



fighting heart disease  
and stroke

european heart network

## Research involving animals – a European Heart Network paper

February 2017

### Introduction

*The aim* of this paper is to provide information about current EU developments with respect to the use of animals in medical research.

Cardiovascular disease (CVD) – the main forms of which are coronary heart disease and stroke – is the main cause of death in Europe, accounting for 3.9 million deaths, and in the EU, accounting for over 1.8 million deaths each year.<sup>1</sup> CVD is also a major cause of disability and a significant economic burden across the EU, estimated to cost the EU economy 210 billion euros every year.<sup>2</sup>

### *About the European Heart Network*

The European Heart Network (EHN) is a Brussels-based alliance of heart foundations and other like-minded non-governmental organisations throughout Europe. EHN has members in 25 countries in Europe. EHN plays a leading role in the prevention and reduction of cardiovascular diseases, in particular heart disease and stroke, through advocacy, networking, capacity-building and patient support, so that they are no longer a major cause of premature death and disability throughout Europe.

### Summary

Scientists use animals to learn more about health problems that affect both humans and animals, and to assure the safety of new drugs and medical treatments. Some diseases can only be studied in a living organism and it is not always possible or ethical to use humans.

The research community is constantly developing new techniques to help reduce the number of animals needed for use in medical research. Scientists carry out as much of their research as possible on human volunteers, cells, or computer models.

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<sup>1</sup> Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N (2017). European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels. <http://www.ehnheart.org/cvd-statistics.html>

<sup>2</sup> Idem

However, completely replacing all animals in research is not yet possible. There is no alternative method that can reproduce the complicated working of our hearts and circulatory systems.

All animal studies have to be carried out in compliance with EU legislation. The EU's most recent Directive on protection of animals used in research (adopted in 2010) seeks to improve the welfare of those animals used in scientific research, as well as to firmly anchor the principle of the **Three Rs**: to **Replace, Reduce and Refine** the use of animals, in EU legislation. This Directive took full effect on 1 January 2013.

In 2015, the European Commission (EC) was handed a European Citizens' Initiative (ECI) petition "Stop Vivisection" with more than 1.17 million certified signatures asking for a paradigm shift in the way research is conducted.

The EC responded that it shares ECI's view that animal testing should be phased out. However, the EC highlighted that the Directive takes the right approach to achieve the objectives of the Initiative and proposes no repeal of the existing legislation. It seems likely that the EC will focus on pushing forward the development of non-animal approaches, by means of further funding, rather than amending existing legislation, which will be reviewed in 2017 as part of the normal legislative process.

EHN also considers that changes to current legislation on the use of animals in research are not necessary at the present time.

## Background

The protection and welfare of animals is an area covered by a wide range of EU legislation. All animal studies, whether for the development of new medicines, for physiological studies, for studying environmental effects or for the testing of chemicals or new food additives, have to be carried out in compliance with EU legislation.

### *EU legislation*

Since 1986, the EU has had in place specific legislation covering the use of animals for scientific purposes.<sup>3</sup> On 22 September 2010, the EU adopted Directive 2010/63/EU which updated and replaced the 1986 Directive 86/609/EEC on the protection of animals used for scientific purposes.<sup>4</sup>

The aim of the 2010 Directive is to strengthen legislation, and improve the welfare of those animals used in scientific research, as well as to firmly anchor the principle of the **Three Rs**: to **Replace, Reduce and Refine** the use of animals, in EU legislation. Directive 2010/63/EU took full effect on 1 January 2013.

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<sup>3</sup> European Directive 2010/63/EU

<sup>4</sup> Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. Official Journal of the European Union L276, 20.10.2010, 33–79.

### *European Citizens' Initiative petition "Stop Vivisection"*

At the beginning of 2015, the European Commission (EC) was handed a European Citizens' Initiative (ECI) petition "Stop Vivisection" with more than 1.17 million certified signatures asking for a paradigm shift in the way research is conducted.

The European Citizens' Initiative is a European Union 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. 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. 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.<sup>5</sup> 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 Initiative asks the EC to *"abrogate Directive 2010/63/EU on the protection of animals used for scientific purposes and put forward a new proposal aimed at phasing out the practice of animal experimentation, making compulsory the use — in biomedical and toxicological research — of data directly relevant for the human species ."*

As set out in the Lisbon Treaty and the ECI Regulation, the EC must react within three months of submission of an ECI with one million or more validated statements of support. The EC had until 3 June 2015 to decide whether it would act by adopting legislation, act in some other way to achieve the goals of the ECI, or not act at all. The EC must explain its reasoning through a Communication adopted by the whole College of Commissioners.

#### *Response from the European Commission*

On 11 May 2015, the official hearing of the Stop Vivisection ECI took place at the European Parliament in Brussels. The purpose of this hearing was to provide a platform for debate for Members, the general public, the ECI's supporters and experts in the field. Oral presentations were given by three representatives of the ECI.<sup>6</sup>

As a result, the EC confirmed that it shares ECI's view that animal testing should be phased out. However, the EC highlighted that the Directive takes the right approach to achieve the objectives of the Initiative and proposed no repeal of the existing legislation.

The Directive is needed to ensure a high level of protection of the animals used in research and repealing it would not reduce the number of animals used in research. The Directive will be reviewed in 2017 as part of the normal legislative process.

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<sup>5</sup> Apelblat, M. (2015). European Citizens' Initiative: How to make good on the promise of participatory democracy. Brussels, Belgium: The Brussels Times. <http://www.brusselstimes.com/eu-affairs/3711/european-citizens-initiative-how-to-make-good-on-the-promise-of-participatorydemocracy>

<sup>6</sup> <http://www.europarl.europa.eu/news/en/news-room/20150507IPR53142/agri-envi-itre-peti-11052015-15.00-18.30>

### *Proposed actions*

In its Communication on "Stop Vivisection" from June 2015, the EC sets out four further actions to achieve the goal of phasing out animal testing.<sup>7</sup>

**Action 1** — The Commission will analyse technologies, information sources and networks from all relevant sectors with potential impact on the advancement of the 3Rs.

**Action 2** — The Commission will continue to support the development, validation and implementation of alternative approaches for regulatory and research use.

**Action 3** — The Commission will actively monitor compliance with the Directive, in particular the 3Rs principle, and with the relevant obligations in sector legislation to use available alternatives.

**Action 4** — took place on 6-7 December in the form of the European Commission Scientific Conference "Non-Animal Approaches". The conference engaged the scientific community and relevant stakeholders in a debate on the validity of animal models and how to exploit the advances in science for the benefit of non-animal approaches.<sup>8</sup> The Commission also reported on the progress of actions 1, 2 and 3.

### *Progress*

*Action 1 – The Commission will analyse technologies, information sources and networks from all relevant sectors with potential impact on the advancement of the 3Rs.*

As a first priority the EC has commissioned a project looking into the available information sources surrounding the 3Rs and alternatives to animal testing.

So far, 800 information sources on the 3Rs have been identified which need to be reconciled and consolidated so that researchers can be pointed to one easy and complete information source regarding the use of animals in research.

*Action 2 – The Commission will continue to support the development, validation and implementation of alternative approaches for regulatory and research use.*

Several new alternative methods are expected to come out of Horizon 2020 projects. However, there is a long time lag between the development of the methods, validation and regulatory acceptance.

*Action 3 – The Commission will actively monitor compliance with the Directive, in particular the 3Rs principle, and with the relevant obligations in sector legislation to use available alternatives.*

Since the Directive entered into effect, 25 pre-infringement enquiries have been launched. These are opened when a check has taken place, issues have arisen and more information is

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<sup>7</sup> <http://ec.europa.eu/transparency/regdoc/rep/3/2015/EN/3-2015-3773-EN-F1-1.PDF>

<sup>8</sup> <http://www.euconf.eu/non-animal-approaches-the-way-forward/en/registration/index.html>

needed to ascertain whether an infringement has taken place. From these enquiries one formal infringement has been recorded.

## **EHN work**

In 2015, in the light of the “Stop Vivisection” campaign, EHN, together with leading research associations, scientific societies, universities, and patients groups, signed up to a statement supporting the current Directive 2010/63 on the protection of animals used in research.<sup>9</sup>

This statement called on the European Parliament to oppose the European Citizens Initiative “Stop Vivisection”.

The use of animals in research has facilitated major breakthroughs in medicine which have transformed human and animal health. With the signatories of the statement, we supported research using animals where alternative methods are not available, where the potential benefits to health are compelling, and where acceptable ethical and welfare standards can be met (the 3Rs principle).

## **Use of animals for CVD research**

Scientists use animals to learn more about health problems that affect both humans and animals, and to assure the safety of new drugs and medical treatments. Some diseases can only be studied in a living organism and it is not always possible or ethical to use humans.

The research community is constantly developing new techniques to help reduce the number of animals needed for use in medical research. Scientists carry out as much of their research as possible on human volunteers, cells, or computer models for example.

However, completely replacing all animals in research is not yet possible. There is no alternative method that can reproduce the complicated working of our hearts and circulatory systems.

### *Current uses for animals in CVD research*

Researchers are studying how the heart develops in mice and fish to better understand what can go wrong to cause congenital heart defects. This work is also bringing us closer to being able to repair damaged muscle after a heart attack, which otherwise can lead to heart failure. By finding out how and when the heart first starts to beat, a research team has uncovered some of the “instructions” that may help them to transform stem cells into fully functional cardiac cells in the lab.

When heart medicines are being developed, researchers can gain insight from studying how they affect heart cells in the lab. But animals are also needed to check if the medicine works in a living system, where the heart is exposed to messages from the brain, other organs, or the changing demands of our bodies.

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<sup>9</sup> <http://www.ehnheart.org/publications/position-papers/publication/1037-eara-statement-supporting-european-directive-201063eu-on-the-protection-of-animals-used-for-scientific-purposes.html>

Studying animals can also reveal potential problems with new treatments. This crucial safety screening process means that researchers can call a halt on drugs that may have otherwise caused dangerous side-effects in patients. For this reason, by law, all emerging treatments must be trialled in animals before tests in humans can take place.

### *Types of animals used in research*

Rodents, mice or rats, account for around 80% of the animals used for scientific purposes in the EU. Cold-blooded animals, such as fish or reptiles, account for around 12% and birds for around 6%.<sup>10</sup>

The majority of CVD research also takes place in rodents (over 90% across the EU in 2011<sup>11</sup>), however a small number of essential studies involving larger animals, such as pigs and sheep, also take place. This is because, unlike rodents, larger animals have hearts, lungs and kidneys very similar to those of humans. Trials in large animals are often needed when developing a new surgical technique to make sure it is safe before being performed on patients.

### *Alternatives to the use of animals in research*

#### Organs on chips

Microchips, called “organs-on-chips”, may offer a potential alternative to traditional animal testing. Each individual organ-on-chip is composed of a clear flexible polymer about the size of a computer memory stick that contains hollow channels lined by living human cells.

Mechanical forces can be applied to mimic the physical microenvironment of living organs. A lung-on-a-chip, for instance, might consist of a layer of cells exposed to a blood-like medium on one side and air on the other, connected to a machine that stretches and compresses the tissue to mimic breathing.

The chips push small quantities of chemicals past cells from lungs, intestines, livers, kidneys, or hearts so any changes in the cells can be observed under a microscope.

However, further research needs to be undertaken to provide the full complexity of organ function. These chips are also currently not advanced enough to replicate organ functions which take place due to complex signals from, say, the endocrine and immune systems.

Testing a known drug in a system that combines multiple organ chips might be difficult to validate as researchers might not know what to look for. The potentially toxic effect of the painkiller paracetamol on the liver, for instance, is well characterised, but less is known about how other organs respond to the drug.

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<sup>10</sup> Seventh Report from the Commission to the Council and the European Parliament on the Statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union COM(2013)859/final [http://ec.europa.eu/environment/chemicals/lab\\_animals/reports\\_en.htm](http://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm)

<sup>11</sup> <http://eur-lex.europa.eu/legal-content/EN/TXT/DOC/?uri=CELEX:52013SC0497&from=EN>

## Computer modelling

Computer models can help scientists to predict the properties needed in a new medicine. Research looking at creating “virtual” model of platelet cells, which form blood clots, will increase our understanding of how to prevent heart attack and stroke.

## Stem cell testing

Human-induced pluripotent stem cells are a type of pluripotent (meaning that it can be transformed into any type of cell) stem cell that can be generated directly from adult cells.

Within the cardiovascular research field, much advancement has already been made using human-induced pluripotent stem cells. For example, in November 2016, a group at the University of Cambridge showed that it was possible to take skin biopsies from patients with Marfan syndrome (a rare genetic disease which causes premature mortality due to the formation of thoracic aortic aneurysms) and transform these cells into blood vessel cells in the lab.

The researchers used these blood vessel models to gain more understanding of how the inherited disease can lead to fatal aneurysms. Their results provide insights into why clinical trials of drugs to treat the disease have so far been largely unsuccessful. The team now hopes to use the lab-generated vessel cells to test drugs for people with Marfan syndrome.<sup>12</sup>

## **Conclusions and recommendations**

### *Conclusions*

It is clear that, at present, alternative options cannot fully replace the use of animals in medical research. Progress in the replacement of animal testing with viable non-animal alternatives is being made. However, no current technique is capable of fully replacing the need for animals in research.

It must also be recognised that animals are used not only to confirm the safety of drugs but also in basic scientific research to advance our knowledge of the various mechanisms of disease.

The time-lag between the development of alternative methods and their regulatory acceptance also stands as a barrier to the complete replacement of animals in research.

Improved data sharing could provide one route to reducing the amount of animal experiments which need to take place. There is a recognised bias introduced into the scientific literature by selective publication – chiefly by a tendency to publish positive results but not negative or non-confirmatory results. The lack of research data and information about negative results

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<sup>12</sup> Granata et al. 2016 Nature Genetics <http://www.nature.com/ng/journal/v49/n1/full/ng.3723.html>

can lead to further experiments using animals needlessly. Therefore increased data-sharing and publication of negative results would reduce repetition of experiments.

### *Recommendations*

In Directive 2010/63/EU the EC shows its commitment to eventually erasing the need for animal use in medical research. By emphasising the need to replace, reduce and refine the use of animals for scientific purposes the Directive also ensures that the numbers of animals used is kept to a minimum.

The EHN considers that changes to Directive 2010/63/EU are not necessary at the present time.