

Refinement on the Way Towards Replacement: Are We Doing What We Can?

Kathrin Herrmann

Freie Universität Berlin, Department of Veterinary Medicine, Institute of Pharmacology and Toxicology, Berlin, Germany; current address: Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, United States
kherrmar@jhu.edu

1 Introduction

[R]efinement is never enough, and we should always seek further for reduction and if possible replacement.

RUSSELL and BURCH, 1959, Chapter 4

Russell and Burch introduced the principles of replacement, reduction, and refinement of animal experimentation in 1959 in their groundbreaking book, *The Principles of Humane Experimental Technique*, to eradicate inhumanity towards non-human animals (hereinafter referred to as animals). They utilized the term *inhumanity* to indicate negative mental states experienced by animals used in research and the procedures that cause such mental states. Their goal was to avoid the use of animals wherever possible and to improve significantly the treatment of the animals still deemed indispensable, while improving the quality of scientific and medical research and testing (Russell and Burch, 1959). Since the 1990s, the 3Rs have slowly gained more acceptance within the animal research community. They have been recognized by organizations such as the Council of Europe (1986) and the World Organisation for Animal Health (2018), and they have been implemented in law in several countries, for example in Germany and in the UK (Herrmann, Köpernik and Biedermann, 2009; Zurlo, Rudacille and Goldberg, 1996).

Today, the principles are not only embedded in legislation in the European Union (EU) but around the world (Bayne et al., 2015). In the EU, Directive 2010/63/EU on the protection of animals used for scientific purposes came into effect in 2013, thereby requiring all EU Member States to implement the

3Rs fully. The EU Directive is more far-reaching compared to other legislation since it promotes a strong shift away from animal experimentation, with its goal being “full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible” (European Parliament, 2010, Recital 10). Furthermore, the EU Directive mandates that replacement should be the first priority, followed by reduction and then refinement to be implemented if animal use is deemed absolutely unavoidable (European Parliament, 2010, Recital 11). Russell and Burch (1959, Chapter 7) proposed the following hierarchy: “Suppose, for a particular purpose, we cannot use replacing techniques. Suppose it is agreed that we shall be using every device of theory and practice to reduce to a minimum the number of animals we have to employ. It is at this point that refinement starts, and its object is simply to reduce to an absolute minimum the amount of distress imposed on those animals that are still used.”

As a result of the incorporation of the 3Rs into legislation, which has mainly been driven by ever-increasing societal concerns (cf. Clemence and Leaman, 2016; European Citizens’ Initiative, 2016; Jones, 2017; Pew Research Center, 2015, 2018), it would seem reasonable to expect changes within the research industry, particularly replacement of animals with non-animal models. However, the cumulative effect of any such replacements has not prevented the overall number of animals used from steadily increasing since the 2000s (European Commission, 2013; Taylor et al., 2008; Taylor and Rego, 2016). When looking at the 3Rs and their impact, it seems that refinement, the R of *ultima ratio*, is receiving the most attention by the laboratory animal science community (AALAS, n.d.; FELASA., 2016), especially in basic and applied research where the majority of animals are utilized (in the EU, 65% of animals; cf. Daneshian et al., 2015). A survey conducted with participants of laboratory animal science training courses in four European countries found that refinement was seen as more feasible and more pressing than replacement and reduction of animal use (Franco, Sandøe and Olsson, 2018).

Due to this focus, the chapter starts by exploring the application of several refinement methods in practice, commencing with current housing and husbandry standards and a discussion about the benefits of a “culture of care”, followed by assessing important experimental refinements. To further assess the quality of animal-based research, it reviews necessary refinements in planning, conduct, and reporting practices of animal studies. The chapter then moves on to look at feasible ways to reduce and replace animal use by, first discussing tools to appraise animal studies whose application could lead to a significant reduction of animal experiments and thus numbers of animals used. It subsequently reflects on what the scientific community has