Questions and Answers on Animal Experiments and Alternative Methods

FAQ of the BfR dated 28 January 2016

Animal experiments are conducted in order to answer scientific questions, but not every scientific question justifies an animal experiment. The German Animal Welfare Act specifies the purposes for which animal experiments may be conducted, the organisational and technical requirements that must be met, and the standards regarding qualifications of personnel to be fulfilled.

The main purposes for which animal experiments are permitted are basic research, the diagnosis and treatment of illnesses in humans and animals, and tests on the safety of medicinal products and chemicals. However, the German Animal Welfare Act stipulates that animal experiments may only be conducted if they are essential to answer the scientific question and are ethically acceptable in view of the balance between the expected knowledge to be gained and the expected suffering of the animals.

Whenever there are reliable alternative methods, these must be used in place of animal experiments. The German Centre for the Protection of Laboratory Animals (Bf3R) at the Federal Institute for Risk Assessment (BfR) promotes the development, validation and use of such alternatives to animal experiments.

What are animal experiments?

Animal experiments as defined by the German Animal Welfare Act are procedures or any course of actionon animals which serve to answer a scientific question and which could be accompanied by suffering, pain or harm to these animals or their offspring. Modifying the genetic material of animals and breeding genetically modified animal lines are also considered animal experiments if the offspring could experience pain, suffering or harm as a result of the genetic modifications.

Procedures and treatments on animals that do not serve directly to answer a scientific question are considered animal experiments if they are conducted to produce substances and products (e.g. antibodies) or to multiply organisms (e.g. parasites) with which scientific questions can subsequently be addressed. The removal of organs or tissues for transplants, the creation of a culture and the testing of isolated organs or tissues for scientific purposes, as well as procedures and treatments on living animals for education or training, are also considered animal experiments.

Who may conduct animal experiments?

The German Animal Welfare Act stipulates that animal experiments can generally only be conducted by persons who have the required knowledge and skills. As a rule, a completed university degree in veterinary medicine, medicine or dentistry is required for this.

Animal experiments without surgical procedures can also be conducted by persons with a completed university degree in natural sciences if they are proven to have the required knowledge and skills, as well as persons who have obtained the required knowledge and skills in the course of completed vocational training (e.g. animal keepers, biological laboratory technicians). Before such persons commence work in an experiment, proof that the required knowledge and skills have been obtained must be provided to the authority granting authorisation.

When can an animal experiment be conducted?
An animal experiment can generally only be carried out after authorisation has been granted by the responsible authority. The prerequisite for this authorisation is that the animal experiment is to be conducted for one of the purposes stated in the German Animal Welfare Act. Furthermore the experiment must be essential to achieve it. The scientific question must not have been answered already and it must not be possible to answer it by means of a method other than the animal experiment. In an animal experiment, the pain, suffering or harm inflicted on the animal must be reduced to the absolute minimum. All persons involved in conducting the experiments or caring for the animals must be suitably qualified for this purpose.

How many animal experiments are conducted in Germany per year?
A general distinction must be made between the number of animal experiments and the number of laboratory animals used during the experiments.

2,008,537 animals were used in animal experiments in Germany in 2014. In addition, 789,926 animals were killed and subsequently used for scientific purposes (source: http://www.bmel.de/DE/Tier/Tierschutz/_texte/TierschutzTierforschung.html?docId=7027766)

No figures are available on the number of individual animal experiments. This figure is, of course, far lower than the number of laboratory animals used. Since 2013, approved animal experiment projects in Germany have been systematically recorded by means of the non-technical project summary (www.animaltestinfo.de).

How many and which laboratory animals are used for animal experiments in Germany?
A total of 2,008,537 laboratory animals were used in animal experiments in 2014. Rodents made up the largest group with 1,713,386 (85%), including 1,263,519 (63%) mice and 296,662 (15%) rats. After rodents, fish made up the second largest group with 212,211 (10%) animals. The number of dogs was 4,627 (0.2%) in 2014. The number of cats used was 997 (0.05%). 2,823 (0.14%) monkeys and prosimians were used in animal experiments. Great apes have no longer been used for animal experiments in Germany since 1991. The detailed laboratory animal statistics are published by the German Federal Ministry of Food and Agriculture (BMEL) every year (source: http://www.bmel.de/DE/Tier/Tierschutz/_texte/TierschutzTierforschung.html?docId=7027766)

For which purposes are animal experiments conducted in Germany?
In 2014, classified according to purpose, a total of 43% of the animals were used in basic research, 16% in research on illnesses in humans and animals, 11% in the production or quality control of medicinal products, 14% in tests of toxicological safety, and 16% for other purposes, such as education and training or for breeding genetically modified animals (source: http://www.bmel.de/DE/Tier/Tierschutz/_texte/TierschutzTierforschung.html?docId=7027766)

Which legal regulations apply to animal experiments?
In Germany, animal experiments are regulated by the German Animal Welfare Act, which has been constitutionally based on the constitutional goal of animal protection according to Article 20a of the German Constitution since 2002.

EU Directive 2010/63/EU on the protection of animals used for scientific purposes was enacted in 2010. In 2013, its regulations were transposed into German law with the amendment of the German Animal Welfare Act. The new regulation on the protection of animals used for scientific purposes also came into effect in 2013. This provides specific details on the provi-

sions stated in the German Animal Welfare Act. For example, the German Animal Welfare Act stipulates that a person who conducts animal experiments needs to have the appropriate knowledge and skills. The regulation on the protection of animals used for scientific purposes describes the required qualifications in greater detail. The same applies to the contents of records that need to be kept on an animal experiment.

The German Animal Welfare Act is divided into twelve sections. Section 5 “Animal Experiments” of the German Animal Welfare Act (Arts. 7-9) stipulates that animal experiments should be reduced to an absolute minimum with regard to the pain and suffering inflicted on the animals and to the number of animals used, and that animal experiments may only be conducted when they are essential for a specific purpose. Authorisation is generally required for animal experiments on vertebrates or cephalopods.

Under which circumstances are animal experiments authorised?
Scientists who are planning an animal experiment on vertebrates or cephalopods must apply for project authorisation. They must provide scientific justification proving that the purpose, scope and execution of the experiments comply with the provisions of the German Animal Welfare Act. It must also be proven that the scientific question addressed by the experiment has not yet been answered, for example by an animal experiment that has already taken place. An authorisation is only granted if plausible justification is provided that the expected pain, suffering or harm of the animals is ethically justified by the expected outcome. For example, suffering may only be inflicted on the animal to the extent that is absolutely necessary for the purpose and it must not be possible for the experiments to be replaced by alternative methods (replacement), for their scope to be reduced (reduction) or for the animals’ pain, suffering or harm to be diminished (refinement).

Apart from the German Animal Welfare Act, which legal regulations apply to animal experiments for chemicals?
The European chemicals directive REACH (*Registration, Evaluation, Authorisation and Restriction of Chemicals*, 1907/2006/EC) regulates the registration, evaluation, authorisation and restriction of chemicals in the European Union (http://ec.europa.eu/growth/sectors/chemicals/reach/index_en.htm).

REACH is based on the principle that the producers and users of chemicals must ensure that the chemical substances do not have a negative impact on human health or the environment. In order to minimise the necessity of extensive animal experiment studies for this purpose, animal experiments should be avoided wherever possible and methods not involving animal experiments should be developed and used. Experiments on vertebrates should only be conducted as a last resort. Equivalent studies may not be repeated, but should be shared by different producers.

Apart from the German Animal Welfare Act, which legal regulations apply to animal experiments for plant protection products and biocides?
EU Regulation No. 1107/2009 concerning the placing of plant protection products on the market and EU Regulation No. 528/2012 concerning the making available on the market and use of biocidal products regulate the approval requirements for plant protection products, biocides and their active substances within the European Union. The regulations aim to minimise the required animal experiments in the context of the approval of plant protection products and biocides. Here also, experiments on vertebrates should only be conducted as a last resort. Equivalent studies may not be repeated, but should be shared by different producers.

Apart from the German Animal Welfare Act, which legal regulations apply to animal experiments for cosmetics?
Today, animal experiments for the development of cosmetics are subject to a general ban within the European Union through Regulation No. 1223/2009. The ban applies to cosmetic end products and to components and combinations of components. There is also a ban on placing cosmetic products and components which have been tested on animals on the market.

Cosmetic products are defined as substances or mixtures of substances which are intended to come into external contact with parts of the human body (skin, hair, nails etc.) or with the teeth and mucous membranes of the mouth with the exclusive or main purpose of cleaning, perfuming, changing the appearance of, protecting or keeping them in a good condition or influencing body odour.

Apart from the German Animal Welfare Act, which legal regulations apply to animal experiments for medicinal products for human use?
So-called finished medicinal products for human use, which are intended for sale to consumers and are produced in advance, can only be placed on the market if they have been approved by the responsible higher federal authority (German Federal Institute for Drugs and Medical Devices, BfArM) or the European Community or European Union has granted an approval for placing them on the market. This obligation to obtain authorisation is set down in Article 21, Paragraph 1 of the German Drug Law (*Arzneimittelgesetz*, AMG). To obtain approval for a medicinal product, its quality, safety and effectiveness must be proven.

How can the public obtain information on animal experiments?
Ever since the German Animal Welfare Act came into effect in 2013, the responsible authorities send the associated non-technical project summary (NTP) to the BfR once an animal experiment project has been authorised. This NTP explains, for example, the purpose and benefits of the experiment. The BfR publishes the NPT on its website (www.animaltestinfo.de) within twelve months. This publication serves to make information on animal experiment projects accessible to the public.

Which tasks does the Federal Institute for Risk Assessment (BfR) perform to protect laboratory animals?
In 2015, the German Centre for the Protection of Laboratory Animals (Bf3R) was opened at the BfR. The Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET), which was founded in 1989, is part of the new centre. Bf3R coordinates all activities throughout Germany that serve to limit animal experiments to the absolute minimum and guarantee the best possible protection of laboratory animals. In addition, the centre's work is intended to encourage national and international research activities and to promote scientific dialogue. The centre has the following tasks:

- To intensify research on alternative methods
- To provide advice to authorities and research institutes
- To standardise alternative methods at an international level
- To promote and coordinate research on alternative methods
- To inform the public.

What are alternative methods?
Alternative methods to animal experiments are all procedures which can replace animal experiments, reduce the number of laboratory animals used, or decrease the suffering of laboratory animals used. The generally recognised scientific basis for developing alternative methods is the so-called "3R principle", which was published by British scientists W.M.S.

Russell and R.L. Burch in 1959. According to this principle, an alternative method must meet at least one of the following three requirements:

- *Replacement*: Animal experiments are replaced by procedures not involving animal experiments
- *Reduction*: The number of laboratory animals is reduced
- *Refinement*: The suffering or pain of the laboratory animals is reduced

Alternative methods include, for example, in vitro procedures with isolated human or animal cells, computer systems, and imaging processes such as magnetic resonance imaging or ultrasound technology. Since 1986, the member states of the European Union have been obliged by EU Directive 86/609/EEC on the protection of animals used for scientific purposes to promote the development and validation of alternative methods in their countries.

Which requirements do alternative methods need to fulfil in order to be able to replace animal experiments for toxicological safety tests?
Alternative methods for testing the toxicological safety of chemical substances are only recognised for regulatory purposes if the results provided are just as reliable as those of animal experiments. In order to prove that an alternative method can replace an officially required animal experiment, i.e. can provide results as good as or better than those of the animal experiment and provide the same results in all laboratories, the method must be scientifically validated.

Because there are limitations in some cases regarding the transferability of results of animal experiments to humans due to differences between species, alternative methods can even, under certain circumstances, make more reliable statements regarding the effect of chemical substances in humans. For this reason, the development of cell models of human origin in particular has huge potential. Since alternative methods generally only illustrate individual biological aspects due to the reduced complexity, combinations of different alternative methods are often necessary in order to obtain a reliable experiment result. The development of test strategies and evaluation concepts in which the data from several alternative methods is integrated in a final assessment of a chemical substance is a focal point of international research activity.

How can scientists find out whether there is an alternative to an animal experiment?
To check whether an animal experiment is absolutely necessary, the party applying for approval of an animal experiment project is obliged to systematically exhaust all relevant sources of information. To facilitate systematic research for such applicants, as well as for animal welfare representatives and approval authorities, the European Centre for the Validation of Alternative Methods (ECVAM) published a search guide in 2013 with the title “ECVAM Search Guide - Good Search Practice on Animal Alternatives” http://bookshop.europa.eu/en/the-eurl-ecvam-search-guide-pbLBN124391/.

The search guide provides information on the wide variety of possible sources of information that could be used for research on alternative methods to animal experiments and on the rules for tapping into this variety of sources. The BfR made a significant contribution to the preparation of the guide by incorporating its expertise in the field of information research for alternative methods.

Which alternative methods has ZEBET been able to establish to date?
Since 1989, ZEBET has been supporting the development, validation and implementation of alternative methods which are internationally recognised today and are set down as official test methods in the EU and in the OECD (*Test Guideline*, TG).

ZEBET has, for example, developed a test for phototoxic skin damage (redness, swelling or blistering) that does not involve animal experiments. Today, the test is routinely used around the world to check the safety of medicinal products, chemicals and cosmetics that are exposed to sunlight, which could change their effect. This alternative method has largely replaced distressing animal experiments on mice, rats, guinea pigs and rabbits for testing phototoxicity and also provides more meaningful information on human health than the animal experiments. This test was recognised within the scope of the OECD test guidelines programme (TG 432) in 2004 and is thus used around the world to test chemicals. In addition, the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA) have also approved this method for testing medicinal products.

It was also possible for tests on rabbits for skin irritation or skin corrosion to be replaced by alternative methods. Here, ZEBET was partly responsible for conducting and coordinating the validation of reconstructed models of human skin, as well as for promoting regulatory acceptance. As a consequence, these models were recognised as OECD test methods for detecting skin irritation (TG 439, 2010) or skin corrosion (TG 431, 2004), which means that, today, dermatological testing of chemicals in the EU now only takes place using human skin models.

You can find further examples of alternative methods developed by ZEBET on the BfR website under http://www.bfr.bund.de/en/zebet-58194.html.

Is the development of alternative methods promoted at an international level?
ZEBET was the first national research institute in the world tasked with replacing animal experiments. When it was founded in 1989, there was only a small number of toxicological test methods not involving animal experiments that were accepted by authorities worldwide for testing chemical substances or products. Today, there are institutes similar to ZEBET in other European countries and in Japan, South Korea and the USA.

The European Union directly promotes the development of alternative methods with Directive 2010/63/EU on the protection of laboratory animals, as well as the use of alternative methods with the legal provisions on cosmetics and chemicals. Moreover, the EU coordinates the validation of alternative methods through the scientific centre EURL-ECVAM.

Since 2008, the National Institutes of Health (NIH) in the USA have been promoting a major focus programme (*Toxicology in the 21st Century*) which has the aim of predicting unwanted side effects of medicinal products and other chemicals for humans without animal experiments.

The Organisation for Economic Cooperation and Development (OECD) is the most important international organisation for the recognition of alternative methods to animal experiments in the field of toxicological testing of chemical substances. The legally agreed mutual recognition of data from alternative methods (*Mutual Acceptance of Data*) forms the basis for the international usage of alternative methods.

How is the development of new alternative methods supported in Germany in financial terms?
The German Federal Ministry of Food and Agriculture (BMEL) makes an annual budget of currently approximately 400,000 euros available to the BfR to support research on new alternative methods at German universities and research institutes. To date, more than 140 research projects have been supported since the beginning of the funding programme in 1990.

Every year, ZEBET supports approximately ten work groups for a duration of between one and three years.

Furthermore, the Federal Ministry of Education and Research (BMBF) has been supporting the development of alternative methods since 1980. More than 450 projects have been supported so far with approximately 145 million euros in funding.