



Proposal for a new national research program (NRP)

Better animal protection and careful animal experiments using the 3Rs – Replace, Reduce and Refine

Submitted proposal (January 9, 2014) – **English version**

Precise problem description and research questions

Animal experiments are a topic of intense controversy in Switzerland, and levels of social acceptance have fallen again. On the other hand, the number of animal experiments conducted in Swiss universities is rising and new regulations on the evaluation of foreign substances may cause the numbers in industry to rise as well. This trend can be countered using the 3R principles. 3R comprises three tools which offer maximum protection for experimental animals without impairing the validity of scientific research: Replace stands for finding alternative methods to replace animal experimentation, Reduce for fewer animal experiments, and Refine for less stress on the animals involved.

Swiss institutions rank among the world's top universities. This success brings with it greater research volumes and more research groups. In addition, improvements to research processes and screening methods have accelerated progress in various research areas and hence increased the number of animal experiments. In industry, the effects that the new regulations on risk assessment of chemicals will have on numbers of animal experiments will become clear in the next few years.

The aim of this national research programme is to establish a 3R culture in science within Switzerland by which we can achieve a lasting reduction in numbers of animal experiments and minimise the suffering of the animals involved. Funds will be made available for the targeted research and development of alternatives to animal experimentation, together with new reduction and refinement techniques or procedures. The programme will also evaluate how research, animals, economy and society can benefit from the 3R principles. Based on these results, a strategy for the efficient and systematic implementation of 3R will be devised and put into practice.

Replacing animal experiments and devising innovative techniques for animal experimentation will also reinforce Switzerland's highly competitive position as a centre of research and a business location by creating new business development opportunities.

1. Main purpose, problems

Animal experiments are a topic of intense controversy. Research to promote a better understanding of biological processes in man and animals with the goal of preventing disease or improving treatment has always been based on experiments in the intact organism. Animal experiments are also conducted in order to assess the risks posed by chemicals, medicines and pesticides to human and animal health and to the environment. The majority of the Swiss population accepts animal experiments in research and risk assessment, up to a certain extent. However, acceptance wanes if the animals suffer. According to a recent survey by the Swiss animal protection association (STS), two thirds of the population oppose experiments in which animals suffer moderate pain, stress or anxiety and as many as 92% are against experiments that cause severe suffering.

Society has a moral obligation to help sick people and animals and to protect them from hazardous substances in the environment. At the same time, we are obliged to avoid stress and pain in experimental animals as far as possible. It is therefore essential to improve existing methods, to conduct fewer animal experiments and to replace such experiments with alternatives. The 3R principles Replace, Reduce and Refine are the cornerstones of humane animal experimentation. They were described over 50 years ago by Russell and Burch in their book 'The Principles of Humane Experimental Technique' (1959). 3R has been enshrined in Swiss animal welfare legislation since 1993.

- **Replacement** - methods that avoid animal experiments or replace them with alternatives. Examples of replacement include computer models and in vitro techniques, e.g. using organoid cultures or human or animal cell systems.
- **Reduction** - methods that minimise the use of animals and enable researchers to obtain comparable information with fewer animals or more information with the same number of animals, e.g. the development of imaging techniques that can be used to observe processes repeatedly in the same animal without having to euthanise animals at every measurement point.
- **Refinement** - covers improvements in scientific methods and animal husbandry that minimise actual or potential pain, anxiety, stress and injury, and improve animal welfare in situations which are unavoidable for the animals. It has been demonstrated that careful handling of experimental animals increases the validity of animal experiments.

3R is generally accepted in Swiss universities and in the research industry, and 3R principles are already being put into practice. Many researchers and animal technicians have contributed to a massive reduction in animal numbers and to improvements in animal experiments. As a result, the number of animals involved in experiments has fallen - from 2 million in 1983 to 600,000 in 2012. Since 2000, however, the number of animal experiments has remained relatively constant, and numbers are actually rising again in the universities due to a surge in research activity. New regulatory requirements such as the provisions on the risk assessment of chemicals (Registration, Evaluation and Authorisation of Chemicals - REACH) may also lead to a sharp increase in the number of animal experiments.

According to animal experimentation statistics, the research industry has done better than the universities in replacing animal experiments with alternatives. One reason for this is that animal experiments in product safety testing are now highly standardised and can therefore be replaced more easily. In addition, there are clear economic incentives to replace animal experimentation with alternative methods that permit high-throughput screening in product development. However, faster identification of promising drug molecules can lead - paradoxically - to more animal experiments.

3R is already being put into practice in university laboratories. With end points that lead to a lower degree of stress, animals' suffering is being reduced through refinement methods. In addition, many in vitro methods have been implemented, making it possible to replace animal experiments to a certain extent. Thanks to optimised cell culture techniques and advanced detection methods, high-throughput screening methods have been introduced in many research areas. Highly developed statistical tools have been implemented, allowing researchers to reduce the number of animal experiments without impairing the validity of the experiments.

However, university researchers use experimental protocols that are very different from each other. This situation is the result of the specific demands of the research issues and means that it is more challenging to achieve significant effects with the implementation of 3R. Another important factor is that many researchers see little incentive to research and develop new refinement, reduction or replacement methods. Especially in the case of younger researchers, this can lead to a trade-off between career and 3R considerations. No data are available that would permit a scientific investigation of the extent to which universities' efforts in the area of 3R have influenced reduction or replacement. In contrast, refinement efforts have seen a reduction in degree of severity according to statistics from the Federal Food safety and Veterinary Office.

The 3R Research Foundation has supported 3R research over the past 25 years, albeit with very limited financial resources. Two universities, Bern and Geneva, have established chairs of animal welfare and 3R research. They clearly play an important role, but they cannot deliver an across-the-board implementation of 3R research within scientific practice as a whole.

There has been no concerted nationwide 3R research initiative in Switzerland in the past 25 years. However, there are strong scientific, economic, ethical and social reasons in favour of a national 3R research programme:

- Biomedical research is extremely complex. As a general rule, however, good science needs to formulate precise research questions. The implementation of 3R principles makes it possible to re-

duce the use of highly complex systems with large numbers of uncontrollable variables, to concentrate on relevant research questions, and thereby to minimise variability and increase control over the experiments. Small laboratory animals are often used to study processes in a model. However, physiological differences between species make it difficult to transfer the results to humans and other species of animal. In such cases, irrelevant animal models should be replaced by in vitro technologies which eliminate such limitations. By tapping the potential of 3R, it is possible to focus on aspects of experimental systems that are actually relevant, and greater experimental control enhances the reliability of results obtained in biomedical research.

- From a scientific perspective, there are several important reasons to support the development of a coordinated 3R research strategy. Animal experiments are expensive; in vitro alternatives are often cheaper, less time-consuming and can provide more reliable results and produce fewer toxic waste materials, thus increasing efficiency in various research areas. New and innovative technological 3R developments would encourage up-and-coming biotechnology companies. Alternative technologies also make a major contribution towards future development in biomedical research. In addition, regulations require the research industry and universities to implement alternatives to animal experimentation.
- From an ethical perspective, 3R research leads to a substantial reduction in numbers of animal experiments and animal suffering, without compromising the moral obligation to achieve important goals in biomedical research or the development of new drugs and treatments for sick people and animals. Risk assessments require alternative methods not only in order to obtain mechanistic knowledge but also to evaluate potential risks of chemicals that are already on the market. 3R research promotes humane science.
- In order to meet social expectations, it is necessary to examine public perceptions, scientific knowledge and experience from a 3R research perspective, together with general perceptions of animal experimentation. This will allow us to devise better communication strategies to increase acceptance of research and product development in connection with animal experiments.

2. Precise research questions

The aim is to establish a 3R culture in Switzerland that is based on a strategy for efficient and targeted progress in the 3R principles. This 3R strategy should be supported by results, knowledge and conclusions drawn from 3R research projects funded by this national research programme. By adopting a forward-looking approach, it will be possible to determine future requirements for a 3R culture more realistically than by evaluating past successes which are not fully documented. Analysis of the 3R research efforts funded by the national research programme would make it possible to specify measurement variables, set benchmarks, estimate the costs of a 3R culture and define clear goals.

Examples of 3R research projects arise from the scope of work and the definition of the 3R principles. Funding should be awarded to projects with a clear 3R objective, i.e. projects seeking alternatives to animal experimentation, research projects aiming to reduce the number of animal experiments, and refinement projects focusing on technical improvements and innovations. This also includes projects for the basic characterisation of models that could contribute to 3R.

The research will also focus on how researchers perceive the individual 3R principles and how they put them into practice in their studies: which methods appear workable, which have scientific merit, and how much merit, which factors motivate, facilitate or inhibit the consistent implementation of 3R? This scientific data should be used to develop efficient training and communication tools for researchers.

Innovative 'outside-the-box' thinking will yield new ideas and technologies that can be used to solve problems for which no suitable methods are available at present. Innovation will not only reinforce Switzerland's highly competitive position as a centre of research but will also strengthen its reputation as a business location by creating new business development opportunities.

Finally, relations between animal experimentation, 3R and society will be documented in order to obtain valuable information for the political and scientific decision-making process and for effective communication channels.

3. Practical application of the NRP proposal

We are convinced that a concerted and targeted 3R strategy at national level is the only way to achieve substantial and lasting progress in implementing 3R principles. Implementation of these principles - Replace, Reduce and Refine - will ensure maximum efficiency in the use of experimental animals and at the same time maximum protection for the animals themselves.

The aim of the national 3R research programme is to achieve a substantial reduction in the number of animal experiments and to minimise the suffering of the animals involved.

Highly developed research tools that apply refinement, and less expensive research using alternative methods, will contribute to the strong competitive quality profile of Swiss research and industry. They will enable universities and industry to prioritise established in vitro methods with higher scientific merit over the results of less relevant animal experiments. They will enable the authorities to approve validated alternative methods more quickly. Targeted training for researchers and laboratory staff, and active communication of 3R content, are key elements for the successful implementation of 3R.

At the same time, innovative high-quality research projects will open up new opportunities for the economy. The proposed National Research Programme will generate new technologies with greater economic appeal and increased activity in the biomedical sciences, the biotechnology industry, the chemical industry and in risk assessment. These sectors are vital to the Swiss economy.

Finally, the resulting raised awareness and sound understanding of 3R in society, in the research community and among the public authorities will lead to humane practice in animal experimentation which will meet with general acceptance.

Authors

Prof Pierre Cosson
Physiologie des cellules et métabolisme, Université de Genève

Dr Fabienne Crettaz von Roten
Maître d'enseignement et de recherche, Université de Lausanne

Dr Marcel Gyger
Schweizerische Gesellschaft für Versuchstierkunde, Lausanne

Prof Andrew Hemphill
Experte Stiftung Forschung 3R
Universität Bern, Vetsuisse, Universität Bern, Parasitologie

Dr Ingrid Kohler
Tierschutz Versuchstiere
Bundesamt für Lebensmittelsicherheit und Veterinärwesen, Bern Liebefeld

Prof Klaus Peter Rippe
Ethik im Diskurs, Zürich

Prof Kristin Schirmer
Abteilungsleiterin Umwelttoxikologie, EAWAG, Dübendorf

Prof Martin Wilks
Direktor Swiss Centre for Applied Human Toxicology
Universität Basel