

Frequently Asked Questions (FAQs) on Animal Research

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Purpose of Animal Research

1. What is Roche's position on the ethics of animal research?

As a leading healthcare company, Roche's overall goal is to provide products and services that help prevent, diagnose and treat disease. The use of animals is an indispensable part of biomedical research. Animal research contributes to the development of innovative products that fulfil unmet medical needs and alleviate suffering caused by diseases.

Roche, nevertheless, recognizes that animal research is a sensitive issue. We take animal welfare seriously and are committed to applying high standards of welfare and to using animals responsibly. We conduct rigorous reviews of planned studies that use animals, seeking to ensure that the studies are scientifically justified and that correct species and an appropriate number of animals are selected. It is essential that we use as few animals as possible and avoid all unnecessary pain and distress. In that regard, Roche fully supports the 3Rs approach to animal research – Reduce, Refine, Replace (see questions 17-22).

2. Why is animal research necessary?

Animal research is extremely beneficial in minimising the risks to humans in clinical trials designed to find new and more effective therapies and diagnostic tests to treat serious diseases and improve the quality of patients' lives. Advances in research on complex diseases such as cancer, Alzheimer's disease or Parkinson's disease heavily depend on the use of animal models.

Before human clinical trials for new medications can be conducted, regulatory bodies worldwide, for example, the European Medicines Agency and the U.S. Food and Drug Administration, require efficacy and safety data based on animal experimentation. This pre-clinical testing is aimed at closely mimicking the functioning of a human body in a whole organism, so that clinical trials in humans may be conducted with maximum safety and efficacy.

Approximately 70% of severe adverse effects that would occur in humans are identified during the animal testing stage. The results help researchers to determine which experimental compounds in advanced development are unsuitable for use in humans. Typically 30-40% of all compounds tested are unsuitable, either because the risk of toxicity is too great or the compound doesn't show the desired pharmacokinetic (study of the effect of a body on a drug, in terms of absorption, distribution, metabolism and excretion) profile, thus likely rendering them ineffective.

3. How can test results from animals be applied to humans?

Humans are biologically similar to other mammals, with many of the same organs, such as the heart, lungs, kidneys and liver. These organs perform the same functions and are

controlled by the same mechanisms, such as the blood stream and nervous system. There are also differences, however, which can sometimes be helpful from a scientific perspective. For instance, the revelation of why certain animals do not suffer from a human disease could lead to a new idea for a treatment.

4. How has animal research contributed to advances in medical science?

Animal research has played a vital role in virtually every major medical advance of the last century for both human and animal health. Be it antibiotics or blood transfusions, dialysis or organ-transplantation, vaccinations or chemotherapy, bypass surgery or joint replacement, practically every present-day procedure for the prevention, treatment, cure and control of disease, pain and suffering is based on knowledge obtained through research with animals.

Ample proof of the success of animal research can be found among Nobel Prize winners: 75 of the 98 awarded discoveries for Physiology or Medicine were directly dependant on research from animals.¹

Additionally the use of animals was crucial in many discoveries made in drug development and biomedical research, including monoclonal antibodies, antibiotics, anaesthesia, analgesia and vaccines.

Rules for Animal Research

5. Which legal requirements and guidelines does Roche fulfil in animal research?

Roche is committed to acting ethically and applying high standards of care and use in animal research. Roche adheres to numerous international, national and regional laws and regulations in the countries where it operates. These include the:

- National laws such as the Swiss Animal Protection Act or the U.S. Animal Welfare Act and the U.S. Department of Agriculture's Animal Welfare Regulations.
- EU Directive on the Protection of Animals used for Scientific Purposes (2010/63/EU).
- European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (ETS 123) by the Council of Europe.
- Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guidelines).
- Institute for Laboratory Animal Research (ILAR) Guide for the Care and Use of Laboratory Animals.

¹ Overview of Nobel Prizes awarded for Physiology or Medicine since 1901, available at <http://www.animalresearch.info/en/medical/nobelprize>

6. Which additional standards does Roche follow?

Roche adheres to a number of industry standards governing the use of animals in laboratory research and testing. For example, all major Roche Pharma research centres, as well as Genentech and Chugai, maintain accreditation from the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). This non-profit organisation enhances life sciences by promoting the responsible treatment of animals used in research, teaching and testing through voluntary accreditation and assessment programs.

In addition Roche has developed an internal guidance document, Animal Research – Principles of Care and Use, to ensure that every employee working with animals acts ethically and with respect for the animals in their care. These standards, which comply with existing laws, regulations and guidelines, apply to the use of animals during experimentation, to their housing and care, to the training and education of the personnel involved in their care and use, and to the conduct of investigative staff.

Additionally, Roche seeks alternative methods to animal research, the so-called 3Rs (see questions 17-22).

7. What external controls ensure that Roche complies with applicable laws and standards?

Roche's animal care and use programs are regularly evaluated by external bodies, including the following:

- In the United States, the U.S. Department of Agriculture (USDA)² conducts unannounced inspections of our animal facilities and issues sanctions if rules are breached. Roche fully supports and complies with these inspections.
- All animal research studies in Europe must be approved by regulatory authorities. This process includes an external ethical review.
- Internationally, Roche prepares an annual report for the AAALAC in order to maintain its accreditation (see question 6). In addition, AAALAC evaluation teams visit Roche research sites every three years and conduct a comprehensive review of our animal care and use procedures. This review covers, inter alia, environmental enrichment, housing and veterinary medical care.

8. What internal controls does Roche employ to comply with laws and standards?

The Roche Ethics Committee on Animal Welfare oversees Roche research sites in Basel, Penzberg, Nutley, Shanghai and sites operated by Chugai and Roche contractors. The oversight includes:

- Providing support and ethical advice for dealing with animals, in particular to researchers, animal welfare officers and laboratory animal personnel.

² The agency within USDA dealing with the protection of animals is the Animal and Plant Health Inspection Service (APHIS).

- Providing guidance on the application of the 3Rs – Reduce, Refine, Replace (see question 18).
- Developing recommendations for instance on the use of contractors for animal research.
- Ensuring that studies involving non-human primates are ethically justified and that potential alternatives have been considered.
- Receiving and addressing concerns and questions related to ethical issues raised by Roche employees or any external person.
- Offering the 3Rs Award and evaluating employees' applications for that award, as well as achievements in reducing the number of animals used, refining testing and improving animal wellbeing (see question 21).

Furthermore, the Committee aims to develop strategies for improvements in animal welfare that go beyond local legislation.

Each Roche research site in the United States has an Institutional Animal Care and Use Committee (IACUC). This federally mandated committee is responsible for ensuring compliance with animal welfare laws, policies and internal guidelines, including:

- Reviewing, at least once every six months, Roche's program for humane care and use of animals, using USDA Regulations and the Guide as a basis for evaluation.
- Inspecting, at least once every six months, all of the animal facilities, including animal study areas/satellite facilities, using USDA Regulations/Guide as a basis for evaluation.
- Preparing reports of its evaluations and submitting the reports to the Institutional Official.
- Reviewing specific concerns or complaints about animal care or use.
- Making recommendations to the Institutional Official regarding any aspect of the research facility's animal program, facilities or personnel training.
- Reviewing and approving, requesting modifications (to secure approval), or withholding approval of those components of proposed activities related to the care and use of animals.
- Suspending an activity involving animals when necessary; taking corrective action and reporting to the funding agency and USDA, when appropriate.

Additionally Roche internal procedures allow employees to raise ethical concerns related to animal welfare. These concerns may be raised anonymously.

9. Does Roche monitor animal research conducted by contract laboratories?

Yes, Roche works closely with various contractors in the field of animal research. We pre-qualify contract laboratories and then conduct routine audits to ensure the proper care and use of laboratory animals.

For example, in the United States, Roche requires a contract laboratory to have an attending veterinarian and an Institutional Animal Care and Use Committee to ensure that all research proposals comply with laws and regulations.

For non-clinical safety studies, Roche teams monitor contract laboratories during animal studies. These teams include trained personnel from Roche's non-clinical safety department and research quality assurance group.

In addition, members of the comparative medicine department inspect animal facilities at contract laboratories, evaluating contractors and animal vendors to determine compliance with animal welfare regulations.

Use & Care of Animals

10. What kinds of laboratory animals does Roche use and how many?

In 2011, Roche used 469,004 animals in its own research, while 68,606 animals were used by Roche contractors. Mice and rats comprised 97.8% of all laboratory animals used globally. The remaining 2.2% include other rodents and rabbits (0.7%), dogs (0.3%), non-human primates (0.5%) and other species (fish, minipigs, frogs: 0.8%).

11. How does Roche obtain laboratory animals?

Roche purchases nearly all animals from professional breeders who breed them specifically for research purposes. Exceptionally, some transgenic mouse, rabbit and rat strains are bred in-house. Roche does not use any pound or shelter animals.

12. Why must non-human primates be used in biomedical research?

As independent reviews confirm, there is a moral and scientific case for the carefully justified use of non-human primates in research.³

The areas of biomedical research where use of primates cannot be completely replaced include several vital research programs on infectious diseases (such as Malaria, Tuberculosis, Hepatitis, Influenza), neuro-degenerative disorders (Parkinson, Alzheimer, etc.), mental disorders (schizophrenia, depression, etc.), immune based diseases (diabetes, multiple sclerosis, immunotoxicity, allergy) and on oncology (monoclonal antibodies), which are of particular importance for Roche.

Whenever non-human primates are used, the purpose, in over 90% of the cases, is to evaluate the efficacy and safety of certain drugs and vaccines prior to the testing in

³ Report "The need for non-human primates in biomedical research, production and testing of products and devices" by the Scientific Committee on Health and Environmental Risks (an advisory committee to the European Commission) available at:
http://ec.europa.eu/environment/chemicals/lab_animals/pdf/scher_o_110.pdf

humans. Such studies are required by regulatory authorities worldwide. Roche has been developing treatments specifically designed to mark particular molecules in the human body and thus block their disease-causing effects for years. Such therapies are called monoclonal antibodies (MAbs). As those MAbs are species-specific, negative and/or positive effects must be shown by testing the substances in organisms which are as close as possible to the human body, namely often in non-human primates. In addition, before entering into studies with non-human primates it must be proven that other animal species cannot be used to reach the study's goal.

The remaining 10% of the non-human primates used involve basic research to advance human knowledge, such as the study of the nervous system, including the brain, and inflammatory diseases, including asthma and other respiratory diseases.

13. How does Roche reduce pain and distress among research animals?

Most research involves only slight or momentary pain such as taking blood samples, giving a single injection or having a change of diet. Nevertheless, pain and distress during research must be minimised, not only for ethical reasons, but also to maintain the reliability and reproducibility of results.

However, just as humans might experience pain and distress caused by a disease, a research animal serving as a model for a disease might experience the same. If more invasive procedures are necessary, anesthetics and/or pain relieving drugs are given in nearly all cases – unless their application would endanger the scientific validity of the experiment.

Animal welfare is of vital importance and trained animal technicians look after the animals under the supervision of veterinarians. Each project submitted for approval includes a detailed explanation of the animal research purpose, the likely effects on the animals and why the research cannot be done using other methods.

All research activities, including measures to minimize pain and distress, are closely scrutinised by the Roche Institutional Animal Care and Use Committee or the approving state authority before approval is given for a study.

The research activities are then monitored by internal and external bodies (see questions 7 and 8).

14. What happens to an animal at the end of an experiment?

At the end of a study, most animals are euthanised. This allows for a full examination of their tissues, which is necessary to determine the effects of the compound being tested.

Many of the non-rodent species used for drug metabolism or behavioural studies are re-used following a so-called washout period. This allows the compound they received to be

fully metabolised and excreted. Studies such as these involve the administration of compounds at dosages that are unlikely to cause adverse effects, while still providing useful information regarding pharmacokinetic and/or behavioural effects, with all procedures that are performed (injections, blood collection, etc.) judged as non-painful.

15. If scientists behave within strict guidelines, why do animal rights groups publish images of alleged misconduct and animal suffering?

Many images displayed by animal rights groups aren't examples of current practices. Instead, they portray outdated methods that are no longer considered acceptable by the scientific community. Furthermore, many examples are taken out of context and edited to elicit a negative public response about animal research. Communication practices such as these are unacceptable and undermine trust between researchers and animal rights groups, as they obstruct the pursuit of an open and factual discussion about animal research.

Scientists are concerned about the welfare of all research animals they use. Their concern is both humane and scientific. They have no reason to mistreat research animals and many reasons for treating them well, as the use of unhealthy, stressed or frightened animals reduces the reliability of experimental results. Veterinary staff is responsible for ensuring that research animals are well fed, free of infections and other illnesses and kept in an appropriate environment.

16. Does Roche engage with animal welfare organizations?

Yes. Roche welcomes regular, open and constructive dialogue on this complex issue. We have regular contacts with animal welfare organisations in order to improve mutual understanding and to exchange views on animal welfare related topics. For example, we communicate regularly through Interpharma with animal welfare organisations such as Swiss Animal Protection (SAP) and Animalfree Research.

Animal Welfare & Alternative Methods

17. How does Roche promote and contribute to animal welfare?

Roche has established mechanisms to ensure high standards of animal care and is committed to using animals appropriately and responsibly.

We comply with all laws and regulations and meet or exceed all industry standards. Roche employees and all contractors who perform animal research are required to obey these laws and standards and to conduct their research with respect for the animals. Moreover, all Roche employees involved in animal research continuously receive training in standards of care and ethics on the use of animals in research.

For example, Roche's Ethics Committee on Animal Welfare provides support and guidance on ethical issues raised by Roche employees or external persons, as well as on the application and promotion of the 3Rs. The Committee develops recommendations and oversees in particular that studies involving non-human primates are ethically justified and that potential alternatives have been considered. The Committee also aims to develop prospective strategies for improvements in animal welfare going beyond local legislation.

Additionally, Roche is a founder of the Swiss Charter on Animal Welfare, adopted in 2010 by Interpharma, the association of research-based pharmaceutical companies in Switzerland. The Charter commits Interpharma's members to join efforts for:

- applying high standards of animal welfare,
- discussing and working on internal and external auditing processes, and;
- fostering employee training, stakeholder dialogue and promotion of the 3Rs.

Interpharma reports annually on progress in implementing the Charter. A working group on auditing has been initiated to exchange best practices and join forces in external auditing efforts. Roche contributed also to the development of an interactive trilingual e-learning tool about the 3Rs by the University of Marburg⁴, which provides theoretical and practical training on animal use and care.

18. What are the alternatives to using animals?

The main alternatives are known as the **3Rs**⁵: **R**educe, **R**efine, **R**eplace

Reduce means using the fewest possible number of animals in a study. With careful design, sophisticated statistical techniques and modern imaging, it is often possible to significantly reduce the number of research animals used while still getting valid results.

Refine refers to decreasing the potential for suffering and continuously seeking advancements in animal husbandry, care practices and environmental enrichment, if reduction is not possible.

Replace is the term most often associated with alternatives to animal testing. Research animals are either replaced by methods that don't involve animals (absolute replacement) or by methods that use only the cells or tissues of animals (relative replacement). Such replacement alternatives include cell and bacterial cultures, computer simulations, mathematical modelling and the use of isolated animal organs. Irrespective of their sophistication, these methods are not always a realistic option, as they cannot simulate the complexity and level of coordination and integration of an entire organism with all its cells, tissues and systems. For the foreseeable future, any advanced research requires studies of the whole living organism in order to acquire as much information as possible

⁴ <http://www.vtk-online.de/>

⁵ Russell, W.M.S. and Burch, R.L., "The Principles of Humane Experimental Technique", London, 1959.

about a potential new medicine before taking it into human clinical trials. Therefore, while replacement is an overall goal, it is equally important to promote validating ways of reducing the number of animals used and refining testing procedures.

19. Have alternative methods lead to significantly lower numbers of animals used for research?

Yes. As the following examples show, in spite of growing research activities, the number of experimental animals required for research has fallen significantly:

- In Switzerland, research animals used in industry and academia have declined by over 60% since 1980.⁶ This includes figures from Roche which reflect a similar reduction. This decline would be even greater if a distinction was made between research by industry and academia. While animals used by industry decreased by 49% between 1994 and 2010, the numbers of animals used in academic biomedical research increased by 215% during the same period. Overall, this led to a slight increase in the number of laboratory animals used in Europe since 2001, may also due to more stringent safety regulations for medications.⁷
- In the US, for species covered by the Animal Welfare Act, which excludes mice and rats, the number of animals used by research decreased by 47% from the peak in 1985 to 2010.⁸

20. Which alternative methods has Roche implemented?

Roche is dedicated to implementing the 3Rs – **R**eduction, **R**efinement, and **R**eplacement. Where regulations allow, and where it is scientifically possible and ethical, Roche employs medical testing procedures that do not require animals.

Alternative techniques are incorporated wherever possible, and we continue working on projects designed to identify compounds with specific therapeutic action. We also discontinued the screening of large numbers of compounds on various species of animals, a technique that was much more prevalent in the past. Roche continues to improve upon and uses automated *in vitro* (“in a test tube or artificial environment”) screening methods to identify promising compounds before they are tested in animals. These screening methods help ensure that the compounds that end up being tested in animals are much more likely of being made into useful new pharmaceutical products. *In vitro* screening and other alternative methods help minimise the number of animals being used to test compounds in the early phases of development.

⁶ Statistics published by the Swiss veterinary authorities available at <http://www.tv-statistik.bvet.admin.ch/BasicStatistics.php>

⁷ http://www.forschung3r.ch/data/3r_bro_e.pdf

⁸ Animal Care Annual Report of Activities (Fiscal Year 2007), Appendix 5 available at http://www.aphis.usda.gov/publications/animal_welfare/content/printable_version/2007_AC_Report.pdf and for 2010 http://www.aphis.usda.gov/animal_welfare/efoia/downloads/2010_Animals_Used_In_Research.pdf

In addition, all Roche research sites have implemented a computer program that predicts the absorption of active substances in humans without animal tests. The program utilises data on solubility and cell permeability.

Determining whether a drug is safe without the aid of animal tests is a major scientific challenge due to the complexity of the processes involved. Roche is a worldwide promoter of computerised techniques for determining pharmacokinetics and tolerability using data from cell tests and clinical studies in humans.

21. What is Roche doing to educate and motivate its employees on alternative methods?

All Roche employees involved in animal research follow the guiding principles of the 3Rs. They also receive training in standards of care and ethics on the use of animals in research.

To further advance alternative methods, the Roche Ethics Committee on Animal Welfare sponsors every second year the Roche 3Rs Award. Launched in 2008, the aims are to increase awareness among employees and scientists about the 3Rs, to encourage the discovery of alternative methods and to make Roche a more innovative and productive company. So far, more than 70 entries have been submitted by Roche Pharma research sites, including Chugai and selected contract research organization partners.

3R Awards are given in the following three categories, with recent examples of award-winning projects:

- Scientific Progress
 - An *in-vitro* test for detecting toxic compounds before testing new drugs on animals. Developed by Roche Diagnostics, the test is now available for pharmaceutical preclinical research.
 - A computer-aided prediction tool developed to avoid toxicological effects and reduce the number of animal experiments.
- Laboratory Animal Care and Management
 - A method to gradually rehabilitate individually housed monkeys back into larger groups, increasing their social interaction and improving their wellbeing.
 - New accommodation for laboratory monkeys used in toxicology studies that provides more space to run, jump and climb, giving the animals living in conditions better suited to their needs.
- Surgery, Methods, Training and Techniques
 - A new method producing human antibodies without first having to immunize laboratory animals.

22. Does Roche participate in organizations that promote animal welfare?

Yes, we work with several organisations, including the following:

- Roche was a founding member of the **3R Research Foundation Switzerland**, which was set up more than 25 years ago. We continue to support the foundation and its objective of promoting alternatives and improvements to animal studies by funding research projects for new methods in line with the 3Rs. The foundation's administrative board brings together representatives from the industry, animal welfare organizations, the Federal Veterinary Office and the Parliamentary Group for Animal Experimentation Issues.
- Roche is a member of the **European partnership for Alternative Approaches to Animal Testing (EPAA)**. The partnership promotes the development of new 3Rs-based methodologies and alternative approaches to the use of animals in safety assessment in Europe.
- Roche was a founder of the **Swiss Charter on Animal Welfare**. Adopted in 2010 by **Interpharma**, the association of research-based pharmaceutical companies in Switzerland, the Charter commits Interpharma's members to efforts for applying consistently high standards of animal welfare, developing auditing processes, fostering employee training and stakeholder dialogue, and promoting the 3Rs. Interpharma reports annually on progress in implementing the Charter.⁹

Useful Links & Documents

Roche

Roche Position on Animal Research

http://www.roche.com/animal_research.pdf

Animal Research – Principles of Care and Use

http://www.roche.com/ar_principles.pdf

EU

Statistics on Animal Research in the EU

http://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm

EU Directive on the Protection of Animals used for Scientific Purposes (2010/63/EU)

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF>

Organisations

Animal Research for Life, a website with information about animals used in biomedical research and development of alternatives

www.animalresearchforlife.eu

⁹ See: <http://www.interpharma.ch/de/politik/Charta-fuer-den-Tierschutz.asp>

Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC)

<http://www.aaalac.org/>

Biotechnology Industry Association

<http://www.bio.org/>

European Federation of Pharmaceutical Manufacturers and Associations (EFPIA)

www.efpia.org

EFPIA's website on animal testing perspectives

<http://animaltestingperspectives.org/>

European Partnership for Alternative Approaches to Animal Testing (EPAA)

http://ec.europa.eu/enterprise/epaa/index_en.htm

Swiss Charter on Animal Welfare

<http://www.interpharma.ch/de/pdf/Charter-animalwelfare-E.pdf>