

The Senate Commission on Animal Protection and Experimentation

Animal Experimentation in Research



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Foreword

Animal experiments are essential to basic biological and medical research – creating a classic dilemma as the acquisition of knowledge for the good of mankind places a burden on animals. The protection of animals is high on the agenda of most European countries and sets limits on research. In 2010, following long and controversial discussions, the European Parliament adopted a EU directive on the protection of animals used for scientific purposes. This directive provides new and more stringent regulations in many aspects, while also setting uniformly high standards across Europe for the approval of animal experiments and the accommodation and care of animals used for research purposes.

The first edition of *Animal Experiments in Research* was first published in 2004 by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). Both the German-language and the English version are no longer available. The amendment to the German Animal Welfare Act in 2013 to bring it in line with the EU directive resulted in a number of changes to the approval process, placing a greater administrative burden on applicants than before. With this revised edition, we aim to present an overview of the current legal requirements, including practical information regarding the organisational processes for the application and the performance of tests on animals, as well as explain the legal and ethical principles of research using animal experimentation. In addition to the brochure, the DFG website offers further information – scientific papers, legal texts, application forms, etc. – which can be accessed under www.dfg.de/tierschutz (available only in German).

In our society, discussions around animal experiments are controversial and often very emotional, not least because of the absence of factual information about the purpose of the experiments, the burden they place on the animals, or the results and potential benefits. Within the framework of the Basel Declaration, scientists have committed to engage in more communication with the public and to provide people with more information. This brochure therefore also intends to inform the interested public about the scope and need for animal testing. On the basis of specific examples and explanations of scientific methods, we endeavour to explain the principles of experimental animal research and thereby provide a contribution to a more objective debate on the topic.

The brochure is the result of cooperation between members of the DFG Senate Commission on Animal Protection and Experimentation and the DFG Head Office in Bonn. At this point, I wish to thank everyone who has contributed to the completion of the project by submitting texts and engaging in critical discussions.

I hope that you will find it an illuminating read!



Gerhard Heldmaier
Chairperson of the Senate Commission on Animal Protection and
Experimentation of the DFG



Introduction

The analysis of the hereditary information (DNA) of complex animals – such as the fruit fly *Drosophila melanogaster*, the mouse, rat, pig, cow or the human being – is one of the most important scientific achievements of recent years. Great progress also has been made in other areas of the life sciences, including new insights into the structure of ribosomes (the protein factories of body cells) and into the astonishing plasticity of stem cells. These findings provide new insights into the complexity of vital processes, improve medical care and nutrition for human beings and animals in the long run, and thereby contribute to an increase in the quality of life and life expectancy.

Considerable progress is however not conceivable without the use of animals in research. Only with the help of animal experiments has it been possible to understand human and animal life processes. This includes the function of sensory organs and of the nervous, hormonal and immune systems, as well as that of individual genes, which can only be decoded within the context of the total organism. For research of such complex processes in the intact living organism, animal testing will also be necessary in future.

There have always been opponents to animal testing. Now as well as in the past, opponents have accused re-

searchers of viewing human beings as superior to animals. Another critique states that results from animal experiments are not transferable to human beings and that animals are made to suffer solely to satisfy scientific curiosity. From today's perspective, some animal experiments conducted in the early days of animal research do in fact seem cruel, although the same is true of surgical procedures performed on humans. This is mainly due to insufficient surgical techniques and anaesthetic options at the time. The discovery of anaesthesia in the 19th century was a godsend for humans and animals alike, and today, its use in animal testing is obligatory as well as routine.

The criticism of animal testing has led to the formulation of rules governing the use of animals in scientific experiments as early as the 19th century. These have been continuously expanded ever since. The German Animal Welfare Act is one of the most stringent acts worldwide. It ensures that animal tests are conducted only within the confines of socially acceptable norms and are subject to government control. Every animal experiment for biomedical research purposes requires a written application to the competent authority of the relevant state and must contain a detailed justification for the experiment. An animal welfare committee, consisting of

The genetic material of animals contains similar characteristics to the genetic material of humans. This makes e.g. the fruit fly a suitable candidate for research into human life processes and diseases.



specialist researchers as well as representatives from animal protection organisations, advises the authority. The decision on the proposal is informed first and foremost by an evaluation of the indispensability of the experiment. This means that the proposal must contain plausible arguments providing evidence that the scientific goal cannot be attained without the use of animal tests or alternative methods.

In order to safeguard a high bioethical standard within animal experimental research across Europe, the European Parliament in 2010 adopted Directive 2010/63/EU on the protection of ani-

mals used for scientific purposes. The directive stresses three principles that must be met to ensure animal welfare in scientific research. This is referred to as the Three Rs principle: Reduction and Refinement of experimental methods as well as the development of Replacement and complementary methods of animal testing. In addition, the EU directive contains a number of new regulations on the approval and performance of animal tests. In July 2013, the German Animal Welfare Act was revised and adapted to the European directive. Old regulations were retained and supplemented with new specifications.



Experiments with animals: Definition and figures

What is animal experimentation?

The German Animal Welfare Act defines animal experimentation as interventions and manipulations in animals if this is associated with suffering, pain and injury to the animals. This applies to all procedures subjecting animals to stress “equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice” (Article 3, 2010/63/EU). In reality this means that each procedure carried out on animals for scientific purposes must be recorded as an animal experiment and approved by an authority. Approval is required for all vertebrates, cephalopods (e.g. octopuses) and decapods (e.g. lobsters).

As part of the approval process by the competent authority, the reason for the use of animals as well as their living and care conditions are examined. Approval for an animal test is granted only for the purposes expressly specified in the German Animal Welfare Act. This includes basic research, applied research for the prevention, detection and treatment of diseases, quality and efficacy testing of drugs, forensic investigations, environmental protection, promoting animal well-being, improvement of animal housing conditions, conservation of species, as well as education, training and professional development.

The killing of animals for the sole purpose of organ extraction or the production of cells does not constitute animal experimentation. Cells or organs are either examined directly or used to create cell and tissue cultures. Such in vitro cultures can supplement or partially replace experiments on live animals and make it possible to develop alternatives to animal testing. About one-third of all animals used for research purposes is utilised for these in vitro methods.

How many animals are used in research?

The German Ministry of Food and Agriculture and the Federal Statistical Office annually record the total number of all animals used in Germany. In 2014, 2.798 million animals were used for research purposes. Included in this are 2.008 million animals used in animal testing and 789,926 used for organ extraction. The number of animals needed for research purposes corresponds to 0.35% of all 795 million animals used in Germany – this small percentage is essential for gaining knowledge about the natural basis of life and for medical progress. At 788 million, the largest proportion of animals were cattle, pigs, poultry and sheep; these were slaughtered to provide food for human consumption. Another 4 million animals were killed





by hunting. Fishing and pest control also involve the killing of animals, but these are not counted.

Since 2014, animals used for scientific purposes are registered according to a new Europe-wide reporting procedure. Newly introduced was the registration of independently feeding larval forms. The first count showed that 563,000 animal larvae were used

in scientific research. Fish larvae can be very small, so that direct counting is not possible and the number of larvae can only be estimated. This initial figure is not included in the figures published by the German Ministry of Food and Agriculture.

There has been a slight decrease in the overall number of animals used for scientific research in recent years:

in 2013 by approx. 3% (2.997 million) compared to the previous year, and in 2014 by another 6.6% (2.798 million).

What are animals used for in research?

The majority of animals in science are used in basic research (31.1%) and in “translational and applied research” (11.9%). The latter are projects that test basic research findings for medical applications. Basic research and translational and applied research are closely interconnected, and their combined percentages make up the expenditure for medical research (43%). Animal experimentation in medical research is conducted to clarify previously unknown life processes and fundamental biological relationships. In turn, these findings are used to improve diagnostics and treatment of human illnesses and diseases.

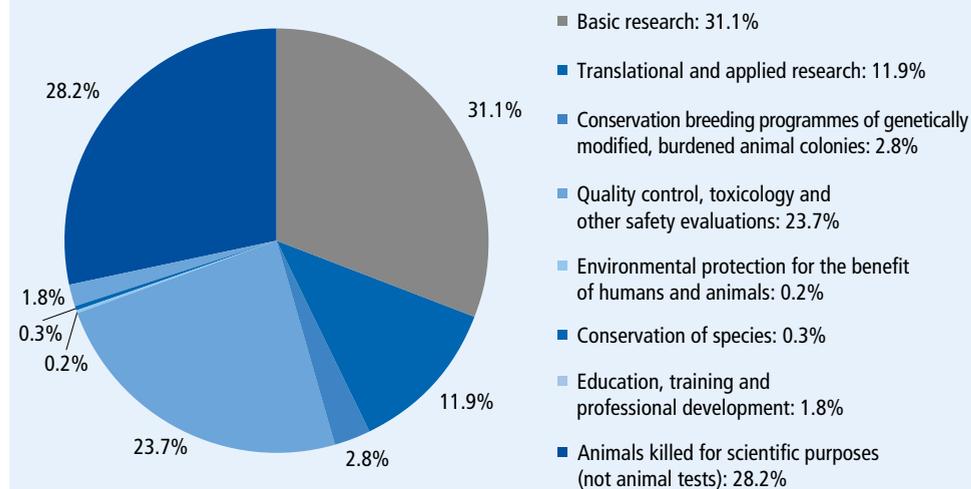
About 28.2% of animals used in research are not exposed to experimental treatments while alive but are put down to gain cells or tissues. These samples are used to examine basic biochemical processes on a cellular level and test new pharmacological treatment methods. Ultimately, this percentage must also be allocated to the cost of medical research.

Numerous animal tests are conducted within the framework of consumer protection and are required by law (so-called “regulatory purposes”). About 23.7% of all test animals in Germany are used for such safety checks, quality controls or toxicological tests in accordance with the legislation on chemicals, medicines and food hygiene. These tests are required for the approval of drugs and other substances with which humans come into contact.

What animal species are used?

Animals used in research are mainly small mammals such as mice, rats, guinea pigs and rabbits; fish and birds are used for specific investigations. Mice (1.901 million in 2014, 68%) and rats (13%) are still the most commonly used animals and are also most often killed for organ extraction. The decoding of the mouse genome a few years ago, and the relatively simple manipulation of this genome from a technical point of view, makes the mouse by far the most important research species as it offers insights into the genetic foundations of life processes and diseases. The slight drop in animal experiment numbers over the last two years is mainly due to a reduction in the number of mice and rats. The use of fish has in-

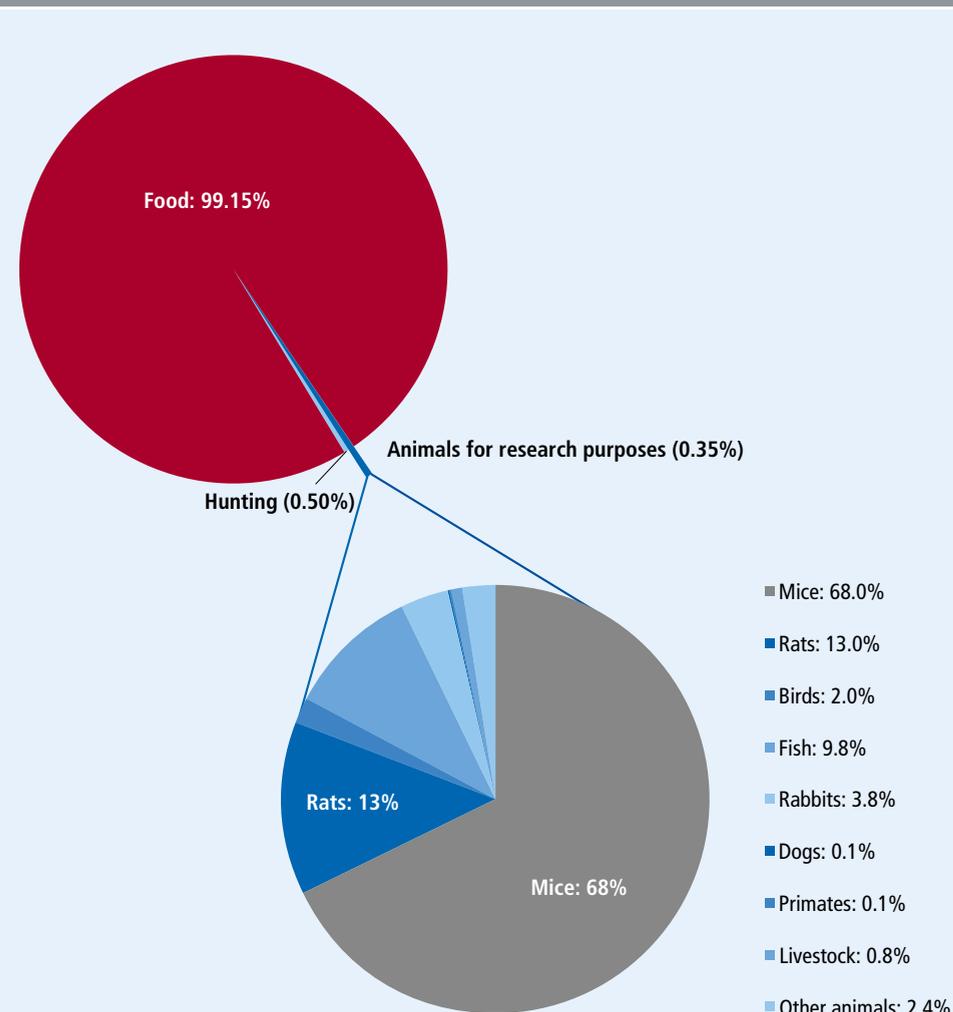
Chart 1:
Percentage of animals used for specific research purposes



Source: Statistics of the German Ministry of Food and Agriculture, 2014



Chart 2:
Animal consumption and animal species used for research purposes



Source: Statistics of the German Ministry of Food and Agriculture, 2014

creased over the last few years (currently 9.8%) as the zebrafish genome was decoded and enabled insights into the origins of the life processes in vertebrates. Other species are used only to a minor extent. Their number may fluctuate slightly, but this has no influence on the overall figures.

Since 1991, experiments on great apes are no longer performed in Germany, and other primates are used only in small numbers. In 2014, the figure was 2,842, which corresponds to about 0.1% of all research animals. The most commonly used monkey species was the long-tail macaque (2,100). In most cases (2,335 animals), primates were used for legally required scientific research, for example in drug testing. Cats played an even smaller role in research (997 animals in 2014), and they too were used mainly for legally required purposes (519).

The use of stray and feral dogs and cats is prohibited in experimental research with animals. They are not suitable for scientific research as their origin, state of health and genetic background, as well as their previous behaviour is unknown. Reliable and reproducible research results can only be achieved under defined and standardised conditions. This applies to the status of test animals as well as all other experimental parameters.

Research on wild animals, however, is possible, but severely restricted and subject to special requirements. To safeguard the protection of species as required by law, additional approval by the relevant nature conservation authorities is required. Wildlife research mainly investigates the behaviour of animals and their interaction with their natural habitats. The findings of such studies are primarily used to protect species. In most cases, the animals are merely being observed and only exposed to low levels of stress so as not to interfere with their natural behaviour.

Developments across Europe

The European Commission also records the number of test animals in order to track the development within Europe. For 2011 – more recent figures were not available at press time – 11.5 million test animals were listed overall. Germany's share in this figure is 2 million animals, because European statistics – in contrast to national records – only count the actual animal experiments and not the killing of animals for organ extraction.

Compared with the last count, there has been a slight increase in the number of test animals in some countries. In most European countries, how-



ever, the number of test animals has remained fairly constant or has fallen slightly, as in France and the UK. Across Europe, mice are also the most commonly used species for animal testing. Their share is 61%, followed by rats, guinea pigs, other rodents, and rabbits. The share of monkeys was 0.05%. Great apes have not been used since 1999. Since 2008, there has been a drop in the number of amphibians (−52%), monkeys (−48%), birds (−26.5%) and rodents (excluding mice) (−19.9%), whereas the recorded numbers of fish (+29%), rabbits (+7.5%) and other mammals (+38%) have increased.

At the European level, more than 60% of animals were used for basic research and for the research and development of medical products and devices for human medicine, dentistry, and veterinary medicine. About 19% of all animals were used for tests and checks of medical products and devices. The number of animals used in toxicological evaluations and other safety tests has remained relatively constant over the last few years, at about 9% – despite the introduction in 2006 of the EU's REACH Directive (Registration, Evaluation, Authorisation and Restriction of Chemicals), which stipulates that all chemicals used in larger quantities within the EU require safety information often based on animal studies.

The number of animal tests with amphibians – including the European tree frog – has more than halved across Europe.





Animal experimentation in practice: Areas of use

Basic research

The aim of basic research is to gain knowledge and insights. Basic research has no immediate application but provides the scientific basis for further research and applications. Because of the similarity between humans and animals in terms of their metabolic processes and function of organs, knowledge gained in animal experiments can provide a better understanding of life processes and their disturbances in both humans and animals. Although the transferability of results from basic research to its application cannot be planned and its direct short-term benefit cannot be predicted, scientific and medical breakthroughs are not conceivable without the knowledge gained from basic research.

Animal testing is a necessity and of particular importance where complex relationships between physiological processes and diseases can only be studied on the living organism. This applies in particular to studies on the functioning of the nervous, cardiovascular and immune systems, as well as the action of hormones. Very dynamic developments are currently taking place in the field of genome and stem cell research. It is hoped that new therapeutic approaches can emerge from stem cell research, using cell and tissue replacement to treat heart at-

tacks or neurological conditions such as Parkinson's disease.

Many results in basic research are obtained using cell cultures, because cultured cells develop relatively quickly and homogeneously and can be directly stimulated with hormones or other chemicals. Cell cultures are always artificial systems and provide only limited insight into life processes. Yet they are the only way to directly manipulate and measure biochemical processes in the cell. In cancer research, for example, isolated tumour cells are used to identify the characteristics and causes of cell degeneration. The true nature of cancer, however, becomes apparent only when its development is viewed in connection with other cells and tissues in the body. In order to trace the development of a tumour in the organism and test therapeutic approaches, animal experiments are necessary in which tumour cells are transferred into mice.

The close relationship between cellular basic research and animal testing also plays a central role in research on infectious diseases. It is the only path to understanding how bacteria and viruses infiltrate and attack the animal organism. Insights into the interaction between viruses and their host cells enable the targeted treatment of virus infections such as influenza, herpes or smallpox, and the development of





preventive measures. A visible result of this type of research is the progress made in the area of vaccinations. Only a few years ago was it discovered that papilloma viruses are involved in the development of cervical cancer. Without animal experiments on mice, sheep, horses and goats, this discovery would not have been possible. A vaccine against the viruses was successfully developed. The German virologist Harald zur Hausen was awarded the Nobel Prize in Medicine for this work in 2008.

Basic research projects initially aimed at gaining information about life processes in animals may translate into medical benefits at a later stage. A case in point is the study on the hibernation of marmots and other small mammals. Initially it was assumed that hibernation is triggered by cold temperatures and lack of food, leading to a failure of the temperature-regulating mechanism. The latest studies of ground squirrels, dormice and marmots however show that these animals actively stifle their metabolism and regulate their body temperature to be near freezing, and that breathing and heart rate come to a near standstill. A new way of regulating metabolism was thus discovered that enables mammals to switch from "normal operation" to "low flame". To understand how this switching process works could be lifesaving in the treatment of severe

injuries or in curbing the effects of a heart attack or stroke. Some clinics are already trying to trigger this process by subjecting patients to low temperatures. Transplantation medicine too (see page 25f.) can benefit by increasing the shelf life of organs.

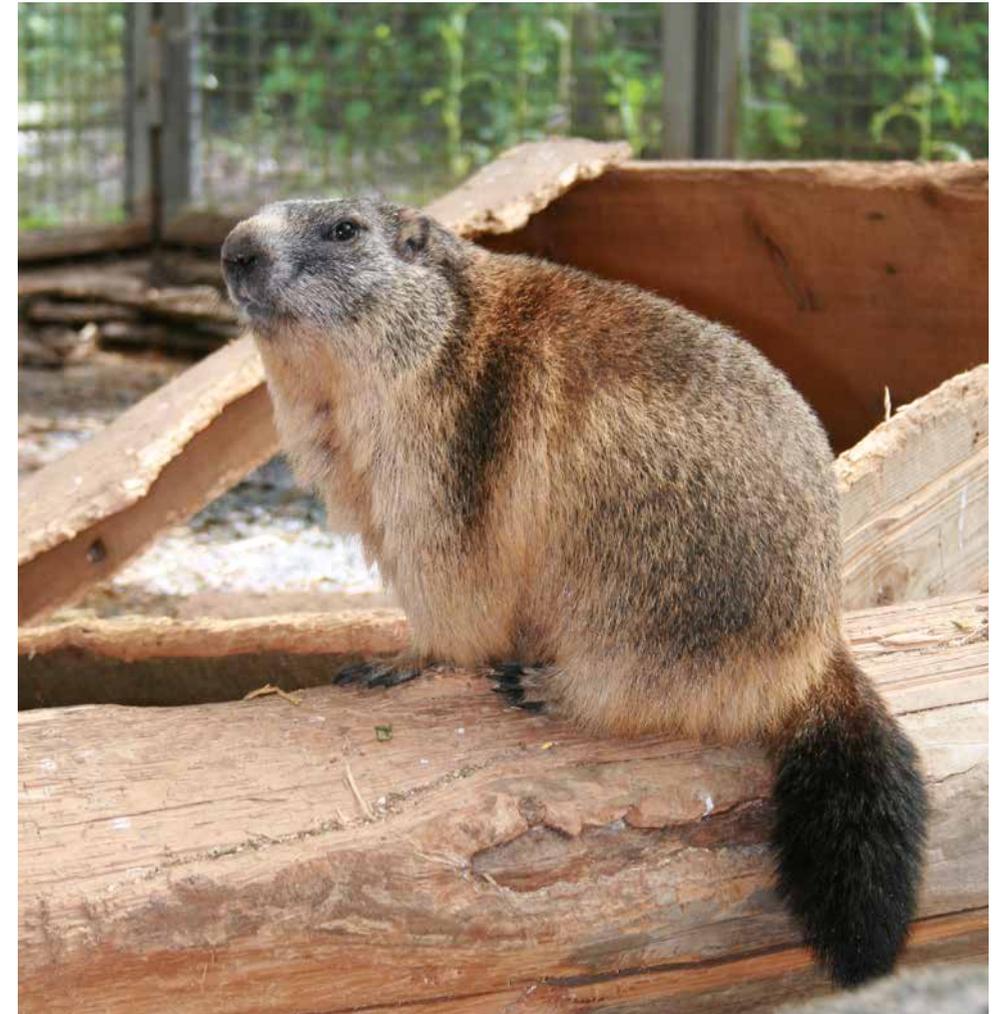
Medical research

Medical progress is inextricably linked with basic research. An example of this is the development of treatment methods for diabetes mellitus. In the 1920s, insulin was identified as a hormone that regulates blood sugar levels. Experiments on rabbits, dogs, pigs and cows helped to understand the effect of insulin on blood sugar levels and thus contributed to the development of new therapies. In 1923, the Canadian scientists Frederick Banting and John J. R. Macleod were awarded the Nobel Prize for their discovery of insulin. Rabbits, dogs and other mammals have been largely replaced by rats and mice in physiological research. The rapid reproduction of these species permitted specific breeding for individual clinical presentations. This includes, for example, the "diabetes mouse" with raised blood sugar levels and the "Zucker rat" that develops obesity.

Immunology provides numerous examples of the utilization of findings from animal experimentation for



Marmots reduce their body functions to a minimum during hibernation. A better understanding of this process could be conducive to saving the lives of seriously injured people.



therapeutic applications in humans. Among other topics, immunology examines resistance to pathogens and the rejection of transplants after implantation. Pioneering advances in

medicine include the development of the antiserum to diphtheria (in which experiments with guinea pigs were instrumental), vaccines against yellow fever and polio (mouse and monkey),



studies on the pathogenesis of tuberculosis (sheep and cattle), typhus (mouse, rat and monkey), malaria (dove), as well as antiretroviral agents to combat AIDS (monkey).

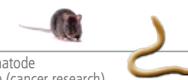
The discovery of the effects of vitamin C was studied in the guinea pig and led to the insight that the effect of vitamins is the same in animals as in humans. Hormones such as calcitonin from salmon are used in the medical treatment of osteoporosis. Animal experiments have led to the development of new surgical techniques and to the refinement of operating methods. The first experiments on tissue transplantation were performed in the mouse as early as the start of the 20th century. These days, animal models (mainly pigs, but also dogs and sheep) are used for kidney transplantation, bone marrow transfer and heart surgery, to develop new methods for the cure or alleviation of organ diseases in humans. Artificial replacement organs, having first been subjected to standardised technical checks, are tested for their biological compatibility in large animals such as pigs.

Nobel Prize worthy: Outstanding scientific findings

Since the beginning of the 20th century, extraordinary achievements in the area of physiology and medicine

have been awarded the Nobel Prize. The first Nobel Prize went to the physiologist Emil von Behring in 1901 for his work on the treatment of diphtheria. At the end of the 19th century, nearly every second child died from the disease. In 1890, von Behring and his Japanese colleague Kitasato found that injecting low doses of the diphtheria toxin triggered the formation of antibodies in rats, mice and rabbits. The animals were then protected for life. Injecting the serum of immunised animals also prevented the outbreak of the disease in other animals. Von Behring thus discovered one of the basic principles of immunology – immunity – and paved the way for the development of vaccinations.

The immense importance of animal experiments in biomedical research and the resulting knowledge gain for medicine is revealed by the fact that the Nobel Prize in Medicine and Physiology (with one exception, i.e. Barbara McClintock for her studies in the area of plant genetics) in the last 40 years has always been awarded to scientists whose studies included the use of animals (see timeline at the top of the page). Outstanding scientific findings that have been awarded the Nobel Prize in Physics or Chemistry have also made substantial contributions to progress. Two chemists, Robert Lefkowitz and Brian Kobilk, received the award for their research on an important class



Emil von Behring was the first person to be awarded the Nobel Prize in Medicine in 1901. His serum therapy, which was tested on animals, is the basis for vaccinations today.



of receptor proteins in the cell envelope of vertebrates, which plays an important function in various physiological processes. In 2008, Osamu Shimomura, Martin Chalfie and Roger Y. Tsien were awarded the prize for the discovery of the green fluorescent protein (GFP) in the bioluminescent jellyfish *Aequorea victoria*. This protein and several different variants are now used as universal molecular markers in biological and

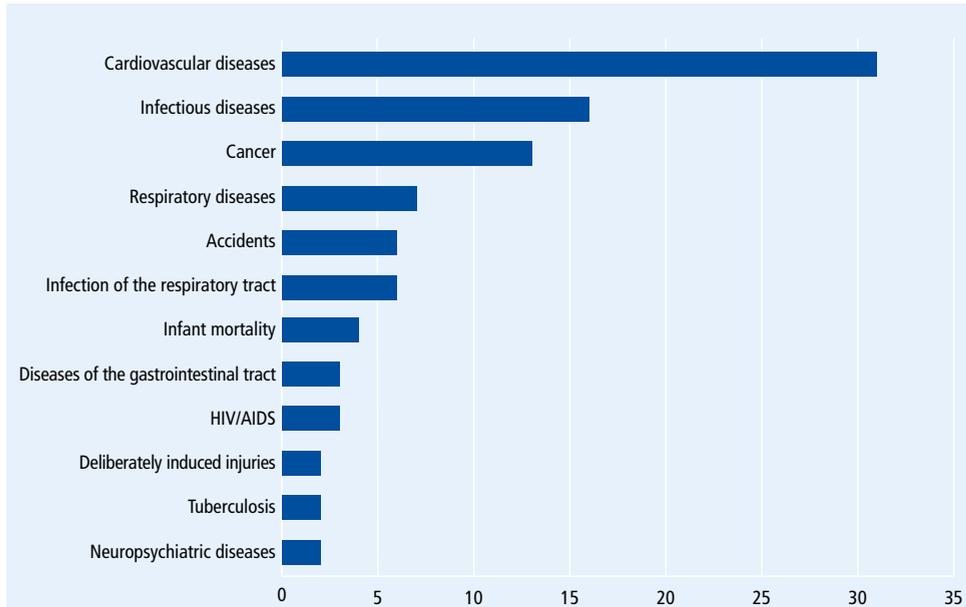
medical research, and enable microscopical analysis of cellular processes that underlie the physiological functions of the organism and its diseases.

Diagnostics

In countries of the Western world, better hygiene conditions and medical care have led to a decrease in neo-



Chart 3:
The most common causes of death worldwide in percent



Source: Berlin Institute for Population and Development (Berlin-Institut für Bevölkerung und Entwicklung): S. Kröhnert, M. Karsch; Lebensspanne und Todesursachen früher und heute (Past and present life-spans and causes of death) (current as of 2013 on the basis of WHO data, 2008)

natal mortality and increased life expectancy. Despite this progress, many diseases can only be treated symptomatically as their development has not yet been adequately researched. Accordingly, society continues to have high expectations of future medical advances and medical care.

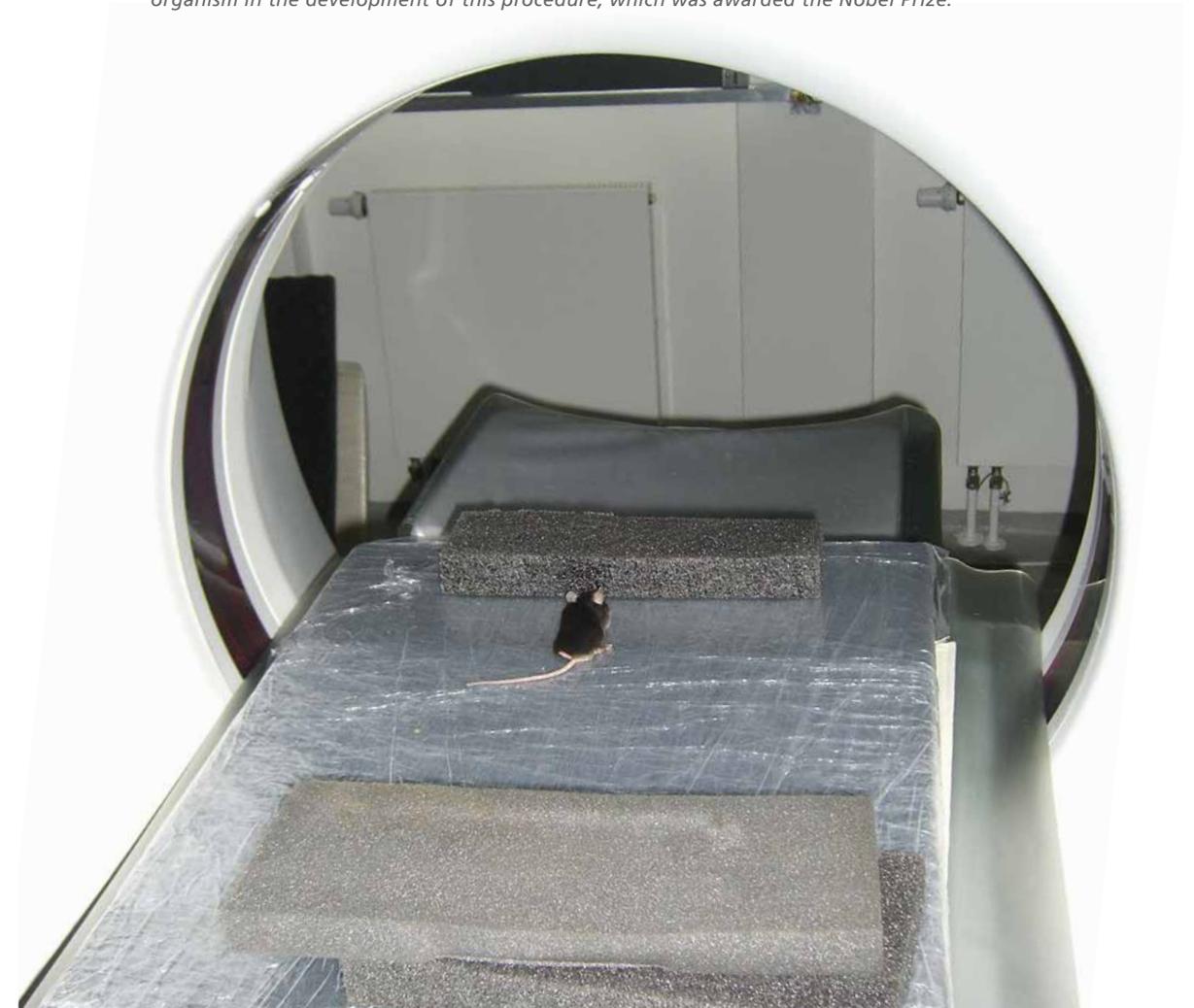
The successful treatment of many diseases depends on early diagnosis.

Refinement and improvement of diagnostic processes is therefore one of the focal points in research. Non-invasive examination techniques such as computer tomography (CT), positron emission tomography (PET), magnetic resonance tomography (MRT) and functional MRT (fMRT), as well as the development of contrast agents and biomarkers (indicators of abnormal processes) open up

new diagnostic options. In 1979, the American Allan M. Cormack and the Englishman Godfrey N. Hounsfield were awarded the Nobel Prize for developing computer tomography. They mainly used pig models in their studies.

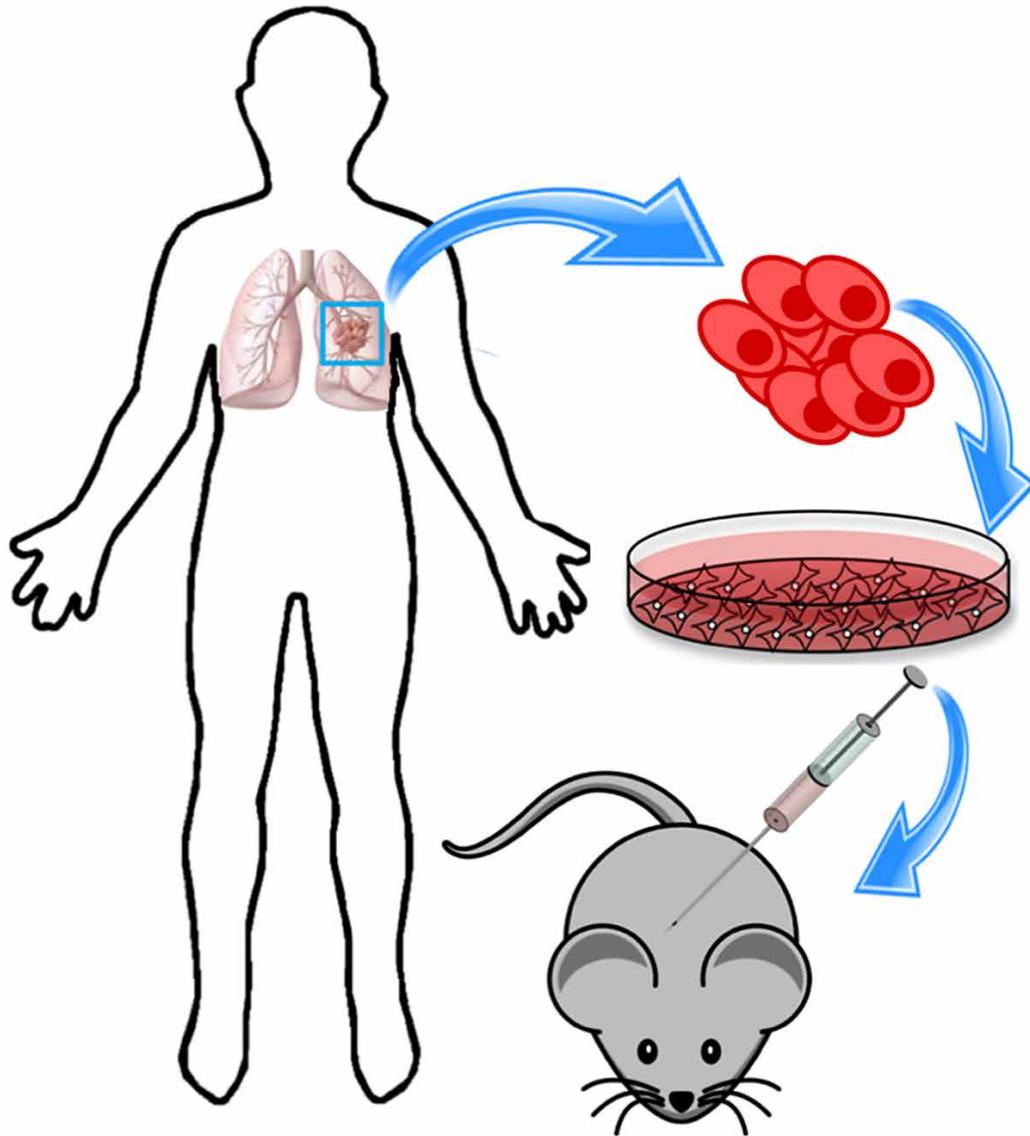
In veterinary medicine, these highly sensitive diagnostic procedures are of particular benefit to cats and dogs. Experience in human medicine with ultrasound diagnostics, X-rays and other imaging methods is also leveraged in modern veterinary medicine.

Computer tomography (CT) provides sectional images of the body. The pig was used as the model organism in the development of this procedure, which was awarded the Nobel Prize.





In xenotransplantation, cells or organs are transplanted from one animal species to another. At present, cancer cells in particular are inoculated into nude mice for research purposes.



Transplantation medicine

In 2014, 3,169 organ transplantations were performed in Germany. At the same time, 11,000 gravely ill patients were waiting for a life-saving donor organ. The surgical techniques and all procedures to avoid rejection reactions were mostly developed in animal experiments after years of research. Of great importance for organ transplantation are new findings on immunosuppression, i.e. methods for suppressing immune reactions against donated organs to minimise complications in organ recipients.

New ways of replacing organs are being studied because the number of donor organs is not sufficient. Xenotransplantation (from the Greek *xenos* = foreign), i.e. the transplantation of organs from one animal species to another, or from an animal to a human, occupies a special position in transplantation research. It could alleviate the shortage of donor organs. The research aims to identify species whose organs are suitable for transplantation due to shared biomedical or physiological properties. For anatomical and physiological reasons, the domestic pig is currently regarded as the most promising organ donor for humans. Animal experimentation is therefore an important interface to livestock research. While the transplantation of whole animal organs has

not been possible until now, transplantations of organ parts and tissues have produced some very good results, e.g. heart valve transplants of porcine origin.

The possibilities of xenotransplantation are currently controversial, primarily because of ethical considerations and the potential risk of immune rejections. For the future it is hoped that genetically modified animals can be bred whose immune system is even more similar to the human one, thereby reducing the potential for rejection of the transplanted organ. Current research in this area is at a very early stage. An obvious way this technique could be used is already on the horizon: in clinical emergencies where no suitable human donor organ is immediately available.

Cell and tissue replacement in humans

Many of the diseases known today are due to the loss of cells or tissue, or loss of their function. Neuro-degenerative diseases, such as Parkinson's or Alzheimer's disease, as well as arthritis and myocardial infarction, entail the loss of cells and tissue, with major consequences for the patient's quality of life. Drug treatment, surgical correction and implantation of skin or nerve cells, or of heart valves, artificial



hearts, heart pacemakers or artificial joints, are all procedures that were developed with the help of animal experimentation. Artificial cultivation of replacement tissue from the patient's own body, known as "tissue engineering", might be used in the future to replace damaged cells or organs with "material" from the patient's own body.

Stem cells have already been successfully used in bone marrow transplants. This approach offers the possibility of allowing some types of tissue to regrow. Moreover, in the so-called "biohybrid implants", the body's own cell structures and functions are combined with electronic or mechanical implants.

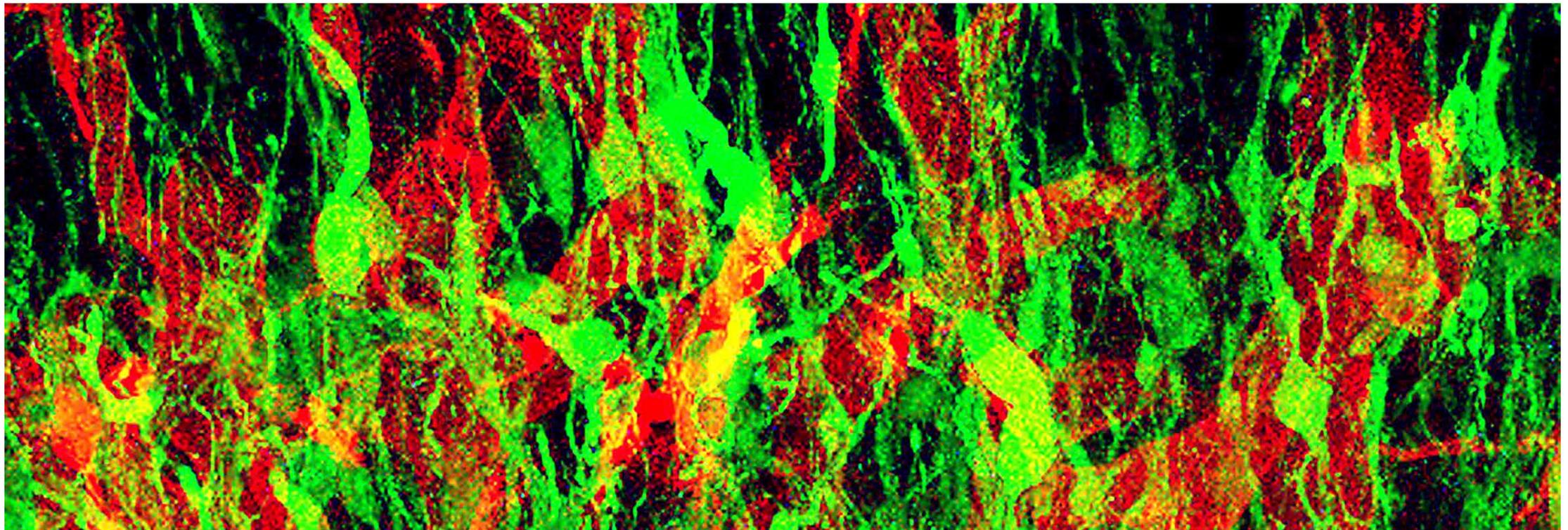
Stem cells have great potential in medicine as they provide fresh cell material that can be used to remedy diseases that have been difficult or impossible to treat up to now.

Stem cell research

The aim of stem cell research is to decipher the principles of cell differentiation and to discover the possibilities of how to control it. Stem cells are cells which are still largely capable of dividing and developing and have the ability to develop into specialised cells, tissues and organs.

There are different types of stem cells. Embryonic stem cells are cellular all-

rounders and have the ability to develop into any type of cell. They are referred to as "pluripotent", meaning that any organ or tissue of a mammal can be developed from this type of cell. In adult organs such as bone marrow, skin, or central nervous system, adult stem cells can repair the damage in the organism. These are referred to as "multipotent" as they only produce cells from an individual organ or tissue. Foetal stem cells are a mixture of embryonic and adult





stem cells that are no longer fully adaptable, but grow faster and better instead. In 2012, the stem cell studies performed by the Japanese Shinya Yamanaka and British John Gurdon were awarded the Nobel Prize. They discovered how mature, differentiated cells can be reprogrammed into stem cells, which in turn can produce various types of tissue. Their insights into induced pluripotent stem cells (iPS cells) were based on experiments with mice.

Animal experiments in stem cell research pave the way for new therapeutic approaches to currently incurable diseases such as Parkinson's, Alzheimer's and diabetes. In cancer therapy, insights into the differentiation processes in cells have contributed to the understanding of the mechanisms involved in the creation and division of cancerous cells. The medical application of cell and tissue replacement by stem cells has already been tested on animals. Adult stem cells from the pancreas, liver and bone marrow could be successfully reprogrammed into insulin-producing cells and were able to alleviate type 1 diabetes symptoms in mice. The transplantation of muscle stem cells in mice not only led to the repair of damaged tissue in mice but also stimulated new muscle growth. 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.

Genome research

Genome research investigates the genetic make-up of living organisms. This involves not only the genetic code – the sequence of nucleic-acid building blocks in DNA – but, more importantly, the function of the genes, as these hold the key to the arrangement and structure of the body and to the interactions between different organs. To be able to analyse these interactions in a complex organism, it is necessary to induce specific changes in the genetic material, i.e. the genome, by means of animal experiments. Effects on the “phenotype” of an animal – its appearance, behaviour, organ function or blood count – enable conclusions about the genetic basis for these changes.

Genome research uses both genetically modified animals (transgenic animals) as well as animals exhibiting spontaneous changes to the genome (mutations) that are the result of natural changes or produced by breeding. Genetic modification of flies, round worms, zebrafish, mice, rats and even large animals such as pigs is now possible. The mouse is especially important in research on human dis-

eases, as the mouse genome and the human genome exhibit major similarities. Both the human and the mouse genome have now been fully decoded. Today, a variety of genetically modified mouse strains exist that can be used as model systems for studying human diseases.

The German Animal Welfare Act demands that, before genetically modi-

fied animals are produced, there must be an ethical evaluation and consideration of the stress for the parent animals and subsequent generations. This is irrespective of whether the animals are produced by technical manipulation or solely by breeding a new line. Operations, such as the transfer of egg cells to surrogate mothers or cutting the spermatic ducts in male animals, are

*The Californian lumpfish (*Aplysia californica*) is an important test model in the field of neurology due to its exceptionally large neurons and manageable nervous system. The Nobel Prize winner Eric Kandel used its synapses to study learning at cellular level, among other things.*

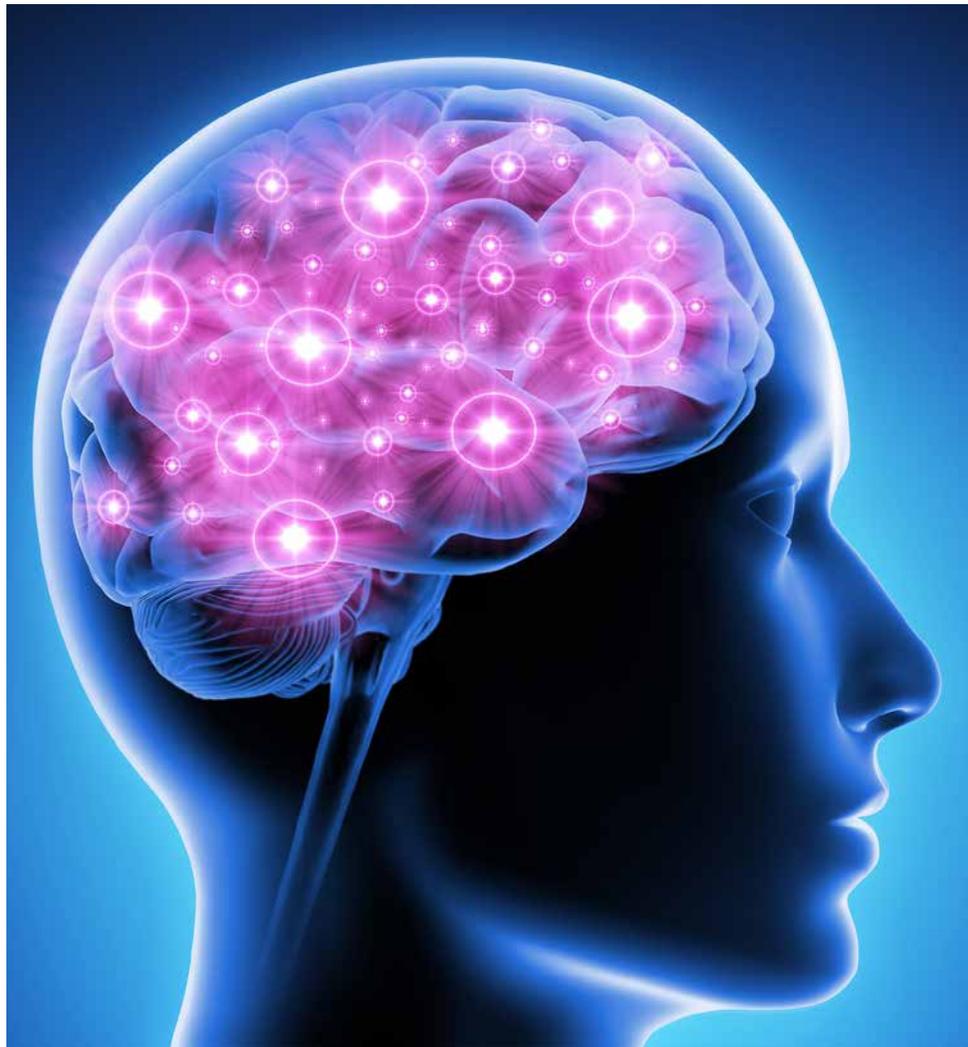




performed under anaesthesia with subsequent pain management and are associated with medium levels of stress in the individual animals. The degree of stress in the offspring is often not predictable and can vary

from slight to severe. Embryonic development can be so severely disturbed that the embryos or foetuses die before birth. However, experience has shown that the appearance of transgenic animals is often hardly

Complex scientific questions such as brain processes can only be studied on the intact and living organism.



different – if at all – from that of the wild type. Evidently the functional impairment of a gene is compensated by other genetic, biochemical or physiological processes, so that deviations can only be detected upon more detailed analysis.

Recently, genome research with pigs is also gaining in importance. It is now possible to specifically modify the genome of an individual oocyte and consequently breed animals that can be used for studies on the genetic principles of diseases, for example in research on degenerative muscular disorders. Another objective is to alter the immune system of pigs so that they can produce replacement organs for human use.

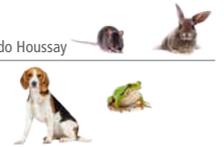
Neuroscience

Neuroscience investigates the structure and function of the peripheral and central nervous system. Their principal focus is the question how nerve cells communicate with each other and how they are connected, in order to gain a better understanding of the highly complex processing of sensory information, the control and coordination of behaviour, and the processes of thinking and feeling.

In 2000, the researchers Eric Kandel, Paul Greengard and Arvid Carl-

son were awarded the Nobel Prize in Medicine for their discoveries regarding signal transduction in the nervous system of mice, rats, rabbits, guinea pigs and marine gastropods. In 2013, James E. Rothman, Randy W. Schekman and Thomas C. Südhof were awarded the Nobel Prize for their discoveries of the transport processes within a nerve cell and their significance for the transmission of signals between nerve cells. They employed rats, hamsters and genetically modified mice in their research. In 2014, John O'Keefe and the married couple Moser were awarded the Nobel Prize in Medicine and Physiology for their research on spatial orientation in mammals. They were able to identify specialised brain cells, the so-called place and grid cells, responsible for spatial orientation, and could verify their interaction. The network of grid cells and their spatial organisation is similar to a 3D coordinate system, and enables orientation and navigation in time and space. These studies were performed using rats. Further studies confirm that comparable structures of the biological orientation system exist in other species, such as mice, bats and primates, and also in humans.

Currently, studies on the functioning of the nervous system and the brain are being intensively pursued. The US is investing in large-scale re-



search projects such as the Brain Activity Map Project (BRAIN initiative) while Europe is spending billions on brain research with the Human Brain Project. Only greater insight into the basic functions of nerve cells will enable researchers to understand what causes diseases of the nervous system and to develop treatment methods for stroke, Alzheimer's and Parkinson's disease, multiple sclerosis, epilepsy, depression, schizophrenia, anxiety disorders and paraplegia.

A substantial number of therapeutic approaches are based on knowledge gained from animal experiments. For example, stem cell transplantations into the brain of mice, which were previously genetically modified or subjected to chemical substances producing pathologies similar to human diseases such as Parkinson's disease, multiple sclerosis or stroke, led to improvements in the general condition and the disappearance of typical symptoms. Chip-based retina implants providing basal vision to the blind, or cochlear implants for the deaf, are based on scientific experiments with chickens, rabbits, cats, pigs and non-human primates. Deep brain stimulation combines neurosurgical and electrophysiological approaches, which were mainly developed on the basis of non-human primate models. It is now used successfully in patients with Parkinson's

disease and its concomitant movement disorders.

Knowledge gained from animal experiments is also used in the development of prosthetic devices and the treatment of paralysis. For example, using electrical stimulation of the spinal nerves, non-human primates suffering from paralysis of their limbs due to spinal cord injury were able again to move their hand and grasp objects. Nerve conduction could be partially restored in paraplegic rats by transplanting embryonic stem cells into their spinal cord. However, the molecular and cellular processes involved are not yet understood well enough to be applied to humans. In the same vein, there are promising initial approaches to using stem cell therapy for the transplantation of specific stem cells into affected areas of the brain.

Veterinary research

The findings from animal experiments are of use not only in human medicine, but also in the development of new diagnostic and therapeutic procedures in veterinary medicine. Certain diseases occur both in animals as well as humans. Among these are arteriosclerosis and congenital deformities of the spine in rabbits, diseases of the visual system in cats, and specific forms

Hygiene is of utmost importance when dealing with animals. Animal keepers and scientists must wear protective clothing when entering animal spaces to prevent the potential risk of infection to the animals.



of cancer, diabetes, ulcers and blood disorders. Dogs with a naturally occurring blood clotting disorder, leading to profuse and life-threatening internal bleeding, can be treated for haemophilia A on the basis of a gene therapy developed for humans, which stops their bleeding in the long term.

Tumour therapy in small animals is another example.

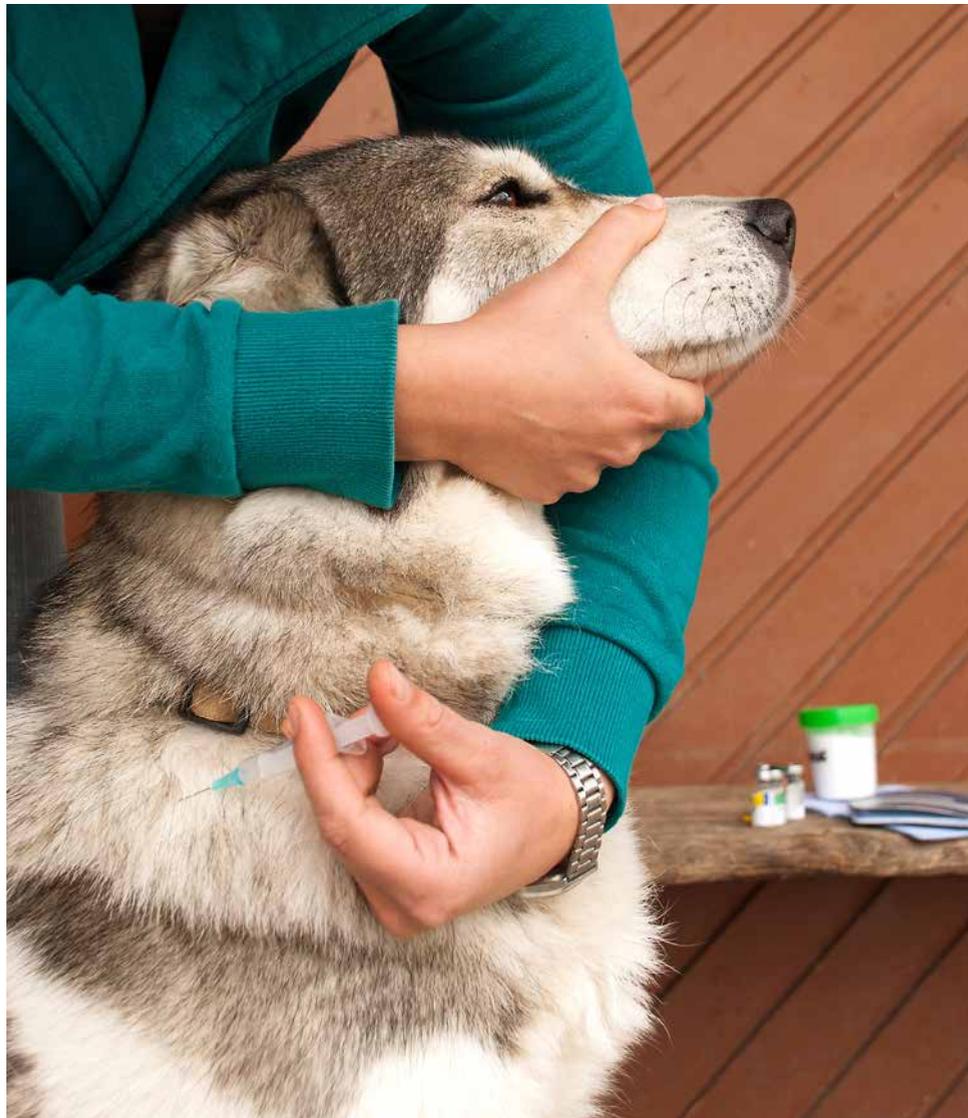
A transfer of treatment methods is generally possible without difficulties, as the methods practised in human medicine were developed in animal experiments. However, veterinary



medicine likewise cannot dispense with the use of experimental animals in basic research and in the development of new treatment methods. The

studies are usually designed such that the target species, i.e. the potential patient, is the subject of the investigation.

Veterinary medicine was able to develop vaccination strategies against fatal diseases such as distemper and leukosis by using test animals.



Vaccination strategies for fatal diseases such as leukosis, distemper and bovine tuberculosis were successfully developed on this basis. Vaccines and veterinary medicines help to reduce livestock losses as a result of diseases. Additionally, these medicines are used in nature preservation projects for the protection of endangered species and especially to prevent the spread of diseases.

Animal experiments in education, training and professional development

Proper handling of experimental animals by researchers and animal keepers needs to be learned. This includes the routine tasks of animal keeping as well as blood sampling, injections and surgical procedures. Careful and comprehensive training of personnel should ensure that any suffering in animals is reduced to a minimum. This is also necessary from a scientific point of view. In order to obtain reliable and reproducible results, stress and pain symptoms must be minimised as much as possible.

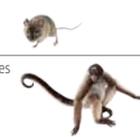
In human medicine, especially in the fields of surgery and anaesthesia, practical training with large animals is an important element of education. Such practical training units,

which are difficult to teach in the context of clinical routine, enable physicians to expand their skills for surgical procedures on humans and to learn new techniques. The German Animal Welfare Act treats the handling of experimental animals as part of a training programme in the same way as animal experimentation, i.e. as subject to application and approval.

The basic assumption of transferability

The components of body cells and the biochemical mechanisms necessary for the processes of life are very similar across different animal species. Molecular genetics can demonstrate that all organisms living today have 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 throughout the geological eras. These similarities even allow comparisons of human genes and metabolic processes with those of bacteria, fungi and yeasts.

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 the resulting compound is toxic to 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 (using alternative methods, see page 51ff.), but also always studies of the complete organism to check both the efficacy and side effects of a substance.

Animal experiments make it possible to predict the desired as well as about 70% of the adverse effects on humans. One example is acetylsalicylic acid (the active substance in the analgesic Aspirin®). It alleviates pain in both rats and humans, but can increase bleeding in both species. Other examples are the effects of building materials and of solvents, which have damaging effects on both rats and humans. Asbestos causes lung cancer in rats and humans, and plastic solvents cause liver cancer in both. From these experiences it can be concluded that safety and efficacy tests on animals can significantly reduce the risk of new treatment methods for humans. 36% of substances tested in preclinical animal studies

Examples of animals used in research.

Mouse, rat
Cancer research
Metabolic disorders
Efficacy testing of drugs
Genome research

Dog
Transplantation surgery
Osteosynthesis
Emergency surgery
Diabetes research
Cardiovascular diseases
Osteoporosis research
Veterinary research

Non-human primates
Basic and applied research in neurobiology
Vaccine development
SIV/HIV research

Rabbits
Development of vaccines
Efficacy testing of drugs

Cattle, horse, pig
Vaccine development and isolation
Veterinary research

Cat
Heart surgery
Neurophysiological studies
Development of hearing aids
Research on feline leukaemia
Veterinary research

are not used in subsequent clinical tests on humans due to undesirable side effects and safety risks, and are excluded from the development process. Animal experimentation thus prevents the administration of potentially harmful or life-threatening substances to humans.

However, there is no such thing as absolute safety. The Thalidomide catastrophe in the 1960s made this tragically clear. Prior to this event, the potential of a drug to cause developmental malformations was not investigated. It was only after the scandal, in 1978, that the German Drug Law was tightened and the effect on embryonic development was added to the testing catalogue for drug safety and efficacy.

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 as well as the conduction of pain stimuli and their perception in the central nervous system are similar in higher animals. This permits analogies to be drawn regarding pain sensitivity and possibly even the capacity for suffering. The transferability of results from animal to humans thus also applies in the opposite direction. Drugs that have been successfully used to treat humans can also be used for domestic animals.



Animal experimentation and protection of animals: Ethical considerations

Development of the concept of animal protection in Germany

The idea that humans have a special responsibility for animals in their care is the result of the historical development of the relationship between animals and humans. Cultural, philosophical, social and official standards define the framework for our attitudes towards animals and their needs. The animal welfare laws and regulations that are in place today are an expression of this development, which began in the 17th century. Since then, an anthropocentric view of animal protection has been advocated – with man at the centre.

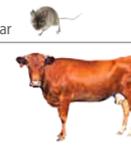
In the 18th and 19th centuries, influential members of a socially and politically active stratum of the population became active. They loathed all forms of cruelty to animals and regarded this attitude as a sign of their level of education. The focus of interest was not the animal, but concerns about the brutalisation of individuals and of society. In Germany, a variety of laws were passed at first, and the Law on the Prevention of Cruelty to Animals was only first included in the German Criminal Code in 1871. This legal harmonisation promoted animal protection as a social goal and led to the formation of numerous societies for animal protection, with the main objective 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. Even back then, people’s reasons for rejecting animal experimentation varied depending on their scientific, religious or societal background.

The first German Animal Welfare Act was passed in the 1930s and remained in force until after the Second World War. For the first time, it laid down regulations for working with laboratory animals. In the 1960s and 1970s, public discussion of the safety of farm and laboratory animals was revived; this encouraged the creation of new laws on animal protection. The Animal Welfare Act adopted in the Federal Republic of Germany in 1972 was based on ethical concepts of animal protection, and exploited scientific findings 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 fellow creatures and strengthened regulation of animal experiments. To enhance the protection of animals as living





creatures in the legal system, animal protection was enshrined in the constitution of the Federal Republic of Germany. In July 2002, the constitution was amended with Article 20a, which reads: “Mindful also of its responsibility toward future generations, the state shall protect the natural foundations of life and animals by legislation and, in accordance with law and justice, by executive and judicial action, all within the framework of the constitutional order.” Ethical treatment of animals has thus been given an unusually high legal status.

Furthermore, the Third Amendment to the Animal Welfare Act was introduced in July 2013, which transposes into national law the Directive 2010/63/EU of the European Parliament and Council of 22 September 2010 on the protection of animals used for scientific purposes. It ensures a higher level of animal protection and raises the minimum standards, taking into consideration the latest scientific findings and developments in keeping with the Three Rs principle (Reduce, Refine, Replace – see pp. 47ff.).

Ethical aspects of animal experimentation and the principle of solidarity

A predominant view within the current ethical discussion on human

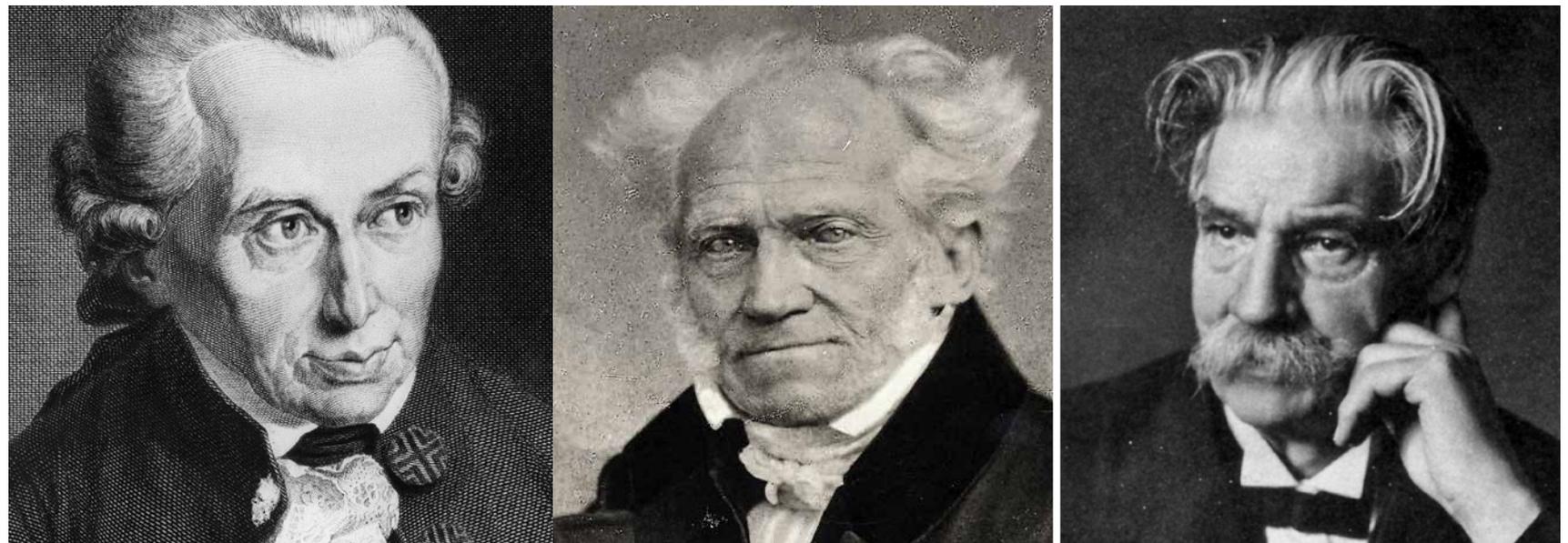
dealings with animals is that humans are vested with the basic moral right to use animals for their own ends. This right, however, is subject to limits where animals are significantly harmed by human actions or are killed without sufficient reason. In the established system of normative positions on animal ethics, this position is classified as “pathocentric”. This means that a living organism’s ability to suffer entails an obligation to protect it. On the other hand, a position is defined as “anthropocentric” if it categorically makes humans “the measure of all things”, including when it comes to the treatment and protection of animals. A third rele-

vant position here is the “biocentric” view, which assigns ethical value to all living organisms, including lower animals and plants. Whilst the extreme versions of these three positions are incompatible with one another, their more moderate forms are generally regarded as reconcilable.

According to the strong variant of anthropocentrism, our treatment of animals should be assessed solely based on human interests, sentiments and feelings. This position has dominated our culture’s philosophical outlook for centuries. Its most prominent advocates were Immanuel Kant and – representing leading Christian moral

theology – Thomas Aquinas. The essential tenet of Kant’s position is that man alone has moral capacity, which results both in prerogatives and obligations. Animal protection is thus ultimately rooted in the self-respect of humans, which forbids acting cruelly.

Immanuel Kant (left) was a follower of anthropocentrism – the belief that humans are the measure of all things but that they have a responsibility to treat animals humanely. According to Arthur Schopenhauer (centre), animals exhibit the same characteristics as humans. This means they are capable of suffering and feeling. Albert Schweitzer (right) represented radical biocentrism, which extends an inherent value to all living things.





However, anthropocentrism was subject to a far-reaching and now generally accepted critique from a pathocentric perspective by Jeremy Bentham and Arthur Schopenhauer. According to Bentham, the point is not whether animals think or speak like humans, but rather whether they can suffer like humans. All sentient beings must be ascribed with intrinsic value.

Biocentrism in turn extends this intrinsic ethical value to all living beings, including lower animals and plants. The most prominent example of this view is Albert Schweitzer's *The Ethics of Reverence for Life*. Many supporters of this view even go so far as to ascribe an equally strong right to life and development to all non-human living beings.

Edward Hicks: *The Peaceable Kingdom* (1846/47).



An ethical system – such as a pathocentric one – that is premised on the position that sentient animals have a moral status alongside humans, occupies a compromise position between the two extremes mentioned above. This compromise ascribes to sentient animals an intermediate moral status that is lower than that of humans, but much higher than that of non-sentient animals and plants.

Patho-inclusive rather than pathocentric: What's the difference?

A pathocentric animal ethics postulates moral obligations towards animals and places the avoidance of suffering at its core. However, it would be incorrect to assert that the avoidance of suffering in its entirety, and therefore also of human suffering, is to be regarded as the most important of all standards. Overall, this approach might more appropriately be classified as a “patho-inclusive” ethics: It is not only reconcilable with valuing human interests over those of sentient animals, but also with the position that other human interests, such as life and health, knowledge gain, and pleasure, may justify causing distress to animals. Moreover, this view does not preclude the killing of animals, but does demand that the killing should not cause fear or suffering, if possible.

Even though patho-inclusive ethics ascribe particular rights to animals, this system is not premised on the assumption that animals possess these rights inherently and independently of their bestowal by man. Rather, the undisputed position amongst animal ethicists of epistemic anthropocentrism – not to be confused with the normative anthropocentrism referred to above – rightly acknowledges that only humans are capable of establishing, understanding and following moral obligations. Even if animals are the subject of human obligation, they depend on the benevolence and the efforts of people to interpret their needs. The obligation not to inflict suffering on humans and to actively relieve it is recognised in all ethical systems. The principal argument for expanding these obligations beyond the sphere of humans is that it is not evident why corresponding obligations should not in principle also apply to sentient animals.

The patho-inclusive position is also the basis for the German Animal Welfare Act. In contrast with older versions, which only afforded animals the amount of protection called for to prevent public nuisances or the potential brutalisation of human beings, the current version protects animals for their own sake. The infliction of suffering is only acceptable where the associated action (such as an animal experiment)



has the potential to protect, secure or realise potential higher values for humans and animals, whilst also being indispensable to that end. This view requires two forms of complex assessment and balancing to justify animal experimentation: a weighing of moral goods, and the determination of indispensability. Both assessments are difficult, but not arbitrary.

Human values such as life and health generally carry a stronger weight than the avoidance of suffering for animals. Moreover, there is also less certainty in relation to animal suffering than there is for human suffering. Since animals cannot help us to interpret their feelings and therefore depend on human empathy, experience and knowledge to determine their welfare, there is a considerable likelihood of error associated with assessing whether an animal suffers and how much. Moreover, individual capacity for suffering will probably differ significantly between animals – as it does between humans. Where there is great uncertainty regarding animal suffering, the “proven” claims of humans take priority from the standpoint of various moral and ethical approaches.

The “indispensability” of inflicting suffering means that no alternative methods are available, that animal experiments are optimised and the suffering of animals is minimised relative to the

scientific, therapeutic or other significance of the experimental objective in accordance with the Three Rs principle (see page 47 ff.). The criterion of suffering capacity thus imposes limits on the experiments that may be performed on sentient animals, although it does not imply any categorical rejection of stressful animal experiments.

Moreover, it may be presumed that only some of the animal experiments carried out are stressful. Keeping cognitively low-developed animals in laboratories, for example, need not be classified as causing suffering in general. In fact, laboratory animals often live longer and are healthier compared to those living in the wild. Furthermore, many laboratory animals are kept in control groups without being subject to procedures, and some are killed for their organs, without having been previously involved in an experiment. In addition, there is also the category of “final animal experiments”. Here, the animals are drugged prior to the start of the experiment and then killed under anaesthesia at the end of the experiment in order to spare them painful experiences.

Patho-inclusive ethics has no fundamental objection against such experiments, provided they are associated with advances in biological or medical knowledge that are expected to benefit humans.

After mice, rats are the most commonly used laboratory animals.



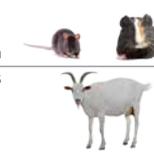
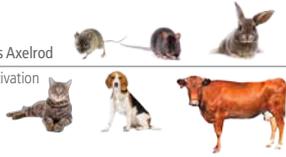
Transferability from an ethical-legal viewpoint

In the public discussion on the ethical evaluation of animal experiments, the direct transferability of findings to humans is often claimed to be a measure of legitimacy. However, this claim underestimates the complexity of transferability. During animal experiments, animal life processes are investigated that can only be indirectly extrapolated to humans. This is also expressed in legislation. Directive 2010/63/EU of the European Parliament and Council of 22 September 2010 on the protec-

tion of animals used for scientific purposes has three aims:

- ▶ to significantly improve the welfare of animals used in scientific experiments,
- ▶ to ensure fair competition within the EU and
- ▶ to strengthen research within the EU.

The transferability of the results from animal experiments to humans is not stipulated in the directive. Instead, it



contains intentions and measures to improve animal welfare and to honour the Three Rs principle. The directive specifies the purposes of the procedures for which animals can be used. These purposes are not restricted to procedures on live animals with results that are transferable to humans. The directive does require an ethical evaluation that weighs the expected harm caused to the animals against the expected benefits. But it leaves open how these benefits are ultimately defined or how soon they should materialise: "... to protect human and animal health and the environment." This unspecific formulation takes into account the experience that it often takes years before discoveries from animal experiments translate into benefits for human and animal health. Requiring immediate benefits for humans is a moral-ethical demand that can hardly ever be fulfilled. Just like humans, animals are extremely complex organisms, but they do differ from humans, despite a few fundamental similarities. These differences are the result of various evolutionary mechanisms which in the past have had an effect on highly complex systems such as animals and humans, and continue to have an effect today via multifactorial mechanisms such as genetic preposition, whilst also being subject to epigenetic and environmental influences. No two peo-

ple are alike and each person is their own ideal model. Human-oriented research is therefore desirable, but it is insufficient.

The conflict between the solidarity principle and animal welfare

Complete prohibition of experimental animal research would also conflict with another valid fundamental moral standard, the solidarity principle. This is the principle of providing the best possible support to the needy, the weak and the sick. The solidarity principle is not only one of the many preconditions for life in human communities; it is a hallmark of human beings to be morally responsible and capable of solidarity.

People who perform animal experiments always experience conflict between two obligations. The first of these is positive: the obligation to use one's knowledge and abilities to reduce human and animal suffering. In contrast, the negative obligation is not to inflict avoidable suffering on other creatures. It is human nature to find it difficult to reach a decision if this means violating one of these obligations in order to meet another. 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. From the standpoint posited here, there will never be a general answer to the question whether an animal experiment is justified – each individual case requires its own answer.

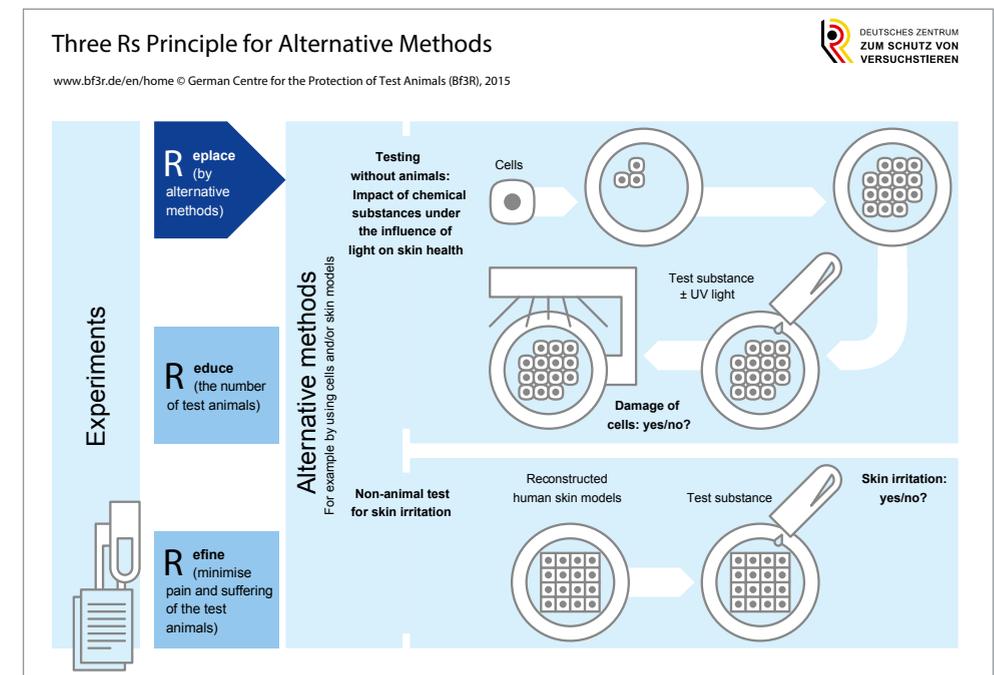
The Three Rs principle

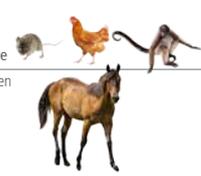
Although animal experimentation cannot be completely avoided in research, there is a general consensus that it must be restricted to the neces-

sary minimum. The Three Rs principle, devised by W. Russell and R. Burch in 1959, can be taken as the guideline for animal experiments. The Three Rs stand for

- ▶ refinement,
- ▶ reduction and
- ▶ replacement.

The aim of the principle is to avoid animal experiments where possible, to reduce their number and to limit





the harm caused to animals during the experiments to the necessary minimum. The consistent and responsible implementation of the Three Rs principle accommodates ethical concerns against the use of animals, and also improves the quality of the test results.

Researchers are challenged time and again to optimise their methods and use objective parameters – such as the animals' behaviour – to estimate the degree of harm caused. This requires both personal sensitivity and good training.

Non-human primates, such as rhesus monkeys, behave similarly to humans. For this reason, the investigation of complex cognitive functions is only possible in these species.

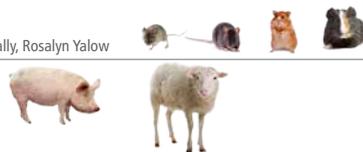


Refinement

The refinement of animal experiments has the objective of minimising the adverse effects of research procedures on animals. An animal's capacity for suffering is central to this assessment. The human obligation to minimise stressful animal experiments must be guided by the extent to which animals are capable of suf-

fering based on their respective level of neuronal development. Particularly important to the gradation of ethically grounded animal protection is the animal's capacity for self-perception. The strongest protection should therefore be given to animals presumed to have the greatest capacity for experience due to their advanced stage of development, such as primates. However, it must also be considered that less developed animals occasionally react to an experimental setup with greater stress than those able to adapt to the stress through training.

By carefully selecting the animal models, alleviating pain using analgesia and anaesthesia, improving the technology used in measurement procedures and developing non-invasive research methods, it has been possible to make great progress in the refinement of animal experiments. Improved animal husbandry conditions, for example thanks to species-specific enrichment of the environment, also help to improve laboratory animals' welfare and give them a greater quality of life. As an example, rodents are provided with nesting materials that help support their thermoregulation, or paper rolls that give them the option to retreat. These improvements are also in the interest of research as they improve the reproducibility of experimental results.



Alternatives to animal testing are encouraged in Germany.



Reduction

Statistical and methodological improvements help to reduce the number of laboratory animals. In addition to carefully selecting suitable animal models and determining the absolutely necessary number of test animals, this entails the consistent application of statistical methods. Even centrally registering and recording results from animal experiments can reduce the need for them.

Replacement

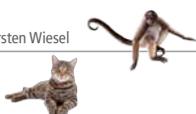
Replacement seeks to substitute animal experiments with alternative methods as much as possible, or to avoid them completely. If the research question permits, simple organisms such as bacteria or invertebrates, cell and tissue cultures, computer models, or other alternative methods will be used.

Alternatives to animal experimentation

Cell lines that have been harvested from animal or human tissue are often used and then bred further in a laboratory culture. These experimental methods outside the organism – known as “in vitro methods” (in vitro = in the test tube) – are of major im-

portance and are widely used, particularly to elucidate cellular processes or the effect of medications on cell metabolism. Significant methodological progress has been made in recent decades in working with in vitro systems. Especially in drug testing and the development of pharmacological substances, they have helped to reduce the use of laboratory animals. However, they cannot completely replace animal experiments as the complexity of the entire organism – i.e. the interaction between organs and tissues – cannot be fully reproduced in these isolated, artificial systems. Furthermore, producing and growing organ and cell cultures requires the killing of animals.

Another method for avoiding experiments on live animals comes from regenerative medicine and is known as “body on a chip”. This method was developed from tissue engineering or bioprinting, whereby replacement organs for humans are grown from human tissue and created using a 3D printer. These mini-organs are placed on a microchip and supported by an artificial maintenance system. Sensors on the microchip measure certain parameters, such as organ temperature and oxygen content, and record changes in the system. The “body on a chip” method is used for testing the toxicity or pharmacological properties of biological and chemical substances.



“In silico methods” (in silico = on a computer) are also becoming increasingly important as alternatives to animal experimentation. These computer-controlled analysis and simulation techniques are used for assessing risk when researching tolerance to substances or theoretically modelling life processes, among other purposes. As a result, experimental data in neurobiology is increasingly being entered in computer models to portray and predict the functions of the central nervous system. Computer simulation is also used in higher education to visualise complex biological relationships. Instructional videos on animal experimentation serve as teaching aids to prepare learners for the work with living animals and promote a responsible approach.

The German Centre for the Protection of Laboratory Animals (Bf3R) is part of the Federal Institute for Risk Assessment in Berlin and coordinates efforts to implement and promote the Three Rs principle across the country. To this end, the Bf3R is divided into several areas of competence that not only assume advisory roles but also conduct research on refinement in animal experimentation and the development of alternative methods. One of these areas is the Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET). Its mission is to record, evaluate and,

where possible, legitimise alternatives to animal experimentation. It is an information centre for alternative methods, and also researches and validates methods not involving animal experimentation in order to promote them. The validation is necessary to obtain 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 (EURL ECVAM) in Rome. The *EURL ECVAM Search Guide: Good Search Practice on Animal Alternatives* also contains numerous information sources on alternative methods and is designed for employees of approval authorities, animal welfare officers and researchers working in animal experimentation. Furthermore, the annex to the European Directive EC 761/2009 and the guidelines issued by the Organisation for Economic Cooperation and Development (OECD) list all officially recognised alternative methods. Within Europe, the following areas no longer require animal testing:

- ▶ acute toxicity
- ▶ eye irritations
- ▶ genotoxicity in mammalian cells
- ▶ acute phototoxicity

The declared aim of research is to reduce the number of laboratory animals and their suffering.



- ▶ skin burns
- ▶ skin irritations
- ▶ skin absorption
- ▶ mutagenic properties
- ▶ properties with hormonal effects.

The Three Rs principle is already widely supported by scientific policy initiatives. As a result, the European Science Foundation (ESF) issued a position paper in 2011 regarding the

EU directive on the protection of animals used for scientific purposes with recommendations for work with experimental animals. In the paper, the ESF calls for recognition of the Three Rs principle and for targeted efforts to reduce and improve animal experiments. The Basel Declaration Society (Basel Declaration, see below), founded in 2011, and its members, as well as the Forum on Animal Experiments in Research, have undertaken to implement the Three Rs principle and other ethical principles wherever animals are used for research

1985

Michael Brown, Joseph Goldstein

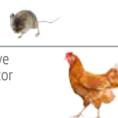
Discoveries on the regulation of cholesterol metabolism



1986

Rita Levi-Montalcini, Stanley Cohen

Isolation and characterisation of the nerve growth factor and epidermal growth factor



1987

Susumu Tonegawa

Discovery of the genetic mechanism that produces antibody diversity



1988

James Black, Gertrude Elion, George Hitchings

Discoveries of important biochemical principles of pharmaceutical therapy



purposes. The forum's statements on refinement and on stress assessment are publicly available.

The Association of Research-Based Pharmaceutical Companies (VfA) in Germany and its member companies also implement the Three Rs principle

Active ingredients can be tested on zebrafish embryos, thereby reducing the number of laboratory animals.

with the aim of reducing the number of laboratory animals and replacing mammals with less developed species. This includes in vitro tests for skin irritation or tests for mutagenic properties of active ingredients using fish embryos, which otherwise would have been performed on rats and rabbits. The methodological development for implementing the Three Rs principle in research is also supported by funding programmes at the

national and state level. Outstanding progress is rewarded with research prizes, such as the DFG's Ursula M. Händel Animal Welfare Prize.

Limitations to alternative methods

In spite of favourable aspects, these alternative methods have a severe disadvantage. The human or animal

body possesses more than 200 different cell types whose interactions are coordinated in organs and tissue structures. To study this complexity is an important part of biological research, and this can only be done on an 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, causing damage in other organs. Conversely, a substance may be inactive in cell culture but effective in an intact organism. For example, without using animals, the synthetic antibiotic Prontosil® would never have been discovered in the 1930s. While Prontosil® showed no effect in the cell culture, it was proven that it has very strong antibacterial properties in a living organism. Gerhard Domagk was awarded the Nobel Prize for this discovery in 1939.

In case of the chronic infectious disease leprosy, it has so far not been possible to cultivate the disease-triggering bacterium *Mycobacterium lepra* in a laboratory. It is assumed that the high ambient temperature in cell cultures limits growth. This means that it is not possible to research this disease in cell cultures. However, the lower body temperature of immunodeficient mice and armadillos favours bacteria growth. For this reason, re-





search into leprosy and possible therapeutic approaches is solely carried out on living animals.

Both in basic research and in application-oriented research, alternative methods and animal experiments are used in a complimentary manner. While individual molecular and cellular aspects of life processes are researched in vitro or in silico as much as possible, scientific work on animals is irreplaceable in order to further our understanding of complex relationships within the entire organism. By carefully considering and selecting the most suitable methods, we have the chance to significantly reduce the number of test animals and the stress caused to them.

The Basel Declaration

The Basel Declaration, adopted in 2010, follows the patho-inclusive approach described above (see pp. 40ff.), which does not prohibit experimental animal research in principle, but seeks to reduce it and make it as gentle as possible on the animals. In line with the Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects (1964), over 2,500 researchers, research institutes and organisations have signed the Basel Declaration so far, and are committed to upholding

standards when handling laboratory animals. Across philosophical views, the signatories hold that animals deserve respect for their own sake and should be kept in a species-appropriate fashion. Not only do they explicitly recognise the Three Rs principle, but they also call for its on-going further development, and for quick and effective implementation of such enhancements. To this end, the basic impetus behind the declaration is regularly substantiated and updated on the Basel Declaration Society's website (www.basel-declaration.org).

To ensure that the commitments of the declaration do not remain empty promises, the signatories have agreed to greater transparency and communication on the purpose and execution of their animal experiments, and thereby hope to build trust among the public and decision-makers. In this spirit, they express their willingness to discuss the sense and purpose of animal experimentation with the public – including critics of experimental animal research. The goals specified on the Basel Declaration Society's website make it clear that this dialogue must not be a one-way street, but rather a mutual exchange. The researchers and their institutions are therefore called upon to be proactive and willing to engage in these discussions, and always be prepared

On the basis of the Basel Declaration, research is committed to greater transparency and communication when it comes to animal experimentation.



to open their laboratories to interested journalists.

The signatories of the Basel Declaration criticise the fact that many human- and veterinary-medicine benefits from experimental animal research are leveraged tacitly, while this research is at the same time constantly being discredited. In this regard, they call on the self-critical public to be more honest and coherent in its attitude and arguments in order to foster mutual dialogue. At the same time, they also signal their willingness to question themselves critically and to make effective pro-

gress – with a view to reducing animal experiments and protecting the animals used.

The limits of dialogue are reached where violence against researchers or research facilities is being perpetrated or encouraged. Regardless of such excesses, however, the signatories continue see a solid basis for justifying experimental animal research in a factual and communicative manner according to the patho-inclusive approach. This task is based on the ethos of science, which sees itself as part of society and is therefore prepared to be accountable for its actions.

Animal experimentation in Germany: From proposal to implementation

European regulations on animal experimentation

As part of the European Union (EU), Germany is bound by EU legislation. This includes the legal framework for carrying out procedures on animals. Regulations on animal experimentation were harmonised in 2010 by the adoption of a directive for all EU members (2010/63/EU). The EU's animal welfare standards are some of the strictest in the world.

Article 1(a) of the Statutes of the Council of Europe, dated 5 May 1949, states: "The aim of the Council of Europe is to achieve a greater unity between its members for the purpose of safeguarding and realising the ideals and principles which are their common heritage and facilitating their economic and social progress." The protection of the environment, including the protection of animals, is part of the Council's mission. Against this background, the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes was passed on 18 March 1986. As a multilateral international treaty, the Convention requires ratification. With the act of assent of 11 December 1990 (BGBl. 1991 II, p. 740), this agreement became binding for Germany. The German Animal Welfare Act corresponds with these Council of Europe guidelines in the area of animal experimentation.

The treaty law for the European Union (EU) also contains Community competence for animal welfare, under the aspect of environmental protection (Article 191 TFEU). As part of the Treaty of Amsterdam of 2 October 1997, the Protocol on Animal Welfare was adopted, which is a binding part of the Community's primary legislation. It expresses the wish to ensure that animal protection is improved and that the welfare of animals, as sentient creatures, is considered.

The EU also ties the allocation of research funds to qualitatively high standards for animal experiments. The same is expected of Member States when they award research funding. Accordingly, the approach to animal experimentation is a result of the EU's authority to standardise legislation. This is the basis on which Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes was passed. Germany implemented this directive on 4 July 2013 with an amendment to the Animal Welfare Act.

Animal experiments subject to authorisation

Animal experiments may only be carried out if they have been approved by the competent authorities. This is

1. Angaben zum Versuchsvorhaben

1.1 Bezeichnung des Versuchsvorhabens (einschließlich der internen Kurzbezeichnung)

1.1.1 Langtitel:

Angabe des vollständigen Titels

1.1.2 Kurztitel:

Kurztitel in Form eines "Keywords"

1.1.3 Zusammenfassung (Abstrakt, 1 Seite):

Was ist das Ziel?

Was wird mit welcher Art und welcher Methode untersucht?

Wie viele Versuchstiere gibt es?

Die Zusammenfassung ist eine Kurzinformation, es brauchen hier keine

Erklärungen zur Relevanz oder Unerlässlichkeit getätigt werden.

1.1.4 Im Falle von Anzeigen: Rechtsgrundlagen des Anzeigeverfahrens anzeigespflichtig aufgrund von

gesetzlich vorgeschrieben Rechtsgrundlagen der Genehmigungsfreiheit
(§ 8a Abs. 1 Nr. 1 TierSchG):

z.B. Gesetz, Rechtsverordnung, Arztbesuch, unmittelbar geltende

EU-Vorschrift, Allgemeine Verwaltungsvorschrift, behördliche oder gerichtliche

Anordnung, Quelle: [www.tierschutz.de](#)

diagnostische Maßnahmen / Impfstoffprüfungen etc.

(§ 8a Abs. 1 Nr. 2 TierSchG)

Versuche an Zehnfußkrebse (§ 8a Abs. 3 TierSchG)

Eingriffe und Behandlungen zur Herstellung, Gewinnung, Aufbewahrung,
Vermehrung von Stoffen, Produkten, Organismen nach bereits erprobten
Verfahren, die nicht Versuchszwecken dienen

(§ 8a Abs. 1 Nr. 3 a TierSchG)



comparable to a building permit or a restaurant licence. Animal experiments are thus subject to a preventive prohibition. This means that they are prohibited in principle and permitted only in individual cases if the legal requirements are met. Therefore, for every animal experiment application received, the approval authorities check whether the comprehensive legal requirements are met and whether the necessity of the procedures is documented and justified.

The last stipulation in particular points to the unresolvable conflict with a fundamental right that is restricted by the preventive prohibition: the freedom of science guaranteed in the constitution. Interferences with this right require special justification according to the system of legal protection of fundamental rights. For fundamental rights – such as the freedom of science – which are not subject to legislation, intervention by law is only permitted for the sake of constitutionally protected rights. Since July 2002, this constitutional justification has been supplied by Article 20a of the constitution: “Mindful also of its responsibility toward future generations, the state shall protect the natural foundations of life and animals by legislation and, in accordance with law and justice, by executive and judicial action, all within the framework of the constitutional

order.” The addition of “and animals” makes it clear that the Animal Welfare Act can constitutionally restrict freedom of research.

However, this does not change the factual 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 legislature to reconcile freedom of research and ethical animal protection. With the Animal Welfare Act and the regulations, the legislature has already done this successfully.

Legal basis

As animal experiments require approval, it must be clear what an animal experiment is. The definition of animal experimentation is based on the purpose of the law as laid down in § 1 of the Animal Welfare Act: according to it, no one may inflict pain, suffering or damage on an animal without good reason.

Any investigation or operation on an animal that could result in pain, suffering or damage is deemed to be animal experimentation and therefore requires approval. In research, animal tests are only justified if they are the only way in which new knowledge can be gained. As a result, seeking

new knowledge is the legally required good reason for conducting research on animals.

The EU directive goes beyond this interpretation and defines any procedure in which animals are used in science as a project subject to authorisation. This definition has been adopted in the German Animal Welfare Act. As a consequence, the number of approval applications for animal experiments in Germany rose significantly.

Seeking new findings may be the driving force behind research, but is not reason enough by itself to approve an animal experiment. The Animal Welfare Act distinguishes between

- ▶ lawful (essential) research purposes,
- ▶ absolutely unlawful (prohibited) and
- ▶ principally unlawful (prohibited in principle) purposes.

Animal experiments are lawful if they are essential for one of the following purposes, for example:

- ▶ in basic research
- ▶ to prevent, recognise or treat illnesses and to recognise physiological conditions in humans and animals

- ▶ to promote the welfare and improve the treatment of farm animals
- ▶ for conservation purposes
- ▶ to protect the environment in the interest of the health or welfare of people and animals
- ▶ to test the quality, effectiveness and safety of drugs, foodstuffs, pesticides, chemicals or other hazardous substances
- ▶ for forensic examinations
- ▶ for education, training and professional development.

Animal experiments are absolutely unlawful, i.e. always prohibited, if they are related to the development and testing of weapons, munitions and related equipment.

Animal experiments are unlawful and prohibited in principle (but with the possibility of specific exceptions) if they are related to the development of tobacco products, detergents or cosmetics.

What is the legal definition of “essential”?

Researchers are expected to be informed about the state of research



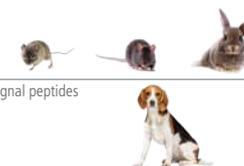
when planning their experiment and to consider whether their planned project can lead to new knowledge. An experiment is only “essential” if there is no equally valid alternative, given the intended purpose. On the basis of available scientific knowledge, it must accordingly be considered whether there is any other procedure that eliminates the need for the animal experiment. All accepted results must be considered, including minority opinions, if they are of adequate scientific quality.

Essentiality must not only be verified to determine the lawfulness of the animal experiment (“whether”), but also for the specific procedure (“how”). The Three Rs principle applies to both (see pp. 47ff.).

What is the legal definition of “ethically justifiable”?

The question of ethical justifiability is concerned with weighing the stress inflicted on the animal during

Since 2013, cosmetic products that were developed using animal experiments can no longer be sold in the EU.



the experiment against the scientific knowledge gain. This is a difficult decision in specific cases, since the benefit of findings in basic research, for example, cannot be known in advance, and the suffering caused to laboratory animals is difficult to quantify.

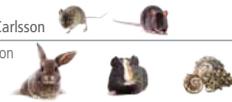
In certain areas, however, animal experiments are required by law. This includes the Drug Law, the Ordinance on Hazardous Substances, the Ordinance on Pesticides, and environmental legislation. In these cases, the question whether an animal experiment is ethically defensible is not subject to an approval procedure. It has already been answered by the legislature on behalf of society – to prevent health risks and to protect people and the environment. It goes without saying that the legal requirement to minimise stress caused to the animals also applies in this area.

Approval procedures

Before an animal experiment can be performed, it must be reported to the responsible authorities and approved by them. In the application, the planned research project must be justified scientifically and it must be proven that the personnel and spatial/technical prerequisites to suc-

cessfully complete the project are in place. The procedure consists of a review on three levels, which determines whether or not applicants will be granted permission.

1. Project-related: The project must be scientifically justified, and its essentiality and ethical defensibility must be demonstrated. In addition, the desired experimental result must not be already available from other sources. The appropriate authorities (such as ministries or state government offices) are responsible for evaluation and reviewing the plausibility of the application. In their decision, authorities may not substitute the applicants' scientifically plausible description of the value of the experiment with their own views.
2. Person-related: Principal investigators and their deputies must possess the necessary professional qualifications and be personally reliable. This implies that they must not have violated the Animal Welfare Act in the past.
3. Facility-related: The structural and personnel requirements for the conduct of the animal experiment must be ensured. These include qualified animal keepers, suitable spaces for keeping animals, and the designation of an animal wel-



fare officer. When it comes to animal husbandry, care must be taken that laboratory animals are kept in a manner that is suitable for their species and needs, and that their medical care is ensured.

If all conditions are met, the approval must be granted. The approval is for a limited time period and may be subject to conditions. In the event of experiments that cause severe stress or experiments using primates, the authorities will demand a retrospective evaluation following the conclusion of the project. In case of violations, financial penalties of up to 25,000 euros or prison sentences may be imposed in justified cases. Bans on experimentation or on keeping animals are also possible.

Conducting animal experiments

The guiding principle of essentiality also affects the performance of the experiments: The number of animals used and the pain, suffering and damage caused to these animals must be limited to what is strictly essential. The Three Rs principle applies here as well (see pp. 47ff.). The following applies as a matter of principle:

- ▶ Where possible, the species that will suffer least under the condi-

tions of the planned experiments should be chosen. Mice and rats are the preferred laboratory animals as they tolerate being kept in cages and reproduce quickly.

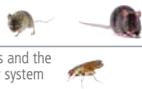
- ▶ Laboratory animals must be bred specifically for experimental purposes to make comparability of results possible. This limitation does not apply to farm animals. If other animals are required for a project, this must be expressly justified – this particularly applies to wild animals and protected species.
- ▶ Primates are under special protection. Their use is strictly limited, and keeping them is subject to particularly high technical and personnel requirements.
- ▶ Painful interventions, such as operations, may only be performed under anaesthesia. If pain is anticipated once the anaesthetic has worn off, additional pain-relieving measures must be implemented. In general, it should be ensured that pain and suffering are kept to a minimum by implementing such measures, which must be taken into consideration when designing the experiment.
- ▶ Highly stressful interventions may not be performed on vertebrates more than once.

Wild animals, such as these field hamsters, are particularly protected – research using these animals is subject to strict preconditions.



- ▶ The use of great apes, as well as carrying out experiments involving long-lasting, severe pain that cannot be minimised, is fundamentally prohibited. If such experiments are absolutely essential, they must be approved by EU authorities. Local

authorities can only provisionally approve this kind of project. Furthermore, the responsible Federal Ministry of Food and Agriculture (BMEL) must be informed and the decision must be justified. The ministry will present such cases to the



Beagles are robust, docile and well-balanced – this is why they are the most commonly used breed of dog for research purposes. All persons who work with animals in research must be competent and trained, and must participate in continuing education – this is prescribed by law.



EU Commission immediately, who can revoke the provisional approval within 30 days.

- ▶ At the end of the experiment, the veterinarian – or in the case of small rodents, another qualified profes-

sional – will decide whether the animal can stay alive. If laboratory animals could only continue living in pain or with damages, they must be killed humanely. If they are returned to full health, they can be given to private individuals or – in

the case of wild animals – be released into the wild. A prerequisite for this is that they are transferred to a suitable type of shelter or habitat. In doing so, it must be ensured that the animals can become accustomed to the new situation and that they do not pose any danger.

Who is allowed to perform animal experiments?

The most important guarantee for the proper conduct of animal experiments is that the researchers and keepers are well trained, prudent, and sensitive to the needs of the animals.

According to German law, animal experimentation may only be performed by persons with the requisite knowledge and skills. These are individuals with a university degree in medicine (veterinarians, physicians, dentists) or natural sciences, or with a professional qualification, such as specially trained biology technicians or laboratory animal keepers. Operations may only be carried out by the first group of persons with the necessary knowledge and skills.

How does the training take place?

Available training in working with laboratory animals varies widely be-

tween different universities. There are no established training plans that are legally binding across all 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. Training may follow the recommendations of the Council of Europe for the education, training and professional development of persons who work with experimental animals. These recommendations are based on suggestions from the international professional organisation FELASA (Federation of European Laboratory Animal Science Associations, London). Depending the scope of tasks, the training takes up to 80 hours.

The DFG recommends taking advantage of such offers and can provide financial support for the professional development of scientists. Numerous universities hold courses that are certified by the Society of Laboratory Animal Science (GV-Solas). This range of courses is supplemented by the online platform LAS interactive (www.las-interactive.de). This platform is available to all universities and research institutions to aid with education, training and professional development regarding experimental animals, and is supported by the DFG.



Qualified monitoring

Effective monitoring of an 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. This documentation must include the number of animals, the species and procedures, as well as the names of the persons who carried out the experiments. In the case of dogs, cats and primates, their gender, any markings, and the procedures must also be documented in such a way that the animal's life from birth to experiment, and beyond, can be traced.

The internal monitoring is carried out by animal welfare officers, who are generally qualified veterinarians. They monitor the experiments and comment on submitted applications. In addition, they advise the researchers and are active within the institution to help implement the Three Rs principle. When fulfilling their duties, animal welfare officers act independently and also provide veterinary care for the animals. In their work, they are also supported by the animal welfare committee, which mainly has an advisory role.

In addition to this internal monitoring, institutions in which animal experiments are performed are subject to monitoring by the responsible

veterinary offices. These may inspect documents and take samples without prior notice. If violations are identified, these authorities can also take the necessary steps. These include instructions to cease animal experiments performed without the necessary approval or in contravention of the Animal Welfare Act. Violations of the regulations are regarded as administrative offences, in extreme cases as criminal offences.

Stress during animal experiments

According to current scientific knowledge, the sensitivity of vertebrates to pain is similar to that of humans. Behavioural responses suggest that animals not only perceive pain, but also suffer subjectively. Legislation recognises this by demanding an evaluation of the consequences for the animal before granting approval of an animal experiment. As part of the evaluation, the duration of the experiment, the frequency of the procedures, the intensity, duration and frequency of pain, and the influence on natural behaviour must be considered.

Many animal manipulations can be minimised by implementing suitable complementary measures. Therefore, providing painkillers and ensuring the best possible husbandry and care con-

Knowledge protects animals: this is the motto of the LAS interactive information and training portal. LAS stands for Laboratory Animal Science.

SUMMARY OF OUR RANGE OF SERVICES

| Free information portal for laboratory animal science | | Fee-based offer for training and continuing education | |
|---|-------------------------------------|---|-------------|
| PRIVATE USER | | PRIVATE USER | INSTITUTION |
| ✓ | ACCORDING TO EU RECOMMENDATION | ✓ | ✓ |
| ✓ | MULTILINGUAL (EN FR DE) | ✓ | ✓ |
| ✓ | EXERCISE QUESTIONS | ✓ | ✓ |
| ✓ | IMAGES & VIDEOS | ✓ | ✓ |
| | ONLINE TESTS | ✓ | ✓ |
| | SELF-STUDY | ✓ | ✓ |
| | BLENDED LEARNING | | ✓ |
| | KNOWLEDGE ACCORDING TO THESISREVIEW | | ✓ |
| | ASSIGNMENT MODULES | | ✓ |
| | FORUMS | | ✓ |
| | SINGLE SIGN-ON | | ✓ |



ditions are crucial for the animal's well-being and absence of pain and anxiety.

Animal suffering is divided into four categories: "non-recovery", "mild", "moderate" and "severe".

Experiments that are carried out entirely under general anaesthesia and from which the animal no longer

Providing painkillers is crucial for the animal's well-being.



awakens are considered stress-free. These experiments are classified separately under "non-recovery".

Procedures regarded as "mild" are those that do not cause significant harm to the animal's welfare and general health, or are expected to cause only low-level pain, suffering or stress for short periods. Such procedures would also be performed on humans in medical practice without anaesthesia or protective measures. This includes, for example, injections and taking blood samples.

Procedures that humans would judge to be unpleasant are classed as "moderate". Both the animal's condition and the pain it experiences are taken into consideration here. This includes operations under anaesthesia that lead to minor consequent stress, such as laying an in-dwelling catheter.

Severe stress would include an organ transplant, during which it is expected that the rejection of the organ could lead to serious adverse effects on the general well-being of the animal. Final efficacy tests for vaccines and acute toxicity tests also fall under this category.

It is inherently difficult to estimate stress, because fluctuations in stress levels within a particular experiment, species-specific differences in reac-



Article 20a Basic Law

"Mindful also of its responsibility toward future generations, the state shall protect the natural foundations of life and animals by legislation and, in accordance with law and justice, by executive and judicial action, all within the framework of the constitutional order."

tion, and an animal's emotional state must be adequately taken into consideration. Significant stress or states of anxiety for laboratory animals, as well as social factors, can have a significant impact on the results of the experiment. To obtain reliable results, it is essential that the laboratory animals are in a normal physiological state and free of pain and fear, if possible. Scientific interests and animal welfare are therefore not in opposition but rather mutually dependent.

Animal welfare group lawsuit

For a long time, animal welfare groups have called for collective action to protect and lend more weight to the rights of animals, who are unable to defend their own rights, against the claims of human beings. They justify this with the constitutional amendment (Article 20a Basic Law). The model is the right to class action in environmental protection: Environmental protection

organisations can take action if environmental law is contravened. Several federal states recently established a legal framework for class actions by animal welfare groups that question the legitimacy of a project and the decision by the competent authorities.

Furthermore, opinions differ on whether class action is even legally possible at the state level. Animal welfare falls within the federal government's concurrent legislation. Federal states only have the authority to legislate to the extent that the federal government makes no use of its jurisdiction. However, in 1972, the federal government already passed the Animal Welfare Act currently in effect. In June 2013, the federal legislature's Committee on Food, Agriculture and Consumer Protection decided by a majority to reject a proposal to introduce the right to class action for animal welfare groups at the federal level. The committee justified this decision by citing the comprehensive animal welfare laws already in force.

Appendix

Questions and answers (FAQs)

Question (Q): Is any unnecessary and senseless animal testing done in Germany?

Answer (A): The performance of unnecessary animal testing is illegal in Germany due to strict laws. Any animal experiment must be submitted to the competent authority and approved before it can be carried out. During the approval process, animal welfare concerns, the necessity of the experiment as well as its ethical justification are examined by an Animal Protection Committee, which also includes representatives of animal welfare organisations.

Q: Can researchers make arbitrary use of experimental animals?

A: Each application for animal testing is evaluated for distress caused to the animals and is controlled by permit from the competent authority. Researchers working in the animal experiment field must be suitably qualified. The necessary skills and knowledge to protect the well-being of the animals and to minimise their pain and suffering is taught in the relevant training programmes. In addition to this, animal welfare officers working at the test sites monitor the experiments.

Q: Is animal testing still performed for cosmetic products?

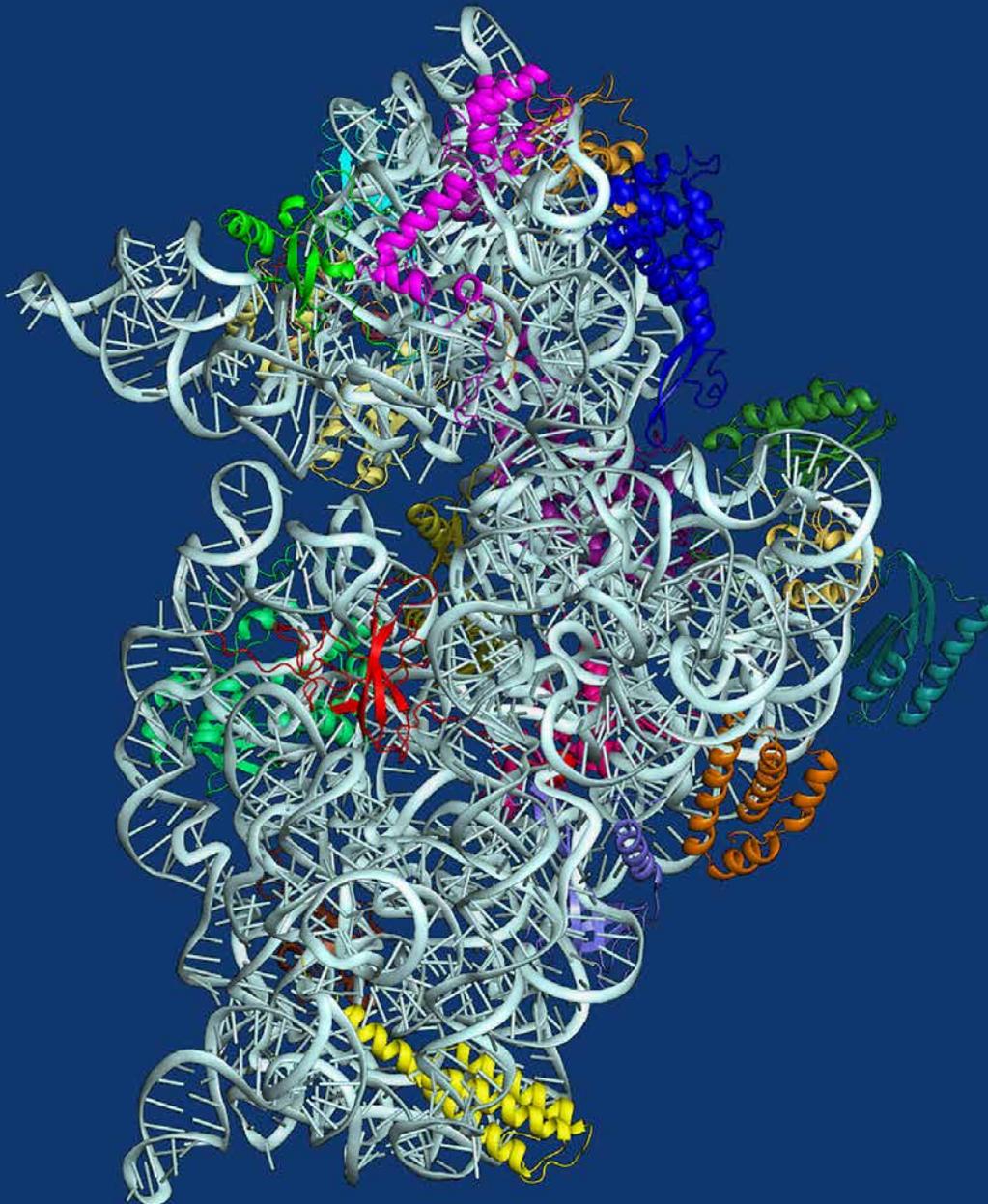
A: Animal testing for the evaluation of cosmetic products has been banned in Germany since 1998. From 2004, animal testing for finished cosmetic products is no longer permissible within the EU. Moreover, since July 2013, animal experiments are no longer permissible for testing the ingredients in cosmetic products.

Q: Is any animal testing involving great apes performed in Germany?

A: There have been no experiments with great apes in Germany since 1991. The use of apes for animal testing is strictly prohibited and may only be approved in exceptional cases (e.g. life-threatening diseases). The European Commission must be informed in such a case.

Q: Are stray and feral dogs and cats captured and used in animal experiments in Germany?

A: The use of stray and feral dogs and cats is strictly prohibited. Animal experiments can only be approved if the origin and health status of the animals is known. Feral populations may only be used for research purposes in exceptional cases, i.e. to protect animal



stocks from epidemics. This only applies to Eastern European countries of the EU, where large populations of feral animals of domestic species still exist and these pose a potential threat to other animals.

Q: Are animals also used for the development of alternative methods to animal testing?

A: In 2014, 789,926 animals (the majority of which were mice and rats) were killed to obtain organs and cells for experiments. This constitutes approx. 28% of all animals that were recorded as test animals. Some of these animals were also used for the research and development of alternative methods to animal testing.

Q: Is it true that results obtained from animal experiments are not transferable to humans?

A: For each experiment, the animal model is specifically selected for its suitability to answer the questions of the particular research. The results from the animal experiment must be analysed carefully and interpreted in relation to their relevance to human beings. Direct transferability is generally not to be expected. However, the same also applies to results from human studies that are equally

not directly applicable to every human being, as each human being is an individual with an anatomy, physiology and genetic make-up all of their own. The interpretation of scientific results from animal experiments is very demanding but makes a substantial contribution to the clarification of the root causes of disease-induced changes and disease mechanisms, and in turn to the improvement the safety and efficacy of drugs.

Q: Is it true that 25 years of AIDS research using primates has not led to any vaccination or drug for human beings?

A: A vaccine against HIV has in fact not been developed to date. The research has however contributed to a marked reduction in the viral load of patients and therefore produced a significant improvement in the quality of life and survival time of patients. This was only possible because the mechanism of action of the virus could largely be clarified, and highly effective drugs and treatment methods could subsequently be developed and applied.

This brochure was prepared by the DFG's Senate Commission on Animal Protection and Experimentation. The section "Ethical aspects of animal experimentation and the principle of solidarity" is based on chapter 3.1 of the ad-hoc statement "Animal Experimentation in Research: Statement on the Transposition of EU Directive 2010/63/EU into German Law" by the German National Academy of Sciences Leopoldina and the Union of German Academies of Sciences and Humanities (2012). The Senate Commission would like to thank Prof. Dieter Birnbacher and Prof. Bettina Schöne-Seifert for their support on this section.

The Senate Commission on Animal Protection and Experimentation

The Senate Commission on Animal Protection and Experimentation deals with current issues in relation to experimental research with animals and animal welfare in research. It has an advisory role to the statutory body of the DFG and authorities at EU, federal and state level. The commission provides advice to researchers as well as universities and research institutions on practical questions and problematic cases. The commission fosters in-depth training of early career researchers in animal research by developing specific training programmes and drives public dialogue through the creation of information materials and organisation of talks and discussions.

Scientific members during the 2014 – 2017 term:

Professor Dr. Gerhard Heldmaier (Chairperson) / University of Marburg

Professor Dr. Peter Dabrock / University of Erlangen-Nuremberg

Professor Dr. Bernd Fleischmann / University of Bonn

Professor Dr. Nils Hoppe / University of Hanover

Professor Dr. Inga D. Neumann / University of Regensburg

Professor Dr. Heiner Niemann / Friedrich Loeffler Institute

Professor Dr. Ingo Nolte / Foundation of the University of Veterinary Medicine in Hanover

Professor Dr. Heidrun Potschka / Ludwig-Maximilian University of Munich

Professor Dr. Ruth Esther von Stebut-Borschitz / University of Mainz

Professor Dr. René H. Tolba / Aachen University Hospital

Professor Dr. Stefan Treue / German Primate Center

Coordinator:

Dr. Cornelia Exner / University of Marburg

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Published by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation),
Senate Commission on Animal Protection and Experimentation, Kennedyallee 40, 53175 Bonn,
Telephone: +49 228 885-1, Fax: +49 228 885-2777, postmaster@dfg.de, www.dfg.de/en

Concept & text: Senate Commission on Animal Protection and Experimentation, DFG

Scientific editors: Dr. Cornelia Exner, Dr. Christoph Limbach, DFG

Translation: oneword GmbH and Norbert G. Kramer

Editors: Diana Fehmer, Inken Kiupel, DFG

Basic layout: Tim Wübben, DFG/ besscom, Berlin

Production layout: Olaf Herling, Warstein/Berlin

Print: Druckerei Hachenburg GmbH

Version dated: 10/15/2016

ISBN: 978-3-527-34355-3

Further information:
www.dfg.de/tierschutz
(available only in German)





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