The silver lining in the Brexit cloud -
Can the UK lead the way to develop a strategy for replacing animals in scientific procedures?

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The release of the UK Annual Statistics on Scientific Procedures on Living Animals seemed to represent a success for the UK government, with declarations that the reduction in animal use (a modest 3% decrease compared to 2018 figures) represented the fourth consecutive year in which animal use had fallen. But how much can we really applaud a decrease of fewer than 120,000 animals used for scientific purposes in the UK when the total number of procedures using animals has remained static at over 3 million for the last 12 years?

The statistics offer some insight into the reason(s) behind continued reliance on animals in laboratories, including where this is driven by government requirements. For example, pre-market toxicity testing for drugs and chemicals is legally required in order to demonstrate safety prior to marketing. However, failures in the capacity of animals to predict human responses are well-documented [1-5], while modern, non-animal methods are increasingly shown to be superior for predicting toxicological hazards to humans [6]. Animal use for toxicity testing purposes has been in decline (less than half a million procedures per year in the UK), reflecting the decades of investment by consumer, pharmaceutical, and other industry sectors in avoiding animal use and embracing novel non-animal approaches to the extent possible within regulatory strictures.

European Directive 2010/63/EU on the protection of animals used for scientific purposes claims a 'final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so,' yet an analysis for the 'Building Back Better' event held on September 10 suggested that, at the current rate of decline, animal use in the EU will not get to zero before the year 2100. Clearly, more ambitious policy targets and investments in human-predictive, non-animal approaches to research and testing are required.

Committing to replace animal use for all scientific purposes respects public and scientific concerns regarding the validity and acceptability of animal models as human surrogates [3, 7-11], could save tens of millions of sentient animals from a sad existence and often painful death, and importantly, advance the non-animal methodologies needed to improve human predictivity for safety testing and health research. What is needed for the UK to drive this forward? Humane Society International suggests the following recommendations as an initial list of what may be required to take advantage of the rapidly evolving scientific and technological landscape [12]:

• Follow the trailblazing vision of the US Environmental Protection Agency and declare the UK's intention to phase out all regulatory animal-based testing requirements by 2035.

• Improve agility of regulatory requirements to allow acceptance of non-animal data and inclusion of these test strategies into guidance to reduce future animal use.

• Prioritise funding for basic biology and human health research using human-based tools and technologies over animal-based research (including the genetically modified, so-called 'humanised' animal models).

• Develop freely accessible education and training courses on the development and application of non-animal methodologies for all stakeholders (researchers from pharma, academia and industry, funders, regulators, ethical review bodies, animal welfare technicians and others).

• Create and maintain updated resources on the development, application and status of non-animal methodologies (e.g. the European Commission's Joint Research Centre project on Respiratory tract Diseases).

• Ensure that all UK-funded studies generating or using human data are collected in collaborative, open-access high-quality databases, according to FAIR principles.

These recommendations are nothing unexpected or out of the ordinary - the SARS-CoV-2 pandemic has shown us how flexible both funding bodies and regulators can be in rapidly shifting priorities, allowing emergency use of potential therapies and redirecting research funding towards vital efforts to better understand the virus. Currently, European funding dedicated to non-animal approaches amounts to a meagre 0.036% of total research awards [13], and clearly this needs to change. Here in the UK, of the £1.8 million awarded to five projects by the National Centre for the 3Rs (NC3Rs) in 2019, only one project was completely focused on the development of fully non-animal approaches. Until we see substantive investment into the development and application of non-animal approaches, and

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improved two-way communication between end-users and developers, we will not improve confidence and application of non-animal methodologies, and we will not attain the goal of full replacement of animals in testing and research.

Leaving the European Union now offers the UK the independence and freedom to demonstrate its commitment to improving science and embracing cutting-edge technologies - this is the UK's chance to lead the world and show that we really can be a hub for innovative, effective science and a nation of animal lovers.

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(1) For the purposes of the UK statistics, the number of procedures is counted, rather than the absolute number of animals - this is likely to be slightly greater than the number of animals used. An individual animal may be re-used in several procedures, depending on the severity of the use. The UK do not publish re-use data but the figures from the EU reveal that re-use represents only around 2% of total use and has remained static for the last three years in which data were collected (2015, 2016 and 2017).