not only the simple sequence of letters in the genetic code, but, more importantly, the function of the genes, as these hold the key to the assembly of the body and to the interactions between different organs. To be able to analyse this in a complex organism, it is necessary to be able to induce specific changes in the hereditary material. This can be achieved by gene transfer or by chemical treatment of hereditary material (mutagenesis). If there are then changes in the so-called "phenotype" of an animal - its appearance, behaviour, organ function or blood count - this permits conclusions about the genetic basis for these changes. These experiments employ so-called model organisms, such as flies, round worms, zebrafish, mice or rats. The mouse is especially important in research on human diseases, as the mouse genome and the human genome exhibit major similarities. Both the human and the mouse genome have now been fully decoded.

Animals in which sections of hereditary material (DNA) have been specifically modified are known as transgenic animals. One goal when establishing breeding strains of this sort is to breed animals with a defined loss of function. Researchers have succeeded in identifying genes which are involved in the origination of diabetes mellitus in both mouse and man. Using the mouse strains, it has been possible to develop new therapeutic approaches for this disease, which is widespread in man.

Breeding strains for research on diseases including cancer, obesity and deafness have already been established. For example, the same gene is responsible for the development of colon cancer in mouse and man and attempts are being made to influence these degenerated cells.

Just as with other animal experiments, the Animal Welfare Act demands that, before genetically modified animals are produced, there must be an ethical evaluation and consideration of the stress for the parent animals and for the subsequent generations. Operations, such as the transfer of egg cells to surrogate mothers or cutting the spermatic ducts in male animals, are performed under anaesthesia and cause low levels of stress in the individual animals. The degree of stress in the offspring is often not predictable. However, experience has shown that the appearance of transgenic animals is often hardly different – if at all – from that of the so-called wild type. Evidently the intact gene or other gene groups counteract the impairment in function. In transgenic animals equipped with the same hereditary material with respect to the inserted characteristics (so-called homozygotic animals), about 5% of the offspring suffer from losses in function. The severity of the stress can range from slight to severe. Embryonic development can be so badly disturbed that the embryos or foetuses die before birth.



Tumour therapy in fish

If the platie hybrids are missing the control genes for a tumour gene, melanomas can form in the skin. The fish then appear to have a very dark pigment and are covered in tumours. After three months of treatment with a hormone which prevents terminal differentiation of the tumour cells, there was a drastic reduction in tumour development

Transferability of the results from animal experiments to man

The components of body cells and the biochemical mechanisms necessary for the processes of life exhibit very marked similarities between different animal species. Molecular genetics can demonstrate that all organisms living today had the same origin. They share genes which are responsible for body structure and which are modified during the course of evolution, thus providing the material basis for the sequence of living creatures during all ages of the earth. These similarities even allow comparisons between human genes and metabolic processes with those of bacteria, fungi and yeasts. It may therefore be assumed in principle that interventions in general metabolic pathways will produce effects which are transferable from microorganisms to animals to man.

However, body functions are much more complex in higher animals and man than in the lower organisms, as body functions in higher animals are based on a multitude of specialised cell types and organs. For example, an active substance may have the desired effect in the liver, but be chemically modified by the liver cells in such a way that a compound is formed which is toxic for the central nervous system. This shows that the transfer of reaction patterns from cell structures to the total organism can be extremely difficult. For this reason, not only studies at the cellular level are needed (complementary methods), but also always experiments with the complete organism. Because of the similarities in cell and organ structure in different mammals, it is assumed that transferability from animals to man is mostly possible. This underlying assumption applies to both the desired and undesired or toxic effects of a substance. Animal experiments make it possible to predict the desired and about 70% of the undesired effects which affect man. One example is acetylsalicylic acid (the active substance in the analgesic Aspirin®). This alleviates pain in both rat and man, but can increase the bleeding tendency in both species. Other examples are the effects of building materials and of solvents, which have damaging effects on both rats and man. Asbestos causes lung cancer in both and plastic solvent liver cancer in both. This experience allows the conclusion that safety and efficacy tests in animal experiments permit a considerable reduction in the risk of new treatment methods in man. The Thalidomide catastrophe in the 1960s made it tragically clear that testing substances in animal experiments does not always lead to complete safety in man. Before then, no-one had recognised the possible reproduction toxicity of this substance.

The transferability of results from animal to man also applies in the opposite direction. Drugs which have been successfully used in man can also be used for domestic animals. The basic assumption of transferability is also an important aspect in the evaluation of pain and sensitivity in animals. The anatomical structure of the brain and the conduction of pain stimuli and their perception in the central nervous system are similar in higher animals. This therefore permits analogies to be drawn about pain sensitivity and about the possibility of suffering.

Veterinary research

The results from animal experiments are not only of use in human medicine, but also in the development of new diagnostic and therapeutic procedures in veterinary medicine. One example for the use of treatment methods from human medicine is tumour therapy in small animals. Transfer is generally possible without difficulties, as the procedures practised in human medicine were developed in animal experiments. However, veterinary medicine cannot dispense with the use of experimental animals in basic research and in the development of new treatment methods. The studies are mostly planned so that animals are involved in the studies for which the procedure is subsequently to be used in practice. The study is performed on the target species – the potential patient.

Laboratory animals help our domestic animals
Studies are often performed and new therapeutic procedures tested on the animals which are to be the patients in the veterinary practice.

Animal experiments &
animal protection:

An ethical balance

Is it possible to dispense with animal experiments?

Since the first use of animal experiments in research, opponents have often demanded that they should be partially or fully abandoned. Instead, they point out the possibilities of natural medicine or the medicine of other cultures, even though the methods and efficacy of these treatments have generally not been scientifically proved. In contrast to so-called experience or alternative medicine, conventional European medicine seeks causally based therapy, to understand the clinical course of the disease and to be able to develop new methods of treatment.

Dispensing with animal experiments would slow medical progress in an irresponsible manner and markedly decrease the chance of a cure for sick people. Biomedical research is currently in a state of rapid development and a multitude of new insights are to be expected in the coming years with the use of new methods. If Germany acted alone and dispensed with animal research, it would very rapidly lose contact with international research and the immediate access to the findings. If the animal experiments were shifted to neighbouring countries, this would have no effect on the overall numbers of animal experiments or on the experiments themselves. This would only mean displacement to countries where the regulations are less strict. This would not improve the protection of the individual animal. We can assume that medical progress from exported animal experiments would also be exploited in Germany. This might justify the accusation of hypocrisy.

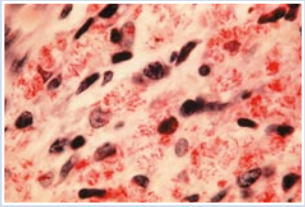
One reason that it is impossible to dispense with animal experiments totally in Germany is that many experiments are performed because of national and international legal regulations. These include chemicals laws, drug guidelines and environmental laws. Legislators have prescribed these substance tests to protect the consumer and for risk assessment. The current requirements for the approval of a drug include animal experiments to test

- *Acute* (immediate) *toxicity*,
- The effects of lower doses applied over a longer period – the *chronic toxicity*,
- Its *carcinogenic activity*,
- Its effect on unborn life, the *teratogenic activity*.

These tests are only possible in the intact organism. Nevertheless, partial aspects of these tests can be submitted to a preliminary study in cell cultures. Research has developed alternatives, which reduce the number of animal experiments and avoid that animals suffer unnecessarily. In many cases, it has been possible to reduce the necessary extent of safety testing by adapting national and international laws. Thus, the so-called LD50 test to test acute toxicity is still demanded in the international guidelines. In these test series, the concentration of a substance is determined at which 50% of the animals in one group die.

Hygiene is the first commandment in the animal house
Before entering the animal house, animal keepers and scientists must put on masks, to exclude the risk of infecting the animals.

Are there alternatives to animal experiments?

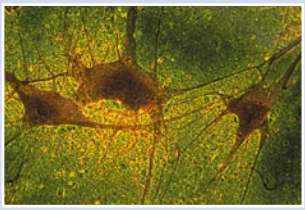


The demand for "alternative methods" or "replacement methods" for animal experiments has become increasingly strident in recent decades. Ideally, these would be methods which would allow the use of animals to be fully abandoned. The talk here is mainly of work with cell lines. This is indeed the ideal case - in the sense of wishful thinking - as the complexity of an organism, with the interactions between organs and tissues, can never be fully replaced by artificial systems. Even now, experimental methods outside the organism, the so-called "in vitro methods" (in vitro = in test tube), are of major importance in research and in public support of research. Cellular and molecular details of drug action and metabolism can be clarified in this way. In recent decades, great progress has been made in the methods used in "in vitro" systems. Nevertheless, in spite of these improvements, the intact organism cannot be replaced and its reaction must eventually be clarified in vivo (in life), i.e. in animal experiments. This is why both basic and industrial researchers study biochemical details in vitro, but usually follow these studies with animal experiments, to clarify the links within the organism. The two approaches are complementary.

Animals must be killed to produce organ and cell cultures. Human and animal cell lines may change over time after storage and culture for many generations. Moreover, they only permit the analysis of specific biochemical detailed questions. For the culture of cell lines, calf serum from slaughtered animals is often needed as nutrient, to stimulate cell division, growth and differentiation. Studies on cell cultures and cell lines have nevertheless led to a reduction in the numbers of animal experiments. This is particularly the case in the areas of drug testing and in drug development.

The demand for alternative methods has a different significance in basic research. Animal experiments are necessary here for the clarification of physiological connections and their disturbances in the organism. These include studies on the central nervous system and the processing of sensory stimuli, interactions within the cardiovascular system, the digestive system, the hormone system, the immune system and behavioural principles. When checking the approval of animal experiments, the authorities examine whether the experiment is essential or whether the desired results can also be attained without using animals.

Computer simulation can be a complement to animal experiments. This is used in biomedical research to depict and map hypotheses about processes and to check them on the basis of theoretical models. This technique is frequently used in neurobiology, to portray the functions of the central nervous system. However, the conclusions of the simulation must always be checked in animal experiments. Computer simulation is also used in higher education, to analyse complex biological situations, to demonstrate them to students and to exemplify the information about animal experiments beyond the content of textbooks. The design and performance of animal experiments can also be demonstrated in learning videos. These simulations then serve as teaching aids and as preparation for working with living animals. Their aim is to increase sensitivity when working with experimental animals.



In Germany, the Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET) in the Federal Institute for Risk Assessment in Berlin was founded to record and evaluate replacement and complementary methods for animal experiments and of achieving their recognition if possible. This institution is also the centre for providing information on alternative methods and is meant to further the validation of methods without experimental animals. This is needed to achieve inclusion in the international testing guidelines for safety toxicology. At the European level, this work is the responsibility of the European Centre for the Validation of Alternative Methods in Rome (ECVAM). European Guideline 67/548/EEC (Annex 5) lists alternative methods which permit the phototoxicity or corrosive effects of chemical substances to be examined on cell culture models. These tests must therefore no longer be performed on animals within Europe. There are efforts to have these test procedures accepted throughout the world and have them included in the guidelines of the OECD (Organisation for Economic Cooperation and Development).

Limits to alternative methods

In spite of favourable aspects, these methods possess a severe disadvantage. The human or animal body possesses more than 200 different cell types and the interactions of these are coordinated in organs and tissue structures. To study this complexity is an important part of biological research and this can only take place in the intact organism. Even if a drug appears to be useful during its development in cell culture, it may turn out to be inactive or even toxic in other cell types, or lead to the formation of breakdown products in the body, which cause damage in other organs. The complementary character of animal experiments and alternative methods nevertheless offers the chance of greatly reducing the number of animal experiments. In particular, this is possible in tolerance studies for man and the environment.

The three Rs

Reduction
Refinement
Replacement

Improvements in measurement techniques and expertise in handling of animals help to reduce the stress on the individual animal. This helps to reduce the numbers of experimental animals and is in keeping with the concept of the three Rs.

Although animal experiments remain essential in biomedical research, there is a general consensus that they must be restricted to the necessary minimum. The three Rs - reduction, refinement and replacement of animal experiments – can be taken as the guideline. Consistent application of statistical procedures and exact experimental planning serve to reduce the number of animals. This is supported by the fact that the official approval and publication of the research results in professional journals are linked to the demonstration that the results are statistically significant and that the studies are original. The refinement of animal experiments has the objective of minimising the adverse effects on the animals from the studies. Great progress has been made in eliminating pain by analgesia and anaesthesia, in technical improvements in measurement procedures and in the development of non-invasive study methods.

The objective in basic research is that animals should only be exposed to low levels of stress if possible. This allows for ethical objections to animal experiments and improves the quality of the test results. Research workers are continually called on to optimise their methods and to evaluate the extent of negative effects on the animals, on the basis of objective parameters, such as the animals' behaviour. This requires both personal sensitivity and good training.

The European Science Foundation (ESF) in Strasburg is the umbrella organisation for all state organisations to support research in Europe and has issued a policy paper with recommendations for work with experimental animals. This appeals to members to accept the principles of the three Rs and also to undertake specific efforts to reduce and to improve animal experiments.

Acceptance of animal experiments

An independent opinion research institute has evaluated and assessed nine studies performed throughout Germany in the 1980s and 1990s.

This study showed that animal experiments which serve the good of mankind were accepted by most of those questioned.

This becomes clearer once the purpose of the research is intelligible. In this case, 10-11% of those questioned supported the performance of animal experiments without reservations. With some reservations – depending on the purpose of the experiments – 71-75% of those questioned tolerate the ani-

mal experiments (EMNID 1985, 1996).

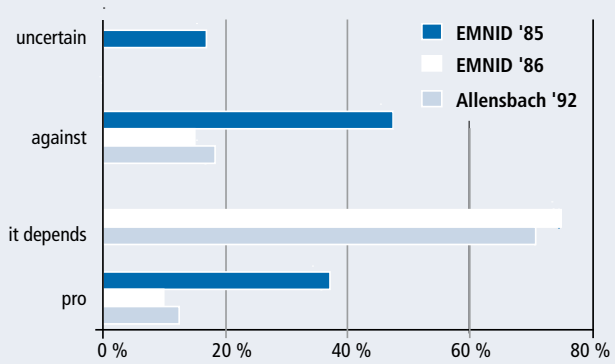
For example, in the 1993 study performed by the Allensbach Institute, 50% of those questioned supported animal experiments, if human life could be saved with their help; 24% could not decide and 26% tended to oppose animal experiments.

Many of those questioned did not connect scientific experiments with torturing animals. 30% had no general reservations about animal experiments; for 49%, it depended on the type of experiment (EMNID 1985, 1989). Hardly any of those asked considered that there were superfluous areas of medical research. In addition, more than 75% were not prepared to forfeit the development of new drugs to prevent the use of animals (EMNID 1985, 1986, 1989).

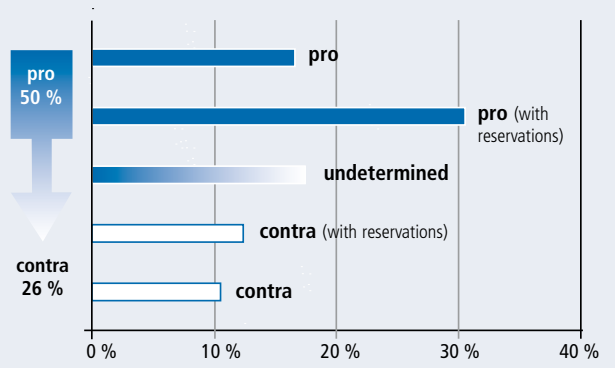
Animal experiments are required by the legislator for testing pharmaceuticals and other medicinal products before they are applied in humans. The EMNID polls dealt particularly intensively with the issues of drug research and animal experiments. The results showed that experiments of this sort are not only tolerated, but even demanded, by those questioned. The acceptance of animal experiments in drug safety and research is mainly based on the wish for safe and reliable medical care. Most of those questioned thought that it was a matter of course that animals were used for the good of man. 75% of those questioned in the EMNID poll (1985) and about 50% in the GfM GETAS Study (1993) could not conceive of doing without meat products. Although the use of animals as food was unambiguously advocated, most of those questioned were unwilling to express a clear opinion on the use of animals in experiments.

As commissioned by the DFG and the Max Planck Society, a poll of experts was performed in 1999 on the issue of animal experiments. The experts came from the fields of economics, science, politics, the press and animal protection. The results of the poll show that there is a great demand for information on animal experimental research within society. The dominant impression in the population is that public research institutions operate defensive information politics and this was confirmed by this expert poll. It is therefore particularly important that these institutions should inform the public about animal experiments, as the public has a great deal of trust in the independence of the Max Planck Institutes and universities, in comparison to commercially orientated industrial research. It has been shown that firms and research institutes enjoy greater acceptance if they maintain intensive dialogue with the population about their animal experiments.

Results of the EMNID and Allensbach polls



Results of the GfM GETAS poll (1993)



Attitude of the population to animal experiments

The development of ideas on animal protection in Germany

Operation on the open chest

Ferdinand Sauerbruch successfully used the so-called pressure difference procedure to prevent the collapse of the lung in the opened chest. The first trial operations took place in the dog. With this method, operations on the heart and lung were possible for the first time.

The idea that man has a special responsibility for animals in his care is the result of the historical development of the relationship between animals and man. Cultural, philosophical, social and official standards define the limits of our attitudes to animals and their needs. If current laws and regulations on animal protection are considered, it becomes clear that these are based on a basic conception of ethical animal protection.

Since the 17th century, an anthropocentric view of animal protection has been evident – with man as the centre. In the 18th and 19th centuries, influential members of a socially and politically active class of the population became active. They loathed all forms of pain to animals and regarded this as a mark of their level of culture - the animal protection movement. The focus of interest was not the animal, but concerns about the brutalisation of individuals and of society. As Germany consisted of many small states, a variety of laws were passed. National criminal legislation on the protection of animals from cruelty was only passed in 1871. This standardisation of the law supported animal protection as a social goal and led to the formation of numerous societies for animal protection, with the objectives of preventing cruelty to animals and "vivisection" (operations on living animals). As experimental research and consequently the number of animal experiments increased within the same period, this inevitably led to conflict between science and animal welfare. Various different reasons led to the rejection of animal experiments. Either animal experiments were totally rejected for ethical reasons, or a reduction in the numbers of animals was demanded. Religious groups coupled their disapproval of animal experiments with their rejection of scientific ideas on progress. However, the opinions of physicians were also divided and some considered that animal experiments were an unsuitable way of solving medical problems, as they doubted the transferability of the results.

The first German Animal Welfare Act was passed in the 1930s and this remained in force till after the Second World War. This laid down regulations for working with experimental animals for the first time. In the 1960s and 1970s, public discussion of the safety of farm and experimental animals was revived. This encouraged the creation of new laws on animal protection. The Animal Protection Law passed in 1972 is based on ethical concepts of animal protection and exploited scientific knowledge on species-specific and behaviourally correct standards and the needs of the animals as criteria for evaluation. Subsequent changes in the law in the 1980s and 1990s were influenced by economic, scientific and political considerations. These changes increased the emphasis on animals as creatures like man and increased the strictness of the regulation of animal experiments. To enhance the protection of animals as living creatures in the legal system, animal protection was laid down as an official goal in the national constitution. This was added as an addendum to the constitution in July 2002 under § 20a. This legal status is unique anywhere in the world; the demand that man deals with animals in a morally responsible manner has thus acquired an unusually high status.

Ethical aspects of animal experiments and the principle of solidarity

Karin Blumer

The question of the ethical acceptability of scientific animal experiments was first systematically discussed in philosophical ethics in the 1970s. The discussion was mainly triggered by the writings of the Australian philosopher Peter Singer, who laid the foundation for the new movement on animal protection with his 1976 work - Animal Liberation. Philosophy has been occupied for centuries with the question of man's responsibility for non-human life. Philosophers have used various theoretical approaches to address the complex theme of the relationship between animals and man.

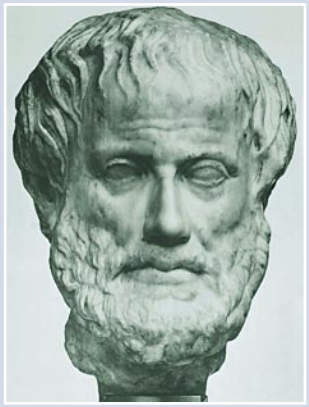
In classical anthropocentrism, animals have no inherent value at all; this can now be regarded as out-dated. It was traditionally supported by such important philosophers as Aristoteles and Immanuel Kant, together with the Christian moral theologians. Its basic assumption is that only man is worth protection, as only man is a rational and reasonable being (or in the image of God). This led to the justified accusation of speciesism, first made by Jeremy Bentham in 1789. Bentham proved that this was egoistic group behaviour, as solely the membership of the biological species Homo sapiens served as the ground for justification. At least since the general acceptance of the theory of evolution in the mid 19th century, the thesis of man's biological uniqueness can no longer be maintained.

However, many other ethical positions on the relationship between animals and man are equally unsatisfactory. Thus, holism, which demands an independent right of existence for even mountains or rivers, suffers from its highly metaphysical premises, which assume, for example, that nature is "animated". The Nobel Peace Prize winner Albert Schweitzer developed the concept of radical biocentrism, which includes all forms of life in the moral community. Although this appears plausible at first sight, it is based on an extremely deontological standard. It forbids the damage of all forms of life - whether animal, plant or bacterium - and thus places the active agent before irresolvable dilemmas.

Finally, pathocentrism, as propagated by Peter Singer and many other proponents of animal protection, is incapable of providing a clear proof as to why only animals with an intact central nervous system may possess an inherent moral value. What however is a much greater problem is the proposal by many pathocentrics that some animals should be declared to be "persons" and to refuse to accept the personality of some humans. Peter Singer has been particularly prominent on this issue. For him, great apes, whales and dolphins are certainly, and all other mammals very probably, persons, whereas newborn babies, persons with severe mental handicaps and comatose persons are degraded to "mere members of the species Homo sapiens".

"Moderate biocentrism" or "moderate anthropocentrism" is a moral theory which might be widely acceptable and plausible these days. Both theories ascribe a moral status to all forms of life, although the binding inherent value of this increases with the position of the species on the evolutionary ladder (hierarchy of the organisms). Thus, for example, there would be more reason to protect the health of a dog than of a hamster or of a

Albert Schweitzer (1875-1965)
His radical biocentrism includes all living creatures in the moral order. According to this, harm to any form of life - whether animal, plant, parasite or bacterium – is forbidden.



According to **Aristoteles** (384-322 B.C.) possess both a "vegetative" and an "animalistic" soul. They are capable of fulfilling their own needs in a deliberate manner, but cannot act reasonably. **Arthur Schopenhauer** (1788-1860) considered that animals possess the same characteristics as man. This means that they are capable of suffering and feeling.

worm. However, the human being retains a special position even within "moderate biocentrism" or "moderate anthropocentrism".

A principle objective of philosophical ethics is to develop standards for human actions and to provide reasons to justify these. On the basis of formal guidelines, every violation of animal interests must be justified by a balanced consideration of values. This does not only apply to animal experiments, but to all actions in which animals are used for human requirements.

Animal experiments have a special status in the discussions of the relationship between animals and man. This is not only because many people regard them more critically than, for example, slaughter of animals for meat or the specific breeding of beautiful but anatomically or physiologically sick races. A much more important consideration is that the motive of the scientific animal experiment is to increase knowledge. This increase in knowledge is by no means an end in itself, but has a concrete objective: the maintenance and furtherance of the health and quality of life of men and animals and the increase in the knowledge of nature. Although this goal cannot be attained in each individual experiment, philosophical considerations indicate that it possesses greater value than, for example, excessive supplies of animal proteins to people in industrial countries or the aesthetic demands of the owners of domestic dogs or cats. As in our society an increase in knowledge possesses a high moral value, animal experiments can be justified if the following conditions are fulfilled:

- The increase in knowledge is essential and serves ethically justifiable objectives.
- The increase in knowledge can be achieved in no other manner. Alternative methods cannot be used.
- This is not an *unjustified* repeated experiment.
- No more animals are used than is absolutely necessary.
- The animals used are as low on the evolutionary ladder as possible.
- No *avoidable harm* is inflicted on the animals. This particularly applies to care, husbandry and possible use of analgesia.

Committees on animal protection comply with these guidelines when approving animal experiments.

This argumentation is also both permissible and necessary for animal experiments in basic research. The fact is often overlooked that the balanced evaluation does not simply compare the interest of the animals with the increase in knowledge as an aim in itself. It is rather the case that the interests must be included of the innumerable people who suffer from diseases which cannot be treated or cannot be treated adequately. With these premises, a massive restriction in biomedical research, as is sometimes demanded, becomes ethically indefensible, as not only actions, but their omission, must be morally justified. It would only be conceivable to dispense with animal experiments completely, if increases in scientific knowledge in wide areas of biomedical research could be sacrificed. This sacrifice would be of possible therapies for many diseases, which are not peripheral phenomena, but very common. These include cancer, HIV infection and AIDS, cystic fibrosis, cardiovascular diseases and Alzheimer's and Parkinson's diseases.

A complete prohibition of experimental animal research would also be in conflict with another valid fundamental moral standard,

the solidarity principle. This describes the principle of providing the best possible support to all those requiring help - the weak and the sick. The solidarity principle is not only one of the many preconditions for life in human communities; it is a special characteristic of man as a morally responsible being capable of solidarity.

People who perform animal experiments always experience conflict between two obligations. The first of these is positive and is the obligation to use one's own knowledge and abilities to reduce human and animal suffering. In contrast, the negative obligation is not to inflict avoidable suffering on other creatures. In the context of human activity, we often find it difficult to reach decisions when we are compelled to violate one obligation. As long as it is scientifically impossible to unravel complex causal activity relationships in living animals without animal research, this conflict between obligations will remain the theme of ethical discussions. There will never be a general answer to the question of whether an animal experiment is justified. Only specific individual answers are possible.

The author is a veterinary physician, has a doctorate in philosophy and currently works in the pharmaceutical industry.

Animal experiments
in Germany:

From application to performance

European regulations on animal experiments

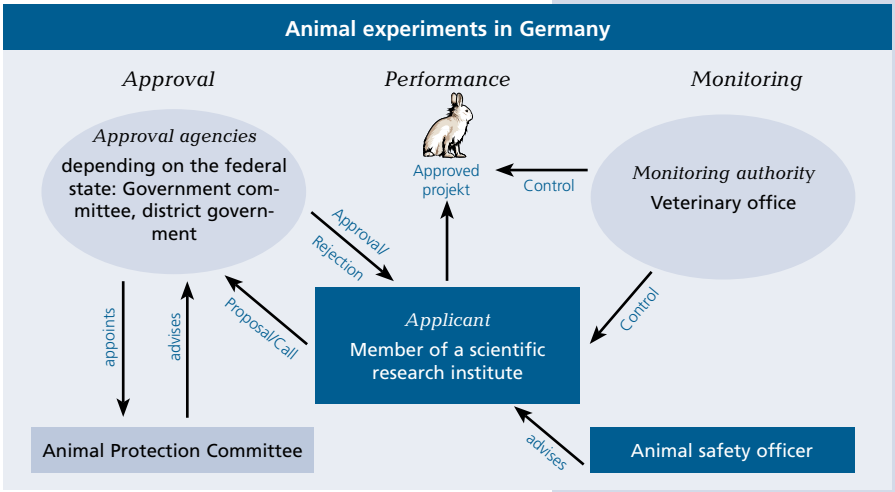
As part of Europe, Germany is bound by the laws of the European Union. This applies to both the laws on animal protection and to the regulations on the performance of animal experiments.

Council of Europe

The Council of Europe is a regional organisation for all of Europe and has the general political responsibility of implementing the common political ideals of the member states and of furthering their collaboration. The Council of Europe considers that this includes environmental protection, which also covers the theme of animal protection. With this background, the "European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" was passed on 18 March 1986. This is a multilateral contract in international law, which requires ratification. As a consequence of the ratification of 11 December 1990 (BGBl. 1991 II, p. 740), this agreement became binding for Germany. The German Animal Welfare Act is in accordance with these Council of Europe guidelines for the area of animal experiments.

European Community

The contract law for the European Community also contains community authority for animal protection, under the aspect of environmental protection (Art. 174 EU Contract). Clause 10 of the Amsterdam Contract of 2 October 1997 is entitled "Protocol on protection and welfare of animals" and this is a binding component of the primary law of the Community. This expresses the wish to ensure that animal protection is improved and that the well-being of animals, as sentient creatures, is considered. For example, the Community may couple the award of research funds to qualitatively high standards of animal experiments. The same is expected when member states award research funds. According to this, the influence on the issue of animal experiments is a result of the Community's authority to standardise legislation. This is the basis on which the "Council Directive on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes" of 24 November 1986 (86/609/EEC ABl. No L 358, p. 1) was passed. The legal force of this directive in individual EU countries depends on its implementation by national legislators.



Animal experiments with the preconditions of approval

Testing heart valves
After implantation of the heart valves, the operated sheep are returned to the herd and can continue to live in their accustomed social environment. The implant function is medically monitored.

No-one can build a house without building approval or run a restaurant without a licence. It is equally true that no-one can perform animal experiments without approval. This is a so-called "preventive prohibition". This implies that animal experiments are permitted in principle, but may be forbidden in specific cases, if the legal preconditions are not met. To allow regulation by the authorities, the performance of an experiment is preceded by an approval procedure (§ 7 of the Animal Welfare Act).

The constitution guarantees scientific freedom. However, the preventive prohibition restricts the researcher's freedom. In accordance with the principles of constitutional protection of basic rights, this must be justified. For constitutional rights - like scientific freedom - for which no reservations were planned by the legislator, legal intervention is only permissible if this is in favour of constitutionally protected objects of legal protection. Since July 2002, this constitutional justification has been supplied by Article 20a of the constitution, with the formulation "and the animals" in the context of the national goal of "the environment". This makes it clear that the Animal Welfare Act can constitutionally restrict freedom of research.

However, this makes no difference to the objective or legal character of the current regulations. As animal protection is a national goal in the context of the constitutional order, it is an exclusive duty of the legislator to reconcile freedom of research and ethical animal protection. This duty has been addressed by the legislator with §§ 7 to 9 of the Animal Welfare Act. The approach has been effective, although it is somewhat less secure with respect to the dogma of the constitution.

Interpretation of the Animal Welfare Act for the area of animal experiments

If animal experiments require approval, it must be clear what an animal experiment is. The definition of animal experiments is based on the purpose of the law as laid down in § 1 of the Animal Welfare Act. According to this, no-one may inflict pain, suffering or damage on an animal, without a good reason. The approval procedure, in accordance with the Animal Welfare Act, will then test whether there is a good reason that pain, suffering or damage are inflicted.

An animal experiment has the following characteristics:

- The purpose of the experiment: The objective of the experiment is to gain knowledge. There is no gain in knowledge if the question put has already been clarified;
- The operation or procedures on the animal may be linked to pain, suffering or damage,
- The operation or procedure on the animal may be linked to pain, suffering or damage for the genetically modified animals or their carriers.

According to the German Animal Welfare Act, the purposes of animal experiments may be lawful, absolutely unlawful and principally unlawful.

- Animal experiments are *lawful*, if they are related to knowledge of human or veterinary medicine, for example
  – In the development of new drugs,
  – In detecting environmental risks,
  – In testing the safety of drugs, pesticides, plants, foods or consumable objectives, chemical or other hazardous substances
  – in basic research.
- Animal experiments are *absolutely unlawful*, if they are related to the development and testing of weapons, munitions and linked equipment.
- Animal experiments are *principally unlawful*, but with the possibility of specific exceptions, if they are related to the development of tobacco products, detergents or cosmetics.

Principles of orientation
Like bees, locusts find their orientation from the pattern of polarisation in the sky

What is the legal definition of "essential"?

It is expected that the researcher will collect information on the status of current research when planning his experiment and will consider whether his planned study may lead to new knowledge. An experiment is only "essential" if there is no equally valid alternative, given the planned purpose. On the basis of available scientific knowledge, it must accordingly be considered whether there is any other procedure which allows the animal experiment to be dispensed with.

All accepted results must be considered, including minority opinions, if they are of adequate scientific quality. The essentiality must not only be checked for the lawfulness of the animal experiment ("whether"), but also for the specific procedure ("how"). The principle of the three Rs applies to both.

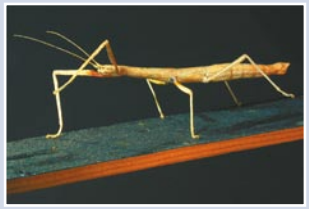
What is the legal definition of "ethically justifiable"?

When considering ethical defensibility, the stress to the experimental animal during the experiment must be balanced against the question as to whether this is justified by the increase in scientific knowledge. The evaluation of the experiment must then weigh the expected benefit against the expected burden to the animal. In the specific case, this is a difficult decision.

Additional measures for ethical defensibility are provided by the standards contained in laws related to animal experiments – such as the Drug Law, the Hazardous Substances Regulation, the Pesticides Regulation or laws on waste water. These no longer require approval and illustrate specific evaluation of the relative benefits and stresses. The performance of these experiments is based on the purposes of these laws and the demands of our society. In the final analysis, society decides which risks it is prepared to tolerate.

Undisturbed measurement
The marmots' body temperature and oxygen consumption are measured during their winter sleep.

Approval procedure



How do you move through rough territory, without falling over?
The stick insect is used as a model in the decoding of coordinated movements. Results from these studies are used in robot technology.

Before an animal experiment can be performed, it must be reported to the responsible authorities and approved by them. The notification or application must include comprehensive scientific details and expert documentation. The approval procedure must include three elements for the applicant to be granted or refused permission.

- *Project-related:* The project must be scientifically justified and the essential character and ethical defensibility demonstrated. In addition, the desired experimental result may not be already available from other sources. The appropriate authorities (such as ministries or state government offices) are responsible for evaluation and they check the plausibility of the application. In the course of their decision, the authorities are not to replace the authors' scientifically plausible description of the value of the experimental objective with their own views.

- *Person-related:* The responsible manager of the research project and his deputy must possess the necessary professional qualifications and be personally reliable. This implies that they may not have violated the Animal Welfare Act in the past.

- *Facility-related:* The personal and structural preconditions for the performance of the animal experiment must be given. These include qualified animal keepers, suitable rooms for keeping animals and the designation of an animal safety officer. For animal husbandry, care must be taken that the experimental animals are kept in a manner which is suitable for their species and needs and that their medical care is guaranteed.

If the preconditions are fulfilled, the authorities must award the approval within three months. The approval is for a limited time period and may be linked to conditions. Should violations be established and where there is due reason, financial penalties of up to 25,000 Euro or prison sentences may be imposed. Prohibitions to perform animal experiments or to keep animals are also possible.

Performance of animal experiments

The guiding principle of essentiality (§ 9 Animal Welfare Act) also influences the performance of the experiments:

- Experiments on animals with "advanced nervous systems" may only be performed when experiments on animals without advanced nervous systems are inadequate.

- Experimental animals must be specially bred. The use of stray dogs and cats is forbidden in Germany and "animal catchers" may not sell animals they have caught to laboratories.

- Experiments on animals taken from nature are only allowed if specifically bred ani-

mals are not available. They require special permission.

- More animals may not be used than necessary.
- Pain, suffering and harm may only be inflicted on the animals to an extent that is inevitable. Anaesthesia of the experimental animals and the obligation to reduce pain have priority.
- Major operations may not be performed more than once on vertebrates.
- If death is expected, the period of suffering must be kept as low as possible.
- Follow-up medical care must be provided by a veterinarian, who can decide after an experiment whether the animal can continue to live without pain and suffering.

Monitoring of the experiment

Effective monitoring of the animal experiment by the authorities is only possible if the experiment is properly documented. For this reason, the details of the experiment must be recorded, including the number of animals and their species. The previous owners of dogs and cats must be given, to protect strays (§ 9a Animal Welfare Act). In addition, § 11a of the Animal Welfare Act lays down that the breeder must record and mark the animals, so that the history of the animals can be followed up to the experiment and beyond.

The internal monitoring is performed by the animal welfare officer, who monitors animal husbandry and is obliged to comment on the submitted applications. In addition, he must provide advice to those participating in the experiments and be active within the institution to further the development and introduction to avoid or restrict animal experiments. When fulfilling his duties, he is not obliged to follow instructions.

In addition to this internal monitoring, institutions in which animal experiments are performed are subject to monitoring by the responsible veterinary offices. Without prior warning, these can inspect documents and take samples. If violations are established, these authorities can give instructions to have these eliminated. These include instructions to cease animal experiments performed without the necessary approval or in contravention of a prohibition in the Animal Welfare Act (§ 16a Animal Welfare Act). Violations of the regulations are regarded as administrative offences, in extreme cases as criminal offences.

Stress during animal experiments

Use of new transplantation procedures

So-called minipigs play an important role in transplantation surgery, in the development of new operative techniques. These two pigs were submitted to a lung transplantation, which they survived without harm. Today, one year after the operation, the animals live in an agricultural unit and are given regular follow-up controls.

According to current scientific knowledge, the sensitivity of vertebrates to pain is similar to that of man. The closer the evolutionary relationship is to man, the more reliable is the assumption that the animals not only perceive pain, but also suffer subjectively. The legislator recognises this by demanding an evaluation of the consequences for the animal during the approval of an animal experiment. In accordance with the general rules on the Animal Welfare Act, the stress is classified into four degrees (none, slight, moderate and considerable). To facilitate the evaluation of this stress, the DFG and the Max Planck Society have performed a classification of conventional operations and procedures. This was based on the categories suggested by H. P. Schnappauf („Kriterien für die Beurteilung des unerlässlichen Maßes bei Eingriffen und Behandlungen im Rahmen der Hochschulforschung“ [“Categories for the evaluation of the inevitable extent in operations and procedures in university research”], Tierärztl. Umschau 39, 1984; 870-879). Procedures were regarded as being of low stress if they could be performed in man without anaesthesia or protective measures. These include, for example, injections and short term fixation of the animals. Measures causing intermediate or moderate stress were those which humans would judge as unpleasant, but not damaging to tissue. This also includes operations under anaesthesia which lead to low consequent stress, such as laying an in-dwelling catheter. Considerable stress was split into two subclasses. The stress is high when pain requiring analgesia can be expected after the operation. The stress is very high when the resulting pain cannot be eliminated. Both the duration and frequency of repetition of the procedures must be considered in the evaluation.

Correct evaluation of the stress to which an experimental animal is exposed assumes familiarity with its species-specific facial expressions and behavioural characteristics, particularly in experimental situations. There are however no international standards to assess this. It is recommended that evaluation of pain to rodents should be based on the FELASA report “Pain and distress in laboratory rodents and lagomorphs” (Laboratory Animals 28,1994; 97-112).

In some animal experiments, the animal serves as a model for specific clinical presentations in man. Such experiments are of particular significance in biomedical research, although they may result in the animals experiencing pain or suffering. For reasons of animal protection, the expected states of pain and fear are alleviated with the help of analgesics or sedatives. Experiments coupled to high stress are usually performed under total anaesthesia. These are often so-called final experiments, in which the animals remain under anaesthesia and are killed under anaesthesia after the tests have been completed.

The criticism is often made that possible fluctuations in stress within the experiment are not allowed for and that the emotional state of the individual animal is not considered. However, intense stress or states of fear influence all organic functions and affect the results of the study. Results from experiments with frightened or suffering animals are scientifically worthless and are not accepted internationally in basic research. To

obtain reliable experimental results, it is essential that the experimental animals are in a normal physiological state and are free of pain and fear, if possible. Scientific interests and animal welfare are therefore not in opposition.

Who is allowed to perform animal experiments?

The most important guarantee that animal experiments are properly performed is that the scientist and his personnel are well trained, cautious and sensitive to the needs of the animals. According to the German Animal Welfare Act, animal experiments may only be performed by persons with the requisite knowledge. These are persons with a university degree in veterinary medicine, medicine or natural sciences, or persons with specific professional training, such as specially trained biology technicians or laboratory animal keepers, who have been individually examined. There are additional severe restrictions on the persons who may perform operations. These may only be performed by veterinary surgeons, doctors or biologists specialising in zoology. They must be employed in scientific institutions. Specific exceptions may only be approved after professional qualifications have been examined.

How is the training performed?

Available training in working with experimental animals differs greatly in different universities. There are no current binding training plans for the different federal states. Students are generally provided with the necessary training during advanced practical courses and lectures at the university or in courses presented by scientific societies. The training can be orientated on the recommendations of the Council of Europe for the training, further training and postgraduate training of persons engaged in work with experimental animals. These recommendations are based on suggestions from the international professional organisation FELASA (Federation of European Laboratory Animal Science Asso-ciations, London). Up to 80 hours of comprehensive advanced training (for study managers) are recommended, depending on individual responsibility.

The DFG recommends that training offers of this sort should be taken up and can accordingly provide financial support for postgraduate training for young scientists. For example, the Centre for Animal Welfare in Hanover University and the Animal Protection Information Centre in Munich University regularly offer supraregional training courses at their own initiative.

Summary

Responsibility to animals and man

Discussion in society on the pros and contras of animal experiments is often very emotional. The spectrum ranges from general rejection through the large group of people who accept a restricted number of animal experiments, to advocacy. The differences in views become particularly obvious when changes in the Animal Welfare Act or in the constitution are being discussed. As research bears responsibility towards society, it must analyse and discuss these different positions. Animal experiments on risk evaluation of pharmacological and chemical substances are prescribed by national and international law. The scientist can act as an advisor here. The demand for reducing the number of animal experiments has already led to a marked reduction in animal numbers in this area. Alternative procedures for testing toxic substances have been developed by basic researchers and have made great progress. However, advocacy of the international acceptance of these methods and their validation with accepted procedures is not only a matter of science, but mainly of politics and society.

Numerous scientific insights have been won with the help of animal experiments. The methods used by researchers to approach biomedical principles do not only include studies on the whole organism - the classical animal experiment - but also studies on lower organisms, such as round worms, or cell cultures, as so-called alternative methods. Each of these approaches has advantages and disadvantages. For example, complex problems, such as metabolic performance, behaviour or sensory processing can only be clarified in animal experiments. On the other hand, cell cultures permit detailed studies on strictly isolated and defined systems. The overall performance of the organism can however not be recorded. The decision as to which procedure is most suitable for clarifying a specific problem must be made when approaching the experiment. It is not in the interest of science to perform animal experiments when more suitable methods are available which could reduce or eliminate the use of animals. Science in general has accepted the principle of the three Rs (reduction, refinement, replacement).

Experimental animal research is regulated by the Animal Welfare Act and the corresponding rules - to an extent hardly seen in other areas of animal husbandry or use. Research with experimental animals is accompanied and monitored by the Animal Protection Committee, animal safety officers and veterinary offices. Approval or rejection of animal experiments is accompanied by ethical consideration. This attempts to consider both the animals' concerns and the solidarity principle - the moral responsibility of humans for each other.

Squirrel monkeys in research in tropical medicine

Monkeys are only rarely used in animal experiments in Germany. They make up only 0.08% of experimental animals. For example, squirrel monkeys are used in research on malaria and on sleeping sickness.

The DFG Senate Commission on Animal Protection and Experimentation

It is a central concern of the Senate Commission on Animal Protection and Experimentation to issue comments on themes related to the use of animals in scientific work and to fulfil the commission of the DFG to advise and inform politicians and the public on themes relevant to research. In recent years, the Commission has followed the changes in national and international law and accompanied their implementation in Germany. Members of the Commission are active as experts in bodies dealing with animal protection and research with experimental animals. These include the Animal Protection Committee of the Federal Ministry of Food, Agriculture and Consumer Protection, the National Ethics Council, the European Science Foundation and the Board of Trustees of the Foundation for the Promotion of Research on Replacement and Complementary Methods to Reduce Animal Testing.

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ISBN 978-3-932306-87-7