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Aligning the 3Rs with new paradigms in the safety assessment of chemicals

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ABSTRACT

There are currently several factors driving a move away from the reliance on *in vivo* toxicity testing for the purposes of chemical safety assessment. Progress has started to be made in the development and validation of non-animal methods. However, recent advances in the biosciences provide exciting opportunities to accelerate this process and to ensure that the alternative paradigms for hazard identification and risk assessment deliver lasting 3Rs benefits, whilst improving the quality and relevance of safety assessment. The NC3Rs, a UK-based scientific organisation which supports the development and application of novel 3Rs techniques and approaches, held a workshop recently which brought together over 20 international experts in the field of chemical safety assessment. The aim of this workshop was to review the current scientific, technical and regulatory landscapes, and to identify key opportunities towards reaching these goals. Here, we consider areas where further strategic investment will need to be focused if significant impact on 3Rs is to be matched with improved safety science, and why the timing is right for the field to work together towards an environment where we no longer rely on whole animal data for the accurate safety assessment of chemicals.

1. Introduction

Within the last two decades there has been a growing interest in, and enthusiasm for, the identification of alternative approaches for toxicity testing that reduce or refine the use of animals in safety assessment, or obviate the need for animals altogether. There have already been some successes, and a variety of new test methods, including *in vitro* methods, have been developed and validated. Nevertheless, it is still the case that the regulatory safety assessment of new chemicals continues to rely heavily on *in vivo* testing.

There are scientific, ethical, legislative and regulatory reasons why it is timely to seek to move away from traditional approaches for safety assessment and to develop alternative paradigms that exploit rapid advances in biomedical sciences, and that also deliver lasting benefits with respect to the replacement, refinement and reduction of animals (the 3Rs).

Abbreviations: 3Rs, replacement, refinement and reduction of animals in research; AOP, adverse outcome pathway; EURL-ECVAM, European Union Reference Laboratory for Alternatives to Animal Testing; ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods; ILSI-HESI, International Life Sciences Institute – Health and Environmental Sciences Institute; NC3Rs, National Centre for the Replacement, Refinement and Reduction of Animals in Research; NRC, US National Research Council; OECD, Organisation for Economic Co-operation and Development; PBPK, physiologically based pharmacokinetic; QSAR, quantitative structural activity relationship; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; SEURAT, Safety Evaluation Ultimately Replacing Animal Testing; TTC, threshold of toxicological concern.

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To facilitate the realisation of these aspirations, the UK National Centre for the 3Rs (NC3Rs) recently convened an expert Chemicals Brainstorming Workshop to review the current landscape and identify innovative opportunities to reduce the need for animals in the toxicological evaluation of chemicals, and in the safety assessment process. The workshop brought together 21 international experts from industry, academia and governmental and regulatory agencies, who collectively identified current opportunities and priority areas for future research.

2. Setting the scene: why is now the right time to take advantage of alternative paradigms?

Recent years have witnessed significant and exciting developments in biomedical science. Those that have already impacted on toxicology and safety assessment, or which clearly have the potential to do so in the future, include stem cell biology, bioinformatics and systems biology, cell–matrix interactions, and the application of computational chemistry and mathematical modelling to biological systems. This list is not exhaustive, and such has been the progress in some areas it is clear that presently there exist many opportunities to harness and exploit new science and emerging technologies to drive lasting change in toxicology. Work aimed at developing new scientific strategies to assess the safety of chemicals and drugs is being driven by the need to improve the relevance for humans of model systems used for safety assessment, to incorporate greater mechanistic understanding, and to reduce, refine and replace the need for animals; a landmark publication in this field was the US National Research Council report 'Toxicity Testing in the 21st Century: A Vision and a Strategy' (NRC, 2007).

The development and regulatory acceptance of *in vitro* skin and eye irritation tests (*e.g.* OECD Test Guidelines 437, 438, and 439) are testament to the possibilities of a future where non-animal methods are a requirement, rather than an alternative. The development of tests such as these represents a real achievement. However, it has to be acknowledged that within the context of the broader landscape of toxicology they address more tractable endpoints (*i.e.* acute effects in discrete tissues), but nevertheless required a substantial international investment of time and resource. It is important, therefore, not to underestimate the challenges that will need to be addressed if non-animal methods for the assessment of other more complex endpoints are to be developed successfully, although there are increasing opportunities to overcome these challenges through the application of intelligent science. For example, there is potential for the issues surrounding the extrapolation of quantitative predictions from *in vitro* to *in vivo* scenarios to be addressed through systems-level computational modelling; furthermore, the development and utilisation of higher order tissue culture systems such as organ-on-a-chip technology illustrate the efforts being made to overcome the inherent difficulties associated with replacing the integrated nature of the intact organism with non-animal test methods (Wikswo et al., 2013).

The most demanding of challenges which continues to require focussed efforts will likely be the development of approaches that permit evaluation of the potential for systemic adverse health effects in humans following repeated systemic exposure. The range of effects that may potentially derive from such exposure is clearly very extensive. With the intention of addressing these challenges, several large-scale collaborative initiatives have been established, which include the SEURAT-1 cluster in the EU (www.seurat-1.eu) and the ToxCast Programme in the US (www.epa.gov/ncct/toxcast). The development of non-animal approaches also provides industry with the tools to address the requirements and opportunities offered by many legislative frameworks – both those which stipulate that animal testing should be carried out only when no other suitable alternative is available (*e.g.* the EU REACH Regulation; EU, 2006), and where there are regional bans on animal testing, particularly for cosmetic products.

The benefits that derive from the successful development of non-animal methods for safety assessment can therefore be summarised as (but are not limited to):

(a) The potential to reduce uncertainty and increase the relevance of human safety assessments, by basing safety decisions on human biology (*e.g.* using data from tests on human cells), rather than on outcomes from traditionally applied rodent models.
(b) The establishment of robust strategies that exploit all of the knowledge currently available which will ultimately enable the application of alternative paradigms that accelerate and reduce the cost of safety assessment, while at the same time better meeting health protection goals.
(c) Addressing societal concerns related to the use of animals in toxicity testing, particularly in instances where methods are associated with high severity/suffering or where high numbers are used.
(d) The meeting of legislative requirements within regulations around the marketing of chemical products and the use of animals for scientific purposes, which stipulate that animal tests should be avoided wherever possible. This is especially pertinent to the personal care products industry, due to the recent and planned geographical bans on the marketing of cosmetic products and ingredients tested using *in vivo* methods.
(e) The potential to reduce the time and cost associated with chemical safety assessment, which remains a resource intensive process, whilst at the same time driving innovation.

But it is really the combination of an appetite for change and the opportunities to exploit new science and technology, alongside an appreciation that embracing 3Rs approaches will inevitably improve the quality of toxicology, which will be the most important driver of developments in this area. We are now at a scientific tipping point where concerted efforts within the toxicology community have the scope to genuinely transform this field, towards a vision of improved safety assessment which relies less and less on the traditional practices, and embraces the advancements in science that alternative paradigms can offer.

3. Translating the use of alternative paradigms into innovative opportunities to reduce, replace and refine animal use

Embedded within the vision of improved toxicity testing and safety assessment are the 3Rs principles. Not only could the increased application of novel *in vitro* and *in silico* techniques contribute to the reduction and perhaps replacement of whole organism testing, but the incorporation of the principles into everyday science may actually perpetuate technological advances and innovation (as exemplified by the NC3Rs CRACK IT scheme; www.crackit.org.uk). Many opportunities exist within the field of toxicology to develop and apply non-animal methods, and at the very least to improve the quality and utility of data obtained from the *in vivo* tests which continue to be undertaken; for example, through efforts to improve the predictivity and increase the number/types of relevant measurements taken in short-term animal studies. Changes to *in vivo* approaches could help to address several endpoints for which otherwise additional animal studies would have to be performed, and lead to a decrease in the extent of chronic testing necessary.

The important question is, can the application of the 3Rs principles improve the science of safety assessment; that is, improve the relevance of toxicity information to humans by