Basel Declaration Society | Allschwilerplatz 1 I Postfach | CH-4009
Basel www.basel-declaration.org | contact@basel-declaration.org

Use of Higher Mammals in Research

Almost 85% of the animals used for medical, veterinary and basic research across Europe, covered legally by the EU Directive 2010/63/EU, are mammals. Additional, legally regulated animal models include fish, birds, amphibians and reptiles. This position paper discusses how the research community should meet the needs of higher mammals used for basic and applied research. Of the total number of animals used for research in the EU in 2008 (most recent statistics), 79.4% were rodents (primarily mice [59.3%] and rats [17.7%]). The majority of the other mammals were rabbits and pigs. Cats, dogs, non-human primates, equids and horses accounted together for less than 0.4% of all animals - see http://ec.europa.eu/environment/chemicals/lab_animals/pdf/sec_2010_1107.pdf

The role of mammals in research:

The history of medical and veterinary research shows that using mammals has been essential for many important medical breakthroughs as illustrated by few select examples:

- Mice and higher mammals played a key role in the development of the breast cancer drug Herceptin, which is based on a humanised mouse protein.
- Higher mammals, in particular non-human primates have played a critical role in understanding many aspects of biology relevant to human physiology and disease, from the Rhesus factor in blood to the development of Deep Brain Stimulation, a treatment strategy for Parkinson's disease and dystonia.
- Rabbits, dogs and cows were necessary for developing the human papillomavirus (HPV) vaccine, which is very effective in reducing incidents of cervical cancer in women.

Although the last hundred years have seen many medical breakthroughs, many more diseases remain incurable. For example, Alzheimer's and degenerative motor neuron diseases will become more prevalent as Europe's population continues to age. Research using mammalian species remains key to facing down some of these new challenges, which includes:

- Research on rodents aimed at breaking down the tau protein tangles associated with Alzheimer’s disease. Furthermore, genetically modified mice help scientists to gain insight into the basic mechanisms that underlie normal organ development and physiology and the fundamental causes and potential prevention of human diseases.
- Non-human primates are also key models to study cognitive and fine-tuned motor abilities that are relevant for gaining insight into important human conditions such as neurodegenerative diseases, neural plasticity after damage to the nervous system, or the neural bases of the reward system and its pathologies, e.g. addiction.

- Studies using non-human primates also provide novel insight into infectious diseases that continue to claim many human lives (e.g. tuberculosis, malaria and HIV).
- Research on genetically modified pigs, another higher mammalian species, helps to understand and alleviate genetic and degenerative diseases such as Cystic Fibrosis and Duchene's muscular dystrophy.

Animal welfare issues:

Each species has different welfare needs that must be met when they are kept in captivity and used for scientific research. It is important that scientists address the specific needs of the species, strain or breed they have selected for their research. This will allow them to take best care of their animals and recognise signs of potential pain, suffering and/or distress. The greater sentience of mammals means that they need a different level of care, and that there must be a special focus on sound justification for using them for research. Some higher mammals may have needs that are difficult to meet in a laboratory setting, which must be considered in planning and evaluating such studies.

Before beginning a research project that uses animals, harm-benefit analysis must determine whether the potential suffering of animals is weighted by the expected gain of knowledge and/or benefits of the study. Benefits may include scientific, medical, and veterinary knowledge that can be translated to improving the understanding of normal and pathological mechanisms, which form the basis for developing scientific evidence-based treatments. Ultimately scientific knowledge is the major means whereby the health and welfare of humans and animals can be improved and protected. It is important to stress that advances in basic research which may, at the time of discovery, have little direct benefit to humans and animals, are an essential part of future clinical developments.

One of the key principles of animal welfare and good scientific practise is the 3Rs - Replacement, Refinement and Reduction of animals in scientific research (see Workshop 3). This principle is increasingly well-established and endorsed by the scientific community. It is also enshrined in both national and international legislations, such as the EU Directive 2010/63/EU. This principle and other ethical and legal constraints must be adhered to and respected wherever possible in all research using animals.

Choosing an experimental model:

A large variety of cellular and animal models are used in life-science research as the majority of medically relevant research topics cannot be investigated directly in human subjects for ethical reasons (see below) or because human tissues and cells are either not available or not suited. In veterinary and basic research, where understanding of animal development, physiology and/or pathophysiology is the goal, the use of animal models is often still the only valid approach. Whenever possible, studies using animals must be complemented by *in vitro* cell- or tissue models (of human and/or animal origin) and *in silico* computer simulations (based on data gathered using animal and/or cellular models). In any case, the use of animals must be limited to the necessary minimum. However, the Nuremberg Code

(1947) and the Declaration of Helsinki (1964; sixth revision 2008) state that experiments involving humans must be based on scientific knowledge, some of which will depend on experiments using animals. Thus, while many questions can be answered using our more distant evolutionary cousins, the analysis of closer relatives is also required to understand human conditions. Animal species that have contributed significantly to our understanding of living systems include invertebrates (e.g. fruit flies and nematode worms) and vertebrates (e.g. zebrafish, mice and non-human primates, typically macaque monkeys). Great apes - chimpanzees, bonobos, orang-utans and gorillas - are no longer used for invasive research in the EU.

Any ethically responsible and scientifically sound research relies on selection of the ***most appropriate*** animal model, which in return contributes to the 3Rs by improving the statistical reliability of the analysis and by likely achieving the best possible correlation with the study aims. While many basic biological questions can be answered using invertebrates or lower vertebrate models, mammalian models are required to study complex biological processes and model conditions relevant to both humans and mammalians. In addition, the knowledge obtained by studying different key members of the animal kingdom is vital to understand the evolutionary relations between different species, to connect this knowledge, and to provide synergy in our insights and concepts of the fundamental processes of life.

Position Statements:

- Scientific research is a vitally important part of medical and veterinary progress and increases our basic understanding of the underlying complex biological processes. Research involving animals remains an essential aspect of medical and veterinary progress and for increasing our understanding of complex biological processes. As long as no scientifically validated animal-free alternative approaches exist, the use of animals must be allowed in a legally regulated framework as has been implemented in the EU (EU Directive 2010/63/EU) and Switzerland.
- The decision on which animal or non-animal model to use must be made on the basis of their suitability for the research aims in question. Research involving animals must be subject to careful ethical evaluation, which weighs potential harms to the animal with the expected benefits.
- All animals have intrinsic value and deserve the highest standards of animal welfare. The evolved nervous systems of higher mammals demands special attention with respect to their individual care and animal welfare. Researchers and their team members, veterinarians and caretakers, as well as the relevant administrative authorities, must continue to work to continuously improve animal welfare based on novel scientific findings, which includes social housing of animals in sufficient space. Experiments, which cause more severe levels of pain, suffering or distress should be replaced or at least reduced continuously and as much as possible. It is essential that all staff working with animals is adequately trained in the experimental techniques and welfare needs of the specific animal species entrusted to them. In particular,

they must be able to establish a positive and compassionate relationship with the animals under study.

- The high level of concern that the public has for the higher mammals used in research, in particular cats, dogs, pigs and non-human primates, requires that scientist embrace an equivalently high level of accountability and transparency in communicating and publishing their research.