Plenary Lectures

Living the good life – how far can Refinement go

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Refinement is typically viewed as a means of reducing the harms to animals used in laboratory research, a key example being improved use of analgesics following experimental surgery. I review other similar examples of recent research on refinements, including improved methods of handling and euthanasia, to show how science can be used to assess the effects of these refinements on the welfare of animals. Focus in the animal welfare literature is now shifting from simply reducing harms we cause to animals to promoting positive experiences. The question has now become: Do the animals under our care experience "a good life"? Achieving a good life might require that we provide environments that allow animals to express natural behaviours that they are motivated to perform and provide opportunities for positive emotional experiences. The goal is that, on balance, positive experiences far outweigh any negative experiences. Our challenge now is in developing scientific methods that can address the question of a good life. Thus I also review recent research in animal welfare science that has begun to develop methods of identifying and assessing positive emotional states and assessing how the animal views its own condition. I conclude that refinement research should increasingly focus on providing laboratory animals a good life, and that research focussed only on reducing harms should be viewed as insufficient.

Engineering performance or performing engineering standards? Globalization and the application of the Three Rs

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This paper reflects on the insights a geographer might bring to understanding the international application of the 3Rs. The landscapes of scientific research are increasingly extensive, with established research centres in Europe and North America now supplemented by the emergence of new scientific initiatives in China, India and elsewhere. Scientific research is also becoming more interconnected, with an intensification of patterns of international collaboration. The use of laboratory animals is following similar patterns, perhaps most notably through a series of initiatives for generating, characterizing and archiving mutant mice across the international scientific community. Whilst publication metrics and other quantitative data give a sense of the patterns of these emerging collaborations, qualitative research is essential for understanding the processes through which such collaborations are forged and the challenges they present to established research practices and the governance of science in different localities. This paper outlines these processes, drawing on in-depth interviews and participant observation with researchers and stakeholders involved in the changing practices of laboratory animal research in North America, Europe and South-East Asia. In particular, it explores the often-entrenched debates between the use of performance and engineering standards to argue for animal welfare in the USA and Europe. It suggests both are linked to these specific landscapes of laboratory research, and the debate between them may need revision to further both animal welfare and meaningful research within the increasingly global landscapes of laboratory animal research.

A challenge to the ultimate 3Rs – *In silico* approach to evaluate chemical safety for humans

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The safety assessment of chemicals is one of the most important issues in regulatory science. Until recently, at least in Japan for industrial chemicals, the safety assessment process has been hazard-based. The toxicity of chemicals has been evaluated mostly using rodents and extrapolated to humans. Because of animal welfare and the requirement of high-throughput, *in vitro*, omics, and also *in silico* systems have been developed and introduced. Our final goal is the assessment of safety for humans, and of the many assay systems only *in silico* systems can focus directly on human beings. Any one (Q)SAR alone cannot do this task, but evaluating mutagenicity of chemicals by a combination of models revealed an acceptable performance, because of the relative simplicity of correlating chemical structure with mutagenicity. However, general toxicity is not easy to evaluate because of the many factors that can affect the results. Any single SAR or (Q)SAR cannot evaluate general toxicity of chemicals. Our project sponsored by NEDO/METI aims at the safety assessment of chemicals evaluated *in silico* and the final goal is to assist toxicology experts in making safety assessments of chemicals for humans accurately and efficiently. We constructed databases containing not only the results of animal repeat dose toxicity tests but also metabolism of chemicals, and of mechanisms of toxicity. We are constructing a platform to integrate these databases and are also including categories of chemicals to assess, based not only on structure but also on activities. We are also building a Bayesian network to incorporate the knowledge of experts.

Alternative training methods for clinical education – considerations

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The use of animate models in medical education and clinical training continues to be a controversial subject often clouded with emotion and experiential bias. On one side, there is clear feeling that it is ethically wrong to sacrifice animals for educational purposes. This position argues that medical and surgical skills needed to perform clinical procedures can be effectively acquired by alternative methods and will provide equivalent or superior results to training with animate models. The opposing viewpoint believes that appropriate exposure to concepts within an animate laboratory setting results in a level of understanding that is different and superior to other learning methods. The belief here is that hands-on animate experience allows mastery of interrelated complex concepts, where other methods cannot. This presentation will explore information available in the open literature comparing animate vs. inanimate training models, limitations of the available data, and considerations of necessary models based on approaches to learning.

Pursuing Medawar's challenge for full Replacement

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William Russell and Rex Burch, who pioneered the Three Rs approach in the 1950s, considered refinement and reduction of animal use in biomedical procedures as interim steps on the path towards replacement. In the 1960s, Peter Medawar, a Nobel Prize winning scientist who helped guide Russell and Burch's work, predicted that scientific innovation would someday completely replace animal use in science. Medawar correctly forecast the leveling off and subsequent decline in animal use in the last quarter of the 20th century. That decline has been checked by a rise in the breeding and use of genetically engineered animals in recent years, but this probably will be a temporary pause in a long-term trend of declining animal use. A 2007 report by the U.S. National Academy of Sciences, *Toxicity Testing in the 21st Century*, proposed a strategy that is likely to replace routine animal testing in toxicology with innovative methods within one to two decades. While replacing animals in biomedical research is more challenging given its diverse nature and larger scale, full replacement is a goal worth pursuing for a host of reasons. This presentation will call for coordinated, targeted, and sustained efforts to fully replace animals in research and testing, review current replacement initiatives, and offer policy and programmatic proposals for moving forward. Such replacement efforts will advance scientific progress and animal protection, and help steer the animal research controversy into a more productive phase.