



# Background to the Montréal Declaration on the Synthesis of Evidence to Advance the 3Rs Principles in Science, as Adopted by the 8<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Sciences, Montréal, Canada, on August 25, 2011

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## Summary

The participants of the 8<sup>th</sup> World Conference on Alternatives and Animal Use in the Life Sciences adopted the “Montréal Declaration on the synthesis of evidence to advance the 3Rs principles in science,” calling for a change in the culture of planning, executing, reporting, reviewing, and translating animal research. Synthesis of evidence (e.g., systematic review, meta-analysis, expert panels, narrative analysis, etc.) has been carried out in human medicine since the late seventies. Arguably, using similar processes of knowledge synthesis to methodically review animal studies would: a) improve the scientific quality of animal studies, b) better inform the ethical review of animal studies, c) help to achieve the Three Rs, and d) increase the transparency of the translation of animal-based research. There is evidence to suggest that reporting of animal studies may be lacking. Therefore, to improve synthesis of evidence for animal studies, it is important to improve scientific reporting.

*Keywords: reduction, refinement, animal studies, humane science, systematic review*

## 1 Introduction

To fully implement the principles of humane science, including the unifying concept of the Three Rs (Replacement, Reduction, and Refinement of animal use) (Russell and Burch, 1959), there is universal agreement that animals should only be used for scientific purposes when no Replacement alternative is available. Where animals continue to be used, it is both a scientific and ethical imperative to ensure that all animal studies are of relevance and quality.

To achieve this objective, a thorough inventory and analysis of all previously performed studies relevant to the question at hand, not only as individual studies but also in relation to one another, is an important step prior to the use of an animal model in support of a particular research question. In other words, a synthesis of evidence is called for. Within medicine, synthesis of evidence (e.g., systematic reviews) is used in order to evaluate and synthesize the outcome of individual study results. For the purpose of the Montréal Declaration, which focuses on animal studies, synthesis of evidence is defined as the contextualization and integration of research findings of individual research studies within the larger body of knowledge on the topic. Ac-

ording to Grimshaw (2010), synthesis of evidence can take a variety of forms: for example, meta-analysis, outcomes from a consensus conference or expert panel, or a literature-based review. Whatever its form, however, a synthesis of evidence must be reproducible and transparent in its methods, using quantitative and/or qualitative methods<sup>1</sup>. The current paper reflects on the origins of synthesis of evidence for human medicine, then goes on to outline the importance of conducting similar processes for animal-based studies. Recommendations are given on the steps that should be followed to achieve systematic reviews for animal studies.

## 2 The origins of knowledge synthesis and the Cochrane Collaboration

In 1972, British medical researcher Archie Cochrane published an influential book entitled, “Effectiveness and Efficiency: Random Reflections on Health Services,” in which he emphasized the importance of targeting limited resources towards health care that had been shown to be effective through properly designed evaluations.<sup>2</sup> Building on Cochrane’s work, a group of

<sup>1</sup> CIHR Report (2011). <http://www.cihr.ca/e/39033.html#Synthesis> (accessed 05.01.2012).

<sup>2</sup> <http://www.cochrane.org/>



Oxford-based health service researchers initiated a program of knowledge synthesis (“Cochrane Reviews”) on the effectiveness of health care interventions. Systematically assessing and summarizing research meant that health care decisions could then be made based on the best available research, paving the way for evidence-based medicine (Sackett et al., 1996). The Cochrane Collaboration began in 1992 as an international network of researchers, academics, practitioners, and users committed to making Cochrane Reviews (syntheses of research evidence that take the form of systematic review) available for health care decision-making.

While narrative reviews of healthcare research had existed for many decades, systematic methods had not been used routinely (Mulrow, 1987). The Cochrane approach involves systematic review using predefined, rigorous, and explicit methodology. Thus Cochrane Reviews are themselves scientific investigations. According to Grimshaw (2010), systematic reviews typically begin by stating the objectives of the research, then defining eligibility criteria for the studies that are to be included. All potentially eligible studies then are identified by applying the eligibility criteria. From the identified studies, the most complete data set feasible is assembled, including data extractions and quality appraisals of included studies. Data analyzed using statistical analysis (if appropriate), and a structured report of the research is prepared. Overall, this systematic review process promotes the use of transparent, explicit, and scientifically structured study approaches to answer a defined question, limiting random bias and systematic errors of bias (Mulrow, 1994). Though currently used mostly for human health care research, systematic reviews could be beneficial to animal research.

If the process outlined above were to be used to evaluate animal studies prior to starting a new program of work, it would contribute to the most appropriate choice of treatment and/or animal model, based on appraisal of all available scientific arguments. Systematic reviews also would require transparency with respect to animal studies, thus allowing for more rigorous application of the Three Rs and better addressing the concerns of society and policy makers.

Currently, there are no clear guidelines for writing a systematic review in the animal experimentation field, and because many papers are incomplete in reporting the necessary details or are of poor scientific quality, systematic reviews cannot be performed easily (Hooijmans et al., 2010a). For this reason, participants at the 8th World Congress on Alternatives and Animal Use in the Life Sciences (WC8) were of the opinion that it is premature to insist on systematic reviews, preferring instead to focus on encouraging other kinds of synthesis of evidence, recognizing that they may, of necessity, not involve the rigor of a systematic review. A step-by-step guide to systematically identifying all relevant animal studies was developed recently to facilitate a thorough inventory and analysis of all previously performed animal studies (Leenaars et al., 2011). To ease retrieval of animal-based studies, two filters were developed, one for PubMed (Hooijmans et al., 2010b) and one for Embase (de Vries et al., 2011).

### 3 The importance of systematic reviews of animal studies

Animal-based research is expensive, and it is important that public monies are directed to high quality science, and that the intended benefits to human, animal, or environmental health or well-being are achieved. It is reasonable that the value gained from a particular research area, project, or animal model should be subject to detailed analysis periodically in order to improve potential outcomes.

Empirical studies analyzing the quality of animal-based research indicate that the conduct of animal studies may not be as sound as is generally presumed (van der Worp et al., 2010). Scientific progress is driven by developing and testing novel hypotheses. If these are built on shaky foundations, however, and if subsequent translation of results from animal studies to treatment for human disease is not based on trustworthy data, there should be cause for concern. As an example, Pound et al. (2004) examined six systematic reviews of animal studies that had been carried out to determine how those studies had informed the clinical research. Their analysis showed that much animal research into potential treatments for humans is wasted because it is poorly conducted and not evaluated through systematic reviews. Similarly, Mignini and Kahn (2006) found that, where systematic review of animal studies has been attempted, the outcomes have been poor due to the lack of reporting in the original papers and the poor methodology employed for the reviews.

#### *Improving the scientific quality of animal studies*

Some recent publications have highlighted the poor quality of animal studies being reported in the literature. The reasons for this have been explored by Mcleod (2011) among others, and concerns have been raised that emphasis on a rapid publication rate is leading to lack of attention to experimental design or statistical analysis, and negative results or equivocal data are not being reported at all. To improve the translation of knowledge from animal studies, it is important that the conclusions drawn are not based on inaccurate information. For example, while the random allocation of experimental units to treatment groups and blind assessment of the treatment effects are standard and obligatory in human clinical trials, they still are not widely applied when performing animals experiments (van der Worp et al., 2010). In publications of animal studies, features of experimental design such as randomization and blinding often are not mentioned, and one can only presume that these have not been performed (Kilkenny et al., 2009). Sena et al. (2010a), among others, have pointed out that, in studies where there is poor experimental design, the positive effect of drugs and treatments tends to be overestimated. For example, within the field of stroke research, CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) focused on performing systematic reviews of animal studies due to the bad predictability of animal studies in this particular field (Sena et al., 2010b).

### *Better informing the ethical review of animal studies*

Research studies generally are built on work already published in the scientific literature. However, if there has not been systematic review of previous work, it is entirely possible that proposed animal studies are trying to answer questions that have already been answered (Pound et al., 2004). Unless the investigator and the animal ethics committee reviewing the study are aware of previous work, the basis for their decision to move forward with the study might be flawed.

A systematic review of previous work in the area also offers the opportunity to review the appropriateness of the treatments or animal models used in order to make a more evidence-based choice. A systematic review may be particularly valuable at the start of a program of work where a treatment or model new to the investigator is under consideration. A recent review by Bateson (2011) is a good example of how synthesis of evidence can be used to assess the use of a particular species (non-human primates) and the value of using that particular species in particular research areas. The Bateson review also highlighted the current difficulty in performing systematic reviews for animal-based studies.

### *Help to achieve the Three Rs*

Signatories to the recent Basel Declaration<sup>3</sup> committed to “*respect and protect the animals entrusted to us and not inflict unnecessary pain, suffering or harm to them by adhering to highest standards of experimental design and animal care.*” This declaration, made during a conference entitled “Research at a Crossroads,” brought together scientists who were committed to greater transparency in biomedical research, pledging to be more open about their research and to engage in more public dialogue (Abbott, 2010).

The initiators of the Basel Declaration were keen not only to have the importance of adherence to the principles of the Three Rs made front and center of their efforts, but they also wanted to emphasize that systematic reviews of animal experiments would contribute to implementation of the Three Rs: “*Systematic literature searches for animal experiments help to avoid their unnecessary duplication and thus reduce the number of laboratory animals used.*”<sup>4</sup>

An earlier declaration signed by participants at the Third World Congress on Alternatives and Animal Use in the Life Sciences, held in Bologna in 1999, affirmed a universal commitment to promotion of the Three Rs. Now, 13 years later, the Montréal Declaration is fulfilling that commitment by encouraging more rigorous examination of animal studies. Studies that have not been properly designed may result in invalid data and use of too many animals. A systematic review of previous studies can lead to better information concerning treatment groups, thus increasing the precision of estimates of treatment effects and reducing the number of animals needed in future experiments (Pound et al., 2004). Conversely, for

some experiments, the number of animals required may prove to be greater than is currently employed. Sena et al. (2010b, p. 5) also pointed out that “*non-publication of data derived from animals means those animals cannot contribute to accumulating knowledge and that research syntheses are likely to overstate biological effects, which may in turn lead to further unnecessary animal experiments testing poorly founded hypotheses.*”

In addition, Hooijmans et al. (2010a, p. 167) argue, “*Besides producing high-quality research, Systematic Reviews of animal experiments will result in direct implementation of the Three Rs. Systematic Reviews may provide the proper argumentation to decide which animal model will give the best answer to the (clinical) research question and to detect whether there are gaps in scientific knowledge that require new animal experiments (Replacement and Refinement). This also will aid in preventing unnecessary duplication of animal experiments (Reduction) and thus discourage unnecessary animal use and time loss.*”

Good examples of how synthesis of evidence might be used to facilitate implementation of the Three Rs may be found in recent papers by Hooijmans (2010b) and de Vries et al. (2011).

### *Increasing translational transparency*

According to Hooijmans (2010a), systematic review of animal studies will lead to a better interpretation of the already existing scientific results from animal experiments, through which a more transparent translation to the clinic and more guarantees for patient safety can become reality (Pound et al., 2004). An increasing number of studies being added to the scientific literature highlight the assumptions that have been made in moving to clinical trials based on little or poor synthesis of animal studies. For example, Sena et al. (2010b) and Mcleod et al. (2008) report that the documented efficacy of treatments in animal stroke studies is confounded due to publication bias and poor study quality.

### *Improving scientific reporting*

While it may not be possible currently to carry out systematic reviews of animal studies, there has been a recent call to improve scientific reporting through editorial policy (Osborne et al., 2009). The ARRIVE guidelines (NC3Rs, 2010) have been adopted by many journals, and these guidelines no doubt will contribute to better reporting of details. In addition, the Gold Standard Publication Checklist (Hooijmans et al., 2010a; Leenaars et al., 2011) has been published, which gives a detailed checklist with recommendations to use the checklist at the planning stage of experiments. We support the development of similar criteria for reporting experiments, compliance with which could be stated in full publication or abstract at minimal cost in space (Mcleod et al., 2005). Improvement in reporting will result in the ability to conduct systematic reviews for all animal studies.

<sup>3</sup> <http://www.basel-declaration.org/>

<sup>4</sup> Basel Declaration Annual Report (2010-2011), p.7.

[http://www.basel-declaration.org/basel%20declaration%20en/assets/File/Annual\\_Report\\_2011\\_en.pdf](http://www.basel-declaration.org/basel%20declaration%20en/assets/File/Annual_Report_2011_en.pdf) (accessed 05.01.2012)



#### 4 Main conclusions and recommendations of the Montréal Declaration

At the WC8, held in Montréal, Canada on August 21-15<sup>th</sup> 2011, a declaration was discussed and put up for adoption. This Declaration calls for a change in the culture of planning, executing, reporting, reviewing, and translating animal research via the promotion and coordination of synthesis of evidence, including systematic review of animal studies. By signing this Declaration, WC8 delegates agreed to actively promote the use of structured ways to achieve this. At the conference an exploratory meeting of scientists interested in the field of systematic reviews of animal studies was held, and it was agreed to start an international collaboration to further develop this field.

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