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## BURSARY REPORT - ZEN AND THE ART OF SYSTEMATIC REVIEWS

### **Zen and the art of systematic reviews**

My book **The Costs and Benefits of Animal Experiments**, published in 2011 by Palgrave Macmillan, examined the human clinical, toxicological and educational utility of invasive scientific animal use, and reviewed alternative research, testing and educational strategies. It relied primar-

ily on systematic reviews (SRs) of large numbers of animal studies selected randomly, to provide insights into the contributions of animal research to human healthcare.

Accordingly, I was intrigued to learn of the First International Symposium on Systematic Reviews in Laboratory Animal Science, hosted by the 3R Research Centre (3RRC)

at the Radboud University Nijmegen Medical Centre, in The Netherlands in February. The symposium focus on SRs appeared to concord strongly with the themes of my book.

As she explained during her lecture, her desire to focus on SRs had arisen as the answer to the personal 'zen koan' of laboratory animal scientist Prof. Merel Ritskes-Hoitinga, who founded the 3R Research Centre (3RRC) in 2006. Zen koans are riddles designed to focus the mind. Merel's koan had been the question, "How can we improve science and animal welfare concurrently?" Although she believed other factors, such as open access publication of experimental results, were important she considered the most beneficial development would be the much wider use of SRs.

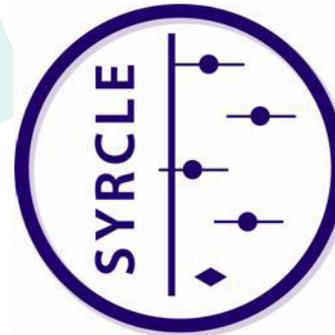
The use of SRs in human medicine is already well established, where they are internationally recognised as informing the highest standards in evidence-based health care. Since its establishment in 1993, these have been championed by the Cochrane Collaboration ([www.cochrane.org](http://www.cochrane.org)), which is an international network of more than 28,000 scientists in over 100 countries. These collaborators investigate the accuracy of diagnostic tests and the efficacy of prophylactic and therapeutic clinical interventions, and advocate evidence-based decision-making. Their SRs - which numbered over 4,600 by Feb. 2012 - are published online in The Cochrane Library, and in appropriate journals, such as Systematic Reviews.

Such SRs differ from traditional narrative reviews in several important respects. As defined by Prof. Ritskes-Hoitinga, "A systematic review is focused on a single question which tries to identify, appraise, select and synthesise all available high-quality research evidence relevant to this question." The research question should be clear and specific, and at least two bibliographic biomedical databases should be searched using a thorough and clearly-defined (i.e., transparent) strategy. Publications should be assessed for scientific quality, and poor quality studies excluded. Exclusion criteria should be clearly specified. Where amenable to such statistical analysis, the data from the included studies may be pooled to give the truest available indication of factors such as effect size (meta-analysis).

To assist researchers conducting SRs, the 3RRC has developed a step-by-step search guide, two Animal Studies Search Filters for Pubmed and Embase, and a Gold Standard Publication Checklist. The publications describing these may be accessed via [www.umcn.nl/Research/Departments/cdl/SYRCLE/Pages/default.aspx](http://www.umcn.nl/Research/Departments/cdl/SYRCLE/Pages/default.aspx).

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This new URL also reflects the importance the 3RRC accords to SRs. In fact, they consider them so important



that their entire focus has shifted to SRs, and their name has also just changed, to become the SYSystematic Review Centre for Laboratory Animal Experimentation (SYRCLE). Their new, circular logo is based on that of the Cochrane Collaboration.

The application of SRs to animal research is just beginning, and indeed, this conference is the first dedicated to this subject. Yet they offer profound benefits. They may not only provide the best available indication of effect size, but also frequently encourage better experimental quality.

As demonstrated by several speakers, including Dr Malcolm Macleod from the University of Edinburgh, Prof. Ian Roberts of the London School of Hygiene and Tropical Medicine, and Prof. Michael Braken from Yale University, poor experimental quality is a common feature of animal studies. These problems were described in my poster presentation entitled 'Systematic reviews of animal experiments demonstrate poor human clinical and toxicological utility', based on my Alternatives to Laboratory Animals 2007 paper of the same name. As described in my paper and book (which has an entire chapter dedicated to exploring factors limiting the human utility of animal models),

*"At least 11 systematic reviews [among all those identified during a comprehensive search] demonstrated the poor methodological quality of many of the animal studies examined, and none of the reviews demonstrated good methodological quality in a majority of studies... Common deficiencies included lack of: sample size calculations, sufficient sample sizes, appropriate animal models (e.g. aged animals or those with appropriate comorbidities), randomised treatment allocation, blinded drug administration, blinded induction of ischaemia in the case of stroke models, blinded outcome assessment, and conflict of interest statements. Some studies also used anaesthetics that may have altered the experimental outcomes, and substantial variation was evident in the parameters assessed."*

Prof. Braken surmised that the poor human predictivity of animal models was due both to their methodological

flaws, and also to the lack of applicable systematic reviews. However, animal models have additional, intrinsic qualities that may also limit their human predictivity and as stated by Dr Macleod, *“The intrinsic limitations of animal models are amplified by the way in which they are used.”*

Because SRs require evaluation of study quality and the exclusion of poor quality research, they focus attention on study design and methodological quality. Accordingly, they improve future experimental quality, thereby decreasing unnecessary duplication of animal studies. Dr Macleod also proposed a registry of animal studies, similar to those extant for human clinical trials, that researchers might con-

sult to prevent unnecessary experimental duplication.

On the second day participants were able to receive guidance in the practicalities of conducting SRs during a workshop. Financial constraints unfortunately prevented my attendance, but I’m nevertheless grateful to LASA for contributing towards my costs for attending the first day of this extremely important symposium.

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