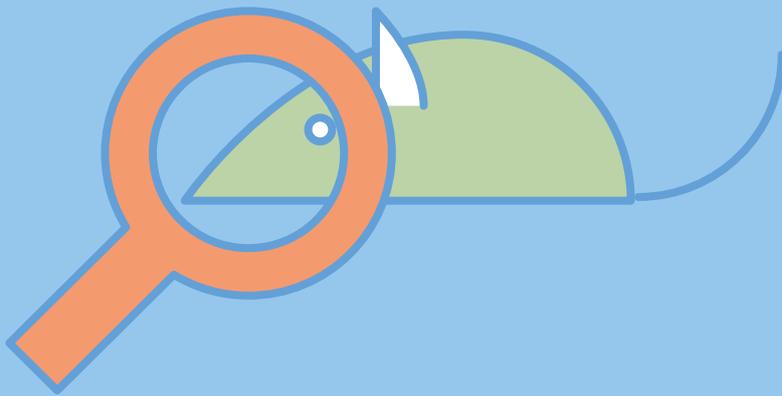


Protection of Laboratory Animals

Fields of research for more animal welfare





The German Centre for the Protection of Laboratory Animals (Bf3R) at the BfR

The Centre combines the various areas of alternative method research on a national level in line with the 3R principle. The Centre coordinates activities all over Germany with the goals of restricting experiments with animals to a level which is absolutely necessary and affording laboratory animals the best possible protection. In addition, impetus is to be given to national and international research activities through the work of the Centre while encouraging scientific dialogue at the same time. Bf3R was established in 2015 in the course of the Animal Welfare Initiative of the Federal Ministry of Food and Agriculture. It is an integral component of the BfR which is subdivided into five areas of competence.

www.bfr.bund.de

> German Centre for the Protection of Laboratory Animals

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“We are creating more transparency in animal experiments”

A focus on animal welfare: Professor Dr. Gilbert Schönfelder heads the German Centre for the Protection of Laboratory Animals at the BfR. In this interview, he reports on the duties of the centre and the search for alternative methods.

Professor Schönfelder, how did you become interested on the topic “Protection of laboratory animals” and the development of alternative methods to animal experiments?

It is our ethical obligation to avoid unnecessary experiments and spare animals from suffering. On the other hand, we still need animal experiments to achieve medical progress and cure sick people. Working within this field of conflict is a tremendous challenge from both a scientific and a social point of view.

Critics say that the results of animal experiments cannot be translated to humans.

Reality isn't only black and white. It's true that the results of some animal experiments can only be translated to humans with difficulty, but this can't be generalised. There are some animal experiments which most certainly do permit conclusions with regard to humans. There wouldn't be any medicine without animal experiments!

One of your main aims is the development of alternative methods – is this a way towards fewer animal experiments?

In the long term, definitely. The guiding principle for us is still the 3R principle put forward by William Russell and Rex Burch in 1959, which states that animal experiments should be replaced, reduced and refined. The latter means that the suffering of the animals should be alleviated. The 3R principle also forms the basis of the European Directive 2010/63/EU on the protection of animals used for scientific purposes. It was implemented into German law in 2013 with the amendment of the Animal Welfare Act.

What does that mean for the Centre for the Protection of Laboratory Animals, which was founded in 2015 and of which you are the head?

The range of our tasks has expanded considerably. The Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments, ZEBET, was already established at the BfR. It exists since 1987. What's new is that we now inform the public about every authorised animal experiment in generally understandable form. Four areas of competence have been added to it with the aim of reducing the stress on laboratory animals, identifying alternative methods for toxicological testing and coor-



Professor Dr. Gilbert Schönfelder

is a physician, full-professor at the Institute for Clinical Pharmacology and Toxicology at the Charité Universitätsmedizin Berlin and head of the department Experimental Toxicology and ZEBET, as well as of the German Centre for the Protection of Laboratory Animals (Bf3R) at the BfR. The main focus of Schönfelder's research lies in the field of experimental toxicology, the further development of alternative methods to experiments with animals, and in reproductive and developmental toxicology. He studied Human Medicine at the Freie Universität Berlin, was appointed junior professor at the Charité in 2003, moved to the University of Würzburg in 2007 and returned to the Charité in 2010. Schönfelder has been with the BfR since 2012.

dinating research funding for alternative methods. The National Committee for the Protection of Animals Used for Scientific Purposes is also located at our Centre. It advises the responsible German authorities and animal welfare bodies at the research institutions.

Many legal tasks have been transferred to you, but you conduct also research at your Centre. How do you manage this balancing act?

One of the essential strengths of departmental research is that it promotes important areas of science which may have been neglected up to now. We have benefited from this too. We were able to acquire outstanding researchers and build up the necessary infrastructure at the Centre, such as modern technology.

A centre where alternative methods to animal experiments are developed – that awakens great expectations among the general public.

We have to be honest here – it is not possible to replace all animal experiments within five years. It's simply unrealistic. I hope that in 10 to 20 years the new methods are so good that a measurable decline in animal experiments results.

Which approaches are particularly promising?

Animal experiments for the development of cosmetics are already prohibited in the cosmetics industry. That's why skin tissue tests have already been introduced to test products for their health safety with regard to skin irritation or corrosion, for instance. Another example are three-dimensional cell culture models which are used more and more in basic research.

You mean “miniature versions” of organs like the stomach?

For example. Cell cultures are also becoming more important in brain research. To study the development of the nervous system, it can be more beneficial to observe the processes on cells in detail in a Petri dish. You can't simply look inside an animal's skull, on the other hand. There's also a lot of discussions at the moment about “human” or “organ-on-the-chip” technology. Miniaturised organ systems, such as the liver and brain, are connected on a plastic chip via a kind of blood flow. The interactions between organ systems can be better understood in this way. But the same thing applies here: these methods are not currently capable of completely replacing animal experiments.

What special impulses can emanate from your Centre?

It is important to increase transparency about research conducted on animals, which is of concern. Our database AnimalTestInfo can provide this important information. As we reported in the journal “Plos Biology”, for the first time we were able to provide a more detailed overview about the use of six million animals in experiments. It is important to better understand the purpose why so many animals are used in the research of cancer, disorders of the vascular and immune system? Detailed information can help to make research more efficient. Therefore, we hope to make an important contribution where alternative methods are needed to reduce the suffering of animals. We hope to inspire scientists to dedicate their research efforts more to this subject.

Many thanks for the interview, Mr. Schönfelder. ▣

Fields of research for more animal welfare

What are the benefits of animal experiments? The BfR “AnimalTestInfo” database provides answers and shows how the protection of laboratory animals can be improved.

The questions are obvious: what is the actual purpose of animal experiments? In which areas it is necessary to do more for animal welfare? Since 4 December 2014, it is possible to answer those questions. On this day, the BfR launched the “animaltestinfo.de” website. The AnimalTestInfo database provides transparent and easily accessible information about experiments with animals. Every authorised project in Germany involving animal experimentation is listed in this database

along with easily understandable information in the form of non-technical project summaries (NTS).

Legislation makes transparency mandatory

The legal basis for the publication of information on authorised animal experiments is the European Directive 2010/63/EU on the protection of animals used for scientific purposes. This directive stipulates that every ▶

Animal experiments for the combat against diseases

Number of planned animal experiments per research purpose (evaluation of AnimalTestInfo entries 2014/2015)

Other diseases

2015: **980**
2014: **748**

Cancer/non-malignant tumours

2015: **533**
2014: **419**

Cardiovascular diseases

2015: **302**
2014: **236**

Diseases of the nervous system

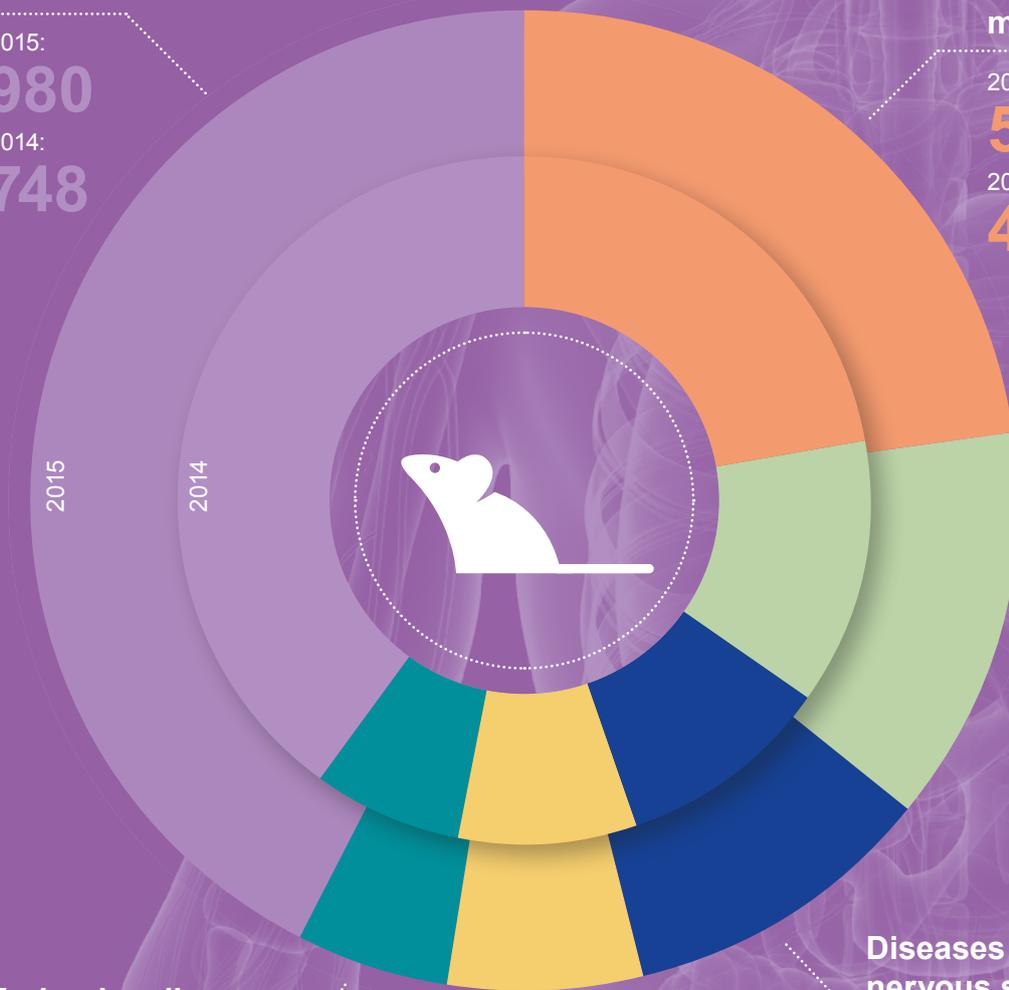
2015: **240**
2014: **186**

Infectious and parasitic diseases

2015: **144**
2014: **156**

Endocrine diseases, nutritional and metabolic diseases

2015: **120**
2014: **128**



“The exemplary evaluation of 5,000 test projects from the years 2014 and 2015 shows that around 80 percent of the animal experiments approved in Germany serve the purpose of investigating the causes, diagnosis and treatment of human illnesses, with main focus on diseases of the cardiovascular and nervous systems, as well as cancer.”

EU member state must inform the general public about animal experiments by publishing generally understandable summaries. The directive was implemented into German law in the summer of 2013 through the amendment of the Animal Welfare Act and the enactment of the Regulation on Laboratory Animal Welfare. Ever since, researchers have to submit a non-technical project summary along with their project application. Among other things, this summary must contain details of the expected benefits, number and species of animals to be used, the severity levels they are likely to be exposed to and information on whether or not the requirements of the 3R principle have been applied (see interview on page 03). Once approval has been granted for an animal experiment, the responsible authorities release the corresponding NTS in the AnimalTestInfo database for publication.

Systematic evaluation of data

Currently, more than 10,000 anonymised non-technical project summaries are listed in AnimalTestInfo and about 2,800 entries are being added every year. Every month, approximately 1,000 users, most of them from Germany but also from other European countries, the USA and Arab and Asian countries, access the database. Although AnimalTestInfo was set up primarily as an information source for the general public, the information contained in the NTS can also be systematically evaluated. And that is exactly what the BfR scientists at the German Centre for the Protection of Laboratory Animals (Bf3R) have done in a study conducted in the third year of the database's existence.

ICD codes as a classification reference

More than 5,000 animal experiments from the years 2014 and 2015 have been systematised with the help of ICD codes. To do so, the experiment purposes described in the NTS were assigned to the corresponding human diseases using the ICD code. The ICD (International Classification of Diseases) code is a classification system used for the precise description of disease diagnoses. For example: an NTS published in 2015 describes an animal experiment examining whether chronic intestinal inflammation increases the risk of colorectal cancer. The plan of the experiment is to switch off some specific enzymes in mice and to transfer certain defence cells. The experiment is intended to help recognise which parts of the immune system and which enzymes contribute to inflammation and cancer. In the Bf3R study, this authorized animal experiment was assigned to the ICD code C15-C26 for malignant tumours of the digestive organs.

More alternative methods required in cancer research

The exemplary evaluation of 5,000 test projects from the years 2014 and 2015 shows that around 80 percent of the animal experiments approved in Germany serve the purpose of investigating the causes, diagnosis and treatment of human illnesses, with main focus on diseases of the cardiovascular and nervous systems, as well as cancer. As the ICD codes deliver a very precise description, the evaluation shows in detail which diseases are researched with animal experiments. Where cancer is concerned, for instance, a great number of the authorised animal experiment projects in this field was dealing with malignant tumours of the digestive system and therapeutic treatment thereof.

In the study, for the first time the concrete fields of research were determined in which a consistently large number of animal experiments were approved over the years, such as the research and treatment of colorectal cancer. The information obtained from the database shows the fields of research in which there is a special need for the development of alternative methods to experiments with animals in line with the 3R principle. The information serves science, research funders and politics as a comprehensive data source opening up areas of action for more animal welfare in the future. ■

More information:

Bert et al. 2017. Rethinking 3R strategies: Digging deeper into AnimalTestInfo promotes transparency in in vivo biomedical research. PLoS Biol. 15 (12): e2003217. (Open Access)

Schönfelder et al. 2015. Laboratory animals: German initiative opens up animal data. Nature. 519: 7541, 33.

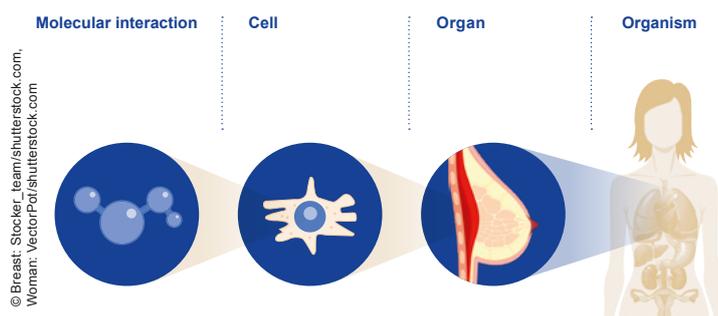
Spectrum

Understanding health hazards without animal experiments

How can hazards and the effects of environmental chemicals be observed without the necessity of animal experiments? Adverse Outcome Pathways (AOPs) were conceived in recent years in order to gain a better understanding of the toxic effects of chemicals on organs and use this knowledge for the development of new, animal-free test methods. AOPs describe on a molecular level how a human or animal body might react to environmental chemicals to cause serious harm to human health. Above all high throughput methods and systems biological approaches are best suited for the implementation of the AOP concept in the risk assessment of chemicals and to target research of alternative methods. The combination of these technologies permits the comprehensive analysis of a large number of chemicals within a short period of time. BfR is now also using these methods to an increasing extent.

More information:

Burgdorf et al. 2017. The AOP Concept: How novel technologies can support development of adverse outcome pathways. *Appl In Vitro Toxicol.* 3: 271–277



Adverse Outcome Pathways depict diseases in detail right down to the level of molecular processes. The AOP of breast cancer looks like this, for instance: bonding to the estrogen receptor activates gene expression, stimulates cell proliferation and cell migration, thus contributing to the occurrence of breast cancer.



Commitment to the systematisation of animal data

What chances and what limits are there for the use of laboratory animals to research diseases? Neurologist Malcolm Macleod of the University of Edinburgh has dedicated himself to this topic. This spring he was awarded the Maria Sibylla Merian Fellowship by the BfR for his interdisciplinary research achievements and contribution towards improving animal welfare. In the field of stroke research, Malcolm Macleod's systematic studies will enhance the reliability of animal experiments and evidence-based transferability to humans. In this way, unnecessary animal experiments can be avoided in future and new, innovative therapy approaches found. Bf3R will collaborate scientifically with Malcolm Macleod in order to advance research in the field of meta-analysis. With the fellowship programme, awarded for the first time, the BfR honours researchers who have excelled themselves through their extraordinary scientific achievements.

More information:

www.bfr.bund.de/en > Research > Fellowship-Programmes

Bf3R research funding 2017: Sponsored projects have been selected

The BfR included eight external work groups in its current Bf3R research funding programme for the development of innovative alternative methods. Among other projects, the scientists are developing training models for use in animal experimentation courses, as well as improved, cell-based skin models for research on the healing of wounds. The individual projects are scheduled to run for up to three years and are each being sponsored with an average sum of 35,000 euros per annum. The BfR invites bids for the Bf3R research funding every two years. Universities, non-university research institutions and companies with research and development capacity in Germany are all entitled to apply. A high priority is given to methods to substitute or reduce animal experiments in basic biomedical research, as well as research approaches to recognise and alleviate the suffering of laboratory animals. Eight of the 47 applications submitted achieved this priority in 2017. The next invitation for bids for Bf3R research funding will be in spring 2019.

More information:

www.bfr.bund.de/en > German Centre for the Protection of Laboratory Animals (Bf3R) > Bf3R Research Funding



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