Comment

The European Citizens' *Stop Vivisection* Initiative and the Revision of *Directive 2010/63/EU*

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Summary — Animal experimentation is presented to the public as an ongoing debate between research scientists on one hand, and the animal protection community on the other. An opportunity to break out of this mindset presented itself in the form of a European Citizens' Initiative, *Stop Vivisection,* which challenged *Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals for scientific purposes*. The manifesto of the initiative called upon the European Commission to replace the existing Directive with a new proposal that does away with animal experimentation, and instead makes compulsory the use of human data as a predictive modality for the study of human diseases and responses to drugs. Although the Initiative succeeded in gathering the required one million signatures, the European Commission ultimately rejected the proposal. However, some of the lessons learned from the Initiative may well be relevant to the revision of *Directive 2010/63/EU*, due to take place by 2017.

Key words: *animal experiments, Directive 2010/63/EU revision, European Citizens' Initiative.*

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Introduction

The European Citizens' Initiative (ECI) is a European Union (EU) instrument in participatory democracy, introduced with the Treaty of Lisbon in 2007, the principal aim of which is to enable ordinary citizens to participate directly in the development of EU policies (1). In order to qualify, an ECI must obtain the support of one million EU nationals belonging to at least one quarter of the Member States (2). Between April 2012 and June 2015, a total of 51 ECIs were officially submitted to the European Commission (EC), and of the 31 that were registered, only three ECIs succeeded in being heard at the European Parliament (3). One of them, the *Stop Vivisection* ECI, with 1,173,131 validated registered signatures, was submitted to the EC on 3 March 2015 and was subsequently heard in the European Parliament on 11 May 2015.

The manifesto of the *Stop Vivisection* ECI stated that (4): *Considering clear ethical objections to animal experiments and solid scientific principles that invalidate the 'animal model' for predicting human response, we urge the European Commission to abrogate* Directive 2010/63/EU *on the protection of animals used for scientific purposes and to present a new proposal that does away with animal experimentation and instead makes compulsory the use — in biomedical and toxicological research — of data directly relevant for the human species*. The legislation mentioned in the manifesto, i.e. *Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals for scientific purposes* (5), was adopted on 22 September 2010. According to the European Commission website (6), *The Directive is firmly based on the principle of the Three Rs, to replace, reduce and refine the use of animals used for scientific purposes. The scope is now wider and includes foetuses of mammalian species in their last trimester of development and cephalopods, as well as animals used for the purposes of basic research, higher education and training. It lays down minimum standards for housing and care, regulates the use of animals through a systematic project evaluation requiring* inter alia *assessment of pain, suffering distress and lasting harm caused to the animals. It requires regular risk-based inspections and improves transparency through measures such as publication of non-technical project summaries and retrospective assessment. The development, validation and implementation of alternative methods is promoted*

through measures such as establishment of a Union reference laboratory for the validation of alternative methods supported by laboratories within Member States and requiring Member States to promote alternative methods at national level.

This present Comment will examine two issues: a) the strategy underpinning the ECI; and b) how the ECI might impact on *Directive 2010/63/EU*, which is due for revision by 2017.

The Strategy Underpinning the *Stop Vivisection* ECI

The strategy underpinning the *Stop Vivisection* ECI was to review the use of animal models in the light of evidence-based science and scientific theory. The use of animal models is the current paradigm in biomedical research (7–10). Animal experimentation is presented to the public as an ongoing debate between research scientists and the animal protection community, or alternatively, as a cost–benefit exercise in which animal suffering must be balanced against human medical progress. Both of these approaches are problematic, because the format of the debate is inherently asymmetrical. In the former approach, research scientists tend to argue in terms of medical progress, while animal protection groups argue in terms of animal suffering. In the latter approach, one cannot measure animal suffering and potential human benefit with the same currency. The harm–benefit analysis procedure remains a 'comparison between apples and oranges', but improvements in the ethical review process have been suggested as a way forward (11). For example, the inclusion in the review process of individuals with expert knowledge of non-animal replacements would signal a more-level playing field than the current system (12).

Society does, however, accept animal suffering on the understanding that it will result in significant benefit to humanity. In the words of Giles (13): *In the contentious world of animal research, one question surfaces time and again: how useful are animal experiments as a way to prepare for trials of medical treatments in humans? The issue is crucial, as public opinion is behind animal research only if it helps develop better drugs. Consequently, scientists defending animal experiments insist they are essential for safe clinical trials, whereas animal-rights activists vehemently maintain that they are useless.*

Animals are also used in science in ways that have nothing in common with their use as predictive models. Examples include the use of animals to provide heart valves or as bioreactors to produce monoclonal antibodies, to which valid alternative replacements exist (human heart valves and phage display, respectively). Semantically, however, there is no *alternative* to a process that is ineffective. A paradigm that is not effective or functional should be abandoned, and should not be pursued solely because of tradition. The miasma theory of disease was abandoned, as was bloodletting, despite the fact that bloodletting supposedly cured diseases for which we still have no cure. Hence, the emphasis of the *Stop Vivisection* ECI on the need for predictive modelling based on human data.

Although *Directive 2010/63/EU* is concerned primarily with the application of the Three Rs (*Replacement*, *Reduction*, *Refinement*), it should be noted that the Directive clearly acknowledges the use of animals as models for the testing of products destined for human use. Specifically, Paragraph 3 of the Directive refers to *Decision 1999/575/EC* concerning the conclusion by the Community of the *European Convention for the protection of vertebrate animals used for experimental and other scientific purposes* (14). *Decision 1999/575/EC* states, *inter alia*: *Whereas the provisions of the said Directive and Convention affect the conditions of production and placing on the market of products and substances the development of which involves the experiments referred to therein; whereas those provisions therefore contribute to the establishment and functioning of the internal market, the completion of which constitutes one of the chief objectives of the Community* (15).

Directive 2010/63/EU is the overarching legislation for the protection of animals used for scientific purposes, whereas specific legislation covers different sectors in which animals are used as test subjects (for example, the Biocidal Product Regulation *528/2012/EU*, the REACH Regulation *1907/2006/EC*, and *Directive 2003/63/EC*, relating to medicinal products for human use).

Paragraph 4.2.2 of *Directive 2003/63/EC*, relating to medicinal products for human use states, that: *The pharmaco-kinetic program shall be design [sic] to allow comparison and extrapolation between animal and human.* Paragraph 4.2.3 refers to single-dose and repeat-dose toxicity. In the category of reproductive toxicity, reference is made to the use of two animal species: *Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent* (16).

Therefore, the overall strategy of the *Stop Vivisection* ECI was to challenge the assumption inherent in *Directive 2010/63/EU* — that the use of animal models is valid as a means of predicting human outcomes with respect to pharmaceutical drugs, industrial chemicals and human diseases. The current use of animal models is founded on the notion that one species has predictive value for another. This dates back to the 19th century, when species were being studied on a level of biological organisation of similar gross morphology (17). Currently, various animal models are used to

ascertain how a perturbation, such as a drug or disease, will affect humans at higher levels of organisation. Greek *et al.* have critiqued this point at length (18–28).

It has long been widely known that mechanisms for toxicity are frequently quite different between species, and yet, animal testing remains the 'gold standard' for historical reasons. The US Food and Drug Administration (FDA) and other regulatory agencies are in the process of evaluating alternatives to animal testing, with the aim of developing models that are truly predictive of human mechanisms of toxicity and limiting *in vivo* toxicology testing (29).

The ECI proposed that the Directive be replaced with legislation that reflects current evidence-based scientific knowledge. Indeed, the opening sentence of Paragraph 39 of the Directive states that: *It is also essential, both on moral and scientific grounds, to ensure that each use of an animal is carefully evaluated as to the scientific or educational validity, usefulness and relevance of the expected result of that use* (5).

On 11 May 2015, the official hearing of the *Stop Vivisection* ECI took place at the European Parliament in Brussels. Oral presentations were given by three of the representatives of the ECI: Gianni Tamino, professor of biology and bioethics at the University of Padua, Italy; Claude Reiss, physicist and cellular biologist and president of a non-profit NGO (Antidote Europe); and Andre Menache, veterinary surgeon and director of Antidote Europe (30). In addition to the oral presentations, a 107-page dossier was submitted to the EC (31). The dossier contained 10 proposals aimed at phasing out animal experiments and accelerating the application of validated non-animal methods. The ECI also challenged the validity of the use of animal models to predict human responses with respect to drug testing and disease modelling. Finally, the dossier examined the impact on public health and the environment of EU policies that are guided and formulated on the basis of safety data generated through animal tests (for example, the Biocidal Product Regulation *528/2012/EU*, the REACH Regulation *1907/2006/EC* and *Directive 2003/63/EC,* relating to medicinal products for human use).

The *Stop Vivisection* ECI derived its arguments to challenge the validity of the use of animal models from empirical evidence, complexity theory and evolutionary biology. Empirically, animal data can be evaluated on the basis of sensitivity and specificity, notably in the field of regulatory toxicology (27). Both *in vitro* and *in vivo* data suggest that animals are not predictive of human outcome and *vice versa*: several studies, including systematic reviews, have shown that animal data predicted human outcomes only around half of the time (32–35). Huang *et al.* (36) observed that human *in vitro* cell line data were not predictive when compared to animal toxicity data within the framework of the Tox21 10K programme and by using quantitative high-throughput screening.

In terms of animal numbers, the category 'biological studies of a fundamental nature' is responsible for the greatest use of animals in the EU (46.1%; 37); in terms of funding, basic research involving animals continues to receive considerable financial support. Between 2007 and 2013, the 7th Framework Programme for Research and Technological Development (FP7) had a total budget of over €50 billion at its disposal (38). Currently, Horizon 2020 is the biggest EU Research and Innovation programme ever, with nearly €80 billion of funding available over seven years (2014 to 2020) and "promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market" (39).

The revision of *Directive 2010/63/EU,* scheduled for 2017, is a timely opportunity to evaluate the claims of breakthroughs and discoveries attributed to basic animal research studies with respect to translation into clinically useful treatments. To paraphrase the earlier statement by Giles (13), the issue is crucial, as society is behind animal research only if it helps develop better treatments — and yet, few scientific audits exist in this field. An overview conducted by Contopoulos-Ioannidis *et al.* (40) examined the translation rate of 25,000 "highly promising" basic research articles published in leading science journals between 1979 and 1983. Crowley (41) analysed the findings of this overview and suggested that the transfer rate of basic research into clinical use is very low, in this case 0.004%. Ioannidis concluded that: *Evidence-based medicine does not seem to have penetrated basic and preclinical science, while basic and preclinical research is often performed in a clinical and methodological vacuum* (42).

The low rate of translation of findings in animal models into clinical applications is underscored by our current understanding of evolutionary and systems biology. For example, Seok *et al.* (43) reported that mouse models poorly mimic human inflammatory diseases, and observed a random correspondence between murine genomic responses to inflammation and their human gene counterparts. Mestas and Hughes (44) pointed to important species differences in the immune systems of mice and humans (45), while Yue *et al.* explained these species differences in terms of species-specific gene regulation (45). Such species differences also extend to the use of non-human primates (46, 47). In addition, the existence of polymorphisms within species (and not least, in humans) has implications for the preclinical evaluation of new drug candidates (48, 49).

Finally, although human and non-human mammalian systems may share conserved

processes at lower levels, or modules, of biological organisation (for example, *hox* genes), such modules are insufficient for inter-species extrapolation when studied at higher levels of organisation, such as body systems (50). Evolved complex systems are much more than the sum of their parts and are not amenable to reductionist methodologies in the same way that simple systems are (51). It is well known that evolved complex systems display emergent properties, making extrapolation between different animal species virtually impossible (27). According to Koch, such systems (for example, the mammalian immune system) are "characterized by large numbers of highly heterogeneous components, be they genes, proteins, or cells. These components interact causally in myriad ways across a very large spectrum of space–time, from nanometers to meters and from microseconds to years" (52).

In the USA, the National Institutes of Health (NIH), the biggest biomedical research organisation in the world, recently announced that it "will no longer fund biomedical research on chimpanzees" (53). The NIH announcement comes in response to a 2011 scientific report commissioned from the US Institute of Medicine (IOM), in which the IOM could not find a single area of disease research for which chimpanzees are essential (54). If the NIH is prepared to abandon the "best animal model" available, what are the implications of funding research that uses animal species evolutionarily more distant to humans, including other primates, dogs, rats, mice, zebrafish and finches?

Was the *Stop Vivisection* ECI Successful as an Exercise in Participatory Democracy?

The hearing on 11 May 2015 in the European Parliament was an opportunity for the organisers of the ECI to present their case. The hearing was organised under the auspices of four parliamentary committees (Agriculture and Rural Development, AGRI; Environment, Public Health and Food Safety, ENVI; Industry, Research and Energy, ITRE; and the Committee on Petitions, PETI). Opening remarks were made by the EC Vice-President, Jyrki Katainen, and the ENVI Director-General, Karl Falkenberg, followed by three rounds of discussions. Each round began with a presentation by one of three experts appointed by the AGRI Committee: Ray Greek, president of Americans for Medical Advancement (afma-curedisease.org); Françoise Barré-Sinoussi, winner of the 2008 Nobel Prize for physiology or medicine, who spoke on behalf of the European Federation of Pharmaceutical Industries and Associations (efpia.eu); and Emily McIvor of Humane Society International (hsi.org/world/europe). Greek and McIvor spoke in favour of the ECI, while Barré-Sinoussi spoke against.

Unlike the two previous ECI hearings (Right2Water and One of Us), the *Stop Vivisection* ECI was organised along the lines of a debate, with speakers for and against. As a result of the debate conditions, the organisers of *Stop Vivisection* ECI received just 34 minutes, collectively, of speaking time during the three and a half hour hearing. The entire proceedings are available on the official EU website (http://www.europarl.europa.eu/news/en/news-room/20150507IPR53142/AGRI-ENVI-ITRE-PETI-11052015-15.00-18.30).

Other drawbacks inherent in the ECI have included legal constraints and bureaucratic hurdles. For example, nearly half of proposed ECIs were declared inadmissible by the Commission on the grounds of narrow legal interpretations, while many citizens were put-off signing because of excessive personal data requirements in the case of some EU Member States. A lack of any impact on EU legislation, as the three first 'successful' ECIs have demonstrated, suggests a lack of transparency and accountability on the part of the EC. Calls for improvement aimed at simplifying the registration requirements and urging the EC to respond to successful ECIs with concrete actions, including legislative proposals, have been put forward by the campaign group "for a European Citizens' Initiative that works" (55). Although the EC ultimately rejected the *Stop Vivisection* ECI, including all ten proposals contained in the dossier submitted on 11 May 2015, the parliamentary hearing that took place in Brussels generated much lively public and scientific debate, in addition to wide media coverage (56–63).

Michael Balls, a former director of ECVAM noted that: *The Citizens' Initiative highlights two important points: many animal models are not valid for predicting human responses, and biomedical research and testing do desperately need procedures which are more directly relevant for the human species* (64). The European Parliament's Intergroup on the Welfare and Conservation of Animals commented that: *An EU strategy is necessary to promote innovation and uptake of more humane state-of-the-art methods. This should also contribute to a paradigm shift to stop relying on the use of animals as the golden rule and recognise that advancing medical progress, research and innovation is possible with methods which do not rely on animals* (65).

In the official EC press release issued on 3 June 2015, Vice-President Jyrki Katainen justified the Commission's decision by saying that: *The 'Stop Vivisection' Citizens' Initiative comes at a time of transition — thanks to major technological advances, Europe is reducing the use of animal testing. However, a complete ban on animal research in the EU would be premature and it*

would risk chasing out biomedical research from Europe (66).

Also, according to the EC, *The Directive has not been in force long enough to draw conclusions on its effectiveness*. The Commission plans to review it in 2017 and will emphasise the availability of alternative approaches. In addition, the Directive requires an implementation report in 2019. These reports will be the first assessments of the extent to which the Directive is reaching its objectives (66). The revision process (as outlined above by the EC) appears to ignore the urgency of bringing existing legislation into line with current evidence-based science. Animal-based research has remained largely immune to scientific audit since its inception; indeed, most animal experiments have never undergone formal validation. In the words of a former FDA official: *Most of the animal tests we accept have never been validated. They evolved over the past 20 years and the FDA is comfortable with them*. (Anita O'Connor, of the FDA Office of Science, personal communication, 1998). In addition, animal tests have rarely been subjected to meta-analysis and systematic review. Of the few examples that do exist, systematic reviews of animal experiments demonstrate poor human clinical and toxicological utility (19, 67). There have also been calls for a formal *invalidation* process as "many currently-accepted animal tests and candidate animal and non-animal tests do not, and could never, meet the agreed criteria for necessity, test development, prevalidation, validation and acceptance" (68).

Conclusions

The revision of *Directive 2010/63/EU* is a fresh opportunity to critically examine the validity of the use of animal models in light of current scientific knowledge. The editorial views expressed recently in the *British Medical Journal* are important contributions to the debate: "How predictive and productive is animal research?" (69), and "Is animal research sufficiently evidence based to be a cornerstone of biomedical research?" (70). The revision of the Directive is also an appropriate time to discuss the concept of proof and where the burden of proof lies in science. "As in law, it lies on the claimant. The null hypothesis demands that we assume there is no connection between events until such causation is proven. Thus, those claiming animal models are predictive of human responses in the context of biomedical research must show that what they are claiming is true" (28).

The *Stop Vivisection* ECI was intended as a win–win exercise, in which needless animal suffering is replaced by evidence-based science to the benefit of humans. At the public hearing on 11 May 2015, the *Stop Vivisection* ECI position was summed up thus: "The biggest challenge to the European Citizens' Initiative is not science, it is communication. The idea behind the ECI was to raise the level of the debate from simply animal welfare to the validity of the animal model, and what we've done today is touch very superficially on the science. And what we would like to ask the European Commission is to organize a scientific public debate similar to a public jury, not where the experts have 10 minutes, but where we have 3 or 4 or 5 days to discuss the science with experts from both sides. If we do not do this, if we do not have a serious scientific debate, we are letting down the 1.17 million people who signed the ECI, we are letting down the animals, and we are letting down patients who want cures based on personalised medicine, not animal tests." (71).

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