Cruelty Free EUROPE

Reducing and replacing animal experiments: Europe needs an action plan

Without pro-active targets, more animals will suffer in laboratories in Europe

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Introduction

Testing on animals is slow, unreliable, unethical, costly, and not what we need in Europe to deliver the objectives of the European Green Deal and a resilient NextGenerationEU.

Despite an oft-cited commitment to replace animal experiments in the European Union (EU), and widespread public unease about the scale and persistence of animal testing, there is no proactive strategy to phase out animal testing in place and, in practice, no one body that feels a responsibility to make this happen. Each decade passes with only slow, incremental change at a rate that could see animal experiments persist in Europe for the best part of another century.

The standard response is that we cannot end animal experiments until non-animal methods are in place. It's a Catch-22 argument that Europe will remain trapped in unless the development, validation, dissemination and use of non-animal methods is given the leadership, funding and urgency in the EU and its member states, and until we accept that we need to think beyond like-for-like replacements and towards a fundamental change in approach. This does not mean compromising safety or innovation, but the opposite.

It is also essential that Europe use opportunities like the new EU Chemicals Strategy for Sustainability to be clear that the comprehensive levels of protection we all want to see for health and for the environment will never be met by more and more animal testing. That approach would arguably deliver more data and enable us to tick more boxes to say that we have met legal obligations, but it will not deliver real-world protection to change health and environmental outcomes.

In other important areas of policy, the EU argues that unless ambitious and binding targets are set, industry and other stakeholders will not change. There are numerous examples: greenhouse gas emissions; vehicle emissions; targets for green energy; recycling; the representation of women in leadership positions and others. The logic is that targets focus the mind, incentivise and drive change – so why not apply this approach to reducing and replacing animal testing?

The European Commission has always said that setting a date after which ingredients could no longer be tested on animals for cosmetics purposes, irrespective of the availability of non-animal methods, hastened the development of animal-free tests. Why not apply the same approach to more areas of animal testing?

In this report, Cruelty Free Europe makes the case for a targeted and proactive approach to the phase out of animal testing across the EU. We explain why the existing Directive on the protection of animals used for scientific purposes (2010/63/EU) is not sufficient to achieve this, and we provide suggestions for change.

For the first time, we calculate how many animals could be saved if a more rigorous approach were taken, and we suggest legislative, political and funding commitments that could be made. Finally, we provide some concrete actions that the European Commission, its agencies, member states and other organisations could take – many immediately – to bring animal testing to an end.

As Europe seeks to build back better after the Covid-19 pandemic – and with sustainability, human health, the environment and research and innovation at the heart of its agenda – a new humane and human-relevant approach to research and testing that does not rely on live animals is essential.

The use of animals in research and testing in the EU

How animals can be used in research and testing in the EU is governed by Directive 2010/63/EU on the protection of animals used for scientific purposes (the Directive)[1].

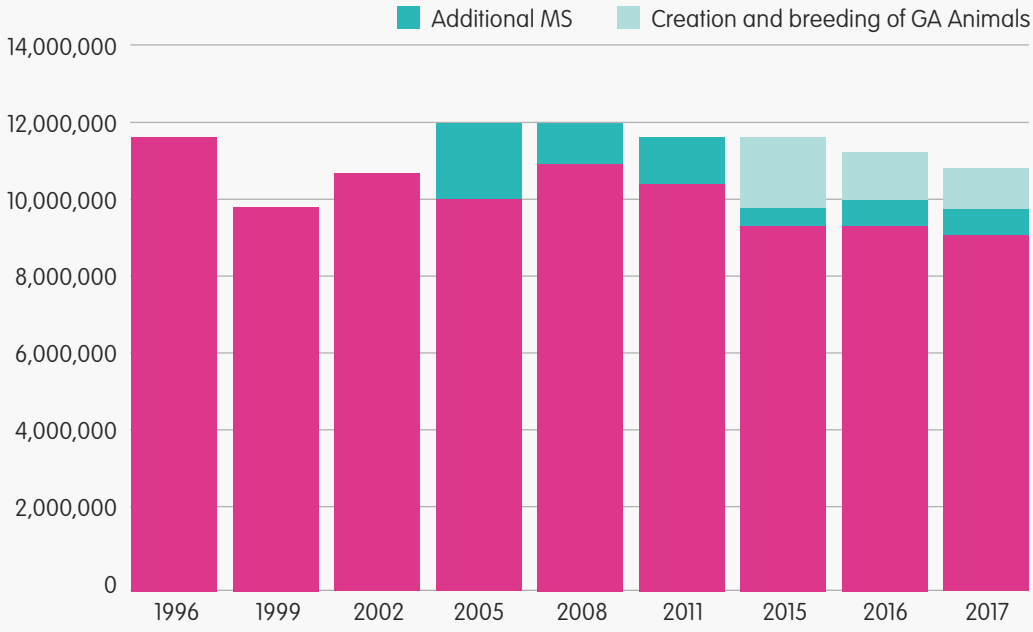


Fig. 1. Uses of animals for scientific purposes across EU member states, 1996-2017. In 2015, reporting changed from number of animals to number of uses. GA: genetically altered.

According to the Commission report under the Directive, in 2017, there were 9.6 million uses of animals in the EU for the purposes of research, testing and education. Note that subsequent years follow on the whole very similar patterns but have not been included in the figure as 2017 is the most recent year that includes all animals, including those bred and not used.

Also note that comparisons cannot be directly made between pre- and post-2015 figures because 'uses' rather than 'animals' are now counted. However, it is important to say that the two are, in fact, very similar as most animals are used only once and then killed.

Reporting of genetically altered (GA) animals with a harmful genetic mutation who are used to create and maintain colonies but are not used in further experiments only began in 2015 (shown in pale teal). However, these are defined as procedures under the Directive and should have been included in the Commission's total. In 2017, this represented 1.3 million animals, bringing the total number of procedures to 10.9 million.

[1] *European Union. 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. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010L0063&from=EN*

According to separate reports from member states in 2017,[2] in addition to the 10.9 million used in procedures:

- 6.1 million conventional or apparently normal GA animals were used to create or maintain GA lines of animals but were not used themselves in experiments, and
- 6.5 million conventional (non-GA) animals were bred and not used and then killed as surplus or for their tissues.

At least 23.5 million animals are bred in laboratories and killed every year in the EU.

The 15 states in membership of the EU when the collection of these statistics was first introduced (shown in pink) continue to account for the vast majority of animal experiments, the number of which has dropped by only 1% on average every year from 1996 to 2016 inclusive.

These trends do not account for the breeding of GA animals with a harmful mutation as we simply do not know the scale of their use prior to 2015. The same applies to the scale of production of GA animals with a non-harmful mutation, or normal animals bred for experiments but not used.

[2] *European Commission. Commission Staff Working Document Accompanying the document Report from the Commission to the European Parliament and the Council on the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes in the Member States of the European Union (SWD(2020) 15 final). 2020. Available at: https://ec.europa.eu/environment/chemicals/lab_animals/pdf/SWD_Implementation_report_EN.pdf*

The Directive

Directive 2010/63/EU establishes the minimum standards that must be adopted by institutions breeding or using animals for scientific purposes.

One of the stated goals of the Directive is to fully replace animal testing. Although a recital, and limited by the interpretation of 'scientifically possible', this is an important commitment.

Recital 10 states:

While it is desirable to replace the use of live animals in procedures by other methods not entailing the use of live animals, the use of live animals continues to be necessary to protect human and animal health and the environment. However, this Directive represents an important step towards achieving the 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. To that end, it seeks to facilitate and promote the advancement of alternative approaches. It also seeks to ensure a high level of protection for animals that still need to be used in procedures. This Directive should be reviewed regularly in light of evolving science and animal-protection measures.

However, the Directive is limited in ambition, seeking to achieve the end of animal testing only through replacement and only when those replacements exist. Furthermore, there is very little within the Directive to ensure that those replacements will materialise.

Development of alternatives

Article 47 of the Directive imposes responsibilities on the European Commission and member states to contribute to the development, validation and uptake of alternative approaches.

Article 47 (1) states:

The Commission and the Member States shall contribute to the development and validation of alternative approaches which could provide the same or higher levels of information as those obtained in procedures using animals, but which do not involve the use of animals or use fewer animals or which entail less painful procedures, and they shall take such other steps as they consider appropriate to encourage research in this field.

Mandatory use of alternatives

The Directive maintains the position first adopted in its predecessor, Directive 86/609/EEC, which is that an animal test must not be authorised when an alternative approach is available.

Article 4(1) states:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.

Article 13(1) states:

Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

However, Article 4 lacks teeth. The use of the term 'wherever possible' is a glaring loophole that provides an opt-out rather than an incentive to hasten change or take actions other than direct replacement. Furthermore, member states tend to authorise large projects involving several procedures on animals. This makes it very hard to judge the genuine opportunities to replace animals. For regulatory testing, whether an alternative approach can be used is often specific to the substance being tested. Project applications may not include the substances to be tested and the Commission has told member states that they can delegate responsibility for determining if an alternative can be used to the institution they are authorising.[3]

The problem with Article 13 is the Commission's interpretation that if an alternative method is not capable of 'obtaining the result sought' for a third country then the animal test can be performed. Oddly, that animal test could not be performed if it were for an EU country. This means that those animal tests for which the alternatives have not yet obtained regulatory acceptance in third countries can and are still being performed in the EU (see Animal tests that have been replaced). This cannot be what the legislators intended.

Harm:Benefit Assessment

Under the Directive, all projects that intend to use animals in research that may cause 'pain, suffering, distress or lasting harm' must undergo a harm:benefit analysis (HBA), where the harms caused to the animals are weighed against the likely benefits to humans or other animals or the environment as a result. If the project passes the test, it is authorised.

Article 36 (2) states:

Member States shall ensure that no project is carried out unless a favourable project evaluation by the competent authority has been received in accordance with Article 38.

Article 38 (2) states:

The project evaluation shall consist in particular of the following:

…a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment…

[3] *Sinkevičius V. Written Answer on behalf of the European Commission to question E-002535/2020, 27 July 2020. Available at: https://www.europarl.europa.eu/doceo/document/E-9-2020-002535-ASW_EN.html*

There is no stated aim in the Directive that animal testing should be reduced per se, that is not dependent on the availability of direct replacement by like-for-like alternative methods. The only potential mechanism in the Directive for limiting the number of animal tests lies in the HBA.

The HBA could be used as a mechanism to limit animal experiments to those that are considered to be essential (high benefit) and/or cause only low suffering (low harm). However, without an imperative to use the HBA in this way all that the HBA does – in our opinion – is act as a crude check that filters out the most egregious experiments. In fact, there has been no assessment of how the HBA works in practice in member states.

In the meantime, the HBA – as it stands on paper – has been criticised in the academic literature.[4,5,6]

Problems include that:

- there are no clear guidelines for how it is to be performed,
- it is not quantitative but instead entirely subjective,
- it is not transparent,
- the assessment is often done by the institution wishing to do the research,
- the institution itself may be the competent authority authorising the assessment,[7] and
- it is almost always done by a limited number of scientific persons who are advocates for animal testing.[8]

Tests that are often outside the acceptability factor of the group of people authorising animal experiments are arguably those that are not permitted anyway; for example the use of great apes, testing finished cosmetic products and tests causing prolonged, severe suffering.

In practice, the harm benefit assessment is not used as a tool to *change* where the line is drawn but is a bureaucratic exercise to show that the line (wherever that is) has not been crossed.

[4] Taylor K. Harms versus Benefits: A Practical Critique of Utilitarian Calculations. In: Linzey A. and Linzey C. ed. The Ethical Case against Animal Experiments. 2018. University of Illinois Press, pp. 148-159.

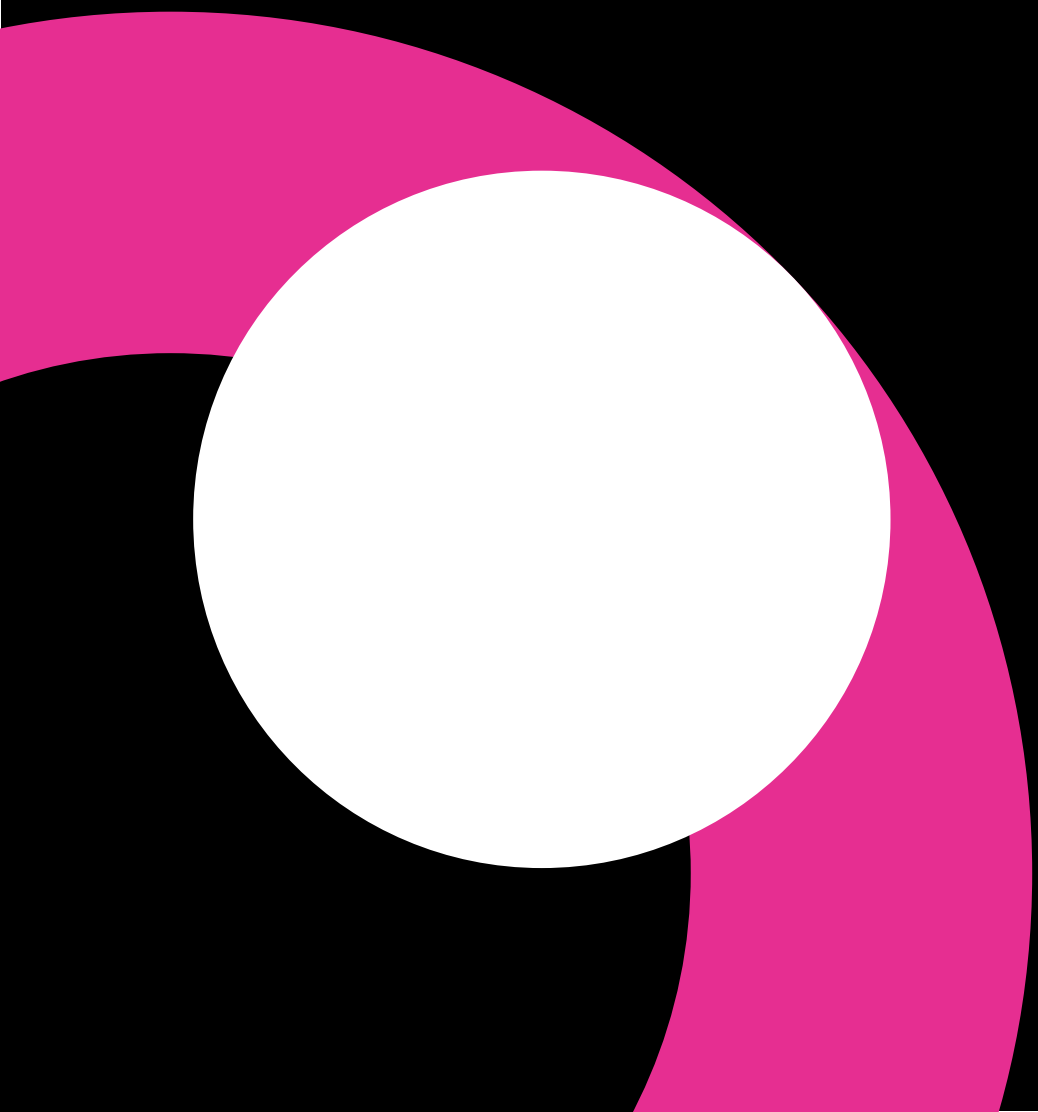
[5] Grimm H. Turning apples into oranges? The harm-benefit analysis and how to take ethical considerations into account. Altern Lab Anim. 2015;43(2):22-4. doi: 10.1177/026119291504300211.

[6] Grimm H et al. The Road to Hell Is Paved with Good Intentions: Why Harm-Benefit Analysis and Its Emphasis on Practical Benefit Jeopardizes the Credibility of Research. Animals. 2017;7(9):70. doi:10.3390/ani7090070

[7] European Commission. Implementation Report 2020.

[8] Taylor, K. Harms versus Benefits. 2018.

Why we need a proactive targets-based strategy to phase out animal testing



Directive 2010/63/EU is not the mechanism for change

The basic difficulty in the EU approach is that it is a demand-led system, in which the number of animal experiments is ultimately decided by the number of researchers who would like to conduct them. Since new types of animal experiment continue to be proposed, the replacement of older types of experiment tends to be balanced or exceeded by the addition of new ones.

This is evident in the fall of on average only 1% per year over the last 20 years in the numbers of experiments.

Assuming animal tests continue to follow a linear decrease at around 1% per year, it will be another 100 or more years (around 2126) before there are no more animal experiments in the EU.

At current rates, it will be another

100

YEARS

before animal experiments are ended in the EU

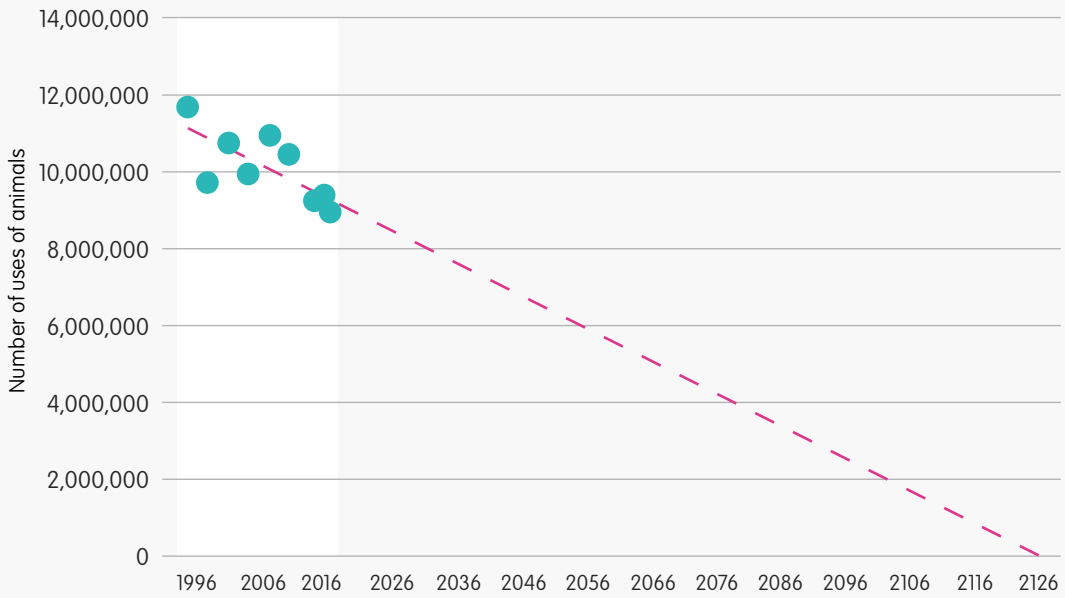


Fig. 2. The number of animal experiments (discounting GA animals) in the 15 member states of the EU at the time reporting began has decreased by 20% in the last 20 years and at that rate may not reach zero for 100 years.

Although the Commission now frequently claims that the Directive is the EU's strategy for ending animal testing, this claim is fundamentally flawed. Whilst the Directive has full replacement of animal use as an aim within its recitals, recitals themselves are not legally binding and the only mechanism it provides for achieving this is via the use of like-for-like alternatives. Without specific targets for its achievement, full replacement will depend entirely on the normal speed of scientific progress with all the inherent hurdles and barriers entailed in challenging the status quo. There is nothing in the Directive to help speed that up.

Furthermore, it cannot be possible that all 23.5 million animals used each year across the EU are absolutely essential to scientific progress, regardless of one's views on the scientific validity of animal testing.

There must be elements of duplication and redundant testing in the system. The Directive does not speak to this issue either.

Not only does the overarching horizontal legislation (the Directive) not have targets, actions or provide a clear mandate to reduce animal testing, neither do any of the sector-specific vertical laws that require animal testing.

Furthermore, these sector-specific laws are inconsistent in their treatment of animal testing and the promotion of alternative methods. The most progressive language is found in the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation – which entered into force in 2006. Worryingly, updates to other pieces of legislation since 2006 have not even included the language of animal testing as a last resort nor the need to promote alternatives (see Table 1). This is despite Article 13 of the Treaty on the Functioning of the European Union requiring that animal welfare be considered when formulating and implementing relevant policies.[9]

The problem with relying on waiting for the replacement of animal testing with like-for-like alternatives as the only mechanism to end all animal testing is that:

1) It will take a long time, which is unacceptable to many,

2) It assumes all animal testing is essential, which is not the case, and

3) It doesn't consider the fact that new animal-based test methods are being developed as fast if not faster than replacements.

Table 1. Examples of sector specific legislation and their treatment of animal testing

Sector	Primary legislation	Last amended	Mandate to reduce animal testing	Animal testing as a last resort	Mandate to promote alternative methods	Data sharing to reduce duplicate animal testing
Chemicals	REACH Regulation 1907/2006	2020	No	Yes	Yes	Yes
Veterinary medicines	Veterinary Medicines Regulation 2019/6	2019	No	No	No	Yes
Biocides	Biocidal Products Regulation 528/2012	2019	No	No	No	Yes
Pesticides	Plant Protection Products Regulation 1107/2009	2019	No	Yes	No	Yes
Food	Novel Food Regulation 2015/2283	2018	No	No	No	Yes
Human medicines	Medicines Directive 2001/83	2012	No	No	No	Yes

[9] *European Union. Consolidated version of the Treaty on the Functioning of the European Union. 2012. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12012E/TXT:en:PDF*

Progress with the development of alternatives

The last 20 years has seen a dramatic increase in the development of non-animal methods. In the scientific literature, the use of *in vitro* (cell-based) methods is continuing to grow, whilst the use of animals may have plateaued (see Fig.3).

The European Centre for the Validation of Alternative Methods (EURL ECVAM), part of the European Commission, has recently been commissioning reviews of disease models to track the progress of the development of alternative methods in basic and applied medical research. The aim is to identify and describe specific research contexts where animal models have been put aside in favour of novel non-animal techniques that use, for example, *in vitro* methods based on human cells and engineered tissues, or *in silico* approaches employing computer modelling and simulation. The first review, on respiratory disease research, found almost 300 non-animal models had been used for the development of new drugs and therapies.[10] The second review, on breast cancer research, found 935 non-animal models.[11] Reviews on immunogenicity of advanced medicinal products, neurodegenerative disorders, immune oncology, autoimmunity and cardiovascular disease will follow.

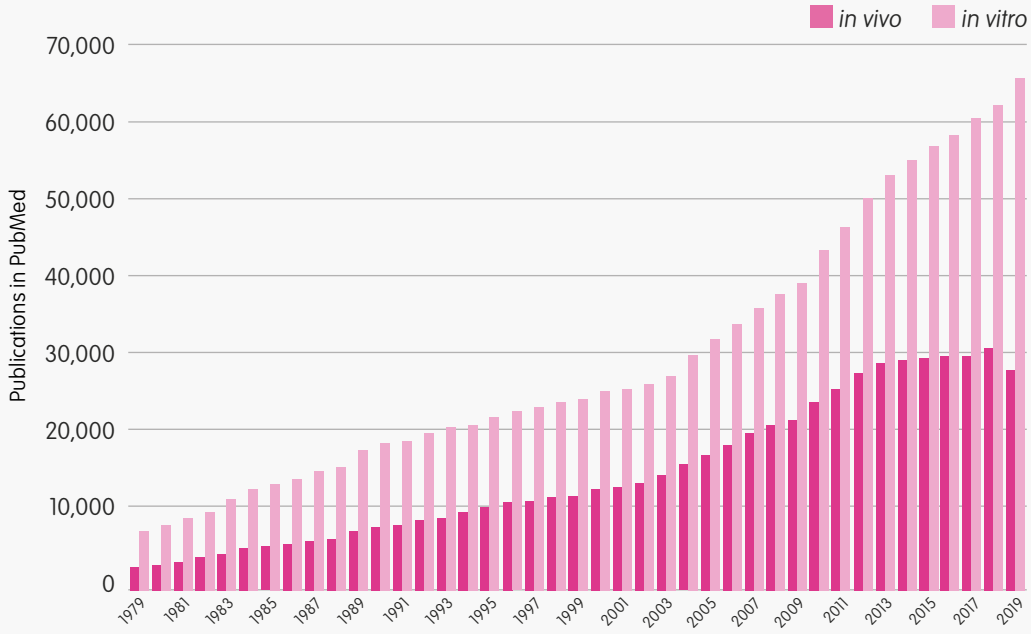


Fig. 3. Number of publications in PubMed based on *in vitro* (cell-based) methods and *in vivo* (animal-based) methods, 1979-2019.

[10] *European Commission. Respiratory tract diseases. Available at: https://ec.europa.eu/jrc/en/eurl/ecvam/knowledge-sharing-3rs/life-science-research/respiratory-tract-diseases*

[11] *European Commission. Breast Cancer. Available at: https://ec.europa.eu/jrc/en/eurl/ecvam/knowledge-sharing-3rs/life-science-research/breast-cancer*

Within regulatory testing, we now have replacement methods for skin absorption, skin irritation, eye irritation and skin sensitisation, and there are cell-based methods that could soon replace acute toxicity tests in mammals and fish. On a case-by-case basis, computer models and expert approaches can obviate the need for a specific animal test like repeated dose or reproductive toxicity. And for quality control, we now have replacements for various vaccine batch safety tests, pyrogen tests, batch potency tests and shellfish toxin safety tests.

Replacements for animal tests are more advanced in the field of regulatory testing because it is this area that has received the most attention. This is partly because it is the only use of animals that is in any way mandated and – due to the standardised nature of the tests – replacement of just one test has a permanent effect on the use of animals in that area and is therefore particularly worthwhile. Annex 1. outlines the status of alternatives for the most common endpoints for toxicity testing that have traditionally, and in most cases still do, use animals.

However, as is evident by the numbers, animals are still used in huge quantities and the trajectory downwards is minimal.

There are several reasons why, despite the growth in the use of non-animal methods, there has not been more progress in achieving full replacement:[12]

- There has not been enough investment in the development of non-animal methods, sufficient to overcome the significant scientific and technological hurdles;
- Non-animal methods may be being used in addition to animals, not replacing but supplementing their use;
- Bureaucratic hurdles are slowing down the implementation of non-animal methods once they are developed; and
- The desire for international harmonisation is causing further delay to the implementation of any replacement method developed in the EU.

[12] *Taylor K. Recent Developments in Alternatives to Animal Testing. In: Herrmann K. and Jayne K. ed. Animal Experimentation: Working Towards a Paradigm Change. 2019. Brill, pp. 585-609. doi:10.1163/97890043911192_025*

Central funding

The Commission is required to report on 'the amount and distribution of funding made available by the Commission for the development and evaluation of alternative test methods' every five years under the reviews of REACH provided for in Article 117(4) of the REACH Regulation. There is a great deal of overlap in the analysis given by the Commission in its first[13] and second[14] REACH Reviews and no clarity on the method by which it considered a project was contributing to the development of alternatives, including whether the project focused on animal methods that reduce suffering or numbers (highly likely). Most of the funding comes through the EU research Framework Programmes. The Framework Programmes are funding streams created to support and foster research in the European Research Area.

An analysis of the two Commission REACH revies reports suggests that the amount of funding provided for non-animal methods under the Framework schemes has not been increasing over time.

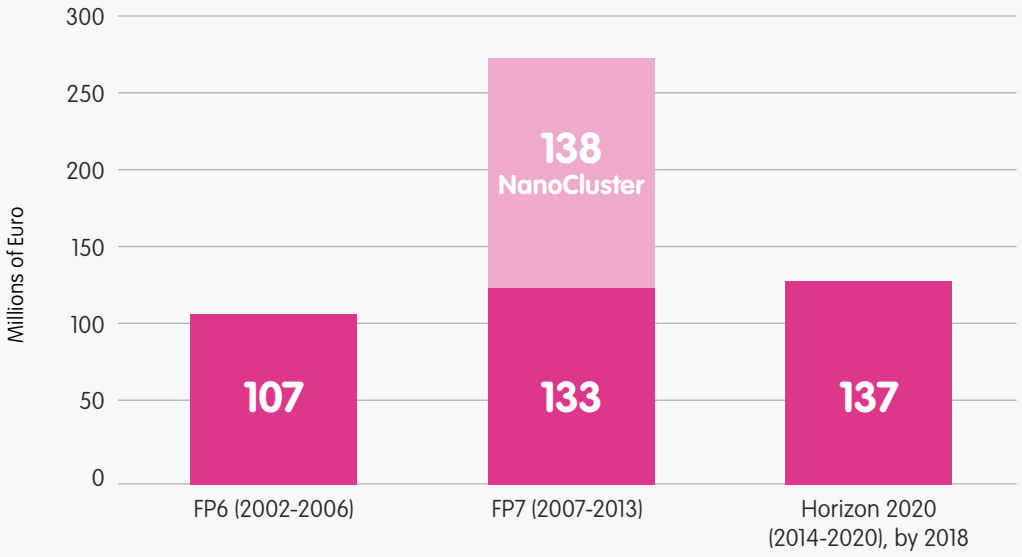


Fig. 4. EU framework funding related to alternative methods, provided in the first and second REACH Review reports, millions of euro.

[13] *European Commission. Commission Staff Working Document General Report on REACH Accompanying the document Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions (SWD(2013) 25 final). 2013. Available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=SWD:2013:0025:FIN:EN:PDF*

[14] *European Commission. Commission Staff Working Document General Report on REACH Accompanying the document Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee (SWD(2018) 58 final) – part 5. 2018. Available at: https://eur-lex.europa.eu/resource.html?uri=cellar:2834985c-2083-11e8-ac73-01aa75ed71a1.0001.02/DOC_4&format=PDF*

According to the REACH reviews, under the sixth Framework Programme (FP6; 2002-2006), 107 million euros were given to 26 projects related to alternatives. This constituted just 0.6% of the total budget for FP6, which was 17.5 billion euros.[15]

Under the seventh Framework Programme (FP7; 2007-2012), 271 million euros were given to 57 projects on alternatives and also on nanomaterials. The basis for including 25 projects totalling 138 million euros under the NanoCluster as contributing to alternative methods is, however, unclear. The larger figure constituted 0.6% of the total 45.3 billion euros invested overall under FP7.[16]

By 2018, only 137 million euros had been allocated to 23 projects related to alternatives to animal testing and also on nanomaterials under Horizon 2020 (2014-2020).[17] Whilst Horizon 2020 projects continued to be approved through to 2020, by 2018 this only constituted 0.2% of the 80 billion euro project.[18]

In a recent written parliamentary answer, the Commission claimed that 'In Horizon 2020, more than EUR 45 million are estimated to be committed each year to research projects on the development of non-animal alternative methods – more than EUR 270 million for the period 2014-2019. The annual budget for this activity in Horizon 2020 is 1.5 times higher than in FP6 and 4 times higher than in FP5.'[19]

The basis for the claim is not given, and it is notable that the Commission does not claim that Horizon 2020 funding of alternatives is greater than the previous FP7 scheme.

Our analysis of Horizon 2020 funding (conducted in March 2020)[20] suggests that, to date, 48 projects which have the development of alternatives as a primary or secondary aim have been awarded funding totalling 93 million euros.

The methodology and details of the projects are given in our report. In comparison, 300 projects cited the use of 'animal models' as part of their methodology. Ninety-three million euros constitutes approximately 0.1% of the total 80 billion euro programme.

Whilst there are some disparities in the number of projects funded under Horizon 2020 to date, and no final figure available yet, it is clear that the percentage of funding is unlikely, by a long stretch, to exceed or even match that of the previous Framework Programme.

The previous and current level of central funding, whilst appearing significant, compares poorly to the funding given to equally ambitious projects. For example, the U.S. government invested 3.8 billion dollars in the Human Genome Project.[21] The EU has pledged 2 billion euros for development of innovative low-carbon technology under the NER 300 programme.[22] And, to respond to the urgency and ambition of the European Green Deal objectives, Horizon 2020 launched a call worth close to 1 billion euros.[23] The final tranche of the Horizon 2020 budget – 11 billion euros – will also focus on new solutions for societal challenges and drive innovation-led sustainable growth. The amounts given to innovation in non-animal methods are 10 to 100 times less than this. Clearly, the rate of change is likely to be slow unless levels of funding significantly increase and are proportionate to the scale of the problem being addressed.

EU central funding also compares poorly to the level of U.S. government funding, especially given these two regions have close to the same share of the world's gross domestic product. Single agency grants on specific projects have included a five year 37 million dollar grant in 2010 from the federal Defense Advanced Research Projects Agency (DARPA), the National Institutes of Health and the FDA to develop human organs-on-chips,[24] followed by a further 35.5 million dollars over five years, pledged in 2020.[25]

[15] *European Commission. The 6th EU Research Framework Programme. 2002. Available at: https://ec.europa.eu/commission/presscorner/detail/%20en/MEMO_02_152*

[16] *https://ec.europa.eu/research/fp7/pdf/fp7_evaluation/2_fp7_expost_evaluation_snapshot_overall_findings.pdf [No longer accessible]*

[17] *European Commission. Commission Staff Working Document General Report on REACH. 2018*

[18] *European Commission. Horizon 2020: First results. 2015. Available at: https://ec.europa.eu/programmes/horizon2020/sites/default/files/horizon_2020_first_results.pdf*

[19] *Gabriel M. Written Answer on behalf of the European Commission to question E-003804/2020, 31 August 2020. Available at: https://www.europarl.europa.eu/doceo/document/E-9-2020-003804-ASW_EN.html*

[20] *Public Impact Limited. Research into and promotion of alternatives to animal testing in the EU Budget and prospects for the 2021-27 MFF (Report Prepared for Cruelty Free International). 2020. Available upon request.*

[21] *Grosjean M. Evidence: $3.8B Investment in Human Genome Project Drove $796B in Economic Impact Creating 310,000 Jobs and Launching the Genomic Revolution. 2015. Available at: https://ec.europa.eu/futurium/en/content/38b-investment-human-genome-project-drove-796b-economic-impact-creating-310000-jobs-and.html*

[22] *European Commission. NER 300 programme. Available at: https://ec.europa.eu/clima/policies/innovation-fund/ner300_en*

[23] *European Commission. European Green Deal Call: €1 billion investment to boost the green and digital transition. 2020. Available at: https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1669*

[24] *CNBC. It sounds futuristic, but it's not sci-fi: Human organs-on-a-chip. 2017. Available at: https://www.cnbc.com/2017/08/14/fda-tests-groundbreaking-human-organs-on-a-chip.html*

[25] *U.S. National Institutes of Health. NIH Awards $35.5 Million to Use Tiny, Bioengineered Organ Models to Improve Clinical Trials' Development and Design. 2020. Available at: https://ncats.nih.gov/news/releases/2020/nih-awards-tiny-bioengineered-organ-models-to-improve-clinical-trials-development-and-design*

It is also notable that EU Framework projects tend to be broad projects involving a number of partner organisations. Their value, in our opinion, is in supporting academic research and training young researchers. They have not proven to be good sources of technologies that have developed into validated, accepted non-animal methods. The most recently validated, accepted methods – the skin and eye irritation and skin sensitisation models – were developed by industry. There has been little progress in the development of a testing strategy using the 10 *in vitro* tests for reproductive toxicity suggested by the RePROTECT project, nor was there great uptake of the testing strategies developed for REACH under the OSIRIS project, to give two examples. It is unclear what has come out of the NanoCluster projects related to alternatives to animal tests.

The other notable element of central funding of alternatives is support for EURL ECVAM. Even here, funding of EURL ECVAM appears to have been reduced from an average of 6.5 million euros per year, reported in 2017/8,[26] to 5 million euros for 2019/20.[27]

Member State funding

According to Article 47(1) of Directive 2010/63/EU, member states should 'contribute' to the development of alternative methods. How they should contribute is not detailed, and in fact it has been difficult to determine how member states have been contributing since the entry into force of the Directive.

Analysis of the five year operation reports required under Article 117(1) of REACH[28] shows that only ten out of the then 28 EU member states reported funding of alternative methods, totalling 7 million euros in 2015 – a one million euro decrease overall from 2010. Two-thirds of member states stated that they had 'no information' on the amount of funding they were providing.

Cruelty Free International conducted a survey in 2013 to obtain more information on member state direct funding of all alternative methods for all purposes, not just in relation to REACH. The total reported was only 18.7 million euros annually coming from seven member states. The amount provided by the most generous provider (the UK; approximately 11 million euros) was still only 0.04% of its national science research and development expenditure for that year.[29]

According to the Review of Directive 2010/63/EU in 2017,[30] only 14 member states had submitted voluntary reports detailing their efforts towards the development, validation and promotion of alternative methods required under Article 47(1) of the Directive. An analysis of these reports[31] shows that the annual total may be 20.6 million euros also from only seven contributing countries. Only eight of the reports are more recent than 2015.

Only a proportion of member states are contributing to the development of alternative methods and the amounts of funding provided are small. There is incomplete information for approximately half of the EU member states.

[26] *European Commission. Commission Staff Working Document General Report on REACH. 2018.*

[27] *Gabriel M. Written Answer on behalf of the European Commission to questions E-004076/2020 and E-004077/2020, 4 September 2020. Available at: https://www.europarl.europa.eu/doceo/document/E-9-2020-004076-ASW_EN.html*

[28] *European Commission. Member States Reports on the operation of REACH (Art. 117). 2020. Available at: http://ec.europa.eu/environment/chemicals/reach/reports_en.htm*

[29] *Taylor K. EU member state government contribution to alternative methods. ALTEX. 2014;31(2):215-8. doi: 10.14573/altex.1401061.*

[30] *European Commission. Commission Staff Working Document Accompanying the document Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions (SWD(2017) 353 final/2). Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=SWD:2017:353:REV1&from=EN*

[31] *European Commission. Animals used for scientific purposes: Development, validation and promotion of alternative approaches by Member States. Available at: https://ec.europa.eu/environment/chemicals/lab_animals/3r/advance_en.htm*

Citizens support a phase out of animal testing

A 2009 opinion poll of citizens of six EU countries found that 79% agreed that Directive 2010/63/EU should prohibit all experiments on animals which do not relate to serious or life-threatening human conditions.[32] Furthermore, 84% agreed 'the [Directive] should prohibit all experiments causing severe pain or suffering to any animal'.

An EU-wide poll by Eurobarometer in 2010 found that, when asked whether scientists should be allowed to experiment on larger animals like dogs and monkeys for the improvement of human health and wellbeing, only 44% of respondents agreed.[33]

agreed the [Directive] should prohibit all experiments causing severe pain or suffering to any animal

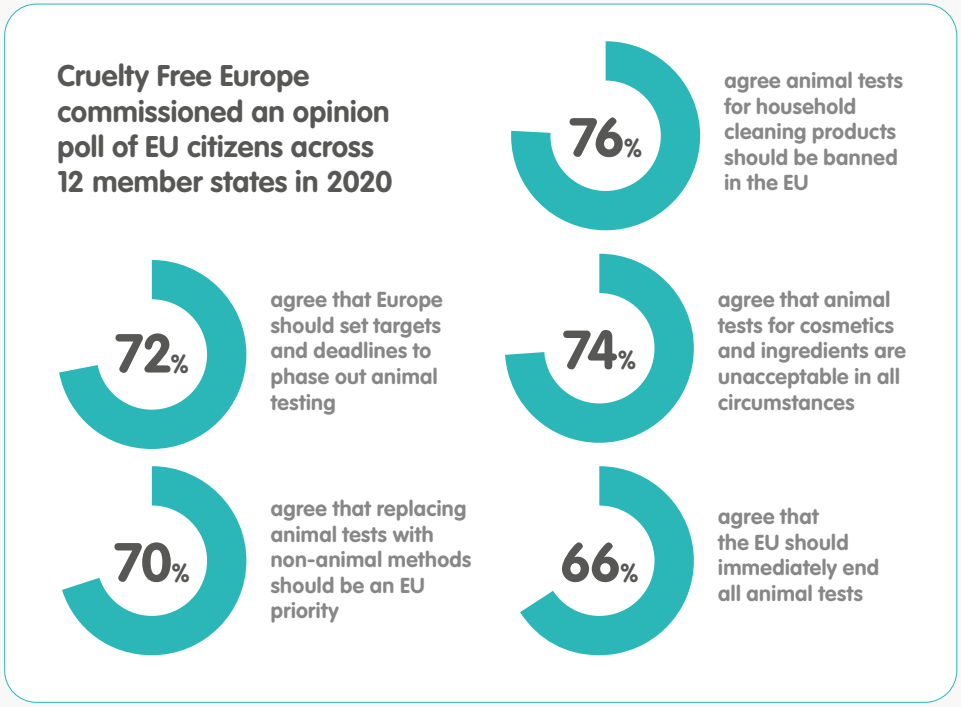


Fig. 5. Responses to Cruelty Free Europe opinion poll on animal testing, 2020.[34]

[32] *BUAV/You Gov. Opinion poll on animal experiments. 2009. Report available on request.*

[33] *Eurobarometer. Special Eurobarometer 340: Science and Technology. 2010. Available at: https://data.europa.eu/data/datasets/s806_73_1_ebs340?locale=en*

[34] *Savanta: ComRes. Cruelty Free Europe – Animal Testing in the EU. 2020. Available at: https://comresglobal.com/polls/cruelty-free-europe-animal-testing-in-the-eu/*

Furthermore, the following percentage of adults agreed that the EU should end experiments conducted for medical research on dogs, (72%), horses (72%), cats (71%) and monkeys (69%).[35]

As further evidence of the public's disquiet with animal testing:

- Following 'One of Us' and 'Right2Water', 'Stop Vivisection' was the third European Citizens' Initiative to reach the necessary threshold. It was submitted to the European Commission on 3 March 2015, signed by 1.17 million citizens and with the active support of 50 MEPs. It asked the European Commission 'to abrogate Directive 2010/63/EU… 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.'
- In 2018, Cruelty Free International and The Body Shop collected over eight million signatures in support of a global ban on animal testing for cosmetics. It was the largest animal related petition in the world and the second largest the UN had ever received on any issue.
- An online petition following an investigation of a German contract testing facility (LPT) in 2019 gained over a million signatures within only a few weeks, in support of closing the facility.
- In 2019, prior to being elected, 89 successful MEPs and considerably more candidates signed the Eurogroup for Animals Vote for Animals pledge to 'promote the adoption of a comprehensive and concrete EU strategy with milestones to phase out the use of animals in research, testing and education'.

It is clear that the public has only limited support for animal research and is in fact opposed to much of the testing that is going on in the EU and wishes to see a proactive phase out strategy in place.

[35] *Ibid.*

Animal testing is not working

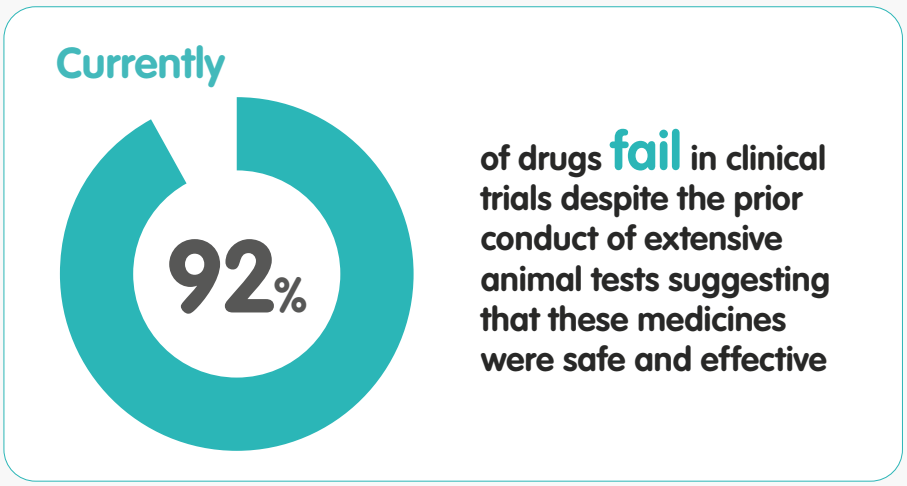
Drug development is in crisis. Currently, 92% of drugs fail in clinical trials despite the prior conduct of extensive animal tests suggesting that these medicines were safe and effective;[36] 55% of failures are due to lack of efficacy, while 28% are due to toxic effects in humans.[37] This general failure rate is bad enough, but for drugs aimed at treating complex and poorly understood conditions, failure is almost a certainty. For example, the failure rate for Alzheimer's drugs is estimated to be higher than 99%.[38]

Only a handful (approximately 20) of novel medicines are released onto the market every year,[39] and withdrawals and warnings of adverse effects commonly follow as the drug is tested in the wider human population.[40] The efficacy of the drug can also prove to be more limited than initially thought based on the animal test data. For example, out of 48 cancer drugs approved by the European Medicines Agency from 2009 to 2013 to treat 68 types of cancer, almost half showed no survival benefits, and even in cases where benefits were seen, the difference was judged to be 'clinically insignificant'.[41] This tells us that the animal testing paradigm is failing.

In addition to the low approval rates, the discovery and development of new drugs is an excruciatingly long and expensive process and typically takes an average of ten to 15 years to complete,[42] at a cost of $2.6 billion per drug.[43]

The situation in basic and applied medical research is even worse. A review of 101 high impact basic science discoveries based on animal experiments found that only 5% resulted in approved treatments within 20 years.[44] A study of 17 animal research programmes licensed in Germany in the early 1990s which promised new therapies, or at least direct clinical impact, found they had resulted in 'no clinical relevance' 17 years later.[45] A systematic review of highly cited animal studies from the top seven science journals found that of 76 qualifying animal studies, only eight led to therapies approved for clinical use.[46]

A recent analysis of claimed 'medical breakthroughs' reported in the mainstream British media in 1995 found that some 25 years later only one out of 27 had resulted in clinical use and even then, with significant caveats. Twenty-one of the 'breakthroughs' failed outright to translate to human benefit, while the remaining five were classed as inconclusive (one case) or, at best, partially successful (four cases).[47] Given this level of failure, it is clear in hindsight that both the media articles, and often the scientific papers themselves, were wrong to claim that the animal-based breakthrough would lead to human benefit. The scientific literature is replete with concerns over the current drug testing paradigm, as well as calls to transition to more predictive and more human-relevant approaches as a matter of urgency.



[36] *Biotechnology Innovation Organization. Clinical Development Success Rates and Contributing Factors 2011-2020. 2021. Available at: go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf*

[37] *Lee BY. The NIH Microphysiological Systems Program: Tissue-on-chips for Safety and Efficacy Studies in Drug Development. Presentation given at ICCVAM Public Forum, 23 May 2019. Available at: https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2019/06-lee-ncats_508.pdf*

[38] *Alteri E, Guizzaro L. Be open about drug failures to speed up research. Nature. 2018;563(7731):317-319. doi: 10.1038/d41586-018-07352-7.*

[39] *Biotechnology Innovation Organization. Clinical Development Success Rates 2006-2015. Available at: https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf*

[40] *van Meer PJ et al. The ability of animal studies to detect serious post marketing adverse events is limited. Regul Toxicol Pharmacol. 2012;64(3):345-9. doi: 10.1016/j.yrtph.2012.09.002.*

[41] *Davis C et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ. 2017;359:j4530. doi: 10.1136/bmj.j4530.*

[42] *Marchetti S, Schellens JH. The impact of FDA and EMEA guidelines on drug development in relation to Phase 0 trials. Br J Cancer. 2007;97(5):577-581. doi:10.1038/sj.bjc.6603925*

[43] *DiMasi JA et al. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012.*

[44] *Contopoulos-Ioannidis DG, Ntzani E, Ioannidis JP. Translation of highly promising basic science research into clinical applications. Am J Med. 2003;114(6):477-84. doi: 10.1016/s0002-9343(03)00013-5.*

[45] *Lindl T, Voelkel M. No clinical relevance of approved animal experiments after seventeen years. ALTEX. 2011;28(3):242-3. doi:10.14573/altex.2011.3.242*

[46] *Hackam DG. Translating animal research into clinical benefit. BMJ. 2007;334(7586):163-164. doi:10.1136/bmj.39104.362951.80*

[47] *Bailey J, Balls M. Clinical impact of high-profile animal-based research reported in the UK national press. BMJ Open Science. 2020;4:e100039. doi: 10.1136/bmjos-2019-100039*

Promises that have been made

In 1999, a European Council Decision[48] made the EU party to the Council of Europe's Convention ETS 123 on the protection of animals used for experimental and other scientific purposes, Recital 3 of which says:

The use of primates for experimental and other scientific purposes carries the risk of suffering for those animals and therefore has to be reduced.

Three years later, in 2002, the European Parliament returned to the issue,[49] resolving that it:

Considers that the need for the continued use of non-human primates in research and testing should be critically evaluated in the light of scientific knowledge, with the intention of reducing and eventually ending their use…

There have been two reports by the Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), in 2009[50] and 2017,[51] looking into the use of non-human primates (NHP) in medical research, partly as a response to these calls. Both failed to set any clear proposals for reduction and were widely criticised by animal protection groups as being written by those in favour of NHP experiments.[52]

The first report however did recommend that:

The predicted degree of severity for NHP work should be limited to moderate.

This was ignored; there is no timetable, programme or even concrete policy commitment to eliminate severe NHP experiments.

SCHEER also recommended that:

The anticipated benefits of NHP studies and scientific progress in developing alternative methods should be regularly assessed to ensure that validated alternatives are adopted as soon as they are reasonably and practical available. This also has not been done.

The second report made two other relevant recommendations:

It is also necessary to reduce the timescale and bureaucracy associated with the process of formal validation and to overcome the lack of regulatory harmonisation both within and across sectors.

The EC should instigate strategic research funding initiatives to support the scientific and technological development required to achieve NHP replacement, or at least considerable progress towards it. This would also help the scientific community meet the policy objectives of the Commission.

The revision of the then animal experiments Directive 86/609/EEC in 2009 was set to tighten the restrictions on the use of primates but was amended by the Council. Directive 2010/63/EU placed some limits on uses of primates; a timetable for moving away from the use of wild caught animals and a ban on the use of great apes. Other NHPs may only be used in applied research with a view to the avoidance, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical conditions in human beings. They are not permitted to be used for forensic enquiries, education and training or protection of the natural environment. However, NHPs can be used for basic research for any purpose, rendering the restrictions of very limited meaning.

[48] *European Council. 1999/575/EC: Council Decision of 23 March 1998 concerning the conclusion by the Community of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31999D0575*

[49] *European Parliament. Resolution on Council Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes (2001/2259(INI)). 2002. Available at: www.europarl.europa.eu/sides/getDoc.do?reference=P5-TA-2002-0594&type=TA&language=EN&redirect*

[50] *Scientific Committee on Health and Environmental Risks. The need for non-human primates in biomedical research, production and testing of products and devices. 2009. Available at: ec.europa.eu/health/archive/ph_risk/committees/04_scher/docs/scher_o_110.pdf*

[51] *Scientific Committee on Health Environmental and Emerging Risks. Final Opinion on The need for non-human primates in biomedical research, production and testing of products and devices (update 2017). 2017. Available at: ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_004.pdf*

[52] *Bailey J, Taylor K. The SCHER report on non-human primate research - biased and deeply flawed. Altern Lab Anim. 2009;37(4):427-35. doi: 10.1177/026119290903700412.*

In 2003, the Seventh Amendment to the former Cosmetics Directive (76/768/EEC) banned the testing of finished products on animals and set a final deadline of 2013 for the testing and marketing of ingredients that had been tested on animals.[53] This target date of 2013 was maintained even though alternative methods were, at the time, not considered available for all of the animal tests. There is wholesale agreement that the impending animal test bans provided renewed enthusiasm and investment in the development of alternative methods to the betterment of cosmetic science and other sectors.

The momentum set by the legislators in the Cosmetics Directive has sadly not been carried forward to any other concrete commitments to reducing and replacing animal testing since then.

In response to the successful Stop Vivisection European Citizens' Initiative in 2012, the European Commission stated that:

> *The EU shares the Citizens' Initiative's conviction that animal testing should be phased out. This is the ultimate goal of EU legislation.*

The Commission outlined some commitments related to phasing out animal experiments but using the development of alternatives as the main mechanism (see below).[54] This seems like a far from adequate response to the concerns of Europe's citizens.

In 2016, the Commission hosted a conference on alternatives,[55] reiterating that it:

> *Supports the ultimate goal that all animal testing should be phased out and replaced by scientifically valid alternatives.*

The conference report did include in its conclusion that:

> *There is also potential in considering deadlines to phase out animal testing in specific areas, where possible …*

In recent years, national governments and agencies have started making some promising commitments towards phasing out animal tests.[56]

Notably,

- The Netherlands made an initial commitment towards ending toxicity testing on animals by 2025 and has followed this up with their Transition Programme for Innovation without the use of animals (TPI).[57]
- The US Environmental Protection Agency has committed to ending mammalian toxicity testing by 2035.[58]
- The US Interagency Coordinating Committee on the Validation of Alternative Methods has committed to a Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States in 2018.[59]
- The US FDA has launched a Predictive Toxicology Roadmap on viable ways to foster the development and evaluation of emerging toxicological methods.[60]

Despite statements in support of a phase-out of animal experiments, in comparison with other territories, including the US, the EU has no proactive and horizontal strategy to end the use of animals in research and testing.

[53] *European Commission. Ban on animal testing. Available at: ec.europa.eu/growth/sectors/cosmetics/animal-testing_en*

[54] *European Commission. Communication from the Commission on the European Citizens' Initiative "Stop Vivisection". 2015. Available at: ec.europa.eu/environment/chemicals/lab_animals/pdf/vivisection/en.pdf*

[55] *European Commission. Non-animal approaches the way forward: report on a European Commission Scientific Conference held on 6-7 December 2016 at The Egg, Brussels, Belgium. 2017. Available at: ec.europa.eu/environment/chemicals/lab_animals/3r/pdf/scientific_conference/non_animal_approaches_conference_report.pdf*

[56] *Alliance for Human Relevant Science. Accelerating the Growth of Human Relevant Life Sciences in the United Kingdom: A White Paper. 2020. Available at: humanrelevantscience.org/white-papers/*

[57] *Nationaal Comité advies dierproevenbeleid. NCad opinion Transition to non-animal research. 2016. Available at: www.ncadierproevenbeleid.nl/documenten/rapport/2016/12/15/ncad-opinion-transition-to-non-animal-research*

[58] *U.S. Environmental Protection Agency. EPA New Approach Methods: Efforts to Reduce Use of Animals in Chemical Testing. Available at: www.epa.gov/research/epa-new-approach-methods-efforts-reduce-use-animals-chemical-testing*

[59] *U.S. National Toxicology Program. A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. 2018. Available at: ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy/index.html*

[60] *U.S. Food and Drug Administration. FDA's Predictive Toxicology Roadmap. 2017. Available at: www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap*

EU targets in other areas

The EU regularly uses targets in other important areas of policy to drive innovation and change. Why is there reluctance to apply the logic of targets with deadlines to bring animal testing to an end and hasten the use of human-relevant science?

The Kyoto Protocol was signed by 37 industrial countries as well as the European Union in 1997 and set the goal of a 5% reduction in carbon emissions below 1990 levels by 2012. The target was met.[61] No one suggested that, in order to meet this target, manufacturing of cars ceased, or power was turned off. Instead, goals to reduce emissions are being met by increased efficiency and innovation spurred on by targets and the need to be better.[62] One can see that the reduction and replacement of animal testing could similarly be achieved through more efficient use of and investment in technology.

Europe made further commitments to reduce carbon emissions levels by 20% by 2020.[63] In 2014, the Commission proposed further targets as part of the EU's 2030 climate and energy framework:[64]

- At least 40% cuts in greenhouse gas emissions (from 1990 levels).
- At least 32% share for renewable energy.
- At least 32.5% improvement in energy efficiency.

The European Green Deal proposes an increase to 55% from the 40% cut in greenhouse gas emissions.[65]

In 2019, the European Green Deal set out a roadmap with actions, including the target to become a climate neutral continent by 2050. Ways it will achieve this include:

- Investment of 35% of the near 100 billion euro Horizon Europe budget in climate objectives, through the development of innovative and cost-effective zero-carbon solutions.[66]
- Requiring member states to develop national long-term strategies to achieve the greenhouse gas emissions reductions.
- A European Climate Law to turn this political commitment into a legal obligation.
- A strategy for sustainable and smart mobility that will achieve a 90% reduction in transport emissions.

Other targets include:

- CO_2 emission performance standards for new passenger cars and for new vans in the EU in Regulation (EU) 2019/631/EU.
- A zero-pollution action plan for air, water and soil.[67]
- 2030 goals for energy efficiency and deployment of renewable energy in Directive 2012/27/EU and 2018/2001/EU.

[61] *United Nations. Kyoto Protocol - Targets for the first commitment period. Available at: unfccc.int/process-and-meetings/the-kyoto-protocol/what-is-the-kyoto-protocol/kyoto-protocol-targets-for-the-first-commitment-period*

[62] *European Commission. 2020 climate and energy package. Available at: ec.europa.eu/clima/policies/strategies/2020_en*

[63] *Ibid*

[64] *Ibid*

[65] *European Commission. A European Green Deal. Available at: ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en*

[66] *European Commission. Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee, theCcommittee of the Regions and the European Investment Bank. A Clean Planet for all A European strategic long-term vision for a prosperous, modern, competitive and climate neutral economy (COM/2018/773 final). Available at: eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A52018DC0773*

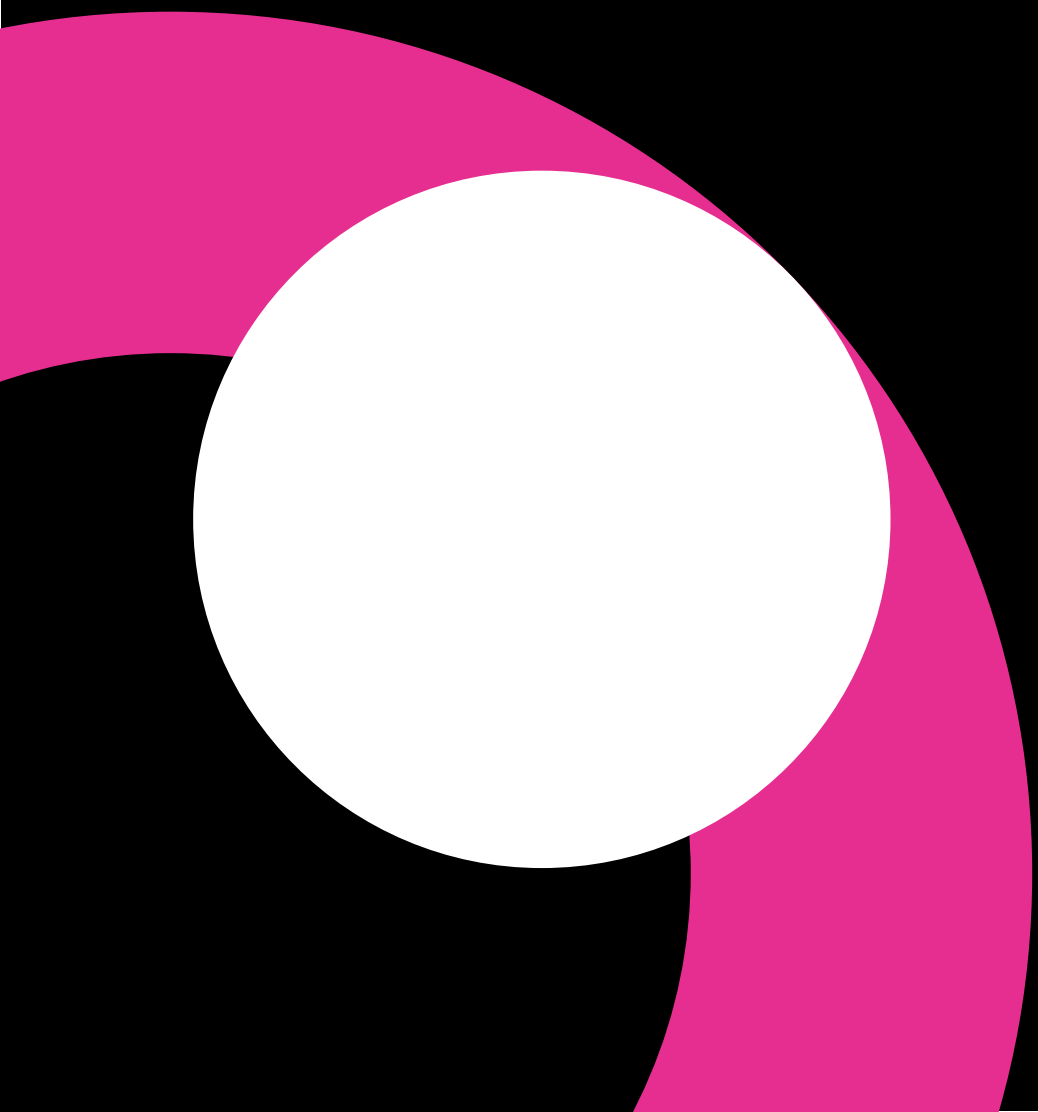
[67] *European Commission. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. Pathway to a Healthy Planet for All. EU Action Plan: 'Towards Zero Pollution for Air, Water and Soil' Brussels, 12.5.2021. COM(2021) 400 final*

Summary

In summary:

- The current legal framework does not have appropriate mechanisms in place to reduce animal testing, except passively and is solely dependent on the development of alternative methods. Directive 2010/63/EU does not provide that mechanism.
- The development and implementation of non-animal methods are limited by comparatively low levels of funding, bureaucratic hurdles and poor enforcement, and no pressure or incentives.
- Public opinion demands that animal research be significantly more limited.
- There is evidence of an appetite for change within the scientific community and in industry.
- A political commitment is needed to ensure that minds are focused on reduction, replacement and new ways of tackling challenges like a toxic-free environment and some of the major health issues of the day, rather than passively waiting to solve the problem, much as we have had to in other areas like carbon reduction.

Where could reductions come from?



Voluntary research (7.7 million animals)

Regulatory testing, mainly related to determining the safety of products, accounts for only 20% of all animal experiments. This is the only area of testing that companies could argue 'must' be done (although of course they can decide not to produce any new products that require testing).

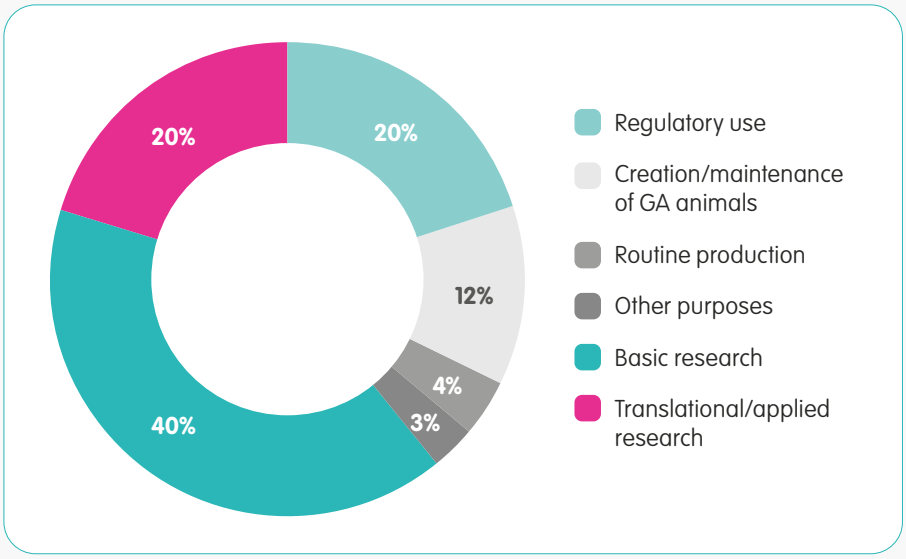


Fig. 6. Purpose of animal use in 2017 across the EU, N=10.9 million uses.

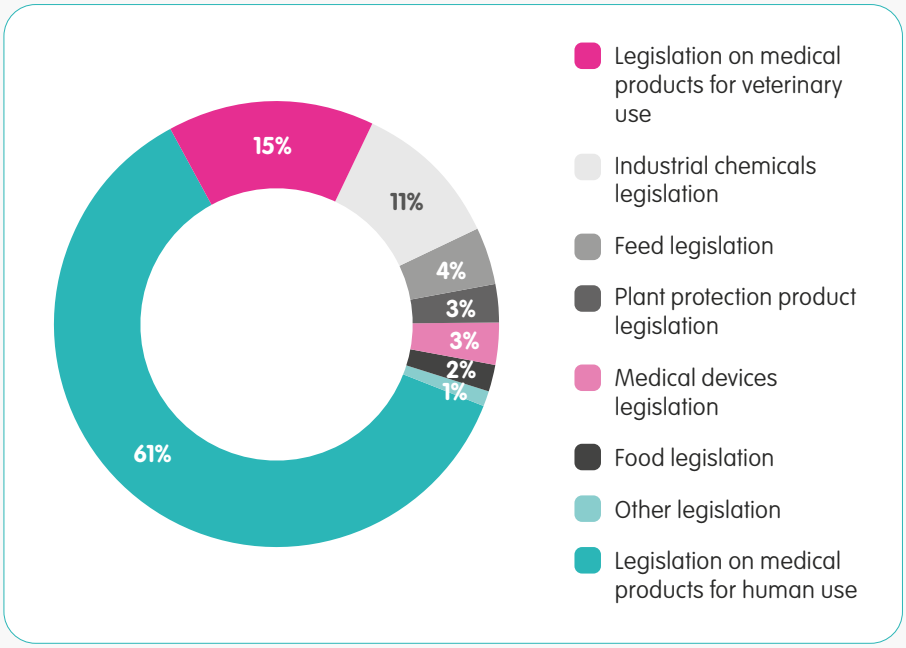


Fig. 7. Legislative purposes, % out of all regulatory use (N=2,186,859 uses)

Furthermore, out of the 2.2 million uses for regulatory purposes, 1.3 million were regulatory tests for human pharmaceuticals (only 12% of the total uses of animals).

At least 80% of the EU's animal testing is therefore entirely voluntary.

The decision to do an animal test usually starts with the researcher. They are then supported by their institution in that decision or because they are acting on behalf of their institution's wishes. The decision to test on animals may be further supported by any external funding bodies and finally endorsed by the government that is authorising it under the national animal experiments legislation. Along the way, internal and external ethical review committees may also agree that the experiment is worthwhile.

Just because several different groups (all interrelated, all science-focused, some with a conflict of interest and generally of the same mindset) agree that an animal experiment is needed to satisfy the researcher's or institution's objectives does not mean that it 'must' be done. Furthermore, just because an ethical review body or competent authority agrees the experiment meets the HBA also does not mean that it is indispensable and must be done for society to progress.

If a commitment is made to reduce animal testing, then there is wide scope to tackle the 80% of testing that has a much more voluntary element.

What is needed is an appreciation that not all science that could be done is being done - there is already a limit on the amount of scientific research that is being done. It is constrained by the scale of funding and the capacity and imagination of the scientific community.

Already, the scientific community collectively on a daily basis makes decisions about what research should be done and therefore what should not.

This decision is made in an uncoordinated manner by individual scientists (in their own heads) but is shaped very much by the priorities of funding bodies. How and why funding bodies make decisions about what research topics are the most important and what are the most appropriate methods to use is a black box which needs to be opened.

It is long suspected that the scientific community shapes its own approach as scientists move from research into governance in their careers. Old ideas can persist. Research projects are typically so specialised and complex that only those scientists involved or recently involved in such research can decide if the research is worth funding. This is the same situation in the peer review of journal articles[68] – the whole system is in fact very insular.

Very large, national or international funding streams such as the EU's Framework projects tend to have very broad research themes dictated by emerging threats as well as exciting opportunities. It is up to researchers already in academia to make the more specific project proposals. They will naturally propose to do the same kind of research that they already tend to do, and the work will be reviewed by their peers. The entire process is not given enough scrutiny and it is possible there is a significant amount of conflict of interest, malaise, and inertia in the system that should be tackled.

Once it is appreciated that not all research that has high value is being done then it becomes less uncomfortable to decide that some types of research that cause suffering to animals will not be done, except in very specific circumstances. Other types of research will be done in their place, and these could lead to greater benefits for humankind.

The HBA under the Directive is a tool that could be used in conjunction with a target-based approach to reduce animal experiments. If member states are under some potentially self-imposed limitation as to the number of animal tests they can authorise, then the HBA becomes the tool to decide which tests should be permitted and which ones should not.

The 3D cube suggested by Bateson that features in Appendix II of the Directive Working Document on Project Evaluation,[69] is still the best visualisation of how the HBA could work. Experiments are notionally classified as of low, medium or high benefit and causing low, medium and high suffering. The cube allows the evaluator to see that experiments considered to be of low benefit and yet cause high suffering should not be permitted.

However, there is currently little quantitative assessment of harms (numbers of animals and level of suffering) and benefits (including chances that the benefit will be realised) being done in practice by ethical review bodies across Europe.[70] If those conducting the HBA were tasked with not only being more quantitative in their approach but under some pre-determined constraints then it is possible to see how the HBA can be used to achieve reductions. The HBA is the tool however, it is not the complete answer.

[68] European Commission. Scientific Conference Non-Animal Approaches. 2016.

[69] National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes. Working document on Project Evaluation and Retrospective Assessment. 2013. Available at: ec.europa.eu/environment/chemicals/lab_animals/pdf/Endorsed_PE-RA.pdf

[70] Taylor, K. Harms versus Benefits. 2018.

Tests of limited benefit from the outset

There are at least four types of animal test that could be considered of low benefit from the outset; in other words, it is known in advance that the outcome of the research is likely to be of low benefit. This includes:

1. **Tests using animal 'models' that have been heavily criticised in the scientific literature.**
2. **Tests in subject areas that are more 'frivolous' than others.**
3. **Duplicated animal tests.**
4. **Tests that the public clearly do not support.**

1. Tests using animal 'models' that have been heavily criticised in the scientific literature

As science progresses there can be evaluation of its success in certain areas. For example, did test A lead to outcome B? This could give us an insight into the value of 'animal models'. Unfortunately, this kind of reflection is not common (science likes to move forward, not look back). Reports are rife with the difficulty of evaluating the value of scientific research.[71, 72] Surprisingly, funding bodies still look more at publication rates than actual outcomes when evaluating research. This is a general issue for science, not just a problem within animal research.

Animal experiments however are a special case in science as most experiments are using the animal as a 'model' to represent a human. They are therefore an approximation of what might happen if you performed the same experiment in a human. When you are relying on a model to mimic what you really want to know it becomes crucial to ensure your model is accurate and reliable. In other areas such as business and technology, it would be unthinkable to not be routinely checking to make sure your model is predicting what it should be. Surprisingly, this is not often done, beyond a justification for choosing that 'animal model' in the first place. It is taken on face value that the animal model is a good approximation of what might happen in humans. Over time however it becomes possible to evaluate using statistics if the animal model was predictive of effects in humans. This is a higher standard of predictivity.[73]

There are a few research groups however that are looking at the validity of animal models (often with a view to improve them rather than end them).[74] They are focusing on disease areas for which the medical community are struggling to find treatments, such as stroke. They are finding areas where animal models have not led to clinical benefit, despite years of effort (see Animal testing is not working) or are so fundamentally flawed that they are extremely unlikely to. Unfortunately, there does not seem to be a coordinated effort to root these methods out of the scientific community. Here are just a few examples of animal models that have been heavily criticised scientifically and yet are still being used:

- Vision research (e.g., on cats and monkeys)[75]
- Alzheimer's disease (e.g., APP and tau transgenic mice)[76]
- Parkinson's disease (e.g., MPTP induced models)[77]
- Stroke (e.g., cerebral artery occlusion model)[78]
- HIV (e.g. SIV model)[79]
- Multiple sclerosis (e.g., EAE induced models)[80]
- Rheumatoid arthritis (e.g., collagen-induced arthritis model)[81]
- Cancer (e.g., graft models)[82]

A more coordinated effort could be made to identify and root out animal 'models' that are accepted to be of limited validity and therefore unlikely to deliver clinical benefit.

[71] NC3Rs. Evaluating Progress in the 3Rs: the NC3Rs Framework. Available at: www.nc3rs.org.uk/sites/default/files/documents/Corporate_publications/Evaluating%20progress%20in%20the%203Rs-%20the%20NC3Rs%20framework.pdf

[72] BBSRC. Review of Research Using Non-Human Primates: Report of a panel chaired by Professor Sir Patrick Bateson FRS. 2011. Available at: mrc.ukri.org/documents/pdf/bateson-review-of-non-human-primates/

[73] Balls M, Combes R. The need for a formal invalidation process for animal and non-animal tests. Altern Lab Anim. 2005;33(3):299-308. doi: 10.1177/026119290503300301.

[74] For example, CAMARADES (www.ed.ac.uk/clinical-brain-sciences/research/camarades/about-camarades) and SYRCLE (www.radboudumc.nl/en/research/departments/health-evidence/systematic-review-center-for-laboratory-animal-experimentation).

[75] Bailey J, Taylor K. Non-human primates in neuroscience research: The case against its scientific necessity. Altern Lab Anim. 2016;44(1):43-69. doi: 10.1177/026119291604400101.

[76] PR Newswire. New model of Alzheimer's derived from skin cells of people with the disease. 2012.

[77] Chesselet MF. In vivo alpha-synuclein overexpression in rodents: a useful model of Parkinson's disease? Exp Neurol. 2008;209(1):22-7. doi: 10.1016/j.expneurol.2007.08.006.

[78] Gladstone DJ et al. Toward wisdom from failure: lessons from neuroprotective stroke trials and new therapeutic directions. Stroke. 2002;33(8):2123-36. doi: 10.1161/01.str.0000025518.34157.51.

[79] Trivedi B. The primate connection. Nature. 2010;466, S5. https://doi.org/10.1038/nature09236

[80] Behan P et al. The Pathogenesis of Multiple Sclerosis Revisited. J R Coll Physicians. 2002;32:244-265.

[81] Firestein G. Rheumatoid arthritis in a mouse? Nat Rev Rheumatol. 2009;5, 1. https://doi.org/10.1038/ncprheum0973

[82] Edwards JC et al. Do self-perpetuating B lymphocytes drive human autoimmune disease? Immunology. 1999;97(2):188-96. doi: 10.1046/j.1365-2567.1999.00772.x.

2. Tests in subject areas that are more 'frivolous' than others

This is the kind of research, usually conducted in universities, that may be considered by some to be more 'frivolous' from the outset than other areas of research. It is usually not directly linked to human medical problems and can be termed 'curiosity-driven' or 'blue-sky' research. The tests are done to investigate hypotheses that often lead to more research. Academics can spend their entire professional lives studying one or two areas, and are able to gain funding, presumably based on publication of papers, training of students and providing evidence for interesting ideas that may move the field on but rarely - in our experience - lead to human medical benefit.

It is contentious of course to weigh the benefit of one area of research over another, but this is precisely what the HBA requires us to do. Furthermore, if public opinion is to be respected, only the most essential research using animals should be done, which means that the less essential research using animals should not be done. It has been argued that knowledge for knowledge's sake may be enough to justify causing harm to an animal in an experiment,[83] but the Directive requires more than this.

Article 38(2)9d of Directive 2010/63/EU requires that the HBA should "assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and ***may ultimately benefit human beings, animals or the environment****;" (emphasis added).*

The Commission in its member state guidance says:[84]

"increased knowledge" as the primary benefit should be linked to a more tangible strategic goal, even though any wider benefits may be much further in the future and less predictable; benefits should go beyond "it would be nice to know".

Animal protection groups have been the most forthcoming in suggesting areas of research that could be of particularly low value (benefit). Often these examples include experiments where the animals also suffer high levels of harm, such as:

- Using animals to investigate human behavioural disorders (e.g., schizophrenia and anxiety) or aspects of human behaviour (e.g., sleep). (basic research)
- Veterinary research linked to other exploitative industries, e.g., racing, intensive food production (applied research)
- Food product health claims (applied research)
- Pet food health claims (applied research)
- Ageing, as distinct from diseases of the older population (basic research)
- Effects of recreational drugs (tobacco, alcohol, drugs) (applied research)
- Defence research (applied research)
- Educational purposes only (education and training)

As part of a targeted approach, the Commission and member states could re-evaluate the 'benefit' of types of research from the outset to inform their decision making.

3. Duplicated animal tests

It has long been assumed that there could be an element of duplication in animal tests, particularly between nations. Given that there are nearly 11 million experiments every year in the EU it is inconceivable that some of these could not be duplicates.

The fact that many scientific experiments give different results when repeated by another researcher is currently a hot topic, the so-called reproducibility crisis.[85] Many scientists claim that it is indeed important that experiments are repeated to show that the results can be trusted. This is a particular ethical problem when it comes to animal experiments. The animal research community is relatively quiet about the need to replicate (not duplicate) experiments. Several studies have shown that there is a huge amount of discord between two studies on the same species[86, 87] so the subject is naturally uncomfortable for animal researchers.Repeating experiments to ensure reproducibility is not (yet) a requirement across science but can be used as an argument when animal groups complain about 'duplication'.

[83] *Grimm H et al. The Road to Hell Is Paved with Good Intentions. 2017.*

[84] *National Competent Authorities. 2013.*

[85] *S86 Harris R. Rigor Mortis: How Sloppy Science Creates Worthless Cures, Crushes Hope, and Wastes Billions. 2017. Hachette UK.*

[86] *Kleinstreuer NC et al. A Curated Database of Rodent Uterotrophic Bioactivity. Environ Health Perspect. 2016;124(5):556-62. doi: 10.1289/ehp.1510183.*

[87] *Braakhuis HM et al. Testing developmental toxicity in a second species: are the differences due to species or replication error? Regul Toxicol Pharmacol. 2019;107:104410. doi: 10.1016/j.yrtph.2019.104410.*

Either animal experiments must be replicated, or they must not. This needs to be cleared up.

There are two types of duplication that are particularly concerning:

Firstly, the kind of duplication when an experiment is proposed (and then conducted) by a researcher in country A when researcher in country B has done, or is doing, the same or very similar work. Researcher A just simply doesn't know. One might argue that this is not a problem if it is relevant to the reproducibility issue described above, but the problem is that researchers A and B may never know they have done the same experiment, especially if the results are not published. The scale of this unwitting duplication is simply not recognised, largely because not all experiments are published, particularly those that are negative or inconclusive,[88] and there is no single database of those that are published. Whilst researchers are very familiar with checking the relevant journal databases like Pub Med, depending on the search terms they may use (and of course the lack of publication) they are not guaranteed to identify all similar experiments that have been done.[89] Duplication may be more likely for postgraduate because PhD student may be more at risk of their experiments going wrong or running out of time to publish the results.

There have been calls for a central database to avoid this unwitting duplication. Suggestions include a database of all proposed animal studies like the clinicaltrials.gov website,[90] containing all results regardless of if they are positive or negative,[91] or of all approved studies. As a consequence of the EU revised implementing decision on the Directive,[92] the Commission has begun publishing the Non-Technical Summaries (NTS) of authorised animal experiments from all 27 member states. Language differences between the member states could be a barrier to effective searching, but there will be key words in English. The problem with this however is that the NTS is simply a summary and may not include the details of particular experiments. In many cases, the projects themselves are so broad and complex that it will be very difficult to identify if there is potential for duplication. In this case, researchers would have to contact the researcher to check the details of their work to determine if duplication is likely. More crucially, unless researchers are forced by their competent authorities to check the database then no-one will know.

Secondly, there is the risk of duplication of regulatory safety and efficacy tests. This used to occur in Europe for batch safety tests of vaccines and other biologicals because there was lack of coordination between member states and a mistrust of the results from one country to another.[93] It is not clear the extent to which this has been resolved and whether this now may still occur between the EU and non-EU countries. Duplication of tests between different pharmaceutical companies that are testing the same or very similar drugs is possible due to the high levels of secrecy. Findings from drugs that get dropped may never be published and could be repeated by others.[94] The UK Nuffield Council on Bioethics report in 2005 raised the issue of duplication in animal testing and suggested strategies to overcome it.[95]

A review of the current potential for duplication of all animal testing should be done to ensure that all efforts are being made to avoid it.

[88] *Sena ES et al. Publication bias in reports of animal stroke studies leads to major overstatement of efficacy. PLoS Biol. 2010;8(3):e1000344. doi: 10.1371/journal.pbio.1000344.*

[89] *EURL ECVAM. Good Search Practice on Animal Alternatives, Re-edition. 2013. Available at: ec.europa.eu/jrc/en/scientific-tool/eurl-ecvam-search-guide*

[90] *STAT. Califf's big idea: Build a database for research done before clinical trials. 2016. Available at: www.statnews.com/2016/06/10/califf-database-preclinical-trials/*

[91] *The Journal of Negative Results in Biomedicine was a peer-reviewed open access medical journal established in 2002 but ceased publishing in September 2017.*

[92] *European Union. Regulation (EU) 2019/1010 of the European Parliament and of the Council of 5 June 2019 on the alignment of reporting obligations in the field of legislation related to the environment. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019R1010*

[93] *Associate Parliamentary Group for Animal Welfare. The use of animals in vaccine testing for humans. 2005. Available from the RSPCA or APGAW.org*

[94] *Prior H et al. Opportunities for use of one species for longer-term toxicology testing during drug development: A cross-industry evaluation. Regul Toxicol Pharmacol. 2020;113:104624. doi: 10.1016/j.yrtph.2020.104624.*

[95] *Nuffield Council on Bioethics. The ethics of research involving animals. 2005. Available at: www.nuffieldbioethics.org/publications/animal-research*

4. Tests that the public clearly do not support

Animal testing of cosmetics is the only area to date where public opinion has been directly considered in the legislative process, and yet there are other uses of animals that the public consistently does not support.

Tests that the public does not support[96] include:

- Tests that cause severe suffering (1,023,138 uses in 2017)
- Tests on monkeys (8,235 uses in 2017)
- Tests on dogs (13,688 uses in 2017)
- Tests on cats (1,879 uses in 2017)
- Tests on rabbits (351,961 uses in 2017)
- Tests on horses (2,414 uses in 2017)

These areas of testing have generally had less political attention paid to them to date, although there has been some focus on the use of monkeys and, to a lesser degree recently, on dogs. Testing on animals of other non-essential domestic products has attracted some attention but that is also yet to be followed up with legislation.

The views of the public should be considered when deciding whether animal tests should be permitted. This could be done by including more members of the public in ethical review bodies so that their voices are heard in the decision-making process on individual animal experiments. More heed should also be given to public opinion when deciding the overall approach to animal testing and prioritisation of types of testing for replacement and reduction. For several years, the UK Government has been tracking the public's view on animal research,[97] but it is yet to incorporate that into its decision making. Clearly, the HBA being done across the EU does not reflect the views of the public.

There is much animal testing that the public does not support, and it is important that this is factored into decisions about which experiments should be authorised.

A regular review of public opinion should be done and used as a guide for those responsible for conducting the HBA and ultimately authorising animal research.

[96] *Ipsos MORI. Views on Animal Experimentation. Available at: https://www.ipsos.com/ipsos-mori/en-uk/views-animal-experimentation. See also other opinion polls referenced in this report.*

[97] *Ipsos MORI. Views on Animal Experimentation.*

Surplus animals (6.5 million animals)

Not much has been known about the scale of and reasons for the breeding of animals who are not then subsequently used in experiments. Until now, there have been only a few estimates of numbers.[98] However, the publication of the Commission's implementation report, in which member states have to count the number of animals bred and not used every five years, now provides the first reasonably accurate figure.[99]

In 2017, the EU member states reported that 6,484,535 animals were bred and not used. This is a huge figure. Of all animals in laboratories in any given year, 28% will be simply bred and then killed. Unfortunately, there is no requirement to report the reasons for the deaths of these animals, but the reports do include animals who were surplus to requirements, were not suitable for testing or were killed for their tissues.

Based on the member state individual reports to the Commission[100], the vast majority of the non GA animals killed and not used were mice, rats and fish. However, 230 dogs were reported to have been bred and not used, including 38 from France and 97 from the UK.

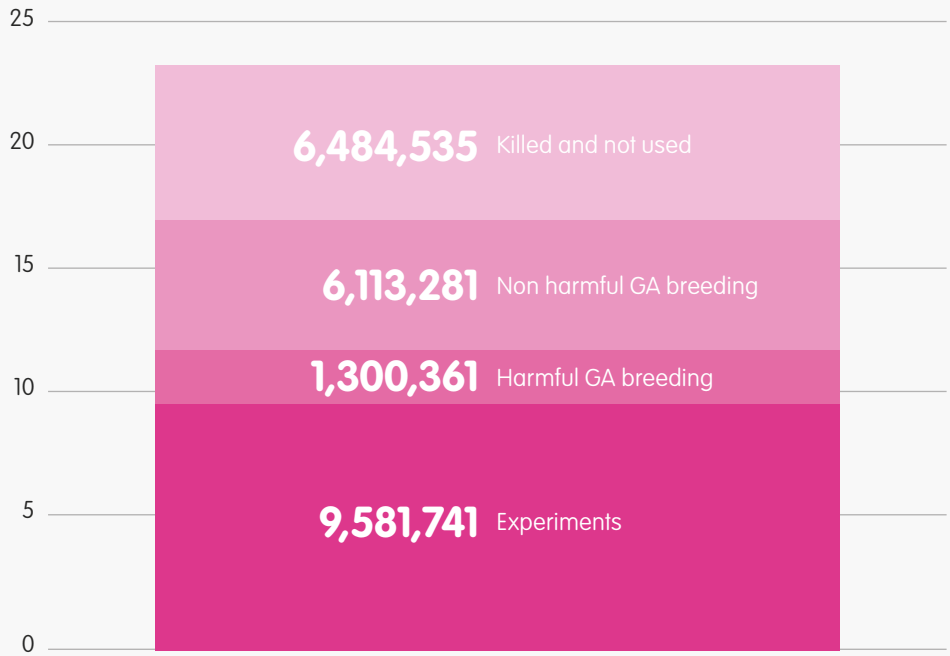


Fig. 8. A total of 23.5 million animals were bred in laboratories and killed in 2017 in the EU according to the European Commission statistical and implementation reports.

[98] *Laboratory Animal Science Association. Usage of dogs, cats and non-human primates that are bred or obtained for scientific purposes but are not subsequently used for that purpose: Report on a survey by the Laboratory Animal Science Association. 2003. In Report of the Animal Procedures Committee for 2003, HC 1017, pp. 51–54. London, UK, The Stationery Office and Taylor K, Alvarez LR. An Estimate of the Number of Animals Used for Scientific Purposes Worldwide in 2015. Altern Lab Anim. 2019;47(5-6):196-213. doi: 10.1177/0261192919899853.*

[99] *European Commission. Implementation report. 2020*

[100] *Ibid*

It is entirely possible that some reduction in this figure could be made by:

- Improving the way breeding facilities communicate with their clients so that the number of animals bred is as close as possible to the number that the client actually uses.
- Improving standards of oversight so that animals are not bred by accident, which can be a problem in less well managed facilities.
- Improving standards of care and breeding so that animals are not rejected for actual use because they are ill or too small.
- Moving away from the use of animal tissues towards using human tissues or cell lines.

Unfortunately, the Commission does not seem inclined to address this issue:

> *Good oversight of breeding programmes is essential to minimise surplus animals as far as practicable, but given the fluctuations in supply and demand, and the specificity of requirements for certain studies,* ***there will always be some animals which cannot be used for scientific studies****.*[101]

The Commission should acknowledge that 6.5 million animals is much more than 'some animals' - this is a crisis that should be recognised as such and tackled.

A review of the reasons behind breeding of animals and subsequent non-use is urgently needed and recommendations followed up by member states.

[101] *Ibid*

Production of GA animals (7.4 million animals)

The number of animals used in the production of new and established GA lines is huge. This area of research has mushroomed in the last 20 years and is now responsible for 43% of all animals bred and killed, with the majority of them not having actually been used in experiments. Out of the 9.6 million experiments conducted in 2017, 2.6 million used GA animals. A further 7.4 million animals were used in GA breeding and not used in experiments. Therefore, only 26% of the GA animals produced are used in experiments.

This scale of animal production cannot all be essential.

The UK Government was asked to look at this issue in 2014. It responded with several recommendations for efficient breeding within institutions:[102]

- Storage of cryopreserved sperm and/or embryos so that a particular strain can be recovered/rederived as needed rather than keeping colonies alive.
- Matching the supply of animals with the scientific demand.
- Efficient colony management.
- Communication and collaboration with other institutions to avoid duplication.

The impact on UK GA production since the project is not known. The Commission services are developing guidance on GA animals. It is hoped it will include further advice on how surplus can be addressed.[103]

A review of the mechanisms for reducing the production of GA animals is urgently needed and recommendations followed up by member states.

[102] *UK Home Office. Efficient Breeding of Genetically Altered Animals Assessment Framework. 2016. Available at: assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773553/GAA_Framework_Oct_18.pdf*

[103] *Sinkevicius V. Answer given on behalf of the European Commission to question E-002719/2020. Available at: www.europarl.europa.eu/doceo/document/E-9-2020-002719-ASW_EN.html*

Animal tests that have been replaced (approx. 1.5 million animals)

Over the last 30 years there have been significant developments in the replacement of tests on animals for regulatory purposes. Alternatives have been developed that can now replace wholly, or in part, several animal tests for several product sectors. However, our experience has been that these methods can become 'stuck' in the process and replacing the animal tests takes much longer than is appreciated because of these delays.

Table 2. below is a list of just ten animal tests for which animal uses were reported in 2017 despite validated alternatives, other examples exist. In most cases, the corresponding animal test has not been deleted from legislation on guidelines, and there may be reasons why regulators or users still prefer to see the animal test data. However, for these ten tests there appears to be a pervasive problem which is exacerbated for batch tests because they involve significantly more animals as they are repeated for each 'batch' of product.

The main issues with achieving complete replacement are:

- **Lack of global harmonisation**
  Companies are reluctant to invest resources in moving to a non-animal test if the animal test is still required by regulators in other countries. Countries need to come together to agree on a way forward to replace these tests worldwide.
- **Lack of regulatory enforcement**
  In the EU it is illegal to conduct animal tests if accepted alternatives exist, and yet these tests may still be conducted. This could be because the regulators are not checking properly that alternatives are being implemented, or they are wilfully allowing the animal tests to be conducted for non-EU purposes (the lack of global harmonisation issue above).
- **Need for a defined approach**
  In more complicated areas where several non-animal methods must be used in combination, there needs to be an agreement about which methods are the most relevant, as well as a clear and defined approach to how the methods can be used in different combinations to obtain the necessary information.
- **Product specific validation required**
  In some cases, regulators will accept the non-animal method, but only after the company/manufacturer validates it for each of its products and demonstrates that it produces results that are comparable with the animal test (which was never validated itself). Some companies will be reluctant to do this as it can be an expensive and time-consuming process and there is poor regulatory enforcement to make them do this.
- **Availability of the alternative**
  Even when a non-animal method has been validated and proven to be superior to the animal test it replaces, it can be difficult to find contract testing facilities that are actually using it or to find manufacturers that are producing and selling it for use.

Table 2. Ten tests that are being conducted in the EU although there are replacements, total 762,788 uses.

	Test	Species used	Number of EU tests[a]	Product area	Progress since 2015
1	Skin irritation	Mostly rabbits	**4,120**	Chemicals	EU REACH legislation no longer demands the animal test (2016)
2	Eye irritation	Rabbits	**814**	Chemicals	EU REACH legislation no longer demands the animal test (2016)
3	Skin sensitisation	Mice, guinea pigs	**47,341** Incl. 30,785 guinea pigs	Chemicals	Defined Approach agreed at the OECD (2021)
4	Pyrogenicity	Rabbits	**35,172**	Medicines (human and veterinary)	The MAT was more strongly encouraged in the Ph.Eur. in 2016 and the rFC method added in 2020. Numbers are decreasing
5	Botulinum toxin batch potency test	Mice	**400,000**[b]	Medicines (human)	Between 2011 and 2019 three major manufacturers have had the cell-based method approved in the FDA and EU
6	Antibody production	Mice, rabbits, sheep, goats	**200,000**[c] Incl.45,024 by ascites	Medicines (human and veterinary)	EU body ECVAM has recommended that companies switch to the 'phage display' alternative method (2020)
7	Leptospira vaccine batch potency	Hamsters	**3,826**[d]	Medicines (veterinary)	The Ph.Eur. was updated in 2015 to include an option to waive the hamster test based on 'consistency of production'
8	Target and laboratory batch safety (veterinary vaccines)	Can include mice, farm animals, dogs, cats	**5,000**[e]	Medicines (veterinary)	In 2019, the VICH released draft guideline GL59, which includes an option to waive the LABST
9	Abnormal toxicity batch test	Mice and guinea pigs	**25,000**[f]	Medicines (human)	The test was completely deleted from the European Pharmacopeia in 2017
10	Shellfish toxin batch safety	Mice	**41,515**[g]	Food	In 2019, the mouse test was removed from EU regulation as the reference method for detecting PSP toxins, allowing for complete replacement

[a] Numbers of tests (not animals) in 2017, unless otherwise indicated, taken from Report from the Commission to the European Parliament and the Council on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017 (COM/2020/16 final).

[b] Based on official national statistics and non-technical summaries as described in 'Taylor K, et al. Botulinum toxin testing on animals is still a Europe-wide issue. ALTEX. 2019;36(1):81-90. doi: 10.14573/altex.1807101'. Furthermore in 2017 there were 892,723 batch potency tests in the EU in which category this test would fall.

[c] In 2017 as well as 45,024 ascites tests, there were 259,780 uses for the routine production of blood-based products (incl. polyclonal antibodies) and 164,554 for 'other product types' (incl. monoclonal antibodies). Since both categories include other products such as sera, a conservative estimate is 200,000.

[d] 2017 uses of hamsters in 'batch potency tests', likely to all be for Leptospira vaccine testing.

[e] Estimated based on expected animal saving per year reported in 'Veterinary Medicines Directorate. Animal usage in quality control tests for the batch release of Immunological Veterinary Medicinal Products (IVMPs) via the UK from 2007 to 2012. 2014.'

[f] The report 'Associate Parliamentary Group for Animal Welfare. The use of animals in vaccine testing for humans. 2005.' indicated that deleting the test in the European Pharmacopoeia would save 25,000 animals. Furthermore, the Abnormal Toxicity Test uses five times as many mice per test as the Target Animal Batch Safety Test, estimated at 5,000 animals per year.

[g] 2017 uses of mice for 'food legislation' requirements, likely to be for shellfish toxin testing.

Another test close to replacement include the acute fish toxicity test, which used 44,915 fish in 2017. The zebrafish embryo acute toxicity (ZFET) test method is a replacement of the acute toxicity test and uses fish embryos rather than young fish. The ZFET has been shown to agree with adult acute fish test results 90% of the time,[105] but it is struggling to gain acceptance by regulatory authorities, including the European Chemicals Agency.[106]

No official animal-based version of the phototoxicity test exists and yet 525 such tests were conducted in 2017. The standard test is actually an *in vitro* test based on a mouse cell line, the 3T3 NRU Phototoxicity Test.[107] However, the European Medicines Agency - supported by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) - appears to be recommending the use of the (unvalidated) animal test in some situations; for example when the *in vitro* test comes back positive.[108] The same 3T3NRU test is also an excellent predictor of lack of acute mammalian toxicity[109] and yet this has also not been taken up.

Other tests can be replaced on a case-by-case basis depending on the substance being tested. It may be that there are other very similar substances that already have the animal test data which therefore can be 'read across' to the substance, avoiding the need for a specific test. For other substances, the activity of the substance, such as its ability to bioaccumulate or be a sensitiser, can be very accurately predicted by its chemical structure, and a database or computer model can be used to predict the animal test result without actually having to carry out the test.

Some alternative methods can only be used if the properties of the substance being tested allows it. For example, some alternatives cannot test sticky substances well, or solids or insoluble substances. What is important in these circumstances is that an independent person checks this for each substance on behalf of the company commissioning the testing. Unfortunately, project applications in the EU do not have to specify the substances being tested and, since they run for five years, the company may not in fact know what they will test in two years' time. Furthermore, the Commission has permitted member states to delegate the responsibility for checking whether, if alternatives become available during the life of the project, they are used by the establishment doing the testing. Thus, the regulatory oversight to ensure that alternatives are used wherever possible is still not there.

The Commission needs to ensure that member states enforce the Directive and have better mechanisms place to prevent animal tests being done where there is a recognised alternative method.

[105] *EURL ECVAM. Recommendation on the Zebrafish Embryo Acute Toxicity Test Method (ZFET) for Acute Aquatic Toxicity Testing. 2014. Available at: publications.jrc.ec.europa.eu/repository/handle/JRC91098*

[106] *European Chemicals Agency. Non-animal approaches: Current status of regulatory applicability under the REACH, CLP and Biocidal Products regulations. 2017. Available at: echa.europa.eu/documents/10162/22931011/non_animal_approcches_en.pdf/87ebb68f-2038-f597-fc33-f4003e9e7d7d*

[107] *OECD. Test No. 432: In Vitro 3T3 NRU Phototoxicity Test. 2019. OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. https://doi.org/10.1787/9789264071162-en.*

[108] *ICH. Guidance S10 on Photosafety Evaluation of Pharmaceuticals. 2014. Available at: https://www.ema.europa.eu/en/ich-s10-photosafety-evaluation-pharmaceuticals#current-effective-version-section*

[109] *EURL ECVAM. Recommendation on the 3T3 Neutral Red Uptake Cytotoxicity Assay for Acute Oral Toxicity Testing. 2013. Available at: publications.jrc.ec.europa.eu/repository/handle/JRC79556*

Redundant animal tests (up to 200,000 animals)

Table 3. Examples of (potentially) redundant animal tests still being conducted in the EU, total uses = 183,610.

	Test	Species used	Number of EU tests[a]	Product area	Redundancy
1	Acute toxicity, oral	Rats, mice	**65,707**[b]	Chemicals Medicines (human) Biocides Pesticides	Has been shown to be redundant for human medicines as companies use the repeated dose test to get the information they need.[c] This progress has not translated to chemicals or other substances.
	Acute toxicity, dermal	Rats, mice		Chemicals Biocides Pesticides	Conducting the test via the dermal route as well as the oral route can be waived in many cases under REACH and Biocides, but still goes on. Similarly, both the oral and inhalation route may be done for REACH.
2	28 day (sub-acute) repeated dose test	Rats, mice	**54,412**[d]	Chemicals Medicines (human) Biocides Pesticides	If it is known that a 90-day test is also needed then 28-day test becomes redundant, but often is still conducted. These kinds of decisions are left to the company which may not be always well advised.
3	90 day (sub chronic) repeated dose test	Rats, mice	**30,819**[e]	Chemicals	For chemical substances showing low toxicity in the 28-day study there is no added value in conducting a 90-day test as well, even though this is still required under REACH.[f]
4	90 day (sub chronic) repeated dose test	Dogs, monkeys	**2,549 dogs** **2,720 monkeys**[g]	Medicines (human)	SCHEER stated it may be possible that data from one species is sufficient for progression of a potential new drug into human clinical trials.[h] Research conducted by Cruelty Free International provided evidence that the second species test does not provide additional confidence in whether a drug is likely to be toxic to humans.[i, j] A follow-up study by the pharmaceutical sector and NC3Rs found that out of 172 drugs studied, two-thirds could have progressed using just one, instead of two animal species in longer-term tests.[k] The recommendations have not yet been implemented.
5	90 day (sub chronic) repeated dose test	Rabbits	**14,910**	Chemicals	There is mounting evidence that testing on two species (the norm) is not necessary. A recent study concluded that the reproducibility error between studies is greater than any potential interspecies differences, rendering the added value of a second species study questionable.[l] No-one has yet looked to see if the same applies for human medicines.
6	Carcinogenicity	Rats, mice	**12,493**	Medicines (human) Chemicals	This assay is known to be unreliable and may add no additional information to other animal and non-animal genotoxicity tests. The ICH has been looking at the redundancy of the test for several years but has yet to formally conclude.[m] Test is rarely asked for under REACH but still goes on.

[a] *Numbers of tests (not animals) in 2017, unless otherwise indicated, taken from Report from the Commission to the European Parliament and the Council on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017 (COM/2020/16 final).*

[b] *Mice and rats used in acute toxicity tests in 2017.*

[c] *Robinson S et. al. A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. Regul Toxicol Pharmacol. 2008;50(3):345-52. doi: 10.1016/j.yrtph.2007.11.009.*

[d] *Mice and rats used in tests up to 28 days in length in 2017.*

[e] *Taylor K, Andrew DJ. The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low (sub)acute toxicity profile in a high quality dataset: An update. Regul Toxicol Pharmacol. 2017;90:258-261. doi: 10.1016/j.yrtph.2017.09.018.*

[f] *Mice and rats used in tests from 28-90 days in length in 2017.*

[g] *Dogs and monkeys used in 29-day studies or longer in 2017.*

[h] *Scientific Committee on Health Environmental and Emerging Risks. 2017*

[i] *Bailey J et al. Predicting human drug toxicity and safety via animal tests: can any one species predict drug toxicity in any other, and do monkeys help? Altern Lab Anim. 2015;43(6):393-403. doi: 10.1177/026119291504300607.*

[j] *Bailey J et al. An analysis of the use of dogs in predicting human toxicology and drug safety. Altern Lab Anim. 2013;41(5):335-50. doi: 10.1177/026119291304100504.*

[k] *Prior H et. al. 2020.*

[l] *Braakhuis HM et al.2019.*

[m] *ICH. Concept Paper S1: Rodent Carcinogenicity Studies for Human Pharmaceuticals. 2012. Available at: https://database.ich.org/sites/default/files/S1%28R1%29%20Concept%20Paper.pdf*

Retrospective reviews have also shown that some animal tests add little extra information to other animal tests done to assess the safety of a substance. In this case, there could be an element of 'redundancy' of one or more tests. If the HBA were used properly, such tests would be of low benefit and would not be authorised, particularly in regulatory toxicology where several animal tests are usually conducted on the same substance, some of which overlap in terms of the toxicities of interest. For example, up to 16 animal tests could be required for a single, high tonnage substance under the REACH Regulation, covering acute, repeated dose, reproductive and environmental toxicity.[110]

Table 3. lists some regulatory tests that are potentially redundant; there may be others. They may have been deleted from one sector but not yet in another, or there may be growing evidence of redundancy for all sectors which is not yet recognised. In some cases, there appears to be a fear to remove the animal test - and replace it with nothing - even in the face of evidence of redundancy. In other cases, there appears to be a lack of communication between sectors which means that advances in reducing animal use are not being transferred as rapidly from one sector to another as they could and should be, for example from the pharmaceutical to the chemicals sector and vice versa.

A review of potential redundancy in regulatory tests should be performed both within and between sectors and guidance for companies updated as necessary.

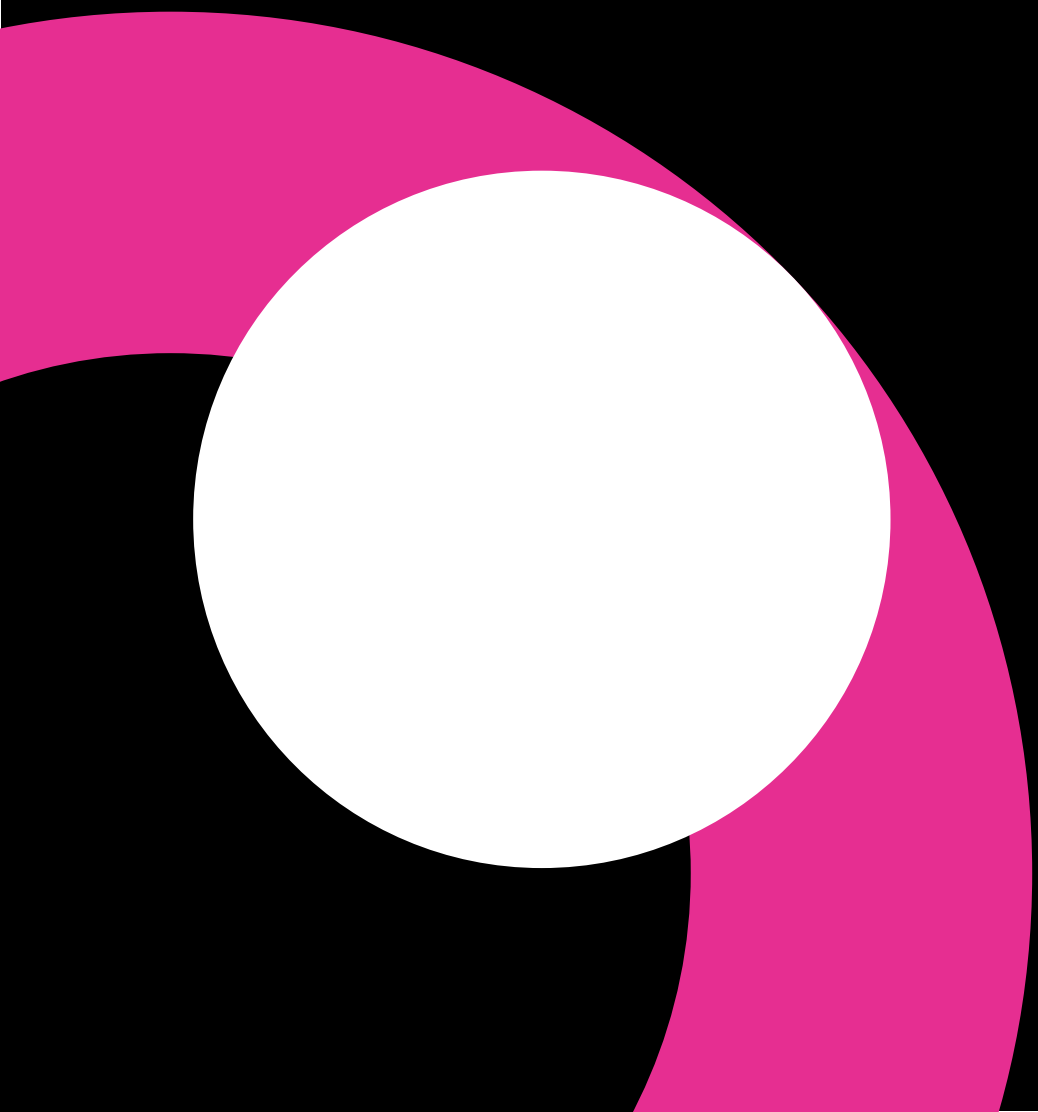
[110] *Our analysis of the tests in REACH Regulation Annexes VII to X.*

Summary

There is plenty of scope for creating a roadmap to phase out animal tests in Europe, starting by:

- Reviewing the utility of animal 'models' to see if they are of sufficient clinical benefit.
- Identifying those tests that are of low benefit from the outset, either due to scientific limitations or clinical need.
- Using the harm:benefit analysis more quantitatively and more strictly, paying due heed to public opinion and rejecting experiments that are likely to cause high suffering and/or be of low benefit.
- Reviewing the reasons behind the numbers of surplus animals and taking measures to reduce them.
- Reviewing the need for the production of so many GA animals and proposing ways to reduce this.
- Ensuring that animal tests are not conducted when an alternative is available by improving communication between the Commission, member states and companies.
- Committing to review potential redundancies in regulatory animal tests and making sure there is a joined-up approach to deleting them where applicable across all relevant sectors.

How could a commitment to a phase-out be made?



Legislative mechanisms

Directive 2010/63/EU

Whilst a directive provides the framework for member states to legislate, it is still entirely possible to insert reduction commitments in the directive itself if the member states agree to that. Animal testing prohibitions, within a specified timescale, were inserted into the former Cosmetics Directive via the 7th amendment to the Cosmetics Directive , now the Cosmetics Regulation. In 2003, a ban on the testing of final products was put in place to be implemented in 2004, and a final ban on testing and marketing of animal-tested ingredients by 2013.

Similar prohibitions on other types of animal testing could be incorporated into Directive 2010/63/EU, or on other sectoral legislation such as the Tobacco Products Directive. Already, Directive 2010/63/EU specifies in Article 10 a mandatory phase-out of the use of wild caught and first generation wild caught primates, five years after a feasibility study that must have been carried out by 2017.

Possible other commitments could include:

- No more experiments involving primates and dogs after 2030 or earlier.
- No more animal experiments for purposes not directly relevant to human or environmental health by 2030 or earlier.
- No more experiments causing severe suffering by 2030 or earlier.

Another option would be to insert targets directed at the member states into the Directive requiring them to reduce their use of animals by a certain percentage by a specified date using the HBA.

Another option would be to strengthen the language around the HBA in Article 38; for example, to say that 'member states shall regularly review the projects they authorise and seek to use the HBA to provide a year on year decrease of X% in animal procedures'.

A fourth option would be for member states to work together to agree a list of experiment types that already would not pass the HBA and add that to a new Annex that would be updated on an annual basis. This could also include procedures that are redundant or have a recognised replacement. This would help avoid the problems with awareness and enforcement that are described above. Animal protection groups have already suggested the creation of an Annex which lists those procedures that would be categorised as causing severe pain, suffering or distress that is likely to be long-lasting and which already should not be permitted under the current Directive. This could be extended to include severe procedures and those with death as the endpoint that should be authorised only in exceptional circumstances, as an improvement on the current rules.

Another way to help achieve a reduction in the amount of animal testing would be for the Directive to be more specific about the contribution that should be made by member states to the promotion of non-animal methods in Article 47. The Article could specify that the contribution should include a *financial* contribution.

Sector-specific legislation

As described in Table 1, there are several pieces of EU legislation that require, directly or indirectly, animal testing. These include the Novel Food Regulation, REACH Regulation, Plant Protection Products Regulation, Biocidal Products Regulation, the Medicines Directive and the Veterinary Medicines Regulation.

Target-based reductions in animal testing would not be appropriate to place in these pieces of legislation as the authorisation of animal experiments lies with member states under Directive 2010/63/EU and not under these laws.

It would be possible, however, to prohibit animal testing in specified sectors, perhaps within a given period of time, as was the case for cosmetics with the 7th amendment to the then Cosmetics Directive. Cruelty Free Europe recently suggested this in its response to the review of the General Product Safety Directive.

Other regulations which could be amended to include animal testing bans include the Novel Food Regulation and the Detergents Regulation. As with cosmetics, new novel foods, general products and detergents are not essential and there are strong ethical grounds to rule out the use of animal testing. Though these changes would likely have a relatively small impact on the overall number of animals used in experiments, they would clearly signal intent and direction of travel and meet growing consumer demand for cruelty free products.

It is disappointing that none of the regulations entering into force post-REACH have included its requirement for animal testing to only be used as a last resort.

There should be a commitment that all new and revised legislation should include these key statements including an aspiration to end animal testing.

Other policy approaches

EU Action Plan to accelerate the transition to innovation without the use of animals in research, regulatory testing and education

In September 2021, the European Parliament adopted a resolution[111] which:

- Calls on the Commission to improve coordination to achieve the goal set out in Directive 2010/63/EU by establishing a high-level inter-service taskforce, involving all key Directorates-General and agencies, to work with EU member states and other relevant stakeholders to draw up an EU-wide action plan, with the aim of driving an active phase-out of animal testing.
- Stresses that a clear and ambitious timeline and list of milestones should be set out to incentivise progress.
- Underlines that the action plan should include ambitious and achievable objectives and timelines to be set under the overarching reduction and replacement goal in order to incentivise change, with concrete and coordinated actions accompanied by indicators.
- Stresses that the plan should include, inter alia, proposals for better implementation and enforcement of existing initiatives, including a well-functioning system of controls.
- Highlights the need for increased and targeted funding under Horizon Europe for advanced non-animal models.
- Calls on the Commission, the Council and the member states to make sufficient medium- to long-term funding available to ensure the fast development, validation and introduction of alternative testing methods to replace animal testing methods, particularly for key toxicological endpoints.
- Calls on the Commission to set reduction goals in consultation with relevant agencies, in particular ECHA and EFSA, through a more proactive implementation of the current regulations on the safety of chemicals and other products, and to support the reduction goals by using a fully connected and interoperable EU chemical safety database.
- Recalls that Article 13 of REACH requires that the test method requirements be updated as soon as non-animal methods become available.
- Urges the Commission to work together with member states to prioritise actions to educate, train and retrain scientists, researchers and technicians in using advanced non-animal models and in sharing best practices, and to raise awareness of validated non-animal models among those involved in evaluating project proposals and attributing funding.
- Highlights the need to work within international structures to speed up validation and acceptance of alternative methods, ensure knowledge transfer and provide financial support to non-EU countries, where scientists may be unaware of alternative methods and where testing facilities may lack the necessary research infrastructure.

With the will of the European Parliament and of Europe's citizens now very clearly expressed, it is beholden on the Commission and on member states to act quickly to produce an EU-wide action plan. The Action Plan on European Democracy or the Circular Economy Action Plan provide good models, introducing legislative and non-legislative measures, actions, timelines and tracking mechanisms.

Commissioner for Animals

At present, none of the European Commissioners have responsibility for animal welfare named specifically within their remits. This would be a positive change that the Commission could make.

A growing number of authorities around the world have or are considering putting in place animal welfare commissioners independent of government to advise on science and ethics. Scotland, for example, now has an Animal Welfare Commission; Berlin has recently appointed a new Animal Welfare Commissioner – a position it has had since 2017 – and Malta has an Animal Welfare Commissioner appointed by the Prime Minister. An EU-wide independent Animal Welfare Commission or Ombudsman could be an idea worthy of consideration.

[111] *European Parliament resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education (2021/2784(RSP))*

Funding mechanisms

Commitment within Horizon Europe

Under FP6 and FP7, the amount given to the development of alternatives (including those methods that still use animals) appears to have been around 0.6% of the total framework budget. It is not yet known if Horizon 2020 matched that.

Under the Directive, reducing the number of animal experiments currently depends on replacement by alternatives If the EU continues without adopting other means to reduce the number of animal experiments - then it will have to investment significantly more to speed up progress.

The Commission should recognise that investment in non-animal methods is not just a means to reduce the amount of animal testing but will also encourage technological innovation to improve the efficiency and productivity of our science and medicine and help to achieve the objectives of the Green Deal.

In its announcement of its final funding tranche under Horizon 2020,[112] the Commission announced that it wanted to prepare the way for Horizon Europe by supporting the future research and innovation landscape. It says it will 'seek greater impact of its research funding by focusing on fewer, but crucial, topics such as climate change, clean energy, plastics, cybersecurity and the digital economy.'

The European Innovation Council – a one-stop-shop for innovation funding to turn science into new business and accelerate the scale-up of companies – will be a new project under Horizon Europe. It is already running in its pilot phase with a budget of 1.2 billion euros. Fifty-eight novel, high-impact technologies have been selected in the last round of investment from the European Innovation Council (EIC) 'Pathfinder Open' Pilot, funded under Horizon 2020, totalling 191 million euros.[124] It is possible this might include some non-animal alternatives, if so, why not make this explicit, if not, then why not use a similar model to support the scale-up of companies developing non-animal approaches?

Greater funding of EURL ECVAM

The support provided by the Commission to EURL ECVAM appears, if anything, to have reduced in recent years, from an average of 6.5 million per year in 2017 to 5 million for 2019/20. Since 2010, EURL ECVAM has had a broad remit under Annex VII of Directive 2010/63/EU to coordinate and promote alternative methods, coordinate validation projects of new alternatives, act as an information portal and a facilitator of dialogue between regulators, industry and stakeholders. These are huge tasks given by the Directive on behalf of the EU. Clearly the more resources it receives the more successful EURL ECVAM can be in delivering them.

Greater funding of the Unit responsible for the Directive

The unit responsible for the Directive within DG Environment is incredibly small. Their ability to execute the recommendations in this report will be extremely limited unless they are given more resource. It is not acceptable that an important piece of EU legislation with obligations to the lives of over 23 million animals and the research capabilities of tens of thousands of researchers is given the little support it is.

Agency support for promotion of alternatives

Neither the European Chemicals Agency (ECHA), the European Food Safety Authority (EFSA) nor the European Medicines Agency (EMA) receive specific funding to promote alternatives to animal testing and none of them claim to have this as a specific mandate. It is therefore not surprising to find that the amount of work these agencies do can be limited and ad hoc, often reliant on the goodwill and dedication of a handful of people. This is insufficient, and there is no accountability. All agencies should be tasked with promotion of alternatives to animals in their remit which will give them grounds to ask for central funding to support these activities.

A Motion for Resolution adopted by the European Parliament on the Chemicals Strategy for Sustainability[114] rightly regretted the fact that there is 'insufficient funding for the research and development of non-animal methods' and … 'requests that action be taken to remedy this situation'… 'including staff within ECHA exclusively dedicated to animal protection and the promotion of non-animal methods across all ECHA activities'.

[112] *https://ec.europa.eu/info/news/commission-invest-eu11-billion-new-solutions-societal-challenges-and-drive-innovation-led-sustainable-growth-2019-jul-02_en*

[113] *https://ec.europa.eu/info/news/european-innovation-council-invests-eu191-million-58-game-changing-technologies-2020-oct-29_en*

[114] *European Parliament resolution of 10 July 2020 on the Chemicals Strategy for Sustainability. (2020/2531(RSP))*

This was underscored by the Parliament's decision on discharge of the ECHA 2019 budget which stated that the Parliament:

> *Regrets the absence in the 2019-2023 strategic plan of any pro-active measures and resourcing for speeding up, improving and quantifying reductions in the number of animal tests and the replacement of such tests by new approach methodologies; reiterates the importance of the principles of the 3Rs (Replacement, Reduction and Refinement) in animal testing; notes the recommendation made by Parliament in its resolution of 6 July 2020 on the Chemicals Strategy for Sustainability a that there should be a team established within the Agency exclusively dedicated to animal protection and the promotion of non-animal test methods; notes with concern the reply given by the Agency's Director in discussion with the Committee on Budgetary Control on 7 January 2021 that the Agency has not followed up on Parliament's call to reduce animal testing; urges the Agency to strongly reduce its reliance on animal testing; calls on the Agency to contribute to international activities aimed at promoting alternative test methods within its mandate and to regularly publish information on the use of alternative methods under REACH.*[115]

Greater support to EPAA

The European Partnership on Alternative Approaches to Animal Testing (EPAA) was set up in 2005 to act as a coordination vehicle between the European Commission and eight industry sectors with a shared vision to apply the principles of Replacement, Reduction and Refinement (3Rs) in regulatory animal testing.[116]
It appears to work on a voluntary basis, a limited number of projects are actioned, and contribution of expert time appears to be in-kind. Projects are created that serve to improve the development or uptake of alternative methods, often in specific areas. There is a focus on coordination, training and communication.

The EPAA could do so much more if it were appropriately supported politically and financially. It is not sufficient to rely on the goodwill of companies to provide their expertise on projects and doing so will naturally lend itself to only those projects which industry favour being prioritised or are investing in anyway.

Pilot projects and preparatory actions

Pilot projects and preparatory actions (PPPAs) are, formerly, experimental programmes that don't require a legal basis, and latterly, preparations for actions that may become the basis of ongoing EU activity (either acquiring or based on a current legal basis).

Until recently, there had been no PPPAs on alternatives to animal testing. However, since 2017, there have been two pilot projects and one preparatory action. The first pilot project adopted in the 2017 EU budget focussed on increasing cooperation and training of scientists on the alternatives to animal testing. One million euros was given to ECVAM and ETPLAS to develop some online training resources. A second Pilot Project in the 2019 budget gave 420,000 euros to conduct a feasibility study on establishing a data-sharing portal between the ECHA and EFSA. In the 2020 budget there was a commitment of 1.8 million euros toward a further preparatory action.

PPPAs are potentially a good mechanism to explore some of the recommendations in this report. For example, they could be used to fund thematic reviews (see below) or support working groups to explore the establishment of reduction targets.

Preferential funding

In addition to greater actual amounts of funding, a decrease in animal experiments could be achieved via other funding related commitments.
For example:

- A pledge within Horizon Europe to not fund animal research, or as a first step, not fund research on dogs or monkeys, for example.
- Further commitments made in a revision to the Ethics Appraisal Procedure for Horizon Europe projects, perhaps following advice by the European Group on Ethics in Science and New Technologies (EGE).
- A quota on the number of animal-based projects funded under Horizon Europe.
- A commitment to preferentially fund non-animal research over animal-based research, for example five times more funding will be given to non-animal methods, or five times as many projects.
- Specific funding calls for non-animal methods to focus attention on the issue.

[115] *European Parliament decision of 28 April 2021 on discharge in respect of the implementation of the budget of the European Chemicals Agency for the financial year 2019 (2020/2170(DEC))*

[116] *https://ec.europa.eu/growth/sectors/chemicals/epaa_en*

Who can help and how?

European Commission

Aside from instigating the legislative, non-legislative and funding mechanisms above, the Commission could also help

Review of the Directive

The review of the Directive required in Article 58(1) in 2017 was only a cursory one as many member states had barely implemented the Directive at that stage. The Commission openly admitted that "there is only limited experience with the Directive's implementation".[117] The review indicated that, "a full REFIT evaluation of the Directive will be undertaken after 2019 when better information is available and sufficient time has lapsed for the Directive's implementation to enable an assessment of any changes in welfare and use practices."[118] This has not begun as yet, however, a review would allow the Commission to consider the proposals in this report.

Thematic reviews

Article 58 of the Directive states:

The Commission shall, where appropriate, and in consultation with the Member States and stakeholders, conduct periodic thematic reviews of the replacement, reduction and refinement of the use of animals in procedures, paying specific attention to non-human primates, technological developments, and new scientific and animal-welfare knowledge.

A thematic review has not yet been carried out, despite several proposals having been sent to the Commission.

Thematic reviews could include:

- looking at areas that are ripe for replacement, e.g., primate neuroscience, antibody production, vaccine batch tests and working out what needs to be done to eradicate animal use.
- looking at how reduction could be achieved across the sectors, i.e., how some of the proposals in this report could be taken up.
- reviewing excess breeding of normal and GM animals and recommending future actions.

Other reviews

Whether as a thematic review or an activity of EPAA or an interservice working group or under a PPPA, or as part of the process for compiling the action plan requested by the European Parliament, the Commission could also undertake specific reviews mentioned in this report that would provide the evidential basis for potential action. For example:

- A comprehensive, transparent review of the amount of funding given to the development of non-animal methods by the European Commission and member states.
- A Eurobarometer survey on animal testing which feeds into recommendations for changes to the Directive and/or advice to member states undertaking HBA.
- A review of the potential for duplication of all animal testing with recommendations for how to reduce this.
- A review of potential redundancy in regulatory tests both within and between sectors with recommendations for changes to legislation.

[117] *https://ec.europa.eu/environment/chemicals/lab_animals/other_reports_en.htm*

[118] *Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions in accordance with Article 58 of Directive 2010/63/EU on the protection of animals used for scientific purposes. COM(2017) 631 final. Brussels, 8.11.2017.*

Enforcement

The Commission could assist member states in their obligations under the Directive by:

- Making statements when alternative methods become available, e.g., those tests listed in Table 3 so that member states are clear about their obligations and can enforce in-country.
- Use the NTS, the statistical and implementation reports to review what procedures are being authorised by member states. Inform and enforce if there are apparent breaches of the existing rules. Advise if there are inconsistencies in authorisation of projects that could be harmonised to improve animal welfare and lead to reductions.
- If member states persist in failing to implement the Directive properly then take infringement action promptly and firmly.

Communication

With more resources, the Unit responsible for the Directive could facilitate initiatives that would lead to reductions in animal numbers. These could include:

- Working with member states to regularly review animal procedures and issue guidance for example that test X 'would not meet the criteria of a successful harm benefit analysis' so that member states can implement this knowing that there is agreement at the EU level, and they are not disadvantaging researchers in their country. Examples of procedures that this could include are listed throughout this report.
- Establishing a high-level inter-service taskforce, involving all key Directorates-General and agencies, to work with EU member states and other relevant stakeholders to draw up an EU-wide action plan, with the aim of driving an active phase-out of animal testing.

EU Agencies

Agencies that regulate substances which may require animal testing such as the EMA, EFSA and ECHA can assist in tasks that can lead to reductions in the numbers of animal used by:

- Proactively monitoring the development of alternatives and making clear statements on their appropriate use.
- Promoting the use of alternative methods to industry and internationally.
- Providing advice on the acceptable use of alternative methods to companies in advance if they request it.
- Regularly reviewing the use of alternative methods in regulatory submissions in order to:
    - o share best practices on new methods between other companies, and other regulators including cross sector.
    - o update guidelines if potential redundancies in animal tests are found, see Table 3.
    - o eliminate animal testing that has been replaced or is redundant and inform enforcement authorities if unnecessary tests have been conducted.
- Making it policy that manufacturers of new biological substances that may require quality control batch tests use an alternative method as the gold standard prior to authorisation.
- Regularly reviewing the use of animals and collaborating with industry and other regulators with an aim to replace and root out ineffective or unethical tests and models.
- Hosting industry-regulator meetings to develop alternatives where data sharing may be necessary, including for product-specific validation studies.

Member states

Member states can also take up the recommendations in this report. They can:

Set national targets for reducing animal tests by:

- Monitoring and enforcing Article 4 and 13 of the Directive, ensuring that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, is used instead of an animal procedure.
- Making sure all authorised users and breeders are aware of developments in alternative methods or policy decisions that would mean that certain procedures are no longer permitted.
- Not delegating the responsibility to establishments to ensure alternatives are used during the course of a project but instead asking to approve all new animal tests on a product-by-product basis in case an alternative method can be used.
- Conducting reviews and consultations regularly to be able to advise project applicants about which animal tests are 'unlikely to meet a successful harm:benefit analysis'.
- Increasing levels of national funding of alternative methods, which may or may not include setting up specific alternative (or 3Rs) centres.
- Tasking National Committees and 3Rs/alternatives centres to work with industry to adopt and implement a target-based approach towards reducing animal tests.
- Where market authorisations for medicines are not done centrally, on a national basis, making it policy that manufacturers of new biological substances that may require quality control batch tests use an alternative method as the gold standard prior to authorisation.
- Reviewing all national pharmaceutical product marketing authorisations to ensure that there are no redundant or replaced animal-based batch tests still being conducted.

Academia, funding bodies and companies

Universities, companies, research associations and funding bodies can of course also set their own targets for the reduction of animal testing. They could include their Corporate Social Responsibility Policy and thereby also improve transparency around the animal tests they do fund or conduct. This would be an important first step in the organisation's understanding of its starting point.

Targets could be achieved by:

- Instilling a quota on the number of animal tests that each ethical review committee can authorise each year, driving the committee(s) to set a more rigorous bar for any project to receive a positive HBA.
- Working with stakeholders and the ethical review committee(s) to make policy commitments about which animal tests they will not approve/fund/conduct.
- Preferentially funding and supporting non animal research over animal research - specifying that, for example, funding of non-animal research will be five times that of animal research.
- Facilitating research areas to work together to evaluate and decide what 'models' are good for what disease area and where animals can be replaced.
- Requiring a thorough review of alternative methods prior to conducting/commissioning or funding any animal research.
- Supporting cross departmental/cross sector dialogue with a view to transfer of knowledge on new technologies and approaches.
- Rewarding projects that achieve a reduction in animal testing.
- Rewarding researchers who promote alternatives or assist in regulatory work related to alternatives to animal testing.
- Investing in humane education of young researchers.
- Having an in-house group dedicated to the oversight of these objectives.

Conclusion

In a demand-led system, targets are indispensable tools in ensuring that meaningful reduction is achieved, maintained and built upon. The field of scientific inquiry is limitless and with it the potential for animal use. Quotas or limits, properly used, can inject discipline into the system and ensure that researchers look beyond their traditional use of animals. It is important to stress that quotas and other tools would be additional to the existing legal obligation to use animals only as a last resort, to not use animals if an alternative method is available, to use as few as possible and to cause as little suffering as possible (the so called Three Rs principle). That principle has been singularly unsuccessful in achieving an overall reduction in animal usage.

It is true that science is complicated, but so are many other policy areas where targets have been agreed and implemented. Complexity of policy simply means that a targets approach has to be reasonably sophisticated, and flexibility built in for unforeseen circumstances, albeit necessarily with a strong presumption that the targets will be met.

There are a number of different possible approaches, and these can be combined. For example, there can be a reduction in numbers in particular areas of research, research using particular species or research causing a particular level of suffering; partial or complete bans of types of research; limits linked to timescales; or a combination of these.

Applying a stricter societal benefit test as part of the harm:benefit assessment, demanding increased scientific stringency and eradicating duplication can help to achieve targets. The result might be that some research would not get done but more likely that it will be done differently. Some products or substances, inevitably the more trivial ones, may not get developed, but again it is more likely that companies will find another way of testing them. The approach of regulators would change, but many need to be shaken out of their ultra-conservative, tick-box mentality, as do companies with a primary eye on pleasing regulators. Targets will increase the incentive for the development of non-animal alternatives and level the presently highly uneven playing-field between animal and non-animal methods. There will be pressure for greater transparency, as with data-sharing for example.

Crucially, there is no reason why targets should lead to any reduction in health protection for people or in environmental protection. Rather, it will mean that proposals to use animals are given much greater scrutiny, both ethically and in terms of possible alternative approaches. The benefits are long term and far reaching as a target-based approach, as for green technology, will result in less damaging, more predictive and more efficient methods for investigating and solving human and environmental health problems.

Recommendations

Commitment

A commitment to a phase-out of animal testing needs to be made alongside a commitment to achieve this within a reasonable timescale and by various means.

Funding

The commitment must be supported by greater funding for the development of non-animal methods as well as for the agencies tasked with delivering it. This should be embedded within Horizon Europe and all other relevant funding streams, as well as in the research and innovation budgets of EU member states.

Action

A range of actions should be put in place to ensure that the phase-out commitment is delivered.

This could include:

- Establishing a high-level inter-service taskforce, as requested by the European Parliament, to mainstream the goal of replacing all animal testing in the EU and to give impetus to a joined-up approach across European Commission directorates general, member states and agencies.
- Incorporating reducing and replacing animal testing into overarching priorities like the Green Deal and post-COVID recovery plans and ensuring there is a consistent approach across legislative and policy activities.
- Conducting thematic reviews as provided for under Directive 2010/63/EU to identify priority areas for replacement and reduction.
- Greater monitoring and enforcement so that animal tests for which there are already valid alternatives in place are not being used in member states.

Annex 1.

Alternative, non-animal methods for standard toxicity tests.

Endpoint	Animal test	Alternative test	Regulatory acceptance?
Skin absorption	The substance is rubbed onto the shaved backs of rats, and they are killed the next day (OECD TG 427).	*Ex vivo* skin based tests that measure the amount of substance that passes through excised skin.	OECD TG 428 (2004). Standalone replacement.
Acute toxicity	Rats are exposed to a very high dose of the substance such that a number of them are expected to die (OECD TG 402,403, 420,423,425,436).	Cell based tests, in particular the NRU3T3, which measures the extent of cell death in the presence of the substance.	Not formally accepted, can be used in combination with other information only.
Skin irritation/ corrosion	Substance is rubbed into the shaved backs of rabbits, and they are killed 2 weeks later (OECD TG 404).	Reconstituted *in vitro* human skin models that measure the extent of cell death in the presence of the substance.	OECD TG 431 (2004) and 439 (2010), plus others. Testing strategies (IATA) formalised in GL 203 (2014).
Eye irritation/corrosion	Substance is placed into the eyes of live rabbits who are monitored for up to 3 weeks (OECD TG 405).	Excised eyes from hens and cattle killed for food (*ex vivo*) can detect non-irritants and severe irritants, human corneal epithelial (HCE) models based on excised human skin or corneas that measure the extent of cell death in the presence of the substance can detect non - irritants.	OECD TG 437 and 438 (ex vivo, 2009), OECD TG 492 (HCE, 2015). A testing strategy (defined approach) is in prep.
Skin sensitisation	The substance is rubbed onto the shaved skin of guinea pigs who are subjectively assessed for allergy (Buehler or GPMT test, OECD TG 406) or painted onto the ears of mice who are killed 6 days later to assess the immune response (LLNA test, OECD TG 429, 442a/b).	Several tests exist that cover the AOP for skin allergy. The peptide reactivity (DPRA) test measures the binding of the substance to proteins (*in chemico*), and the in vitro keratinocyte assay, the human Cell Line Activation Test (h-CLAT) based on human skin cells measure part of the immune response. Testing strategies using these methods in combination are already being used by companies.	OECD TG 442c (DPRA, 2015), 442d (keratinocyte assay, 2015) and 442e (h-CLAT, 2016). Testing strategies are now adopted as a Defined Approach Guideline (GL 497, 2021).
Mutagenicity/genotoxicity	The substance is force-fed or injected into mice or rats for 14 days who are then killed to look at the effects on their cells (OECD TG 474, 475, 483, 486, 488, 489).	Several in vitro tests, including bacteria (Ames) tests, *in vitro* chromosome aberration, cell micronucleus and gene mutation tests are available. A battery of two or three cell based tests is always carried out before conducting an animal test.	OECD TG 471 (1997), 473 (1997), 476 (1997), 487 (2010), 490 (2015). Positive results however still lead to follow up in vivo.
Repeated dose	Rats (occasionally rabbits, mice or even dogs) are force-fed, forced to inhale, or have the substance rubbed onto their shaved skin every day for 28 or 90 days before being killed (OECD TGs 407-413).	*In silico* techniques such as read across can be used if the substance is similar to existing ones that have already been tested. A battery of *in vitro* tests or lab on a chip model are still in the development phase.	Read across is accepted on a case-by-case basis (OECD Guidance on Grouping, GL 194, 2014), battery of *in vitro* tests or lab on a chip are not yet accepted.

Carcinogenicity	Rats or mice are fed the substance for two years to see if they get cancer (OECD TG 451, 452).	Cell transformation assays (CTA) based on cellular changes to rodent cells have been in use for 50 years and can detect 90% of known human carcinogens.	CTA assays have failed to gain international regulatory acceptance and are used for screening purposes only (OECD GL 214, 2015; OECD GL 231, 2017).
Reproductive toxicity	Pregnant female rabbits or rats are force-fed the substance and then killed along with their unborn babies (OECD TG 414).	*In silico* techniques, such as read across, can be used if the substance is similar to existing ones that have already been tested. The *in vitro* Embryonic Stem cell (EST) test is based on mouse stem cells; substances are classed as toxic if they block development into beating heart cells. Other *in vitro* tests are still in the development phase. Receptor binding assays are *in vitro* assays that can detect activation of genes involved in hormone production.	Read across is accepted on a case-by-case basis (OECD GL 194, 2014). However, the EST has failed to gain international regulatory acceptance. Receptor binding assays (OECD TG 455, 2012; 457, 2012; 456, 2011) are accepted to screen for potential endocrine disrupting properties.

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Contact Us

For all enquiries regarding Cruelty Free Europe, please email info@crueltyfreeeurope.org

crueltyfreeeurope.org