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Legal opinion on the regulation of animal testing for scientific purposes

European Union, the United States, Australia, India and New Zealand

Current to: 08.02.2024

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John Curran

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EXECUTIVE SUMMARY

Animal testing is widely used for scientific research, including drug development and safety testing. Although animal research is invaluable to scientific progress, it also raises ethical concerns regarding animal welfare. Regulations aim to minimize animal suffering, balancing scientific advancement with ethical principles. The "3Rs" (Replacement, Reduction, Refinement) guide these efforts, encouraging alternatives to animal testing, reducing the number of animals used, and refining methods to lessen pain. However, outdated laws can hinder the adoption of non-animal alternatives.

This study focuses on the regulatory frameworks in a number of regions and countries around the world, including the European Union, the United States, Australia, New Zealand, and India. It examines how laws in these areas promote or hinder alternatives, provide for mandatory testing, and encourage transparency. European Union regulations have sought to harmonise member state laws to embrace the 3Rs, while laws in other parts of the world, including the United States, have proven slow to adapt to non-animal testing methods. The study also highlights recent developments in the field of animal testing regulation, emphasizing the need for updated legal instruments to reflect scientific advancements.

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SUMMARY

This comparative law study, prepared in response to a request from the *Bundesamt für Lebensmittelsicherheit und Veterinärwesen*, examines the legal regulation of animal testing for scientific purposes and its alternatives outside of Switzerland.

The study principally focuses on the legal frameworks of the European Union ("EU") and the United States ("US"), but also examines a selection of European countries (Denmark, France, Germany, the Netherlands and the United Kingdom) either active in animal experimentation and/or experienced in its regulation. This is complemented with overviews of the relatively developed systems of Australia and New Zealand as well as the legal framework governing animal testing in India. Reference is also made to recent important developments in animal testing regulation in other jurisdictions.

1. Overview: regulation of animal testing and supervisory oversight

Legal rules

Measures aimed at the protection, care and use of animals for scientific purposes are not usually contained in a single law. In Europe and beyond, these matters are often subject to a mix of primary and secondary legislation, but also policies and guidelines of government departments, regulatory agencies and voluntary standard-setting bodies. In many cases, the law even supports systems of self-regulation.

Rules in the European jurisdictions examined are typically contained in an overarching law dedicated to animal experimentation (or a chapter of animal welfare legislation), supplemented by legal instruments setting out detailed rules on implementation. Domestic legislation in all **EU Member States** was amended after 2010 in order to transpose into national law provisions of the EU's *Directive (2010/63/EU) on the protection of animals used for scientific purposes* ("2010 Directive").

The 2010 Directive replaced Directive 86/609/EEC on the same subject and seeks to harmonise the legislative frameworks of EU Member States concerning the regulation of animal testing. Crucially, it prevents EU Member States from establishing stricter measures, although more extensive national protection in place at the time was allowed to be retained, such as the Netherlands' 2003 complete ban on the use of great apes in animal experiments. Overlapping in many respects with the 1986 *Convention of the Council of Europe on the protection of vertebrate animals used for experimental and other scientific purposes* (known as "ETS 123"), the 2010 Directive goes further in its ambitions and explicitly integrates the principle of the replacement, reduction and refinement of the use of animals in scientific experiments ("3Rs") throughout its provisions.

The **US** framework consists of a multilayered network of laws, regulations and guidelines. The principal federal law concerning animal welfare does not extend to the majority of vertebrates used in animal testing (such as purpose-bred birds, rats and mice), but policies and guidelines used by its Public Health Service ("PHS") as well as standards issued by the *American Association of Accreditation of Laboratory Animal Care international* ("AAALAC") do cover these vertebrates, and act as important regulatory instruments in practice. PHS-sponsored projects must comply with the PHS Policy on the care and use of laboratory animals, and many institutions comply with AAALAC standards in order to achieve and maintain accreditation.

In **Australia**, animal testing is principally governed by animal welfare legislation at the state or territory level, but all jurisdictions have incorporated into law principles and guidelines established by a code of practice on the care and use of animals in science published by a national body with responsibility for developing public health standards. Specific sections of national animal welfare legislation in **New**

Zealand and **India** are aimed at the regulation of the scientific use of animals, although subordinate legislation in India establishes more detailed rules regarding supervisory oversight.

Supervisory oversight

Structures for ensuring supervisory oversight of institutions that use animals for scientific purposes vary among the jurisdictions examined, but a number of similarities can be identified. A common feature is the constitution of an in-house committee for overseeing day-to-day compliance with the law. Different rules apply to the composition of such a body, and its work is often complemented by periodic oversight from an independent or public authority.

Requirements of the 2010 Directive mean that, common to all **EU Member States**, a national 'competent authority' ("CA") will have been established with responsibility for authorising and registering breeders, suppliers and users of animals intended for experimentation as well as for carrying out regular inspections; each establishment using animals must also set up an Animal-welfare body ("AWB") to oversee and monitor all activities relating to the welfare of its animals. Benefiting from flexibility in the implementation of these requirements, and with the AWB expected to develop its own terms of reference, domestic arrangements vary among the European countries examined. Some, for example, restrict project evaluation and authorisation functions to a public CA while others designate private bodies and even institutional AWBs as CAs.

In **the US**, dealers and breeders of animals used in testing must be licensed by, and research facilities registered with, the US Department of Agriculture ("USDA"). It is the USDA which also takes responsibility for overseeing compliance and inspecting research facilities. Supervisory oversight, however, is mainly conducted on an in-house basis, with a research facility-appointed Institutional Animal Care and Use Committees ("IACUC") responsible for ensuring compliance with welfare legislation. Although parallels may be drawn with the AWB, the IACUC has a much wider remit within a research facility, overseeing the entire animal care and use program, arrangements for the health of staff and an executive role in authorising the conduct of procedures. In PHS-sponsored projects and AAALAC-accredited institutions, additional oversight to ensure compliance with the PHS Policy and AAALAC standards, respectively.

Committees similar to the AWB and IACUC are responsible for monitoring compliance and the ethical review of establishment projects involving animals in India, New Zealand and Australia. The framework in **Australia** can even be characterised as a system of self-regulation and self-assessment, although periodic independent external reviews of the research establishment are required on a periodic basis and state and territory governments may constitute public authorities for investigating the conduct of animal research. The equivalent committee in **New Zealand** has significant supervisory responsibility but must submit the establishment and itself to periodic independent reviews by accredited inspectors. In **India**, the equivalent committee has similar day-to-day responsibility but must submit research proposals involving larger animals to a national committee with ultimate supervisory oversight.

2. Regulation of alternatives to animal testing

Encouragement of alternatives

Encouraging the pursuit of alternatives to the testing of animals for scientific purposes is an increasingly common feature of the regulation of animal experimentation, particularly in Europe. Explicit reference to the 3Rs principles is contained throughout the text of the EU's 2010 Directive, and an overriding obligation is placed on **EU Member States** to ensure that scientific methods not involving live animals be adopted where possible.

Animal welfare legislation in **the US** does not explicitly encourage alternatives, although other policies and guidelines used by many research facilities do endorse 3Rs principles.

Likewise, the code of practice adopted under state and territory legislation in **Australia** requires consideration of alternatives to animals, as does **New Zealand's** animal welfare law.

Encouragement of alternatives in regulatory laws

Rules concerned with alternatives to animal testing are not just found in animal welfare law. They are also a feature of sector-specific legislation aimed at ensuring that a substance or product meets safety and efficacy standards established by law or by regulators (typically referred to as 'regulatory' laws). Specific methods of testing are often prescribed, and animal studies commonly represent the default method for registrants (such as manufacturers and importers of substances) seeking to satisfy data requirements for assessing the hazards and risks of the substance in question. Increasingly, however, legal provisions and regulator requirements demand that non-animal alternatives be pursued where possible.

Among **EU Member States**, where almost all animal testing undertaken for regulatory purposes arises from EU requirements, it is directly applicable EU Regulations governing the registration and classification of chemical substances (known as 'REACH' and 'CLP') which are at the heart of the regulatory framework. In REACH, several legal provisions stipulate that animal testing should be pursued only as a last resort, while others are designed to encourage those seeking registration to share data and avoid duplicating tests; recently proposed amendments to the CLP Regulation also demand consideration of non-animal testing methods and similar provisions can be seen in pesticides regulation and other regulatory laws.

Regulatory requirements in other jurisdictions are not examined in detail, but it may be noted that **the US**'s *Toxic Substances Control Act* was amended in 2016 to place requirements on registrants to consider non-animal alternatives and, in the case of the relevant regulator, to eliminate vertebrate animal testing "to the extent practicable" when regulating new and existing chemicals. For pesticides, data requirements based on animal studies feature throughout the applicable legislation, but under binding rules promulgated by the responsible regulatory agency, waivers can be granted in relation to data requirements, and guidance has been developed by the regulator describing how animal studies can be avoided where a waiver applies.

Incentives to promote alternatives

Specific incentives to promote alternatives to animal testing mainly arise outside of legal frameworks. Much of the progress in the advancement of the 3Rs at the domestic level is achieved not through legal regulation but through scientific initiatives. Although beyond the scope of this study, these include the work of national 3R centres which promote the use of alternative methods through education and training, communication networks, financial support and development of alternative methods for validation and implementation as recognised test methods.

That said, **the EU's** 2010 Directive does contain a few provisions which encourage this approach: Member States and the European Commission are required to contribute to the development and validation of alternative approaches, and the EU Reference Laboratory ('EURL ECVAM'), an organisation with specific responsibility for promoting the development and use of alternatives in regulatory testing, is given a legislative basis by the 2010 Directive.

Similarly, in **the US**, where the government is recognised for having provided large amounts of funding for developing alternatives, laws regulating alternatives are limited, but inter-agency coordination led

by a legislatively constituted body, ICCVAM, reflects a political willingness to develop non-animal testing methods.

3. Regulatory testing

Various legal instruments in all jurisdictions establish the requirements for assessing the safety and hazards of producing and placing substances on the market, including chemicals, pesticides, medicines and food. Notwithstanding animal welfare legislation designed to reduce animal experimentation for all scientific purposes and the development and validation of reliable alternatives, animal testing is often still required in practice. This is for a number of reasons, common to regulatory laws in the **EU, the US and other countries**.

First, many legal regulations in these sectors continue to be drafted in such a way as to make animal testing mandatory. There are numerous examples of requirements in these legal instruments which are formulated with reference to animal studies, making this the default method for producing the data required. Secondly, although animal testing methods are often required to be adopted only as a last resort, the scientific progress is simply not sufficiently advanced for non-animal technologies, methodologies or approaches (often referred to as new approach methodologies ("NAM")) to be validated by relevant agencies. This requires that a NAM is able to provide information on hazards and risks which are equivalent to, or of better scientific reliability or quality as, that obtained from animal testing. Thirdly, the only type of safety and efficacy information often acceptable to regulators and other authorities is that obtained from tests on animals. This may be directly requested, on a case-by-case basis, of those seeking registration of substances or products, or it may be contained in technical guidance documents produced by the regulator to assist registrants comply with legal requirements. Although such guidance documents increasingly encourage consideration of alternative methods, they still frequently refer to, require and/or set standards for animal tests.

Among **EU Member States**, 95% of regulatory uses of animals are undertaken to comply with regulatory requirements under EU legislation. Regulatory use accounts for around 17% of all uses of animals in experimental procedures, but when considering severe uses of animal, this percentage rises to 32%. Examples of legislative texts which are drafted in such a way as to make, what is typically referred to as, "*in vivo*" testing, mandatory can be found in a range of specific sector legislation. Some of those identified, particularly under EU law, in relation to various sector-specific laws are described in this study:

- *Chemical substances*: for chemical substances, particularly those registered in high tonnages, there is a continued reliance in the **EU's** REACH Regulation on standard test methods using vertebrate animals to predict the effects of chemicals on humans and the environment. Moreover, the classification and labelling requirements for hazardous substances and mixtures under the CLP Regulation also contain frequent reference to *in vivo* testing. Other obligations for tests on animals often come from specific rulings of the European Chemicals Agency (the "ECHA"), but in a 2021 case of the Court of Justice of the European Union ("ECJ") in which the ECHA had required a registrant to conduct a toxicity study on animals, it was held that the animal tests must only be carried out as a last resort, even after the ECHA has made a decision that animal tests must be carried out.
- *Cosmetic Products*: under the **EU's** 2009 Regulation on Cosmetic Products, a wide-ranging ban on testing animals on finished cosmetics products and their ingredients, as well as a marketing ban on such products, is in force across the EU. However, an ECJ ruling in November 2023 has confirmed that ingredients, even when used exclusively in cosmetics, may be tested on animals under REACH to assess the risks to workers' health.

- *Pesticides*: laws in both the **EU** and the **US** make frequent reference to data requirements based on animal studies, making animal testing the standard test method in many cases.
- *Medicinal products*: no medicinal product may be placed on the market without marketing authorisation, and frequent reference to data requirements based on animal testing can be found in the Annexes to the **EU's** Medicinal Products Directive. Although these do not present a formal legal barrier to using alternative methods, guidelines issued by the European Medicines Agency ("EMA") do contain frequent reference to animal testing methods for meeting certain data requirements, and registrants are unlikely to secure approval from the EMA without following guidelines. Moreover, standards adopted by the guidelines, established under the European Pharmacopoeia monographs - the primary source of official quality standards for medicines and their ingredients in Europe - are legally binding and contain frequent reference to animal testing methods. Although the option to use validated alternative methods features as a general principle, the time and expense of validation means that animal testing often continues to remain as the standard method for satisfying certain quality standards.

  In the **US** and in **India**, a strict legal requirement for the testing of all new medicines on animals has recently been removed under amendments to legislation. Adopting almost identical wording, the revised laws in both countries make it clear that in addition to animal tests, non-animal tests may instead be used, where possible, to test the safety and effectiveness of a drug prior to the clinical trial phase.
- *Food and animal feed safety*: as with other **EU** regulatory legislation, there is no formal legal barrier to adopting non-animal methods to comply with data requirements under the various sectoral laws applying to food and animal feed. Many laws however, including REACH and those concerning pesticides are drafted in a way which makes *in vivo* testing mandatory in practice. For the assessment and authorisation of animal feed additives, in particular, animal testing is unavoidable in relation to a particular safety assessment, because a 90-day animal feeding study is necessary to detect possible toxicological effects.

4. Transparency of research and data

Requirements to publish research for scientific purposes

There is no evidence among the jurisdictions studied of legal measures requiring the results of research involving animal testing to be published or for technical data to be made accessible for scientific purposes. Legal duties aimed at transparency rather concern the recording and publication of animal testing statistics as well as, among European Union Member States, non-technical information about scientific projects involving animals.

The 2010 EU Directive imposes two main reporting duties on **EU Member States**: to report, on an annual basis, on statistical information on the use of animals in procedures; and the provision of non-technical project summaries ("NTS") of authorised projects to be submitted for publication within 6 months of the date of project authorisation. This information is stored and made available for public access in the respective "ALURES" databases of the EU. A total of 17 Member States have also transposed into national legislation a requirement for NTSs to undergo retrospective assessments. Another obligation concerning transparency is the data sharing requirement applied as part of the registration process under REACH for substances manufactured or imported into the EU: one of the aims of this duty to share information about the properties of a substance is to reduce the scope for duplication of tests on animals.

Research into jurisdictions outside of Europe indicate that legal duties to publish information on animal testing are typically confined to statistical data. This is the case in the **US, Australia** and **New Zealand**

where annual reports from registered research facilities must keep records and submit to the relevant regulator data on the use of animals for statistical, rather than scientific, purposes. Similar requirements are not known to apply in **India**.

Preregistration of research

As to the preregistration of research involving animals, this is, according to our research, currently not mandated by law anywhere in the world. Although the preregistration of clinical research – that is, research carried out on humans – is already mandatory in the US and EU, there is no similar mechanism applying to pre-clinical research (that which begins prior to testing on humans and which frequently relies on animal experiments).

There are, nevertheless, opportunities for scientific studies involving animal testing to be preregistered on a voluntary basis. Currently, three online platforms are known to cater for the preregistration of animal research. Although the preregistration of studies involving animals is increasingly being incorporated into the editorial policies of scientific journals, there is said to generally be a slow uptake in participation, and calls for mandatory preregistration of studies remain limited.

5. Latest developments

The following latest developments with regard to the regulation of animal testing in Europe and beyond are discussed in the final section of this study:

- European Commission response to European Citizens' Initiative on animal testing;
- European Court of Justice ruling on animal testing for ingredients used solely in cosmetics;
- Revision of the CLP Regulation to contain wording aimed at alternatives to animal testing;
- Proposal to replace existing pharmaceutical legislation with new Directive and Regulation containing provisions aimed at promoting 3Rs and decreasing animal testing;
- European Parliament adopts resolution "*on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education*";
- UK ban on animal testing for chemicals exclusively intended as ingredients in cosmetic products;
- Dutch Government strategy to phase out regulatory animal testing by 2025 is scaled back;
- US passes law removing a requirement for drugs to be tested on animals;
- India amends pharmaceutical legislation to include non-animal methods for drug development;
- Academic and industry experts in South Korea urge the passing of legislation to promote alternative approaches to animal testing;
- Canada amends environmental protection legislation to promote 3Rs in toxicity testing and bans the testing of cosmetics on animals.

I. BACKGROUND AND QUESTIONS

A. Context

Swiss law requires that the use of animals for experiments be limited, conducted only under certain conditions and only to the extent necessary. Moreover, alternatives to the use of animals for testing are to be promoted. Balancing the ethical interests with the needs of science and of the economic competitiveness of Swiss industry has led to a framework of rules that emphasizes the "3R" approach: replace, reduce, refine.

B. Mandate

The Federal Food Safety and Veterinary Office (*Bundesamt für Lebensmittelsicherheit und Veterinärwesen,* "BLV") contacted the Swiss Institute of Comparative Law with a request that we examine the regulation of the use of animals in experiments and the regulation of alternatives to animals for such experiments. Specifically, the BLV requested that the following points be examined in the present study (BLV's own wording):

- *Regelung von Tierversuchen: Wie sind Zulässigkeit, Bedingungen und allfällige Verbote geregelt?*
- *Gibt es rechtliche Regelungen zur Pflicht von Tierversuchen (etwa zur Bewertung von Gesundheits- und Umweltrisiken, z.B. als Zulassungsbedingung für neue Medikamente oder im Chemikalienrecht)?*
- *Wie sind die Alternativen zu Tierversuchen geregelt (bspw. 3R, Organoide)?*
- *Wer entscheidet über die Zulassung von Tierversuchen? Wie wird die Aufsicht gewährleistet?*
- *Gibt es eine Pflicht zur Präregistrierung von Tierversuchen?*
- *Gibt es eine Pflicht zur Publikation von Forschungsergebnissen bzw. wie ist die Zugänglichkeit von Daten zu wissenschaftlichen Zwecken gewährleistet?*
- *Gibt es rechtlich geregelte Anreize zur Förderung von Alternativen zu Tierversuchen?*
- *Welche neuen Entwicklungen gibt es (Bsp. Bürgerinitative der EU, die Mitte 2023 beantwortet wurde; Gesetzesentwurf in den USA) bspw. zum Ausstieg aus gesetzlich vorgeschriebenen Tierversuchen für neue Medikamente oder zur Messung der Giftigkeit neuer Chemikalien)?*

C. Questions

For ease of reference and for structural purposes, these points have, with the agreement of the BLV, been re-formulated and addressed under the following questions:

1. **Overview:** regulation and institutional supervision of animal experiments: How are permissibility, conditions and possible bans regulated, and which bodies have supervisory authority?

2. **Alternatives:** How are the alternatives to animal testing regulated? Are there legally regulated incentives to promote alternatives to animal testing?

3. **Regulatory testing:** Are there legal regulations requiring animal testing?

4. **Transparency of research and data**: Are there legal obligations to make research results and data involving animal testing accessible for scientific purposes? To what extent must research involving animal experiments be pre-registered?

5. **Latest developments:** what new developments are there?

II. INTRODUCTION

Around the world, animals are used on a daily basis in testing for scientific purposes. This takes place principally in the fields of basic and applied research, but also for satisfying regulatory requirements for new chemical substances, medicines, pesticides and others. Research on animals is invaluable in understanding complex questions of science, contributing to life-saving cures and treatments and improving the safety and efficacy of products for humans, animals and the wider environment. Regulation of animal testing is needed to keep the use of animals, and their pain and suffering, to a minimum. Too much regulation, however, can impede scientific progress and may lead to animal research transferring to jurisdictions where less rigorous standards apply. Laws and guidelines therefore tend to strive for a balance which, in theory at least, is underpinned by the core ethical principle that the likely benefits of such research outweigh its costs.

Animal welfare in experimentation is a vast and complex topic, typically subject to a range of laws, rules, guidelines and practices, too numerous and detailed to cover in their entirety. However, regulations often share the same central characteristic: increasingly, they are framed by an approach aimed at the **replacement** of vertebrate animals with non-animal methods, the **reduction** in numbers of animals used for testing and the **refinement** of testing methods in order to reduce pain and suffering of the animals involved: together, these are commonly referred to as the principle of the Three Rs ("3Rs"). Legal frameworks governing animal testing for scientific purposes are however at differing stages of development, with certain jurisdictions praised for their efforts to actively incorporate the 3Rs in rules regulating animal experimentation, while others are slow to adapt and show consistently high animal usage. A particular problem, even for jurisdictions at the cutting edge of animal replacement methodology, is that outdated legal requirements in regulatory laws continue to refer to animal testing as the standard method for demonstrating relevant standards are met. This failure of the law to keep up with scientific developments leaves it acting as a barrier to the implementation of non-animal testing methods.

This study examines the legal systems of a select number of countries and regions for which legal information is easily accessible, which are characterised by advanced or recent regulation in this field and/or which represent large or important markets for the kinds of substances and products on which animals are typically tested. Our principal focus is on the European Union ("EU") and the United States ("US"). The EU has legislated in relation to the testing of animals for scientific purposes with the aim of harmonising Member State laws in this area. The US is at the forefront of scientific advances with regard to non-animal testing methods but remains one of the most active countries with regard to animal experimentation. Reference is also made to a selection of European jurisdictions with important markets and/or long histories of animal testing regulation. Looking further afield, overviews of the relatively developed systems of Australia and New Zealand are provided, as well as the legal framework governing animal testing in India.

Section 1 offers a description of the regulation of animal testing for scientific purposes in Europe. It looks in particular at the rules set out in the EU Directive on this topic. This is complemented with an overview of the source of animal testing regulation in five European jurisdictions – Denmark, France, Germany, the Netherlands and the UK – as well as a description of supervisory oversight mechanisms. Beyond Europe, the regulatory systems of the US, Australia, India and New Zealand are examined, again with particular reference to sources of regulation and oversight.

Section 2 focuses on alternatives to animal testing. The use of alternatives to animal studies is an integral part of the regulation of animal testing, and the analysis here attempts to identify and examine aspects of the law which are specifically aimed at promoting and encouraging them. With regard to European law, we examine three aspects: legal requirements to promote the 3Rs and alternatives;

provisions in EU regulatory testing legislation – in particular chemicals and pesticides laws - requiring alternatives to be considered; and aspects of EU law which deal with incentivizing the pursuit of alternatives. Domestic regulation of alternatives among European countries is then considered, illustrating how much of this takes place outside of the legal framework. Finally, legal regulation of alternatives in the US, India, Australia and New Zealand is examined.

Section 3 concerns the extent to which there are legal obligations to test on animals, commonly referred to as 'regulatory testing'. With 95% of regulatory testing among EU Member States being performed to comply with EU regulatory requirements, the focus on Europe in this section mainly concerns EU laws and guidelines which render animal testing mandatory. Divided among a number of areas in which regulatory testing typically takes place – chemicals substances, cosmetics, pesticides, medicinal products, medicinal device laws, food and feed safety - reference is also made, where possible and by way of comparison, to regulatory testing laws in the US.

Section 4 examines laws and other regulation concerning the transparency of research and data involving animal testing. The first section considers reporting requirements around research and statistical information in Europe as well as in the other featured non-European jurisdictions; the second section looks at preregistration of research involving animal experiments (namely, preclinical research), noting how that, unlike clinical research, this is an area yet to be regulated by law.

Finally, **section 5** identifies some of the most important recent developments regarding the regulation of animal testing in science. This refers to developments in the EU and some European countries, as well as those developments beyond Europe, including South Korea and Canada.

III. ANALYSIS

1. Overview

1.1. European regulation

The rules, principles and guidelines constituting the European framework on the protection, care and use of animals in research, education and testing is to be found principally in documentation issued by the **Council of Europe ("CoE")** and the **European Union ("EU")**. These are:

- the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes,*[1] published in 1986 by the CoE in the European Treaty Series 123 (better known as **ETS 123**); and
- *Directive 2010/63/EU on the protection of animals used for scientific purposes* (the "**2010 Directive**"),[2] published by the EU on 22nd September 2010 (referred to as Directive 2010/63/EU).

The universally binding and more prescriptive provisions of the 2010 Directive overlap with many of the areas covered by ETS 123. However, for EU Member States, it is the 2010 Directive which is considered as having greater precedence in the regulatory framework. This, and other EU legislation with relevance to animal testing[3] will therefore be the main focus of the European legal measures examined in the present study. ETS 123 is nevertheless addressed by way of a brief overview below.

1.1.1. ETS 123

As an international organisation, the CoE cannot make laws. However, it relies on voluntary cooperation among its member countries[4] to set standards in a variety of areas through recommendations, agreements and conventions. Member countries may sign and ratify conventions such as ETS 123 and will subsequently be bound to implement those conventions into their national legislation.

The significance of ETS 123 for EU Member States is that the principles and some of the content in ETS 123 were the **basis for the original EU Directive on the use of animals for scientific purposes**, 86/609/EEC, which, for 25 years, established the minimum legal requirements applicable in this field.[5] In particular, its Appendix A on the guidelines on the accommodation and care of animals, were adopted as recommendations in Directive 86/609/EEC, while many of the definitions and scope of the Directive closely resembled those in ETS 123. The EU itself became a party to the ETS 123 convention in 1998.

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1 *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (ETS 123), available at https://rm.coe.int/168007a67b (06.12.2023).

2 *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*, consolidated version available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02010L0063-20190626 (06.12.2023).

3 As part of the present overview, *Regulation (EC) 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products* (available at https://health.ec.europa.eu/system/files/2016-11/cosmetic_1223_2009_regulation_en_0.pdf (11.12.2023)) will briefly be examined, and in later sections, reference is made to important aspects of EU legislation concerning regulatory testing.

4 Of which there are currently 46, including all 27 EU Member States.

5 Javier Guillén and others, *The European Framework on Research Animal Welfare Regulations and Guidelines*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research,* Academic Press, London, 2018, 2nd edition, p. 118.

Spread across 38 articles in 12 Parts and with 2 Appendices (A and B), it will be seen how ETS 123 is **covered by many of the same areas as the 2010 Directive**, including care and accommodation of animals, the conduct of procedures, the authorisation of procedures and persons, administrative measures for breeding and supplying establishments, requirements for establishments which use animals for experimentation, education and training and statistical information. Its Part III (Articles 6 to 12) concerning the conduct of procedures, provides implicit reference to the implementation of the principles of replacement, reduction and refinement (the "3Rs"[6]), with a focus on the use and promotion of alternative methods, choice of species, minimisation of pain and distress, reuse and euthanasia.[7]

1.1.2. EU legislation

1.1.2.1. EU competence

As a supranational entity, the EU only has the powers provided to it by the treaties of the EU and may only act within the limits of the competences conferred upon it by the EU Member States. In the **field of animal welfare regulation, the EU is authorised to adopt EU-wide laws only to a limited degree**.[8]

The **EU shares competence with Member States** in numerous areas in which animal testing for scientific purposes has particular relevance: regulation of the internal market; agriculture; the environment; common safety concerns in public health matters; and consumer protection.[9] Moreover, Article 4(3) of the TFEU confers on the EU **shared competence in the field of research, technological development and space**.

A**nimal welfare** is not, unlike environmental protection, one of the common goals of the EU. It is nevertheless recognised by the TFEU as a **principle having general application** (along with principles such as consumer protection, the promotion of sustainable development and the protection of health). Notably, Article 13 of the TFEU **recognises animals as sentient beings**, asserting that full regard should be paid to the welfare requirements of animals when formulating and implementing the EU's agriculture, fisheries, transport, internal market, research and technological development and space policies.

The above principles feature heavily in the recitals to the 2010 Directive, in which the EU reiterates its competence to legislate with regard to the protection of animals used for scientific purposes. The first recital, in particular, emphasises a desire **to ensure a proper functioning of the internal market**: namely, by reducing disparities in the laws and regulations of Member States with regard to the protection of animals. Promotion of the 3Rs or legislation on the keeping of farm and experimental animals, for example, might constitute regulatory obstacles, or barriers to trade in products and substances involving experiments on animals. Allowing Member States to implement stricter measures may result in traders based in countries with such stricter regulations being disadvantaged by

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6 "3Rs" or "3Rs alternatives" refers to the replacement, reduction and refinement of animals used in research, teaching, testing and exhibition. First defined by Drs. William Russell and Rex Burch in their 1959 book, "The Principles of Humane Experimental Technique", the goal of the 3Rs Principle is to avoid animal experiments altogether (replacement), to limit the number of animals (reduction) and their suffering (refinement) in tests to an absolute minimum.

7 Javier Guillén and others, *The European Framework on Research Animal Welfare Regulations and Guidelines*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research*, *op. cit.,* p. 118.

8 See Maestri, E., The 3Rs Principle in Animal Experimentation: A Legal Review of the State of the Art in Europe and the Case in Italy, *BioTech*, 2021, 10, 9, p. 4.

9 *Ibid*, Article 4(2). These are areas in which regulatory testing plays an important role (see section 3 of the present study, below).

increased production costs, leading to disruption to the operation of the internal market. Rules on the protection of animals used for testing can therefore only properly be achieved as part of an EU-wide approach if the internal market is to function.

1.1.2.2. Directive 2010/63/EU on the protection of animals used for scientific purposes

The provisions of the 2010 Directive had to be transposed into national law by Member States by November 2012. The Directive itself **constitutes a revision of the original EU Directive** on the use of animals for scientific purposes, Directive 86/609/EEC, which it replaced and repealed. The main aim of the 2010 Directive is to strengthen legislation and improve the welfare of those animals still needed to be used, as well as **explicitly integrating the principle of the 3Rs** for the use of animals for scientific purposes in EU legislation.

Whereas the earlier Directive established minimum standards across the EU and allowed certain Member States to go beyond its provisions, the **2010 Directive seeks to harmonise the legislative framework**. Crucially, Article 2 excludes the possibility for **Member States to establish stricter measures** than those provided for in the Directive. Only stricter domestic measures that were in force on 9th November 2010 and which were communicated to the European Commission by the beginning of 2013 could be retained.

Notwithstanding this common legislative framework within the EU, **differences in the interpretation and implementation of some of the Directive provisions** can be found at the national level, while a number of Member States continue to maintain **stricter measures that were in place prior to the publication of the 2010 Directive**. Some of the more notable divergences from the common framework are discussed below in relation to selected EU Member States.

Scope and applicability

The areas covered by the 2010 Directive are established in Article 1. This lays down rules on:

(a) the replacement and reduction of the use of animals in procedures and the refinement of the breeding, accommodation, care and use of animals in procedures;

(b) the origin, breeding, marking, care and accommodation and killing of animals;

(c) the operations of breeders, suppliers and users;

(d) the evaluation and authorisation of projects involving the use of animals in procedures.

The Directive applies where animals are used or intended to be used in procedures or bred specifically so that their organs or tissues may be used for scientific purposes. According to Article 1(3), the Directive concerns all live nonhuman vertebrate animals as well as live cephalopods. It also applies to animals in procedures at an earlier stage of development, where other conditions are met. The use of testing of non-human primates is subject to restrictions, and the use of great apes (namely, chimpanzees, bonobos, gorillas and orangutans) is forbidden, save only for the purposes of research aimed at the preservation of those species and where action in relation to a life-threatening, debilitating condition endangering human beings is warranted and no other species or alternative method would suffice for achieving the aims of the procedure.[10]

Comprised of 66 articles across 6 chapters, plus 8 annexes, the 2010 Directive covers a comprehensive range of aspects of animal testing for scientific purposes:

[10] 2010 Directive, Article 8.

- Chapter I sets out **General Provisions**, including scope, definitions, the application of stricter measures, the 3Rs principles, the permitted purpose of experimental procedures and methods of euthanasia.
- Chapter II establishes the **provisions of certain animals in procedures**, such as endangered species, nonhuman primates, animals taken from the wild, animals required to be purpose-bred, and stray and feral animals of domestic species.
- Provisions with regard to the **conduct of procedures** are contained in Chapter III, including the choice of methods, anaesthesia, classification on the severity of procedures, reuse of animals and their setting free or rehoming.
- The first part of Chapter IV concerns the **authorisation of breeders, suppliers and users**, setting out requirements in relation to - among others - installations and equipment, the competence of personnel, the creation and role of animal-welfare bodies (an "AWB", providing institutional oversight) and care and accommodation. For this latter, **minimum housing standards** are contained in the Directive's Annex III, which adopts part of the provisions of Appendix A of ETS 123. The second and third parts of Chapter IV establish, respectively, requirements regarding **inspections** and requirements for **project authorisation and transparency**.
- In Chapter V, provisions **aimed at supporting alternative approaches to animal testing** are set out, including avoidance of the duplication of procedures, the creation of the EU's Reference Laboratory (the Commission's Joint Research Centre)[11] and duties on Member States to establish national committees for the protection of animals used for scientific purposes.
- Chapter VI concludes with provisions which include the **requirement for the EU Commission to periodically report** both on the implementation of the Directive and on statistical information submitted by Member States, as well as **obligations on Member States to designate competent authorities** for the implementation of the Directive.

Application of the 3R principles

EU rules on alternatives to animal testing are addressed in section 2 of the present study, but the wider regulation of animal experiments under the 2010 Directive cannot be described without reference to the 3Rs principles. In fact, the **Directive explicitly demands the implementation of the 3Rs principles** throughout the provisions of the Directive, with **specific emphasis given to replacement**. The Recitals refer to the Directive as being a significant step toward achieving the **final goal of full replacement of procedures as soon as it is scientifically possible**,[12] and instruct that the principles of replacement, reduction and refinement should be considered systematically when Member States are implementing the Directive.[13]

Explicit requirements on Member States to implement the 3R principles can be found in the overarching provision of **Article 4 (entitled 'Principle of Replacement, Reduction and Refinement')** and with regard to the choice of methods and testing strategies in **Article 13 ('Choice of methods')**; as will be seen, other references appear in relation to practices concerning the **ethical review process** which apply to oversight, the ethical evaluation and technical evaluation at the procedural level of projects,[14] putting obligations on both Member States and animal-welfare bodies[15] of breeders, suppliers and users to ensure that the 3R principles are applied; further requirements to respect 3R

11 See section 2.1.2. of the present study, below.
12 2010 Directive, Recital 10.
13 2010 Directive, Recital 11.
14 2010 Directive, Article 38.
15 2010 Directive, Article 27.

principles can be found with regard to the **obligation to produce non-technical project summaries**[16] and in relation to minimum requirements for **training and education of personnel**,[17] **accommodation and care**,[18] **anaesthesia**[19] and **reuse of animals**.[20] As mentioned above, Chapter V of the Directive, entitled **"Avoidance of Duplication and Alternative Approaches"** is also specifically dedicated to the avoidance of duplication of procedures using animals and the broader requirements on the EU Commission and Member States to develop and validate approaches which use, no or fewer, animals.

Supervisory authority

Each EU Member State will designate in its national laws its own **supervisory authority** with the competence for ensuring compliance of establishments in which animals are bred or used for scientific purposes. However, the 2010 EU Directive lays down specific requirements with regard to these institutional structures.

In particular, each Member State is required to ensure that there is a **national 'competent authority' ("CA")** and that breeders, suppliers and users are authorised by, and registered with this CA.[21] Authorisation is to be granted only if the breeder, supplier or user and its establishment[22] is in compliance with various requirements of the Directive. Broadly, this means there must be a person on site with responsibility for ensuring such compliance and one or several people responsible for the welfare and care of animals and the provision of prompt veterinary attention when necessary. For those establishments in which scientific procedures are carried out on animals, the Directive **requires CAs to have responsibility for issuing authorisations** to those individuals who design and oversee the conduct of procedures,[23] as well as for **issuing specific authorisation for projects** involving the testing of animals.[24] In order to verify compliance with the requirements of the Directive, Member States are required to ensure that the **CAs carry out regular inspections** of all breeders, suppliers and users, as well as their establishments.[25]

Another important aspect of ensuring the efficacy of the supervisory authority and giving priority to animal welfare considerations is the obligation on Member States to ensure that each establishment sets up a committee, known as an **Animal Welfare Body ("AWB")**.[26] The AWB must include at least the person or people responsible for the welfare and care of the animals, and in the case of a user, a scientific member. The **AWB has a duty to oversee and monitor all activities relating to the welfare of animals** housed or used in the establishment, including their acquisition, accommodation, care and use; among its other responsibilities, it must advise staff on the application of the requirements of the 3R principles and establish and review internal operational processes in relation to the welfare of animals housed or used in the establishment, follow the development and outcome of projects, advise on rehoming schemes and comply with duties imposed on Member States to ensure that records of advice given by the AWB and associated decisions are kept for at least 3 years.[27]

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16 2010 Directive, Article 43.

17 2010 Directive, Annex V.

18 2010 Directive, Article 33.

19 2010 Directive, Article 14.

20 2010 Directive, Article 16.

21 2010 Directive, Article 20.

22 Meaning any "[…] *installation, building, group of buildings, or other premises and may include a place that is not wholly enclosed or covered and mobile facilities.*" (2010 Directive, Article 3(3)).

23 2010 Directive, Articles 23 to 27.

24 2010 Directive, Chapter IV, section 3.

25 2010 Directive, Article 34.

26 2010 Directive, Article 26.

27 2010 Directive, Article 27.

Implementation by Member States of the supervisory oversight requirements of the 2010 Directive is discussed as part of the country summaries below.[28] As a general observation, however, it may be noted that despite the transposition of the Directive into national law achieving a degree of harmonisation among EU Member States, there are **still some notable differences with regard to how oversight and ethical review systems have been implemented**. This is partly due to varied domestic frameworks in operation prior to the Directive coming into force, but also because of different interpretations of the Directive by Member States.[29] One particular issue is that some Member States restrict the project evaluation and/or authorisation functions exclusively to a public CA, while others have designated CAs to include institutional AWBs or other ad hoc ethics committees to carry out project evaluation and even authorisation tasks.[30] That such institutional committees may perform project evaluations alongside their role as an AWB is controversial given that the designation by Member States of non-public bodies as CAs must not result in conflicts of interest.[31]

1.1.2.3. Regulation 1223/2009 on Cosmetic Products

An overview of EU legislation aimed at the regulation of animal testing is not complete without reference to *EC Regulation 1223/2009 on cosmetics* (the "Cosmetics Regulation").[32] As a Regulation of the EU, Regulation 1223/2009 is **directly applicable in all EU Member States** and does not need to be transposed into national law.

Repealing and replacing the earlier Council Directive 76/768/EEC,[33] it **takes over the prohibition** - in force since 2004 - of the **testing of animals on finished cosmetic products** and, since 2009, the **testing of ingredients used in cosmetic products** on animals in the EU.

Additionally, it **implements a marketing ban** - applicable since 2009 - of cosmetics tested on animals: namely, a prohibition on the placing on the EU market of cosmetic products and ingredients contained in cosmetic products that have been tested on animals anywhere in the world. Exemptions to the ban, which still allowed animal testing in relation to the most complex human health effects (repeated-dose toxicity, including skin sensitisation and carcinogenicity, reproductive toxicity and toxicokinetics), were removed in 2013.[34]

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28 Reference is also made in country summaries to national committees, established in accordance with Art. 49 of the 2010 Directive, for the protection of animals used for scientific purposes with the role of advising the CAs and AWBs and ensuring sharing of best practice. Such a committee does not have supervisory duties, however, and will not be discussed further here.

29 Javier Guillén and others, *The European Framework on Research Animal Welfare Regulations and Guidelines*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 149.

30 Article 59 of the Directive permits Member States to, "[…] *designate bodies other than public authorities for the implementation of specific tasks laid down in this Directive…*" albeit only if there is proof that the body: (a) has the expertise and infrastructure required to carry out the tasks; and (b) is free of any conflict of interests as regards the performance of the tasks. (2010 Directive, Article 59(1)).

31 Javier Guillén and others, *The European Framework on Research Animal Welfare Regulations and Guidelines*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 150-151.

32 *EC Regulation 1223/2009 on cosmetics of the European Parliament and of the Council of 30 November 2009, op. cit.*

33 *Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31976L0768 (12.12.2023).

34 European Commission, *Press Release - Full EU ban on animal testing for cosmetics enters into force,* 11th March 2013*,* available at https://ec.europa.eu/commission/presscorner/detail/en/IP_13_210 (12.12.2023).

As discussed below however (section 3.3.), the ban under the Cosmetics Regulation **covers only tests performed to demonstrate the safety of the product to end users** and not to those done for regulatory purposes under EU chemicals legislation, nor to testing undertaken for assessing risks to workers during the production process.

1.2. Selected European jurisdictions

1.2.1. Denmark

Denmark is recognized for its comprehensive legal framework governing the use of animals in scientific research and is **commended as a model for other countries to follow** with regard to its work promoting the 3Rs principles.[35]

The Danish rules on animal testing are laid down in its **Animal Testing Act** (*Dyreforsøgsloven*)[36] and in the **Government Ordinance on Animal Testing** (*Dyreforsøgsbekendtgørelsen*) (the "Ordinance").[37] The Animal Testing Act was introduced in 2022 and replaces the previous 2014 law which implemented the 2010 Directive. This follows **observations by the European Commission that a number of the 2010 Directive's provisions had not been implemented correctly** into Danish law. The changes, which do not significantly alter the application of existing rules, include amendments to the process and content of authorisation for animal experimentation, the evaluation of applications for projects involving animal testing and provisions governing the completion of experiments.

The **3Rs principles feature heavily in Danish legislation**; they are mentioned in several provisions of the Ordinance, which confirms at its section 62 that an application of approval to conduct animal testing must contain information on the use of replacement, reduction and refinement methods in relation to the testing activity. In the Animal Testing Act itself, section 6(4) transposes requirements of the 2010 Directive, confirming that test shall not be performed if another method or testing strategy not entailing use of live animals may be used to obtain the intended results.

The principal supervisory body for animal testing is the Animal Experiments Inspectorate (*Dyreforsøgstilsynet*). The Animal Experiments Inspectorate consists of a secretariat - commonly referred to as The **Animal Experiments Inspectorate** - and the **Animal Experiment Council** (*Rådet for Dyreforsøg*). The Inspectorate carries out inspections of all animal testing facilities in Denmark, as well as advising on the housing and use of experimental animals and legislation. The Animal Experiment Council is specifically tasked with evaluating all applications for permission to carry out animal experiments in Denmark.[38] It is composed of a chairman (who must be a judge) and 10 council members who are all appointed by the Minister of Food, Agriculture and Fisheries on a four-year term. Detailed regulation on the work of the Council is laid down in an Ordinance on the rules of procedure for the Council for Animal Testing (*Bekendtgørelse forretningsorden for Rådet for Dyreforsøg*).[39]

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35 See "Protecting animals used in scientific research in World Animal Protection, *Animal Protection Index – Denmark*, available at https://api.worldanimalprotection.org/country/denmark (09.01.2024).

36 *Dyreforsøgsloven (Bekendtgørelse af lov om dyreforsøg* LBK nr 1107 af 01/07/2022), available in Danish at https://www.retsinformation.dk/eli/lta/2022/1107 (09.01.2024).

37 (Dyreforsøgsbekendtgørelsen) (Bekendtgørelse 2020-12-14 nr. 2028 om dyreforsøg), available at https://www.retsinformation.dk/eli/lta/2020/2028 (09.01.2024).

38 See Ministry of Food, Agriculture and Fisheries of Denmark, *The Animal Experiment Council*, available at https://en.dyreforsoegstilsynet.dk/about/the-animal-experiment-council (09.01.2024).

39 (*Bekendtgørelse 2013-01-29 nr. 82 om forretningsorden for Rådet for Dyreforsøg*, available at https://www.retsinformation.dk/eli/lta/2013/82 (09.01.2024).

1.2.2. France

Like other EU Member States, **France has an extensive legal framework** covering the protection of animals used in scientific research and its legislation actively promotes the 3Rs principles. The objective of pursuing alternative methods in animal experiments for scientific purposes has formed part of the law since 1976, and France's Rural and Maritime Fishing Code (*le Code rural et de la pêche maritime*)[40] contains a number of articles founded on the 3Rs principles along with detailed requirements with regard to the authorization of projects using animals.[41] These provisions are supplemented and amended by secondary legislation in the form of **Decree 2013-118 of 1st February 2013 concerning the protection of animals used for scientific purposes** (*Décret n° 2013-118 du 1er février 2013 relatif à la protection des animaux utilisés à des fins scientifiques*)[42] and **five orders** ("*Arrêtés")*,[43] which serve to transpose into French law the 2010 Directive.

According to these regulations, two different oversight bodies must be set up by an establishment, each having independent but complementary missions: an institutional Ethics Committee and the AWB.[44] **Unlike many other jurisdictions where the AWB has a role to play in project evaluation, in France, this aspect is the sole responsibility of the Ethics Committee**. The AWB is rather responsible for the advisory functions set out in Article 27 of the 2010 Directive. Several establishments may be covered by one Ethics Committee, but each establishment is required to have a specifically designated Ethics Committee which must be registered with the Ministry of Higher Education, Research and Innovation *(Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation,* "MESRI"). All Ethics Committees must be comprised, at the very least, of: one person with skills in the design of experimental procedures on animals; one person who has skills in the field of carrying out experimental procedures on animals; one person who can demonstrate competence in at least animal care and/or the killing of animals; a veterinarian; and a person not specialised in questions relating to the use of animals for scientific purposes.[45] Annual audits are carried out to ensure compliance and include review by a regional representative of the MESRI and inspection by the Ethics Committee. Veterinary inspectors also review animal use and the implementation of the principles of the 3Rs.[46]

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40 *Code rural et de la pêche maritime*, available at https://www.legifrance.gouv.fr/codes/section_lc/LEGITEXT000006071367/LEGISCTA000027039288/#LEGISCTA000027039291 (08.01.2024).

41 *Ibid*, Arts. R214-87 to R215-10 in particular.

42 *Décret n° 2013-118 du 1er février 2013 relatif à la protection des animaux utilisés à des fins scientifiques*, available at https://www.legifrance.gouv.fr/loda/id/JORFTEXT000027037840 (08.01.2024).

43 These may be described as orders with more detailed enforcement instructions. These are: *Arrêté du 1er février 2013 fixant les conditions de fourniture de certaines espèces animales utilisées à des fins scientifiques aux établissements utilisateurs agréés, Arrêté du 1er février 2013 fixant les conditions de fourniture de certaines espèces animales utilisées à des fins scientifiques aux établissements utilisateurs agréés, Arrêté du 1er février 2013 relatif à l'acquisition et à la validation des compétences des personnels des établissements utilisateurs, éleveurs et fournisseurs d'animaux utilisés à des fins scientifiques, Arrêté du 1er février 2013 fixant les conditions d'agrément, d'aménagement et de fonctionnement des établissements utilisateurs, éleveurs ou fournisseurs d'animaux utilisés à des fins scientifiques et leurs contrôles, Arrêté du 1er février 2013 relatif à l'évaluation éthique et à l'autorisation des projets impliquant l'utilisation d'animaux dans des procédures expérimentales* and *Arrêté du 1er février 2013 relatif à la délivrance et à l'utilisation de médicaments employés par les établissements agréés en tant qu'utilisateurs d'animaux à des fins scientifiques.* See Gircor, *Textes en vigueur,* available at https://www.gircor.fr/la-reglementation/ (08.01.2024).

44 See Guillén, J., Robinson, S., Decelle, T. *et al.* Approaches to animal research project evaluation in Europe after implementation of Directive 2010/63/EU, *Lab Anim* 44, 23–31 (2015), at p. 25.

45 *Code rural et de la pêche maritime, op. cit.*, Art. R214-118.

46 Guillén, J., Robinson, S., Decelle, T. *et al.* Approaches to animal research project evaluation in Europe after implementation of Directive 2010/63/EU, *op. cit.*, p. 25.

At the national level, **MESRI takes responsibility for submitting annual statistics to the European Commission**. The Code also establishes two committees, although these do not have supervisory responsibility. The first of these is the **National Commission on Animal Experimentation** (*Commission Nationale de l'expérimentation animale* – "CNEA"). The CNEA reports to the Ministry of Agriculture and MESRI and has the task of advising the competent authorities and others on matters related to the use of animals in experimental procedure. It is also required to exchange information on the functioning of structures responsible for animal welfare and on project evaluations with the national committees of other Member States, for the purpose of sharing best practices. It consists of 23 individuals, including those representing government departments and individuals nominated by the ministers for agriculture and for research from the fields of public research, private industry, animal welfare and science. The second committee is the **National Committee for Ethical Reflection on Animal Experimentation** (*Comité national de réflexion éthique sur l'expérimentation animale* – "CNREEA"). The CNREEA provides advice concerning ethical questions arising from animal experimentation and, in 2008, it created a National Charter on the Ethics of Animal Experimentation, comprising nine articles with regard to the use of methods and techniques underpinned by the 3Rs.

1.2.3. Germany

Germany is **widely recognised for its extensive rules** governing the use of animals in scientific research and its promotion of the 3Rs principles.[47] Articles 7 to 9 of its Animal Welfare Act (*Tierschutzgesetz* – "**TierSchG**")[48] specifically concern animals used for scientific research; these are supplemented by two further regulations: the *Tierschutz-Versuchstierverordnung* (the "**TierSchVersV**")[49] on the use of laboratory animals and the *Versuchstiermeldeverordnung,*[50] a regulation concerning the reporting of animal experiments ("**VersTierMeldV**").

The **TierSchG set out what constitutes an "animal experiment"** (*Tierversuche*) **and the circumstances in which an animal experiment may be conducted.** The permissible purposes of an animal experiment include basic research, the diagnosis and treatment of diseases in humans and animals, and the safety testing of medicines and chemicals. However, the TierSchG states that animal experiments may only be carried out if they are indispensable to provide an answer to a scientific question and appear ethically justifiable in the balance of interests between the expected gain in knowledge and the expected suffering of the animals.[51] Article 7a sets out **specific bans in relation to animal testing**. In particular, animal testing for the development or testing of weapons, ammunition and associated equipment is prohibited; and animal testing for the development of tobacco products, detergents and cosmetics is generally prohibited.[52] Exceptions to the latter may be authorised by ordinance by the Federal Ministry with the approval of the *Bundesrat*, but only insofar as this is necessary to prevent

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47 See World Animal Protection, *Animal Protection Index – Germany, Protecting animals used in scientific research*, where it receives an "A" rating with regard to protecting animals used in scientific research, available at https://api.worldanimalprotection.org/country/germany (08.01.2024).

48 *Tierschutzgesetz*, available at https://www.gesetze-im-internet.de/tierschg/index.html (08.01.2024).

49 *Verordnung zum Schutz von zu Versuchszwecken oder zu anderen wissenschaftlichen Zwecken verwendeten Tieren*, available at https://www.gesetze-im-internet.de/tierschversv/index.html (08.01.2024).

50 *Verordnung über die Meldung zu Versuchszwecken verwendeter Wirbeltiere oder Kopffüßer oder zu bestimmten anderen Zwecken verwendeter Wirbeltiere,* available at https://www.gesetze-im-internet.de/verstiermeldv_2013/ (08.01.2024).

51 See Bundesinstitut für Risikobewertung, *Questions and answers on animal experiments, alternative methods and animal experiment numbers*, available at https://www.bfr.bund.de/cm/349/questions-and-answers-on-animal-experiments-alternative-methods-and-animal-experiment-numbers.pdf (08.01.2023).

52 § 7a (3) TierSchG.

specific health hazards (and the necessary new findings cannot be obtained by other means) or to implement legal acts of the EU.[53]

The TierSchVersV provides further detail on the requirements and principles set out in the TierSchG and **transposes into national law various aspects of the 2010 Directive**. Although the TierSchG establishes the rule that approval of the responsible authority is required for performing animal testing,[54] it is in the TierSchVersV that specific information concerning supervisory oversight and the approval of experimental projects are set out.

The **CAs for approving animal experiments in Germany are divided among the German federal states**, with certain states having two or more authorities across their respective regions.[55] These regional Ethics Committees are composed of expert volunteers with responsibility for project evaluations. It is the Ethics Committees which determine the appropriate party (government body, veterinary authority or state ministry) for reviewing and evaluating the plausibility and ethics of project applications involving animal testing.[56]

At the national level, the **German Federal Institute for Risk Assessment** (*Bundesinstitut für Risikobewertung* – "BfR")[57] has been entrusted with several tasks relating to the protection of laboratory animals, but it performs an advisory, rather than, supervisory role. According to the TierSchG, its tasks include advising the approval authorities and AWBs on all matters dealing with the acquisition, breeding, housing, care and use of animals in scientific procedures. It also acts as "National Committee for the Protection of Animals Used for Scientific Purposes"[58] and has the legal task of sending to the European Commission annual statistics on animals used in experimental projects, this based on a compilation of all reports submitted to it by each of the regional competent authorities. The Committee includes a 'Pool of Experts' consisting of 127 members, including scientists with expertise in the fields of natural sciences, law, human and veterinary medicine as well as ethics, managers of animal facilities and animal caretakers.[59]

1.2.4. Netherlands

The Netherlands is considered as a **leading country with regards to the protection of animals used in scientific research**.[60]

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53 § 7a (4) TierSchG.

54 § 8 I 1 TierSchG.

55 See Bf3R, *Approval authorities*, available at https://www.bf3r.de/cms7/sixcms/detail.php/291355 (08.01.2024).

56 See Guillén, J., Robinson, S., Decelle, T. *et al.* Approaches to animal research project evaluation in Europe after implementation of Directive 2010/63/EU, *op. cit.*, at p. 26.

57 See Bf3R, *National Committee for the Protection of Animals Used for Scientific Purposes of the Federal Republic of Germany*, available at https://www.bf3r.de/en/national_committee_for_the_protection_of_animals_used_for_scientific_purposes_of_the_federal_republic_of_germany-294874.html (08.01.2024).

58 As required of all EU Member States by Art. 49 of the 2010 Directive.

59 See BfR, *Pool of Experts for the German National Committee for the Protection of Laboratory Animals,* available at https://www.bf3r.de/en/pool_of_experts_for_the_german_national_committee_for_the_protection_of_laboratory_animals-295399.html (08.01.2024).

60 See World Animal Protection, *Animal Protection Index – Netherlands, Protecting animals used in scientific research*, available at https://api.worldanimalprotection.org/country/netherlands (19.12.2023).

Dutch law regulating animal experimentation for scientific purposes is principally set out in its **Experiments on Animals Act (*Wet op de Dierproeven*) ("WOD")**.[61] This is **supplemented by a number of legal instruments** to facilitate the regulation of animal testing. The WOD was amended in 2014 to incorporate the requirements of the 2010 Directive, but also relies on the exemption in the Directive allowing EU Member States to retain stricter animal testing requirements that were in force prior to the Directive's adoption.[62] A key example of a **retained stricter requirement** is that the **use of great apes (chimpanzees, bonobos, orangutans and gorillas) in animal experiments has been banned** since 2003, whereas the 2010 Directive allows (under strict conditions) the possibility for such animals to be subjected to testing. **Another concerns the interests which animal experimentation serves**: the 2010 Directive sets out a range of purposes for which animal testing may be undertaken whereas the WOD limits establishment licences to those conducting animal testing (albeit not with regard to basic and forensic research) aimed only at the interests of the health or nutrition of humans or animals. Another surviving provision of the Dutch legislation is the definition of animal testing. **The WOD retains the broader concept of 'animal experiment'**, a concept which includes the killing of animals for the sole purpose of using their organs or tissues: this is something which the 2010 EU Directive specifically excludes in the definition of its preferred term, 'procedure'.

Institutional supervision is overseen by a public body, the **Netherlands Food and Consumer Product Safety Authority** (*Nederlandse Voedsel- en Warenautoriteit*, "NVWA"). The NVWA monitors establishments engaged in the breeding, supply and testing of animals, and **conducts inspections** on a periodic basis to ensure compliance with animal testing regulation.[63] To conduct animal experiments, two permits are needed. Those involved in the breeding, supply and use of animals for testing are required to apply to the NVWA for an establishment licence. For every project, **a project licence must be sought from the Central Animal Testing Committee** (*Centrale Commissie Dierproeven*, "CCD"). This will issue a project licence only if a positive recommendation has been received from the **Animal Tests Committee** (*Dierexperimentencommissie*, "DEC"), an independent advisory committee whose main task is to make an ethical assessment of applications for animal testing. As required by the 2010 Directive, each establishment must set up an AWB, the role of which is to monitor the welfare of animals and to advise staff. Crucially, it is also charged with previewing draft applications for project licences to ensure compliance with the 3Rs principle before evaluation by the CCD and DEC.

1.2.5. United Kingdom

The United Kingdom ("UK") has been hailed as one of the world leaders in animal welfare and is **highly rated overall with regard to animal protection** and incorporation into national law of the animal welfare standards of the World Organisation for Animal Health.[64] However, it **has received criticism** with regard to its transparency concerning the protection for animals used in scientific research,[65] and

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61 *Wet op de dierproeven*, valid from 01.07.2023, available at https://wetten.overheid.nl/BWBR0003081/2021-07-01 (19.12.2023).

62 See Overheid.nl, *Kamerstuk - Wijziging van de Wet op de dierproeven in verband met implementatie van richtlijn 2010/63/EU – Memorie van Teolichting* (explanatory memorandum with regard to implementation of Directive 2010/63/EU), 15.07.2023, available at https://zoek.officielebekendmakingen.nl/kst-33692-3.html (19.12.2023).

63 See NVWA, *Eisen voor instellingen die dierproeven doen of proefdieren fokken*, available at https://www.nvwa.nl/onderwerpen/dierproeven-voor-onderzoek/eisen-voor-instellingen-die-dierproeven-doen-of-proefdieren-fokken (19.12.2023).

64 See World Animal Protection, *Animal Protection Index – United Kingdom*, available at https://api.worldanimalprotection.org/country/united-kingdom (10.01.2024).

65 Notably, section 24 of the *Animals (Scientific Procedures) Act 1986* (see below), which stops the Home Secretary from releasing any information received in confidence under this Act or obtained when discharging functions under the Act and which has made it difficult to obtain information regarding animals used in experiments.

concerns have been raised in recent years about its continued commitment to animal welfare protection in light of Brexit.[66]

Animals used in experiments have long been afforded certain protections under the ***Animals (Scientific Procedures) Act 1986*** **("ASPA")**,[67] and this law was amended and strengthened as part of the UK's transposition of the 2010 Directive.[68] ASPA serves to legalise practices which would otherwise be criminal offences under other laws, such as the *Animal Welfare Act 2006*, which provides specific exemption for acts lawfully done under ASPA. **Since Brexit**, those aspects of ASPA which were introduced pursuant to the 2010 Directive have been retained and other aspects of EU law, notably in relation to cosmetic testing, are not expected to change. On the other hand, the UK has, for example, lost access to certain EU data sharing mechanisms and committees.[69]

The use of animals in science in the UK (save for Northern Ireland) is regulated **through a 3-tier system of licensing** which licenses each establishment, project, and individual involved in undertaking regulated procedures on animals.[70] The Secretary of State for the Home Office (the "Home Secretary") has regulatory power for granting licences, a function which is exercised through the **Animals in Science Regulation Unit ("ASRU")**, forming part of the Home Office.[71]

Following implementation of the 2010 Directive, ASPA was amended requiring the Home Secretary, with regard to project licences, to carry out a harm-benefit analysis to ensure any potential benefits of the results of the experiment outweighs the harm caused to animals, by taking into account ethical factors as well as giving consideration to alternatives and the 3Rs principles. This discretionary process has been utilised to implement what are referred to as **'policy bans' on certain animal experimentation**: instead of legislating to prohibit experiments in particular fields (for example, through ASPA), a policy is formulated according to which licences are simply not awarded for particular experiments.[72] This is the case in relation to great apes (which have not been used in research in the UK since 1986), cosmetic products since 1998, household products and certain testing methods in relation to tobacco and alcohol products.[73]

ASRU also acts as the supervisory authority for animal experimentation in England, Wales and Scotland. As well as responsibility for the operation of the licensing system, ASRU has a policy team, a business support team and a compliance function, assuring compliance of licence holders with the requirements of ASPA and the terms of licences. This is primarily achieved through on-site inspections. ASRU has also published and enforces standards for the care and accommodation of all animals bred, supplied or used for scientific purposes.[74]

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66 See Dunn, R., Brexit: A Boon or a Curse for Animals Used in Scientific Procedures?, *Animals* 2021, 11, 1547.

67 *Animals (Scientific Procedures) Act 1986*, available at https://www.legislation.gov.uk/ukpga/1986/14/contents (10.01.2024).

68 Pursuant to the *Animals (Scientific Procedures) Act 1986,* 2012 (Statutory Instrument 3039 of 2012).

69 See Dunn, R., Brexit: A Boon or a Curse for Animals Used in Scientific Procedures?, *op. cit.*, at p. 11.

70 Gov.uk, *Corporate report – Animals in Science Regulation Unit annual reports 2019 to 2021*, 18th November 2022, available at https://www.gov.uk/government/publications/animals-in-science-regulation-unit-annual-reports-2019-to-2021/animals-in-science-regulation-unit-annual-reports-2019-to-2021-accessible-version (10.01.2024).

71 Although this function, in practice, is carried out through the Animals in Science Regulation Unit ("ASRU") – see further below.

72 Dunn, R., Brexit: A Boon or a Curse for Animals Used in Scientific Procedures?, *op. cit.*, at p. 6.

73 See World Animal Protection, *Animal Protection Index – United Kingdom, op. cit.*

74 Gov.uk, *Corporate report – Animals in Science Regulation Unit annual reports 2019 to 2021*, *op. cit.*

In the UK, the **National Committee**, previously required under Article 49 of the 2010 Directive, is the **Animals in Science Committee ("ASC")**. This consists of 13 members, appointed by the Home Secretary or relevant Minister, and is described as a non-departmental public body providing independent advice to the Home Office on issues relating to ASPA. It advises the Secretary of State on all matters concerning the use of animals in scientific procedures, advises AWBs on sharing best practice in the UK and exchanging information with the EU.

1.3. United States

The regulatory landscape governing the care and use of animals for scientific purposes consists of a **multi-layered network of laws, regulations and guidelines** overseen and enforced by a range of authorities and organisations.[75] The present overview focuses on the principal federal regulatory instruments.

1.3.1. Regulation

Regulation of animal testing on vertebrates is primarily to be found in the ***Animal Welfare Act***[76] **of 1966 ("AWA")** and the ***Animal Welfare Regulations*** **("AWRs")**. The AWA only protects mammals intended for use in research, teaching, testing, experimentation or exhibition purposes, or as a pet; crucially, it **does not cover those vertebrates that constitute the grand majority of those used for scientific purposes** in practice, namely: purpose-bred birds, rats and mice. These vertebrates are therefore **not counted in the annual statistics** and are not covered by the minimal protections provided under the AWA. Although the AWA provides for research facilities to follow professionally acceptable standards for the care, treatment and use of animals during actual research, including ensuring that animal pain and distress are minimised, it also **prohibits the promulgation of rules, regulations or orders related to the design, outlines or guidelines of actual research or experimentation**.[77]

Alongside the AWA and AWRs, another important regulatory instrument is the ***Public Health Service Policy on the Humane Care and Use of Laboratory Animals*** **("PHS Policy")**,[78] issued by the Office of Laboratory Animal Welfare ("OLAW") of the National Institutes of Health ("NIH", an agency of the US Department of Health and Human Services), and applicable to institutions using animals in PHS-sponsored projects. PHS Policy requires institutions that receive PHS funding to additionally comply

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75 These include the Animal Welfare Act, the Animal Welfare Regulations, the Public Health Service Policy on Humane Care and Use of Laboratory Animals (and its implementing guidelines, the *Guide for the Care and Use of Laboratory Animals*), the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training; for agricultural animals used in research and teaching, other guidelines apply, entitled the "Guide for the Care and Use of Agricultural Animals in Research and Teaching"; other guidelines with universal use are the Guidelines on Euthanasia, published by the American Veterinary Medical Association; additional regulations and guidelines apply in specific fields of research or in relation to particular species. See John F. Bradfield and others, *Oversight of Research Animal Welfare in the United States*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 16.

76 *Animal Welfare Act (Laboratory Animal Welfare Act of 1966* (Public Law 89-544), available at https://www.govinfo.gov/content/pkg/COMPS-10262/pdf/COMPS-10262.pdf (12.12.2023). See also consolidated AWA and AWRs in 'Blue Book' of United States Department of Agriculture - Animal and Plant Health Inspection Service, *Animal Care - Animal Welfare Act and Animal Welfare Regulations*, APHIS 41-35-076, July 2023, available at https://www.aphis.usda.gov/animal_welfare/downloads/AC_BlueBook_AWA_508_comp_version.pdf (13.12.2023).

77 See AWA, *op. cit.*, section 2143.

78 USDA, NIH, *Public Health Service Policy on the Humane Care and Use of Laboratory Animals,* revised 2015, available at https://olaw.nih.gov/sites/default/files/PHSPolicyLabAnimals.pdf (13.12.2023).

with the standards of the ***Guide for the Care and Use of Laboratory Animals*** **(usually referred to as the "*Guide*")**,[79] published by the Institute for Laboratory Animal Resources ("ILAR"), now known as the Board on Animal Health Sciences, Conservation and Research ("BAHSCR"), itself a unit of the Division on Earth and Life Studies of the National Academies of Sciences, Engineering and Medicine, a congressionally chartered organisation.[80] Unlike the AWA, this covers all vertebrate species, including rodents, birds and fish. Also, unlike the AWA, the *Guide* contains extensive guidance with regard to the appropriate conduct of experimental procedures, including consideration of alternatives to reduce or replace the use of animals. Finally, it should be noted that a set of principles, referred to as the ***US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*** **(the "US Government Principles")** were promulgated in 1985 by the Interagency Research Animal Committee and adopted by US Government agencies that either develop requirements for or sponsor procedures involving the use of vertebrate animals. Emphasising compliance with federal laws, policies and guidelines, these nine principles feature prominently in the PHS Policy and the *Guide,* among others.

An overview of regulation of the welfare of research animals would not be complete without reference to the **American Association for Accreditation of Laboratory Animal Care International ("AAALAC")**. A private, non-profit organisation, the AAALAC offers accreditation to participating institutions. This voluntary accreditation process allows research programs to demonstrate that they have achieved a standard of excellence in animal care and use as well as meeting the minimum standards required by law.[81] Valued by many institutions[82] in the US and worldwide, the AAALAC uses various standards of accreditation, including the *Guide*, and for European institutions, ETS 123.[83]

1.3.2. Supervisory oversight

The AWRs serve to implement the AWA, and these are enforced by the Deputy Administrator for Animal Care of the **Animal and Plant Health Inspection Service ("APHIS") of the United States Department of Agriculture ("USDA")**. The AWRs require dealers and breeders to be licensed, and research facilities registered with the USDA; standards and regulations must be met by licensees, and research facilities must demonstrate they meet requirements with regard to the structures, qualified personnel, record-keeping and accessibility of premises. Registration must be renewed every 3 years. The USDA-APHIS requires all registered research facilities to comply with the AWRs and conducts unannounced inspections of research facilities by a designated 'Veterinary Medical Officer' on at least an annual basis.

However, **supervisory oversight in the United States is principally undertaken on an in-house basis**. Since 1985, research facilities have been required by the AWA to appoint an Institutional **Animal Care and Use Committee ("IACUC")**, consisting of at least three members including a Doctor of Veterinary Medicine and one member who is not affiliated with the institution. IACUCs effectively act as agents for research facilities in assuring compliance with the AWA; in fact, they play a central role in overseeing the care and use in research of animals in the United States. Among the IACUC's responsibilities, as prescribed by the AWRs, it must inspect all animal facilities and study areas every 6 months, file a report of its inspection with the 'Institutional Official' of the research facility – an individual within the research facility who is legally authorised to commit on behalf of the facility that the regulations and standards will be followed - and must review and approve all proposed activities

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79 National Academies, *Guide for the Care and Use of Laboratory Animals*, 8th edition, 2011.

80 National Academies home page, available at https://www.nationalacademies.org/home (13.12.2023).

81 AAALAC International, *About*, available at https://www.aaalac.org/about/what-is-aaalac/ (13.12.2023).

82 Including those in industry, academia, hospitals, non-profit, and governmental organisations.

83 John F. Bradfield and others, *Oversight of Research Animal Welfare in the United States*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 24.

involving the care and use of animals in research, testing or teaching procedures. The IACUC has particular responsibility for evaluating procedures that minimise discomfort, distress and pain, methods and procedures for euthanasia, living conditions, medical care, ensuring procedures are undertaken by qualified individuals.[84]

For those institutions using animals **in PHS-sponsored projects, it is OLAW which has supervisory oversight** of animal care and use. In particular, it is responsible for verifying that a written assurance of compliance with the PHS Policy (an "Animal Welfare Assurance of Compliance") has been provided and approved. As well as applying to all vertebrate animals, this places obligations on institutions which go beyond those of the AWA and AWRs with regard to the institute's program for the care and use of animals and the composition of its IACUC. Crucially, reviews of the animal facilities and the institutional program are subject to the more demanding requirements of the *Guide*, which supports and elaborates on PHS Policy expectations and procedures for IACUC review and oversight of the care and use of animals. OLAW occasionally carries out on-site inspections of programs to ensure compliance with the *Guide* and PHS Policy, as well as the information provided in the assurance statement.

For AAALAC-accredited institutions, the AAALAC is responsible for supervisory oversight of ongoing accreditation status as part of a voluntary, collaborative peer review evaluation of animal care and use programs, principally by way of a site visit at least once every three years.[85]

1.4. Australia

1.4.1. Regulation

Australia's regulation of the scientific use of animals and animal welfare is **principally governed by animal welfare legislation and supervision at the state or territory level**. Specific legislation varies between the six states and two territories. In New South Wales for example, its *Animal Research Act 1985*[86] sits alongside general animal cruelty legislation, specifically regulating aspects of the scientific use of animals, and requiring that those carrying out animal research or supplying animals for research be authorised in accordance with the Act and accredited as research establishments; other states have specific sections referring to scientific use of animals within broader animal welfare laws. However, **common to all of the state and territory laws are the following requirements**:

(a) **prior licensing or registration** of the scientific establishment that uses animals, and/or premises where animals are bred, held or used for scientific purposes;

(b) **prior ethical review and approval**, and ongoing oversight of the animal care and use by an appropriately constituted Animal Ethics Committee ("AEC"); and

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84 John F. Bradfield and others, *Oversight of Research Animal Welfare in the United States*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 18.

85 AAALAC International, *Accreditation Program - FAQs*, updated June 2022, available at https://www.aaalac.org/accreditation-program/faqs/#H4 (13.12.2023).

86 NSW Government, *Animal Research Act 1985,* No. 123, up to date 30 October 2023, available at https://legislation.nsw.gov.au/view/html/inforce/current/act-1985-123 (14.12.2023).

(c) adherence to the principles and guidelines set out in the Guideline document known as the *Australian Code for the care and use of animals for scientific purposes 2013*[87] (the "**Australian Code**").[88]

Although regulatory responsibility for animal welfare is a state and territory matter, the **Australian Code is recognised in each jurisdiction** and included within the regulatory framework applying to scientific use of animals. Developed and overseen by the **National Health and Medical Research Council ("NHMRC")**, a non-corporate government entity with responsibility for promoting and developing public and individual health standards, it applies to the care and use of all live non-human vertebrates and cephalopods. Although not legally binding in and of itself, **it has been adopted into the respective legislation of all states and territories**,[89] making compliance with it compulsory for obtaining licensing and government funding for research projects.

It should also be noted that since 1st July 2020, the *Industrial Chemicals Act 2019*[90] has **banned the use of data or information from animal tests being used for new cosmetic ingredients**. It is complemented by a non-binding voluntary code of practice,[91] developed for the cosmetics industry in consultation with the Australian Department of Health and other key stakeholders, aimed at helping businesses involved in the making or supplying cosmetics for sale in Australia to comply with advertising laws and to enhance transparency towards consumers.

1.4.2. Supervisory oversight

Supervisory oversight of institutions that use animals for scientific purposes may be characterised as a system of **self-regulation and self-assessment**. Under the Australian Code, **applications for research which use animals must be assessed by an institutional AEC**, a body which includes at least one animal welfare member independent of the establishment, a veterinarian and an animal researcher. An institution that uses animals for scientific purposes must establish an AEC, directly responsible to the governing body of the institution. Small institutions or non-institutional persons with insufficient animal use to establish their own AEC may make arrangements to access an existing external AEC or to share an AEC with another institution. The **two main roles of an AEC are to ethically review proposals to use animals for scientific purposes and to monitor animal care and use**. Supervisory duties include inspecting animal housing and laboratories on a regular basis, inspecting at an early stage any project likely to cause animals harm, including pain or distress and ensuring that activities that are not compliant with the code cease immediately and remedial action is taken.

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87 Australian Government, National Health and Medical Research Council, *Australian Code for the care and use of animals for scientific purposes,* 8th edition 2013 (updated 2021), available at https://www.nhmrc.gov.au/about-us/publications/australian-code-care-and-use-animals-scientific-purposes#block-views-block-file-attachments-content-block-1 (14.12.2023).

88 Denise Noonan and Virginia Williams, *Laboratory Animals Regulations and Recommendations: Australia and New Zealand*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 377.

89 Albeit in different ways: in some, there is mandatory compliance with the entire document; in others, the main principles and terminology are incorporated into the text of the legislation: see Denise Noonan and Virginia Williams, *Laboratory Animals Regulations and Recommendations: Australia and New Zealand*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 381.

90 *Industrial Chemicals Act 2019 (No. 12, 2019)*, available at http://classic.austlii.edu.au/au/legis/cth/num_act/ica2019202/ (18.12.2023).

91 Accord, *Voluntary Industry Code of Practice to Support the Australian Ban on Testing Cosmetics on Animals*, available at https://accord.asn.au/wp-content/uploads/2021/05/Australian-Ban-on-testing-cosmetics-on-animals.pdf (18.12.2023).

The Australian Code also requires an institution to make arrangements for an **independent external review of the institution** and the operation of its AECs by a panel of external people who are independent of the institution and with appropriate qualifications and experience. These are to be undertaken every four years, with the aim of assisting institutions and their AECs to comply with the requirements of the Code and to ensure that high standards of animal welfare are maintained for all animals used for research and teaching purposes.

State and territory governments **may also constitute animal research authorities for the purpose of investigating the conduct of animal research** more broadly, but also with supervisory oversight functions. In New South Wales, for example, its *Animal Research Act 1985* provides for members of an Animal Research Review Panel to be appointed by the relevant government minister. In addition to investigating and evaluating the efficacy of the Australian Code in regulating the conduct of animal research, its responsibilities include investigating applications and complaints referred to it and arranging for inspections of accredited research establishments.[92]

1.5. India

Chapter IV of India's ***Prevention of Cruelty to Animals Act 1960***[93] **is aimed entirely at animals used for experiments**, setting out legal provisions on the sale and acquisition of animals for research purposes. It establishes an exemption from anti-cruelty provisions of the Act, permitting experiments on animals for the purpose of advancement by new discovery of physiological knowledge which will be useful for saving or prolonging life, alleviating suffering or combating disease, whether of human beings, animals or plants. Chapter IV also provides for the constitution of a committee known as the **Committee for the Purpose of Control and Supervision of Experiments on Animals ("CPCSEA")**, with responsibility for regulating all animal experimentation. This is composed of 23 members, 10 of whom are government officials, 11 researchers from life sciences, one veterinarian, and one animal activist.[94] Although the Animal Welfare Board of India ("AWBI") (also established by the Act) regulates all activities related to animal welfare and cruelty, it is the **CPCSEA which has overall supervisory oversight of the use of animals for scientific research**; it has the ability to authorise, control, regulate and supervise experiments on animals, supported by enforcement powers, including mechanisms to revoke or suspend registration of establishments or breeders.

Subordinate legislation in the form of the *Breeding of and Experiments on Animals Rules 1998* (the "BEA Rules")[95] establish rules requiring establishments engaged in animal breeding or experimentation to register with the CPCSEA. Approval of an establishment is subject to an inspection of the facility by a person nominated by the CPCSEA and the establishment of an **Institutional Animal Ethics Committee ("IAEC"), the equivalent of the IACUC in the United States**. The IAEC's primary duty is to review and approve all research proposals involving small animal experimentation and to monitor experimentation during the study and after completion. For larger animals, proposals need to be submitted with the recommendations of the IAEC to the CPCSEA National Committee for approval.[96]

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92 *Animal Research Act 1985, op. cit.*, sections 9 and 10.

93 *The Prevention of Cruelty to Animals Act, 1960,* available at https://dahd.nic.in/prevention-cruelty-animals-act-1960 (29.01.2024).

94 Syed S.Y.H. Qadri, Subbaraya G. Ramachandra, *Laws, Regulations, and Guidelines Governing Research Animal Care and Use in India,* in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 243.

95 Relevant legislation available at Committee for Control and Supervision of Experiments on Animals, *Acts, Rules and Guidelines,* available at https://ccsea.gov.in/Content/54_1_ACTS,RULESANDGUIDELINES.aspx (03.01.2024).

96 Syed S.Y.H. Qadri, Subbaraya G. Ramachandra, *Laws, Regulations, and Guidelines Governing Research Animal Care and Use in India,* in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 240.

The IAEC is required to ensure compliance with all regulatory requirements. It is composed of 8 members, three of which are nominated by the CPCSEA and the remaining five members by the establishment. The IAEC must submit minutes of meetings and inspection reports to the CPCSEA in accordance with the BEA Rules.

In addition to the general regulation of animal experimentation, it may also be noted that the *Drugs and Cosmetics Rules 1945*[97] have been amended – in June 2013 and again in October 2014 – **banning, respectively, the testing of cosmetics and their ingredients on animals** and the import of cosmetics products that have been tested on animals.

1.6. New Zealand

The legislative framework governing the welfare of animals used in research, testing and teaching in New Zealand is established by Part 6 of the ***Animal Welfare Act 1999*** **("AWA")**[98] **and the *Animal Welfare Amendment Act (No 2) 2015*** **("AWAA").**[99] The AWA requires owners of animals and individuals in charge of animals to attend properly to the welfare of those animals and specifies conduct that is or is not permissible in relation to any animal or class of animals. It sets out a process for the approval of the use of animals in research, testing and teaching. In 2015, the AWAA amended the AWA to prohibit the use of animal testing for the purpose of developing, making or testing a cosmetic or an ingredient that is intended exclusively for use in a cosmetic.

Supervisory oversight is principally undertaken by a committee set up by the establishment in which the research, testing and teaching takes place. This committee, known as an **Animal Ethics Committee ("AEC")** is **constituted under a 'Code of Ethical Conduct' ("CEC")** approved under the AWA by the Director-General for Primary Industries, the public service department of New Zealand responsible for overseeing farming, fishing, food, animal welfare, biosecurity and forestry sectors of New Zealand's primary industries. An AEC committee consists of at least 4 members, three of whom are nominated from organisations separate from the institution that has the licence to carry out the licence testing: a member of the public nominated from the regional or territorial authority to represent the public interest; a veterinarian; a person nominated from an approved welfare organisation under the AWA and a senior member of the staff from the organisation that has the CEC. Animal testing cannot generally take place without prior approval by an AEC, properly constituted under an approved CEC. The **AEC is responsible for monitoring compliance with the conditions of approved projects** and for ensuring that the CEC holder collects and maintains records according to the AWA and CEC.

Although the AEC has significant supervisory responsibility, this is subject to certain checks and balances. For example, there is a **duty on the CEC holder to arrange for periodic independent reviews of itself** and the AEC, appointed by the CEC holder, to be conducted by individuals accredited by the Director-General for Primary Industries. Moreover, the **Director-General has authority, under certain conditions, to revoke approval of a CEC** in circumstances where the CEC holder has failed to comply with the requirements of the AWA.

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97 See at *Drugs and Cosmetics Act and Rules,* as amended up to 31st December, 2016, available at https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/acts_rules/2016DrugsandCosmeticsAct1940Rules1945.pdf (18.12.2023).

98 *Animal Welfare Act 1999*, available at https://www.legislation.govt.nz/act/public/1999/0142/latest/DLM49664.html (18.12.2023).

99 *Animal Welfare Amendment Act (No 2) 2015,* available at https://www.legislation.govt.nz/act/public/2015/0049/latest/DLM5174807.html (18.12.2023).

2. Regulation of alternatives to animal testing

2.1. European law

2.1.1. General legal regulation of alternatives

Identifying alternatives to the testing of animals for scientific purposes is central to European regulation concerning the care and use of animals in research. Alternative test methods that are developed to reduce or replace animal experiments are typically based on either *in vitro* systems, on computer-based models (*in silico*) or a combination of these two.[100] **Historically, the 3Rs principles have been implicit** in the more important rules and procedures governing animal testing. This can be seen in the Council of Europe's ETS 123, as well as in the original 1986 EU Directive (86/609/EEC), which did not explicitly refer to the 3Rs principles. For example, Article 6.1 of ETS 123 imposes an obligation on signatories to the Treaty to pursue non-animal alternatives:

> "*A procedure shall not be performed for any of the purposes referred to in Article 2, if another scientifically satisfactory method, not entailing the use of an animal, is reasonably and practicably available*."[101]

This is accompanied by Article 6.2, aimed at the promotion of alternatives:

> "*Each Party should encourage scientific research into the development of methods which could provide the same information as that obtained in procedures*."[102]

Other Articles of ETS 123 show implementation of the principles of reduction and refinement, albeit again on an implicit basis. **More recently, however, explicit reference to the 3Rs principles** and the use of alternatives to animals in scientific testing **can be seen in European law**. This is no more evident than in the EU's current law on animal testing for scientific purposes - the 2010 Directive - where requirements with regard to implementation of the 3Rs principles feature throughout the text of its articles. Particular emphasis is put on the replacement of animal testing with other methods, as evidenced by the preamble to the Directive:

> "*[…] 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.*"[103]

In the main text of the 2010 Directive itself, the principal requirement on Member States to adopt non-animal alternatives is set out at paragraph 1 of **Article 4 (entitled, "Principle of replacement, reduction and refinement")**:

> "*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 places obligations on Member States with regard to the choice of methods, the first paragraph of which concerns the replacement of procedures involving live animals with other methods:

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100 European Commission – EURL ECVAM , *EU Science Hub - Frequently Asked Questions – General,* available at https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/eurl-ecvam-faqs/frequently-asked-questions-general_en (28.12.2023).

101 ETS 123, *op. cit.*

102 *Ibid.*

103 2010 Directive, *op. cit.*, Recital 10.

"[…] *Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining a result, not entailing the use of a live animal, is recognised under the legislation of the Union.*"

Other provisions of the 2010 Directive which establish specific obligations with regard to alternatives to animal testing include the following:

- **Tasks of the AWB**: one of the tasks that an AWB is required to carry out is to advise staff on the application of the requirement of replacement, reduction and refinement, and to keep it informed of technical and scientific developments concerning the application of that requirement;[104] another is to follow the development and outcome of projects, taking into account the effect on the animals used and identify and advise as regards elements that further contribute to the 3Rs.[105]
- **Project evaluation**: the evaluation of projects by the Member State's competent authority ("CA") for the purpose of providing prior authorisation is required to include: "*an assessment of the compliance of the project with the requirement of the 3Rs principles*."[106] Moreover, one of the areas of expertise required for the evaluation by the CA is, "*the areas of scientific use for which animals will be used, including replacement, reduction and refinement in the respective areas*."[107]
- **Retrospective assessment**: where Member States choose to mandate their CA to carry out a retrospective assessment of projects, the CA is required to evaluate documentation submitted by the user with regard to elements that may contribute further implementation of the 3Rs.[108]
- **Non-technical project summaries**: the requirement on Member States to submit to the European Commission of the EU includes an obligation to provide a demonstration of compliance with the requirement of the 3Rs.[109]

Examples of requirements with regard to the replacement of animals as part of implementation of the 3Rs can also be found in the 2010 Directive in relation to areas not directly concerning animal testing, including accommodation and care, anaesthesia, reuse and minimum requirements for training and education of personnel.

2.1.2. Legal regulation of alternatives in regulatory testing

It is in the field of regulatory testing[110] that legal measures concerning alternatives to animal testing - other than those identified in the 2010 Directive - can be found at the European level. As will be discussed in section 3 of this report, **animal testing is still required both directly and indirectly in a number of areas for regulatory purposes** to assess the safety and/or efficacy of substances/products. These include fields such as pharmaceuticals, chemicals, veterinary medicines, plant protection products and food safety. Alternatives to these conventional testing requirements are sometimes referred to as **new approach methodologies ("NAMs")**, namely any technology, methodology,

104 2010 Directive, *op. cit.*, Article 27(1)(b).
105 2010 Directive, *op. cit.*, Article 27(1)(d).
106 2010 Directive, *op. cit.*, Article 38(2)(b).
107 2010 Directive, *op. cit.*, Article 38(3)(a).
108 2010 Directive, *op. cit.*, Article 39(1)(c).
109 2010 Directive, *op. cit.*, Article 43(1)(b). For more information see section 4.1.1. of the present study.
110 "Regulatory testing" refers to testing undertaken for the purposes of ensuring that something, such as a drug, pesticide, medical device or chemical meets a set of laws, regulations, standards and other rules set by authorities.

approach or combination that can provide information on chemical hazard and risk assessment without the use of animals.[111]

Often, the legally binding texts of EU regulations and directives do not define testing requirements at all, but simply refer to a legal obligation to ensure the safety or efficacy of a substance or product. Thus, a reliance on animal testing often does not result from obligations explicitly contained in the text of EU legal instruments, but rather from what might be labelled '**soft law**' (such as the **application of scientific guidelines)** or, on a case-by-case basis, from **requests by European regulatory authorities** such as the **European Medicines Agency ("EMA") and the European Chemicals Agency ("ECHA")** for information and data as part of licensing or other authorisation processes (see section 3 below). As will be discussed, many of these organisations actively support the implementation of the 3Rs principles and collaborate with proponents of the 3Rs principles to review and update scientific guidelines to ensure that reference is not made to animal tests that are no longer considered appropriate.

Legal provisions aimed at promoting alternatives to animal testing, however, remain cautious. The approach taken by many EU legal instruments which govern regulatory testing is to set out **general provisions which demand that non-animal alternatives be pursued where possible**, while acknowledging that animal testing may sometimes offer the only way of securing the information or data needed. The regulatory language therefore often leaves the possibility for manufacturers and the scientific community to rely on animal testing where deemed necessary. Some of the more notable examples are in the fields of **chemical substances** and **pesticide regulation**.[112]

Arguably, the most important area of EU law in which animal testing data plays a central role is that governing chemical substances. The ***Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation*** **("REACH")**[113] together with the ***Classification, Labelling and Packaging of Substances and Mixtures Regulation*** **("CLP")**[114] apply to all chemical substances. Under REACH, responsibility is placed on registrants to manage the risks from chemicals and to provide safety information on substances. Companies must register the chemical substances they manufacture or import into the EU at more than one tonne per year with the ECHA. A number of its provisions concern **how alternatives to animal testing should be pursued**. Article 13(1) of REACH states:

> "[…] *for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across[115]).*"

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111 Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology*, Volume 4, https://doi.org/10.3389/ftox.2022.964553, at p.1.

112 Other examples of requirements to adopt non-animal alternatives can be found in other regulatory legislation (see section 3 of the present study, below).

113 *Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)*, consolidated version available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02006R1907-20231201 (21.12.2023).

114 *Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures*, consolidated version available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32008R1272 (21.12.2023).

115 "Read across" refers to the practice of using information from similar tested substances to deduce toxicity of a substance which is lacking in data.

Other provisions are designed to **encourage registrants to share data and to avoid duplicating tests** already undertaken. Under Title III of REACH, entitled 'Data sharing and avoidance of unnecessary testing', Article 25(1) states:

> "*In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests.*"

Article 26 requires potential registrants to enquire from the ECHA whether registrations of a substance have already been registered and **prohibits the repetition of studies involving vertebrate animals**. For substances registered within the previous 12 years, Article 27 then requires potential registrants to **request from previous registrants all information relating to vertebrate animal testing** that is required for registration of the substance.

Article 13(2) of REACH **allows the European Commission to propose amendments to REACH Annexes** concerning approved test methods to "*replace, reduce or refine animal testing*." One specific area in which rules contained in REACH have been amended are those concerning skin irritation, skin corrosion, skin sensitisation and phototoxicity. Pursuant to the *Test Methods Regulation 440/2008*,[116] **certain REACH annexes** were amended in 2016 and 2017 after the EU's Reference Laboratory (EURL ECVAM)[117] **validated full replacement of animal test methods in these toxicological areas**. These require NAMs such as *in vitro* testing to be used for obtaining standard toxicological information in certain cases, making non-animal testing the default method.

As will be seen below (see section 3.2.), the REACH Annexes setting out the **standard information requirements** for substances manufactured or imported in increasing quantities **reiterate the need for data from alternative methods to be assessed by registrants before animal tests** are conducted. Typical wording is:

> "[…] *Before new tests are carried out to determine the properties listed in this Annex, all available in vitro data, in vivo data, historical human data, data from valid (Q)SARs*[118] *and data from structurally related substances (read-across approach) shall be assessed first. In vivo testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided. Prior to testing, further guidance on testing strategies should be consulted in addition to this Annex."*[119]

Annex XI gives criteria for adapting the standard information requirements and **waiving new *in vivo* tests**.

To assist manufacturers and importers of substances with responsibilities under REACH and the CLP to keep animal tests to a minimum, the **ECHA has published a practical guide** entitled, '*How to use alternatives to animal testing to fulfil your information requirements for REACH registration'*.[120]

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116 *Council Regulation (EC) No. 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No. 1907/2006 of the European Parliament of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH),* available at https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:142:0001:0739:en:PDF (28.12.2023).

117 The European Centre for the Validation of Alternative Methods of the European Commission's Joint Research Centre, originally founded in 1991, was nominated as the EU Reference Laboratory with the acronym, "EURL ECVAM". For more information, see section 2.1.3. of this study, below.

118 'QSARs' refers to mathematical models to relate chemical structure to bioactivity.

119 REACH, *op. cit.*, Annex VIII.

120 ECHA, *How to use alternatives to animal testing to fulfil your information requirements for REACH registration,* Version 2.0, July 2016, available at

Although not legally binding, this sets out how those applying for registration of chemical substances can avoid unnecessary testing on vertebrate animals while continuing to ensure that sufficient information on the properties of the substances is provided for classification and risk assessment.

Similar regulatory provisions concerning alternatives to animal testing can be found in relation to the **regulation of pesticides and biocides**. A number of up-front data requirements apply with regard to the registration of plant protection active ingredients, including studies to assess potential hazards to humans and non-target organisms.[121] Plant Protection Products ("PPPs") and their active ingredients are regulated under *Regulation (EC) No. 1107/2009* (the "Pesticides Regulation"),[122] with toxicology data requirements (that is, the data required to be provided registrants to assess hazards) set out in *Commission Regulation (EU) No. 283/2013*[123] and *Commission Regulation (EU) No. 284/2013*.[124] Article 62(1) of the Pesticides Regulation requires that,

> "[…] *testing on vertebrate animals for the purposes of this Regulation shall be undertaken only where no other methods are available*. […]"

Similar requirements to those found in REACH with regard to avoiding the duplication of animal testing are also set out in Article 62:

> "*(1)* […] *Duplication of tests and studies on vertebrates undertaken for the purposes of this Regulation shall be avoided* […]*"*
>
> *"(2) Member States shall not accept duplication of tests and studies on vertebrate animals or those initiated where conventional methods described in Annex II to Directive 1999/45/EC could reasonably have been used, in support of applications for authorisations. Any person intending to perform tests and studies involving vertebrate animals shall take the necessary measures to verify that those tests and studies have not already been performed or initiated.* […]"
>
> *"(3) The prospective applicant and the holder or holders of the relevant authorisations shall make every effort to ensure that they share tests and studies involving vertebrate animals*.[…]"

Moreover, Articles 8(1)(d) and 33(3)(c) of the Pesticides Regulation require applicants to provide, for each study involving vertebrate animals, a **justification of the steps taken to avoid animal testing and the duplication of tests and studies** on vertebrate animals.

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https://echa.europa.eu/documents/10162/17250/practical_guide_how_to_use_alternatives_en.pdf/148b30c7-c186-463c-a898-522a888a4404?t=1473948556256 (10.01.2024).

121 Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology, op. cit.,* p.17.

122 *Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC,* consolidated version available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1107-20221121 (28.12.2023).

123 *Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market,* available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02013R0283-20221121 (28.12.2023).

124 *Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02013R0284-20221121 (28.12.2023).

As for the Commission Regulations[125] setting out the **data requirements**, point 5.1 of the Introduction section in their respective Annexes states:

> "*Tests on vertebrate animals shall be undertaken only where no other validated methods are available. Alternative methods shall include in vitro methods or in silico methods. Reduction and refinement methods for in vivo testing shall also be encouraged to keep the number of animals used in testing to a minimum.*"

Point 5.2 **requires the 3Rs principles to be taken into account in the design of methods**, allowing for other validated methods to be used as they become available.

Biocides are regulated separately under *Regulation (EU) No. 528/2012* ("Biocides Regulation"),[126] and its Article 62(1) similarly requires that testing on vertebrates shall be undertaken only as a last resort. Requirements similar to those found in REACH on the sharing of data involving tests on vertebrates are also set out in the Biocides Regulation, with duties on applicants to determine whether such tests or studies have already been submitted to ECHA.

2.1.3. Legally regulated incentives to promote alternatives

EU law does not regulate, as such, specific incentives for promoting alternatives to animal testing. As seen above, the 2010 Directive more generally places obligations on Member States to embrace the 3Rs principles, while REACH and other regulatory legislation requires Member States to ensure that animal testing should be a last resort and that duplication of tests should be minimised. The scientific **development of alternatives** to animal testing, however, **arises outside of requirements contained in the formal legal framework**.

The **2010 Directive, nevertheless, contains a number of provisions which encourage this approach**. For example, for the first time, it required the European Commission and Member States more generally to promote and validate alternative methods. Chapter V of the Directive, entitled 'Avoidance of duplication and alternative approaches' spells this out in clear terms. Its **Article 47 ("Alternative approaches")** 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 or which entail less painful procedures, and they shall take such other steps as they consider appropriate to encourage research in this field.*"

Article 48 and Annex VII of the 2010 Directive also establish the **legal basis of the EU Reference Laboratory,** an organisation with specific responsibility for coordinating and promoting the development and use of alternatives to procedures using animals.[127] The European Centre for the Validation of Alternative Methods of the European Commission's Joint Research Centre, originally founded in 1991, was **nominated as the EU Reference Laboratory with the acronym, "EURL ECVAM".** As mentioned above, one of its key roles is in the field of regulatory testing, where its validation of alternative methods to animal testing has led to their adoption in EU law and other forms of internationally accepted test methods.

According to the 2010 Directive, the **main activities of EURL ECVAM** are:

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125 *Commission Regulation (EU) No 283/2013* and *Commission Regulation (EU) No 284/2013*, *op. cit.*

126 *Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products*, consolidated text available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02012R0528-20220415 (28.12.2023).

127 2010 Directive, *op. cit.*, Annex VII.

- to **promote the development and use of alternatives** in the area of regulatory testing but also in biomedical research;
- to **coordinate at the European level the validation of alternative methods**, also by involving the newly established EU Network of Validation laboratories located in different Member States, and to participate with its own laboratories in the evaluation and validation of test methods;
- to **disseminate information on alternative test methods** through databases and other media;
- to act as a **focal point for information exchange** on development, use and acceptance of methods and to promote dialogue between all relevant players in the field.[128]

The **development of incentives for promoting alternatives to animal testing form a central part of its work**, particularly through its collaboration with the CAs of EU Member States, dialogue with EU agencies and European industry associations.[129] This is, however, beyond the scope of the present study.[130]

One specific area of EU law which may be said to incentivise the promotion of alternatives to animal testing is that of **transparency**. As will be discussed below (section 4.1.1.), Article 43 of the 2010 Directive requires anonymised **non-technical summaries of projects** involving animal testing to be provided on a regular basis by EU Member States to the European Commission. These summaries include information on the objectives of the project, including the harm-benefit assessment and the number and types of animals used and a demonstration of compliance with the 3Rs. This serves to hold those with licences for carrying out animal experimentation accountable for their compliance with promoting the 3Rs and **represents an indirect incentive to explore alternatives** to animal testing.

2.2 Domestic laws of European countries

As mentioned above, Article 2 of the **2010 Directive precludes the introduction of national measures that are stricter** than those contained in the Directive itself. National measures which provide for a higher level of protection than those in the Directive may only be maintained if they were in force on 9th November 2010 and notified to the European Commission. Some national measures regulating animal testing which were in force prior to this date are referred to above, but Article 2 of the 2010 Directive means that there should be **no recent EU Member State laws aimed at alternatives to animal testing which result in stricter protection** of animals than that established by the Directive.[131]

For example, the **2022 changes to the Danish Animal Testing Law** aimed at improving aspects of Denmark's transposition of the 2010 Directive into national law (referred to above)[132] were **expressly acknowledged by Danish legislators as going no further than that required by the 2010 Directive**.[133]

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128 See European Commission – EURL ECVAM, *EU Science Hub - Frequently Asked Questions – General*, *op. cit.,* and 2010 Directive, *op. cit.*, Annex VII, para. 2.

129 These include PARERE-EURL ECVAM Network for Preliminary Assessment of Regulatory Relevance, ESTAF-EURL ECVAM Stakeholder Forum, and the European Partnership for Alternative Approaches to Animal Testing ("EPAA").

130 Some of the latest initiatives are discussed in EURL-ECVAM's 2022 status report, available at https://publications.jrc.ec.europa.eu/repository/bitstream/JRC132525/JRC132525_01.pdf (10.01.2024).

131 This does not preclude the possibility that certain Member State laws go beyond EU measures having failed to properly implement the 2010 Directive, nor is it possible to provide an exhaustive overview of Member State policies and other practices which diverge from requirements under the 2010 Directive.

132 See section 1.2.1. of this study, above.

133 An explanatory note accompanying the draft law confirmed that the proposed changes do not go beyond the obligations arising from the 2010 Directive. See: *Retsinformation, Forslag til Lov om*

Indeed, one of the amendments was a newly inserted provision concerning alternatives to animal testing. This new section 6(4) supplements a long-standing existing clause on the use of alternatives[134] by reinforcing the prohibition on animal testing where the intended results can be achieved without the use of live animals, albeit subject to EU law:

> "*Tests shall not be performed if, in accordance with Union legislation, another method or testing strategy not entailing the use of live animals may be used to obtain the intended results*."[135]

In practice, **much of the progress in the advancement of the 3Rs at the national level is achieved** not by governments through legislative developments but through **the initiatives of national centres for 3Rs.**[136] National 3R centres work with research communities to develop and validate methods to replace animal studies and to support researchers in designing experiments to improve animal welfare.[137] Examples include the Danish 3R Center, the British NC3Rs, the French FC3R and the German Bf3R. These **3R centres promote the use of alternative methods through the publication of guidelines and other voluntary tools**, **but also by way of education and training, communication networks and research initiatives such as prizes and funding** for projects aimed at the development of non-animal methodologies.[138] A list of 3R centres and similar organisations throughout the world can be found on the Danish 3R Center website.[139] Although alternative methods to animal testing developed by 3R centres may, as seen above,[140] be formally validated and ultimately incorporated into legal texts governing regulatory testing, the alternatives developed by 3R centres do not constitute legal regulation, and so are beyond the scope of the present study. Nevertheless, for illustrative purposes, **some examples of initiatives** developed at the national level include:

ændring af lov om dyreforsøg og lov om kloning og genmodificering af dyr m.v. (Supplerende implementering af dyreforsøgsdirektivet), 2021/1 LSF 128 (Gældende), 10th February 2022.

134 *Ibid*, section 6(3). This states "*Animals shall not be used in procedures for which the use of cell, tissue or organ cultures or other methods may be assumed to be equally suitable. The applicant shall demonstrate that the knowledge which may be gained from the performance of procedures cannot be gained, in whole or in part, without the use of animals and that it is not already known."* (Author's translation using DeepL)

135 *Dyreforsøgsloven (Bekendtgørelse af lov om dyreforsøg* LBK nr 1107 af 01/07/2022), *op. cit.*, section 6(4). Author's translation using DeepL.

136 See in relation to the UK, Dunn, R., Brexit: A Boon or a Curse for Animals Used in Scientific Procedures?, *op. cit.*, at p. 8.

137 For example, ZEBET, part of Germany's 3R centre, has developed a non-animal test for phototoxic skin damage which was recognised in 2004 under the OECD Test Guidelines Programme and which has been approved for testing pharmaceuticals by the EMA and US Food and Drug Administration. It is now routinely used worldwide for safety testing of medicines, chemicals and cosmetics: see See Bundesinstitut für Risikobewertung, *Questions and answers on animal experiments, alternative methods and animal experiment numbers, op. cit.,* p. 7.

138 Note the European Commission, *European 3Rs Centres*, available at https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/knowledge-sharing-three-rs/knowledge-networks/european-3rs-centres_en (03.01.2024). See for example, the UK's 3R centre, "NC3Rs", website available at https://www.nc3rs.org.uk/ (03.01.2024); the French Centre FC3R, website available at https://www.fc3r.com/en/ (10.01.2024); the Danish 3R-Center, website available at https://en.3rcenter.dk/ (03.01.2024); the German Centre for the Protection of Laboratory Animals ("Bf3R"), and in particular, the work of the Central Office for the Recording and Evaluation of Alternative and Complementary Methods to Animal Experiments ("ZEBET") which forms part of Bf3R and which researches, develops and validates alternative methods in its own laboratory, see BfR, *Task of the ZEBET*, available at https://www.bfr.bund.de/en/task_of_the_zebet-58194.html (08.01.2024).

139 Danish 3R-Center, *3R Organisations,* available at https://en.3rcenter.dk/3r-organizations (24.01.2024).

140 See section 2.1.2. of the present study, above.

- **Making unpublished results available**: providing a portal for unpublished or negative results of data involving animal testing to promote the sharing of knowledge and information and avoid unnecessary and unethical repetition.[141]
- The **award of prizes** to scientists or groups of scientists affiliated with universities or other organisations who have promoted 3Rs principles.[142]
- **Financial support** for projects promoting alternative methods, including specific methods, such as computer modelling.[143]
- **Development of alternative methods for validation and implementation** as internationally recognised as official test methods in the EU and at the Organisation for Economic Cooperation and Development ("OECD").[144]
- **Development of search engines** for scientists to search alternative methods to animal experiments.[145]

In the field of **regulatory testing**, it can also be seen that EU law in this field is predominantly implemented by way of EU Regulations, such as REACH. Various measures regulating alternatives to animal testing, such as those discussed above, are therefore **directly applicable in all EU Member States**. Although Member State regulatory authorities have licensing, monitoring and control responsibilities with regard to the proper implementation of EU Regulations, there is **limited scope for national laws to legislate further** in fields already covered by an EU Regulation.

That said, **interpretation of EU Regulations** by individual Member States **and** the introduction of **non-legal measures can lead to differences at the national level**. It is reported, for example, that some Member State regulatory authorities responsible for PPPs, including those from the Czech Republic, Sweden and Slovenia, publicly adhere to the legal requirement that studies using vertebrate animals must be justified, whereas others, including those from the Netherlands and – prior to Brexit – the UK, interpret the Pesticides Regulation more strictly, stating that applications will not be considered if they are found to have breached the Article 62 requirement to test on vertebrate animals only as a last resort.[146] Likewise, **measures may exist which indirectly regulate alternatives to animal testing but which are not enshrined in law**, such as the UK Government's policy banning the use of animals in

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141 An example of this can be seen at the FC3R: see FC3R, *Unpublished data*, available at https://www.fc3r.com/en/unpublished-data.php (10.01.2024).

142 This is a common initiative, examples include Denmark (see 3R-prisen - Danmarks 3R-center (3rcenter.dk)) and France (FC3R – Remise de prix).

143 An example of this is an initiative by the French FC3R, see FC3R, *Appel a projets du FC3R – Approches Numeriques*, available at https://www.fc3r.com/files/modalites-fc3r-aap3-modalites-novembre2023.pdf (10.01.2024); in Germany ZEBET is said to fund about ten working groups per year and the Federal Ministry of Education and Research has been funding the development of alternative methods since 1980, with up to 600 projects supported and 190 million euros of funding: see https://www.bfr.bund.de/en/questions_and_answers_on_animal_experiments__alternative_methods_and_animal_experiment_numbers-197057.html (10.01.2024).

144 In Germany, for example, ZEBET has developed a non-animal test for phototoxic skin damage (redness, swelling or blistering). The test is now routinely used worldwide for safety testing of medicines, chemicals and cosmetics that could be exposed to sunlight and thereby alter their effects: see *ibid.*

145 The German Bf3R has developed a search engine based on the freely accessible biomedical literature database PubMed (Medline); its search engine, known as SMAFIRA ("SMArt Feature based Interactive RAnking") is designed to enable scientists to find suitable suggestions for alternative methods to a given animal experiment and moreover, ranks the result of the search: see Bf3R, *SMAFIRA is online!*, available at https://www.bf3r.de/en/smafira_is_online_-297119.html (10.01.2024).

146 Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology, op. cit.,* p.17.

testing finished Household Products, implemented (prior to Brexit) as a mandatory condition of being awarded and retaining a project licence.[147]

2.3. Other jurisdictions

In other jurisdictions outside of Europe, laws aimed at the protection of animals used for scientific purposes can include provisions which specifically concern the promotion and deployment of alternatives to animal testing. Some of these are discussed below. As seen above, legal provisions referring to alternatives can also be found in legislation dealing with regulatory testing in particular scientific fields (discussed in more detail in section 3 of this study, below). A number of examples are identified below in relation to US law, but the fragmented nature and complex requirements of regulatory testing laws means this largely falls outside of the scope of the present study.

2.3.1. United States

The United States Government is recognised for having **provided large amounts of funding for developing alternatives to the use of animals in research**,[148] and inter-agency coordination on this subject reflects a political willingness to develop non-animal testing methods.[149] The *ICCVAM Authorization Act*[150] established the **Interagency Coordinating Committee on the Validation of Alternative Methods ("ICCVAM")** in 2000, composed of representatives from 17 U.S. federal regulatory and research agencies, with aims which notably include the promotion of the 3Rs principles in the field of regulatory testing.[151]

Laws specifically targeted at the regulation of alternatives to animal testing appear to be limited. The amended **Congressional statement of policy** recited at the outset of the AWA acknowledges that methods of testing not using animals continue to be developed which are faster, less expensive and more accurate than traditional animal testing for some purposes and that measures which eliminate or minimise the necessary duplication of experiments on animals can result in more productive use of Federal funds,[152] but there are **no further specific provisions of the AWA aimed at alternatives to animal testing**; indeed, it will be recalled that the AWA prohibits the promulgation of rules related to the design of actual research or experimentation.

Moreover, alternatives to animal testing are not specifically addressed in the PHS Policy nor in the US Government Principles, although several of the principles refer to minimising the numbers of animals

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147 See section 1.2. of this study.

148 The NIH has, since 2008, been funding a major program, *Toxicology in the 21st Century*, which aims to predict the adverse effects of drugs and other chemicals on humans without animal testing: see NIH, *Toxicology in the 21st Century (Tox21)*, available at https://ncats.nih.gov/research/research-activities/Tox21 (22.01.2024).

149 See World Animal Protection Index, *USA – Protecting animals used in scientific research*, available at https://api.worldanimalprotection.org/country/usa (03.01.2024).

150 *ICCVAM Authorization Act of 2000*, available at https://ntp.niehs.nih.gov/sites/default/files/iccvam/docs/about_docs/pl106545.pdf (03.01.2024).

151 See National Toxicology Program, *About ICCVAM*, available at https://ntp.niehs.nih.gov/whatwestudy/niceatm/iccvam (03.01.2024). In 2018, ICCVAM published a strategic roadmap to serve as a guide for agencies and stakeholders seeking to adopt NAMs for chemical safety and risk assessments: see National Toxicology Program, *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*, available at https://ntp.niehs.nih.gov/whatwestudy/niceatm/natl-strategy (03.01.2024).

152 AWA, *op. cit.* section 2131, as amended by Pub. L. 99-198, title XVII, subtitle F, section 1751 under the heading, "Congressional Findings for 1985 Amendment") (see United States Code, 2022 Edition, Title 7 – Agriculture), available at https://www.govinfo.gov/content/pkg/USCODE-2022-title7/html/USCODE-2022-title7-chap54.htm (03.01.2024).

necessary and reducing pain and distress. On the other hand, **the *Guide*, the use of which is required by PHS Policy, does recognise that the 3Rs** have become an internationally accepted approach for researchers considering the use of animals in their research studies[153] and it **specifically endorses the consideration of alternatives** (identified as *in vitro* systems, computer simulations, and/or mathematical models) to reduce or replace the use of animals.[154]

Although specifically identified alternatives to animal testing for scientific purposes are not required by US laws, **some references to the aim of reducing animal experimentation can be found in legislation concerning regulatory testing** as well as in rules promulgated by executive departments and agencies of the federal government of the US and guidance notes produced by those executive departments.

In the ***Toxic Substances Control Act* ("TCSA")**,[155] for example, the equivalent of the EU's REACH Regulation, amendments made in 2016 introduced a new duty to reduce testing on vertebrate animals. Its **section 4(h)**[156] places this requirement mainly on the relevant regulator, the US Environmental Protection Agency (the "EPA"). **Three broad duties are set out**, two of which fall on the EPA: first, to reduce and replace, to the extent practicable, the use of vertebrate animals in the testing of chemical substances or mixtures;[157] and secondly, to promote the development and incorporation of alternative testing methods, including through the development of a strategic plan and a (non-exhaustive) list of NAMs identified by the EPA Administrator. The third obligation rests on the regulated community, namely, to consider non-vertebrate testing methods when performing voluntary testing in circumstances where the EPA has identified an alternative test method or strategy to develop such information.

In **another field of regulatory testing – that concerning pesticides and PPP** – principles and procedures permitting alternatives to animal testing are principally found in **binding rules promulgated by executive departments and agencies of the federal government** of the US under authority delegated by the US Congress. These rules and regulations are codified in the *Code of Federal Regulations* ("CFR").[158] The *Federal Insecticide, Fungicide and Rodenticide Act*[159] requires all pesticides sold or distributed in the US to be registered with the EPA unless otherwise exempted. The Office of Pesticide

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153 See John F. Bradfield and others, *Oversight of Research Animal Welfare in the United States*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 26.

154 *Ibid*, at p. 59.

155 *Toxic Substances Control,* as contained in Chapter 53, United States Code, available at https://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53&edition=prelim (03.01.2023).

156 Found at section 2603(h) of the United States Code, *ibid.*

157 Specifically, by: "*(A) prior to making a request or adopting a requirement for testing using vertebrate animals, and in accordance with subsection (a)(3), taking into consideration, as appropriate and to the extent practicable and scientifically justified, reasonably available existing information, including—(i) toxicity information; (ii) computational toxicology and bioinformatics; and (iii) high-throughput screening methods and the prediction models of those methods; and (B) encouraging and facilitating—(i) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under this subchapter; (ii) the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category; and (iii) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests, provided that such consortia make all information from such testing available to the Administrator*."

158 *Code of Federal Regulations*, available at https://www.ecfr.gov/ (17.01.2024).

159 *Federal Insecticide, Fungicide, and Rodenticide Act* ("FIFRA 7 USC section 136), available at https://www.govinfo.gov/content/pkg/USCODE-2022-title7/pdf/USCODE-2022-title7-chap6.pdf (03.01.2024).

Programs ("OPP")[160] has delegated authority from the EPA for pesticide evaluation and registration. Data requirements for pesticide registration are, however, laid out in Part 158 of Title 40 of the CFR.[161] These **allow for waivers to be granted by the OPP in relation to data requirements placed on registrants of pesticides** so long as there are sufficient data to make the determinations required by the applicable statutory standards.[162] Where data requirements typically based on animal testing must be met to register a pesticide, the **OPP has developed its own guidance**[163] describing how animal studies can be avoided by waiving animal testing requirements and/or apply existing toxicological data for similar substances (known as "bridging").[164] Furthermore, with regard to satisfying data requirements, paragraph 158.70(e) of the CFR states that certain toxicology studies may be combined to reduce usage of test animals, citing the example of carcinogenicity studies in rats and rat chronic toxicity studies.

By way of comparison, it may be noted that in **Canada**, the relevant regulator, the Pest Management Regulatory Agency ("PMRA"), is afforded even greater flexibility with regard to the testing methods needed to produce data for the registration of pest control products because specific data requirements are not prescribed in legislation. Although its *Pest Control Products Act*[165] provides the overarching components for assessments (such as health, environment and value), it also provides for policy instruments and guidance documents to set out specific data requirements. This is reported as having allowed the PMRA to take an active role in the development of NAMs, adapting and adopting as part of their implementation for regulatory standards, and in collaboration with stakeholders.[166]

2.3.2. India

We are **not aware of any particular regulation of alternatives to animal testing for scientific purposes** in India, although it is reported that ethical concern and laboratory animal welfare is gaining more importance, in part, due to the strict guidelines established by the regulatory authority, the CPCSEA.[167] Although there is **no explicit reference to the 3Rs principles**, India's BEA Rules were amended in 2001 and again in 2006, with one requirement being that those conducting animal experiments should first consider using animals "*lowest on the phylogenetic scale*", that they should use the minimum number of animals necessary to achieve 95% statistical confidence and that they must provide justification for

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160 The Office of Pesticide Programs, see EPA, *About the Office of Chemical Safety and Pollution Prevention,* available at https://www.epa.gov/aboutepa/about-office-chemical-safety-and-pollution-prevention-ocspp#opp (03.01.2024)

161 CFR, Title 40, Chapter I, Subchapter E, Part 158, available at https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158?toc=1 (17.01.2024).

162 *Ibid*, para. 158.45.

163 OPP, *Guiding principles for data requirements,* 31st May 2013, available at https://www.epa.gov/sites/default/files/2016-01/documents/data-require-guide-principle.pdf (17.01.2024).

164 CFR, Title 40, Chapter I, Subchapter E, Part 158*, op. cit.,* para. 158.70(e). See Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology, op. cit.,* p.12.

165 *Pest Controls Products Act* (S.C. 2002, c. 28), available at https://laws-lois.justice.gc.ca/eng/acts/p-9.01/ (16.01.2024).

166 Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology, op. cit.*, pp. 15-16.

167 Bayne, K. Ramachandra G.S., Rivera E.A., Wang, J., The evolution of animal welfare and the 3Rs in Brazil, China and India, *J Am Assoc Lab Anim Sci*, 2015; 54(2): 181-191.

not using non-animal alternatives.[168] Other legal measures aimed at regulating alternatives to animal testing may be found in laws dealing with regulatory testing in specific scientific fields, but this is beyond the scope of the present study.

2.3.3. Australia

Although differences exist between the laws of the states and territories of Australia, the **common adoption of the Australian Code** means that the overall framework and central principles applying to animals used for scientific purposes are broadly the same.[169] The Australian Code emphasises from the outset the **importance of using animals only when justified and applying the 3Rs at all stages of animal care and use**.[170] The provision of the Australian Code implementing the replacement element of the 3Rs principles is **expressed in broad terms** and forms part of the general governing principles section of the document, but nevertheless **sets out some of the replacement techniques** which should be considered:

> "*1.18 Methods that replace or partially replace the use of animals must be investigated, considered and where applicable, implemented.*
>
> *1.19 Before the use of animals is considered, all existing information relevant to the proposed aim(s) including existing databases, must be examined. Replacement techniques that must be considered include the use of epidemiological data; physical and chemical analysis; computer, mathematical and inanimate synthetic models; simulations; in vitro systems; non-sentient organisms; cadavers; and clinical cases. […]*"[171]

As a largely self-regulatory system, however, it should be noted that much of the responsibility for applying the Australian Code and approving animal use, as opposed to non-animal alternatives, lies with the animal ethics committee of an institution ("AEC"). It is possible that **more detailed regulation of alternatives to animal testing may be found at this institutional level or as part of state or territorial laws**.

2.3.4. New Zealand

Similarly, the treatment of alternatives to animal testing in New Zealand is, in its animal welfare legislation, **limited to general principles embracing the 3Rs** and encouraging the replacement of animal testing where possible. In particular, the AWA states that one of the purposes of its regulation of the use of animals in research, testing and teaching is to promote efforts to replace animals as subjects for research, and testing by substituting, where appropriate, non-sentient or non-living alternatives and to replace the use of animals in teaching by the same methods or by imparting the information in another way.[172] The AWA also **provides AECs with considerable discretion** when determining applications for the approval of a project involving animals; one of the matters listed by the AWA, introduced in 2015, to which an AEC must have regard, is a **consideration of alternatives**, namely:

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168 BEA Rules, *op. cit.*, newly inserted rule 9(bb), pursuant to *The Breeding of and Experiments on Animals (Control and Supervision) Amendment Rules, 2006*, available at https://ccsea.gov.in/WriteReadData/userfiles/file/2006.pdf (04.01.2024), rule 3(1).

169 Denise Noonan and Virginia Williams, *Laboratory Animals Regulations and Recommendations: Australia and New Zealand*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.*, p. 381.

170 The Australian Code, *op. cit.*, sections 1.1 and 1.5.

171 The Australian Code, *op. cit.*, sections 1.18 and 1.19.

172 AWA, *op. cit.*, section 80(2)(b)

"[…] *the extent to which there has been –*

(i) assessment of the suitability of using non-sentient or non-living alternatives in the project; and

(ii) replacement of animals as subjects with suitable non-sentient or non-living alternatives […]"[173]

Two other factors an AEC must take into account which may have relevance to alternatives to animal testing are: whether the project involves the unnecessary duplication of an experiment on animals;[174] and the extent to which there is a commitment to ensuring that the findings of any experiment will be adequately used, promoted or published – potentially avoiding future duplication of the same experiment.[175]

3. Regulatory testing

3.1. Overview

As discussed above, considerable progress has been made in recent decades in the development of alternatives to animal testing, and laws and scientific guidelines in the EU, US and other countries increasingly encourage non-animal methods to be adopted where appropriate. Notwithstanding overarching legislation - such as the 2010 EU Directive - specifically aimed at reducing animal testing across all sectors, **there are still laws, requirements and/or international treaties applying to particular sectors, such as chemical substances or medicines, which directly or indirectly require animal testing**. Commonly referred to as 'regulatory testing', these legal instruments set out requirements for assessments of the safety of producing, placing and maintaining products or substances on the market. Manufacturers, importers, suppliers of products must provide relevant regulators, such as the ECHA, with sufficient information to allow them to assess the risks such products or substances may pose to consumers, workers or the environment.[176] This may also include information to demonstrate that the product is effective for its intended purposes, particularly for medicines and vaccines.

In many cases, the only type of safety and efficacy information acceptable to regulators is that obtained from tests on animals. The requirement for such data may be set out explicitly in the law applying to the particular sector in question. Some examples of these direct requirements will be provided below.[177] Usually however, **legal instruments are not detailed enough to cover all possible testing requirements** for different types of products. Instead, regulators and other authorities produce **technical guidance documents** to assist manufacturers and suppliers to comply with the law as part of a standardised approach to testing. These establish detailed guidance on which tests should be done and how the results should be interpreted. Although, as will be seen, these often facilitate and

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173 *Ibid*, section 100(1)(fa).

174 *Ibid*, section 100(j).

175 *Ibid*, section 100(l).

176 Royal Society for the Protection of Cruelty to Animals, *Animal Testing and the Regulation of Chemicals and Products: an RSPCA information paper*, 2010, available at https://science.rspca.org.uk/documents/1494935/9042554/Animal+testing+and+the+regulation+of+chemicals+%282010%29.pdf/34b47084-ef3a-e122-4723-d732ed45a519?version=1.0&t=1553171380222&download=true (11.01.2024).

177 See R.A.A. Vonk et al., *Legal Barriers for the use of alternatives to animal testing: do current EU regulations and guidelines for regulatory acceptance of medicinal products pose legal barriers?*, National Institute for Public Health and the Environment, Letter Report 2015-0084, 2015, Netherlands, available at https://www.rivm.nl/bibliotheek/rapporten/2015-0084.pdf (11.01.2024), at pp.21-37.

encourage the replacement of animal testing with alternative methods, **such guidelines still frequently refer to, require and/or set standards for animal tests**.[178] Those seeking licensing or other authorisation for a product or substance will often need to provide sound justification for departing from the recommended methods. While not amounting to a formal legal barrier to using non-animal alternative methods, this **can, in reality, make it necessary to undertake tests on animals**.[179]

Experimentation on animals for regulatory purposes continues to represent a significant proportion of all animal testing undertaken. In Europe, the latest statistics[180] from the European Commission on the use of animals for scientific purposes across all Member States of the EU and Norway shows that **regulatory use accounts for 17%** (or 1.4 million out of 8.05 million uses) of all uses of animals for research and testing conducted in 2020; but when considering **severe**[181] **uses of animals, this percentage rises to 32%.**

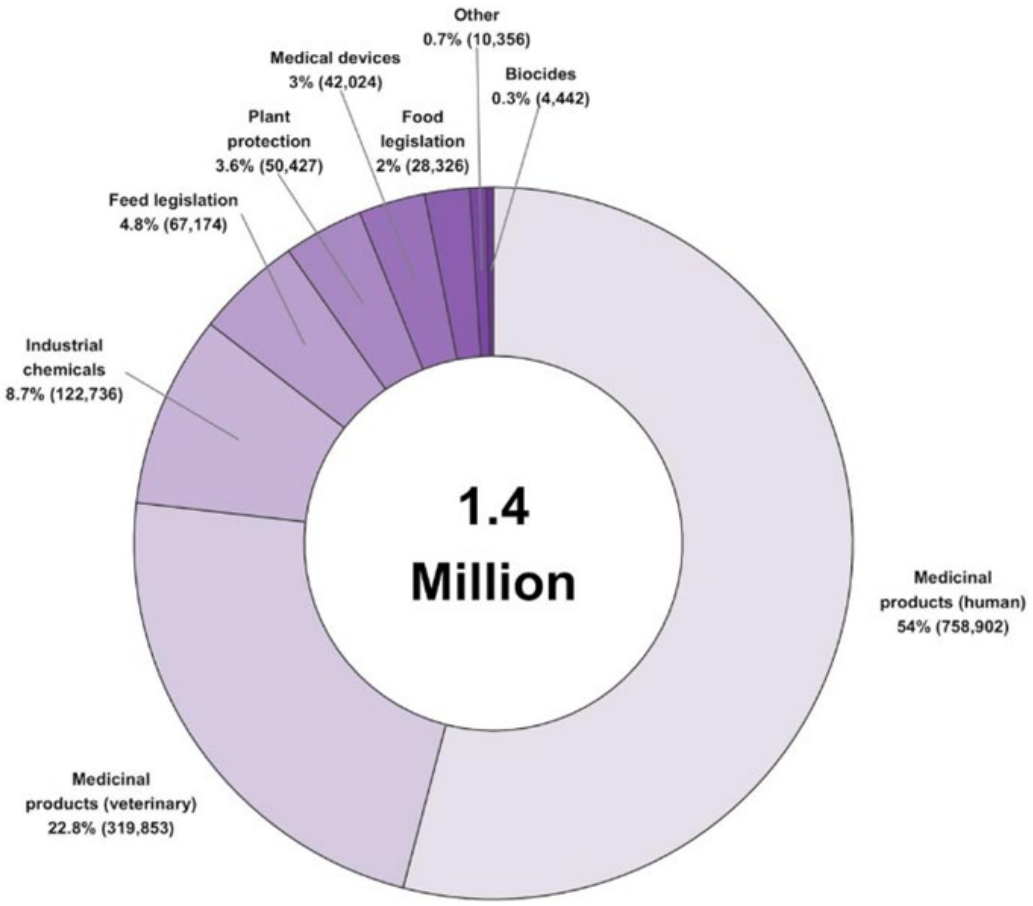
Testing undertaken to satisfy the regulatory requirements applying in different sectors varies considerably; the uses of animals across EU Member States and Norway in 2020 to satisfy regulatory requirements of specific sector legislation are illustrated on the following page.*

178 *Ibid*, at p. 29.

179 Beyond the legal framework, however, it is worth noting that some of the most important barriers to implementation of the 3Rs lie with the current state of scientific knowledge. Most available alternative test methods measure only a single toxic effect and not more complex systemic effects. For this reason, animal tests cannot be replaced by a single alternative method. Before a method can be used for regulatory purposes, it must be validated and entered into official test guidelines by the OECD. Although EURL-ECVAM has successfully validated full replacement methods in the toxicological areas of skin irritation, skin corrosion, skin sensitisation and phototoxicity, the validation of alternative methods remains a slow and expensive process: see Vanessa Zainzinger, *Can animal testing be replaced?*, in C&EN, 2022, 100(28), pp 26-31, August 15th 2022.

180 European Commission, *Commission Staff Working Document – Summary Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union and Norway in 2020*, Part 1/2, SWD(2023) 84 final, Brussels, 31.3.23, available via https://circabc.europa.eu/ui/group/8ee3c69a-bccb-4f22-89ca-277e35de7c63/library/10ad28d6-e17e-4367-b459-20883402cfcc/details?download=true (11.01.2024), p. 10, figure 4.

181 'Severe' meaning animals which have undergone a procedure as a result of which the animals have experienced severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress as well as procedures, that have caused severe impairment of the well-being or general condition of the animals: see 2010 Directive, *op. cit.*, Annex VIII.



* European Commission, *Commission Staff Working Document – Summary Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union and Norway in 2020*, *op. cit.*, Figure 4, p. 10.

The European Commission's statistical report states that **95% of regulatory uses of animals** by EU Member States (and Norway) continue to be performed **to comply with regulatory requirements originating from EU, rather than domestic legislation**.[182] These will therefore be the focus of the present enquiry with regard to regulatory testing among European states.

Examples of legal requirements and the continuing regulatory uses of animals across a selection of different sectors will be examined in more detail below, with particular reference to EU law.[183]

3.2. Chemical substances

Two key pieces of EU legislation, **the REACH and CLP Regulations, form the central pillar of the EU's regulatory system**, applying to all chemical substances. Other sector-specific laws impose additional rules on the chemicals that can be used in particular products, such as pesticides, cosmetics, medicines and foods; some of their requirements are examined below. This complex regulatory framework can

182 *Ibid,* p.10.

183 Note that this does not represent a comprehensive nor exhaustive overview of all sectors in which regulatory testing on animals is undertaken but is used to illustrate the areas in which animal testing is a feature and the types of legal and other regulatory measures which can render it mandatory.

lead to different information and data requirements across sectoral legislation as well as the methods available for generating and/or gathering the evidence.[184]

Under REACH, **companies are required to register substances** that they manufacture or import into the European Economic Area ("EEA") in quantities of more than one tonne by submitting a dossier with information about the properties and hazards of the substance. **The CLP requires companies to classify, label and package their hazardous chemicals correctly** before placing them on the market.

As discussed above (see section 2.1.2.), REACH plays a role in keeping animal testing to a minimum by requiring that such *in vivo* testing can only be used to meet registration requirements as a last resort and by facilitating data sharing of testing results. At the same time however, information requirements for a chemical are increased as production volumes increase and **REACH generally requires *in vivo* tests for chemicals produced in volumes of more than 10 metric tons per year**.[185] Although non-animal testing is the default method for skin sensitization, skin corrosion or irritation and serious eye damage or eye irritation, testing for most other health effects still requires data from animal testing.[186] Those seeking registration can often produce the required animal testing information with reference to toxicity information from similar tested chemicals (known as 'read across'), but this is often not possible.

Although the introduction to the standard toxicological information required of registrants expressly states that alternative existing information (including "*in vitro* data, *historical human data, data from valid (Q)SARs and data from structurally related substances (read-across approach) shall be assessed first* […],") **frequent reference to the need for *in vivo* testing**, particularly in relation to the manufacture or import of 100 and 1000 tonnes or more of chemical substances each year, can be found in the text of the REACH Annexes.[187] In particular, where negative results have been obtained from what are known as 'pre-validated methods' based on *in vitro* methods, they must be confirmed with the relevant *in vivo* tests set out in the REACH Annexes. As the ECHA's own guide to using alternatives to animal testing states:

> "*Alternative test methods such as in vitro tests are continuously being developed and REACH standard information requirements are constantly being adapted. Yet, many of the information requirements, especially for the chemicals registered in high tonnages, rely on standard test methods using vertebrate animals as a model to predict the effects of chemicals on humans and the environment.*"[188]

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184 Cattaneo, Irene and others, Implementing New Approach Methodologies (NAMs) in food safety assessments: Strategic objectives and actions taken by the European Food Safety Authority, *Trends in Food, Science and Technology*, 133 (2023) 277-290 at p. 278.

185 See ECHA, *Information requirements,* available at https://echa.europa.eu/regulations/reach/registration/information-requirements (15.01.2024). Information requirements are mainly set out in Annexes VI to XI of REACH. The types of tests required for a chemical depend on the quantity of the chemical placed on the market, with requirements increasing across defined ranges: 1-10 tons/year (Annex VII), 10-100 tons/year (Annex VIII), 100-1000 tons/year (Annex IX) and more than 1000 tons/year (Annex X).

186 Vanessa Zainzinger, *Can animal testing be replaced?*, *op. cit.*

187 *Ibid*, Annexes IX and X. Moreover, the REACH Regulation is supported by the *Test Methods Regulation 440/2008 (op. cit.*), setting out the OECD Test Guidelines and other testing methods on which animal testing is to be based. This contains numerous references to the conduct of *in vivo* testing.

188 ECHA, *How to use alternatives to animal testing to fulfil your information requirements for REACH registration, op. cit.*, p. 6.

Likewise, the **Annexes of the CLP Regulation make frequent reference to *in vivo* testing** as the principal method for producing required information.[189] In Annex I concerning the 'Classification and Labelling Requirements for Hazardous Substances and Mixtures', the need for *in vivo* testing can be found particularly in relation to the criteria to be satisfied for classification of substances according to their hazards. Although data requirements are not drafted in a way such that *in vivo* data is mandatory, many criteria are based on information extracted from animal studies, rendering animal testing the principal method by which to satisfy many of the requirements.[190]

It should also be noted that, as mentioned above (section 3.1.), many of the obligations to conduct animal testing are not found in the text of EU law, but rather as **a requirement imposed by the relevant regulator on a case-by-case basis**. With regard to the manufacture or import of chemical substances, it is reported that there is an increasing number of cases where the ECHA, following compliance checks of submitted dossiers, is asking companies to conduct animal testing where, in the original submissions, it was deemed scientifically feasible to use non-animal methods for meeting REACH information requirements.[191] However, a **decision of the European Court of Justice ("ECJ")** in recent years has changed how some registrants and chemicals manufacturers respond to requests from the ECHA to generate new animal data: in a 2021 case before the ECJ,[192] the court ruled in favour of *Esso Raffinage,* which had been required by the ECHA to conduct a developmental toxicity study on animals to fill a gap in its data. Esso had argued that it could avoid animal tests by demonstrating the safety of its chemical using evidence from other sources, but the ECHA refused this option. Finding in favour of Esso, the **ECJ ruled that under REACH legislation, animal tests must only ever be carried out as a last resort**, emphasising that this principle applies even after the ECHA has made a decision that animal tests must be carried out.[193] The ECHA also has a duty to consider alternatives put forward by registrants at this stage.

Finally with regard to the EU, it **had been expected that REACH would be reviewed** as part of the EU's 2020 Green Deal and the new EU Chemicals Strategy for Sustainability ("CSS"), leading to an extension of their scope and a potential increase in the use of animal testing. However, these proposals have been left out of a copy of the European Commission's 2024 work programme announced towards the end of 2023 and are understood to no longer be going ahead.[194] **Proposed amendments to the CLP Regulation**, on the other hand, are anticipated to go ahead and are expected to be formally adopted by the European Parliament and Council. These include changes to the legal texts aimed at reducing reliance on animal testing. This is discussed in more detail below (see section 5).

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189 See CLP, *op. cit.*, Annex I. For example: Part 3 Health Hazards, paras. 3.1.2.1., 3.5.2.1., Table 3.5.1.

190 For human health hazards for example, the ECHA states that no *in vitro* tests or Q(SAR) predictions can currently fully replace toxicology studies performed to characterise the health effects of chemicals for a number of endpoints; this limits the alternative data that can be relied on as an alternative to animal testing: see ECHA, *The role of testing in CLP*, available at https://echa.europa.eu/testing-clp (16.01.2024).

191 Julia Fentem and Ors, Upholding the EU's Commitment to 'Animal Testing as a Last Resort' Under REACH Requires a Paradigm Shift in How We Assess Chemical Safety to Close the Gap Between Regulatory Testing and Modern Safety Science, *Alternatives to Laboratory Animals*, Volume 49, Issue 4, July 2021, Sage Journals, Pages 122-132.

192 European Court of Justice, *Judgment of the Court (Third Chamber) 21 January 2021.* Case C-471/18, P – *Germany v Esso Raffinage*, available at InfoCuria, see https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:62018CJ0471 (15.01.2024).

193 *Ibid*, paras. 135 to 139.

194 Guardian Newspaper, *EU abandons promise to ban toxic chemicals in consumer products*, 16th October 2023, available at https://www.theguardian.com/environment/2023/oct/16/eu-abandons-promise-ban-toxic-chemicals-consumer-products (15.01.2024).

As to **regulatory testing of chemical substances in the United States**, legislative provisions of the *Toxic Substances Control Act* ("TSCA")[195] do not contain animal testing requirements for toxicity.[196] This does not preclude the possibility of the relevant regulator, the EPA, from ordering testing on animals, but as noted above (see section 2.2.), the revised TSCA imposes a new requirement on the EPA to reduce testing on vertebrate animals.

3.3 Cosmetic products

As discussed above, substances used in cosmetic products are subject to an animal testing ban under the Cosmetics Regulation (see section 1.1.2.3.). However, those **same substances may need to be registered under REACH** in certain cases, meaning that testing on animals could be required by the ECHA.

First, registrants of **substances that are used for a number of purposes, and not solely in cosmetics**, may be required to perform animal testing, as a last resort, in relation to human health. This is because the Cosmetics Regulation allows *in vivo* tests for assessing cosmetic safety if tests are performed for a non-cosmetic purpose – known as a dual use. Most cosmetic ingredients have a dual use in other industries, such as in pharmaceuticals or as food/feed ingredients. Secondly, as discussed above, REACH requires registration dossiers for all chemicals (including cosmetic ingredients) that are manufactured in or imported into the EU in a quantity of one ton per year. Although cosmetic ingredients are exempted from a full chemical safety assessment for consumer exposure, they are **not exempted in relation to worker exposure** during the manufacture of the ingredient or the final cosmetic product. The ECHA therefore acknowledges that new *in vivo* tests may need to be performed on a cosmetic ingredient to fulfil the REACH requirement for risk assessment for worker exposure. Thirdly, registrants may be permitted to perform animal testing, as a last resort, **in relation to what are referred to as 'environmental end points' –** namely the adverse environmental effects which may occur depending on the type and duration of use of the cosmetic ingredient.[197]

Although REACH demands that registrants use animal testing on chemical substances as a last resort, the ECHA can, as discussed above, require animal testing to be conducted on certain substances in individual cases as part of registration requirements. That such an obligation can be placed on a registrant even in relation to cosmetic ingredients has been **illustrated in recent case law** before the ECJ.[198] In 2018, the German company, Symrise AG, challenged the ECHA's request to test two ingredients in its sunscreen product on 5,500 animals, refusing to carry out further animal testing that undermines the Cosmetics Regulation ban. Confirming the ECHA's position, the **ECJ ruled in November 2023 that ingredients used exclusively in cosmetics may be tested on animals under REACH to assess the risks to workers' health** arising from exposure to the substance in question.[199]

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195 *Op. cit.*

196 Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology, op. cit*.,

197 ECHA, *All news – clarity on interface between REACH and the Cosmetics Regulations*, October 2014, available at https://echa.europa.eu/de/-/clarity-on-interface-between-reach-and-the-cosmetics-regulation (15.01.2024).

198 European Court of Justice, *Judgment of the Court (First Chamber) 22 November 2023.* Case T-655/20, *Symrise AG v ECHA*, available at InfoCuria: https://curia.europa.eu/juris/document/document.jsf?docid=279983&doclang=EN (15.01.2024).

199 See Eurogroup for animals, *Court of Justice of the European Union ruling exposes limitations of cosmetics animal testing ban*, 24th November 2023, available at https://www.eurogroupforanimals.org/news/court-justice-european-union-ruling-exposes-limitations-cosmetics-animal-testing-ban (15.01.2024).

3.4. Pesticides

Requirements to produce data typically based on animal testing can be found in regulatory laws concerning pesticides in both the EU and the US.

In the EU, data requirements for the registration of plant protection active ingredients are listed in *Commission Regulation (EU) No. 283/2013* and *Commission Regulation (EU) No. 284/2013* (see section 2.1.2. above). Although, as discussed, the Pesticides Regulation requires testing on animals to be undertaken only where no other methods are available, many of the data requirements contained in the Commission Regulations are **drafted in a way which make *in vivo* data mandatory**.[200] Notwithstanding introductory provisions which state that tests on vertebrate animals must be undertaken only where no other validated methods are available,[201] the testing requirements, particularly in relation to toxicology and metabolism studies make frequent reference to *in vivo* testing.[202]

In the US, FIFRA[203] and its implementing regulations require substantial 'upfront' testing to register a pesticide. Reference to data requirements based on animal studies feature throughout FIFRA and the regulations set out in the CFR, making animal testing the standard method in many cases.[204] As discussed above however (section 2.3), the relevant regulator, the OPP, is given considerable discretion to make registration decisions based on data that it deems most relevant and processes have been developed to allow studies involving animals to be waived.[205]

3.5. Medicinal products

3.5.1. European Union

In the EU, the relevant rules for marketing authorisation of medicinal products for human use are found in *Directive 2001/83/EC* (the "**Medicinal Products Directive**").[206] For veterinary medicinal products, *Regulation (EU) 2019/6* applies (the "**Veterinary Medicinal Products Regulation**"), although the following will focus on the Medicinal Products Directive.[207] Additional EU legislation provides

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200 See, with regard to food, Cattaneo, Irene and others, Implementing New Approach Methodologies (NAMs) in food safety assessments: Strategic objectives and actions taken by the European Food Safety Authority, *Trends in Food, Science and Technology*, 133 (2023) 277-290, Table 1 at p.279

201 See section 2.1.2. of the present study, above.

202 See, for example, *Commission Regulation (EU) No. 283/2013, op. cit.,* Annex, Part A ('Chemical Active Substances'), section 5.

203 See section 2.3. of the present study, above.

204 See Code of Federal Regulations, *Part 158 – Data requirements for pesticides*, available at https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158 (17.01.2024).

205 Andreas O. Stucki and others (2022), Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health, *Frontiers in Toxicology, op. cit.*, p.13

206 *Consolidated text: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02001L0083-20220101 (16.01.2024). Also regulating procedures for the authorisation and supervision of medicinal products for human use is *Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004R0726-20220128 (16.01.2024).

207 *Consolidated text: Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC,* available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02019R0006-20220128 (17.01.2024).

common rules for the conduct of clinical trials and other rules addressing particularities of certain types of medicinal product. It should be noted that the **European Commission has, on 26th April 2023, adopted a proposal for a new Directive and a new Regulation** to revise and replace the existing general pharmaceutical legislation (see section 5 below).[208]

No medicinal product may be placed on the market without marketing authorisation, and applicants must provide detailed information to authorities about the pharmacological and toxicological effects of a product as well as satisfying requirements for demonstrating that the medicine works as intended. **Frequent reference to data points based on animal testing can be found in the Annexes of the Medicinal Products Directive** with regard to the information to be supplied to apply for marketing authorisation.[209] However, the Medicinal Products Directive – like other EU regulatory legislation - **does not contain any formal legal barrier to using alternative methods** to animal tests.

Test methods are contained principally in guidance documents issued by the relevant regulator, the European Medicines Agency ("EMA").[210] **The guidelines contain frequent reference to animal testing methods** as the standard method for meeting certain data requirements in relation to human[211] and veterinary[212] medicinal products. Moreover, the guidelines adopt many standards in relation to the quality control of certain medicinal products contained in the **European Pharmacopoeia monographs ("Ph. Eur.")**, and **animal testing methods are also a common feature of these scientific standards**.[213] Published pursuant to the adoption by the Council of Europe of the *Convention on the Elaboration of a European Pharmacopoeia*,[214] the Ph. Eur. is the **primary source of official quality standards for medicines and their ingredients in Europe**.[215]

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208 See European Commission, *Reform of the EU pharmaceutical legislation*, 26th April 2023, available at https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en#:~:text=26%20April%202023&text=The%20proposal%20adopted%20by%20the,2000%2FEC%20%2C%20respectively (17.01.2024).

209 For example: (1) in Annex I, part I, module 4, paragraph 4.2.3e concerning reproductive and development toxicity, it is stated that, "[…]*Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent* […]"; (2) in Annex I, part I, module 5, para. 5.2b, it states, "*Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex* […]".

210 Some of the guidelines reproduce those of the *International Council of Harmonisation of Technical Requirements for Pharmaceuticals in Human Use* ("ICH"), originally a cooperative platform of the EU, US and Japan aimed at guaranteeing the safety, efficacy and quality of medicinal products. See ICH, *ICH Guidelines*, available at https://www.ich.org/page/ich-guidelines (26.01.2024).

211 EMA, *Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs,* 18th October 2018, available at https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-providing-overview-current-regulatory-testing-requirements-medicinal-products-human-use-and-opportunities-implementation-3rs-first_en.pdf (17.01.2024).

212 EMA, *Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs,* 21st June 2018, available at https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-providing-overview-current-regulatory-testing-requirements-veterinary-medicinal-products-and-opportunities-implementation-3rs_en.pdf (17.01.2024).

213 Ph. Eur. standards provide a scientific basis for the quality control of a product throughout its life cycle, supporting the pharmaceutical industry and healthcare systems.

214 *Convention on the Elaboration of a European Pharmacopoeia,* Strasbourg, 22.7.1964, available at https://rm.coe.int/168006ff4c (17.01.2024).

215 These apply in relation to certain medical products such as vaccines and hormones with regard to the quality standards of dossiers in which an application for marketing authorisation is contained, and their

As discussed in the overview above (section 3.1.), most of the scientific guidelines are not legally binding but **registrants/applicants are unlikely to secure approval from the relevant regulator if they fail to follow them**.[216] Moreover, the Ph. Eur. standards are of a legally binding character, as recognised by the EU as a signatory party to the *Convention on the Elaboration of a European Pharmacopoeia*, along with 37 Council of Europe member states.

Despite animal studies often representing the standard method for satisfying EMA requirements, applicants are informed that in the relation to the prescribed tests, they may deviate from the guidelines as long as they are able to provide data or argumentation which shows that a 3R approach offers an equivalent level of quality, safety or efficacy.[217] Moreover, editions of the Ph. Eur. in recent decades have shown a clear commitment to the reduction of animal use in accordance with ETS 123 and the 2010 Directive. In particular, the **option to use validated alternative test methods is established as a general principle** and many animal tests have, over time, been replaced with *in vitro* and other alternative methods, or removed after review of historical data.[218] However, validated alternative test methods must show equivalent compliance to the monograph standards and, in general, can only become a pharmacopeial method after exhaustive validation often performed in international standardisation studies.[219] In practice, the **time and expense of validation means that traditional animal testing for certain quality standards often continues to remain as the default method**.

3.5.2. United States

In the US, various **testing of new medicines on animals, until recently**, derived from a mandatory requirement in the original 1938 version of the *Federal Food, Drug and Cosmetic Act* ("FFDCA") that **potential drugs be tested for safety and efficacy in animals**. However, the **FFDCA was amended in December 2022** by what is termed the '*Food and Drug Administration Modernization Act 2.0*'[220] to make it clear that the definition of a nonclinical test or study under the FFDCA includes adjunct and complementary testing methods alongside animal testing. A nonclinical test is defined in the revised FFDCA as follows:

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legally binding character is recognised by the EU as a signatory party as well as 37 Council of Europe member states.

216 The EMA itself describes the guidelines as a, "[…] *harmonised Community position which, if they are followed by relevant parties such as applicants, marketing authorisation holders, sponsors, manufacturers and regulators will facilitate assessment, approval and control of medicinal products in the EU*." See EMA, *Status of EMEA scientific guidelines and European pharmacopoeia monographs and chapters in the regulatory framework applicable to medicinal products*, 11 September 2008, EMEA/42371/2008, available at https://www.ema.europa.eu/en/documents/scientific-guideline/status-emea-scientific-guidelines-and-european-pharmacopoeia-monographs-and-chapters-regulatory-framework-applicable-medicinal-products_en.pdf (16.01.2024).

217 EMA, *Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs, op. cit.*, p. 3. It should be noted that the EMA supports the implementation of the 3Rs principles with regard to the use of animals in medicine testing, and the guidelines are frequently reviewed to ensure that they do not make reference to animal tests that are no longer considered appropriate.

218 R.A.A. Vonk et al., *Legal Barriers for the use of alternatives to animal testing: do current EU regulations and guidelines for regulatory acceptance of medicinal products pose legal barriers?, op. cit.*, pp. 20-25.

219 *Ibid*, pp. 24-25.

220 As an amendment to section 505 of the FFDA by section 3209 of the *Health Extenders, Improving Access to Medicare, Medicaid and CHIP and Strengthening Public Health Act of 2022* located at 'Division FF – Health and Human Services' of the *Consolidated Appropriations Act, 2023*, available at https://www.appropriations.senate.gov/imo/media/doc/JRQ121922.PDF (17.01.2024).

"[…] the term 'nonclinical test' means a test conducted in vitro, in silico or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following:

(1) Cell-based assays.

(2) Organ chips and microphysiological systems.

(3) Computer modelling.

(4) Other nonhuman or human biology-based test methods, such as bioprinting.

(5) *Animal tests."*[221]

It should be noted that this **does not change the regulatory process for drugs (or medical devices and treatments) prior to reaching clinical trials in humans, nor does it eliminate animal testing**. Rather, it clarifies that data from the use of certain alternatives to animal testing can be used to submit an application for a new drug to the relevant regulator, the Food and Drug Administration.[222]

3.5.3. India

A recent change to India's pharmaceutical law (see section 5 of the present study) also **authorises researchers to use non-animal methods in relation to the development of drugs**.[223] Introduced in March 2023, the amendment to the *New Drugs and Clinical Trials Rules, 2019* is worded almost identically to the clause inserted into the US's FFDCA,[224] listing the non-clinical testing methods by which the safety and efficacy of new drugs may be assessed.

3.6. Food and feed safety

Requirements for food and feed safety **in the EU** form part of a complex regulatory framework affected by various sectoral laws, the implementation of which is **overseen by the European Food Safety Authority ("EFSA")**.[225]

Data and information requirements feature in a number of EU Regulations, including REACH and CLP and those concerning pesticides, food additives, feed additives, food contaminants, novel foods and genetically modified food and feed. **Many of these laws promote implementation of the 3R principles** and allow for the possibility of food and feed safety to be assessed using data based on NAMs and other alternatives not requiring animal testing. However, **certain of the data requirements** set out in

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221 *Ibid*, section 3209.

222 See, Coco Lederhouse, *New law clarifies alternatives to animal testing for safety, efficacy of drugs*, American Veterinary Medical Association, 21st March 2023, available at https://www.avma.org/news/new-law-clarifies-alternatives-animal-testing-safety-efficacy-drugs (17.01.2024).

223 See *New Drugs and Clinical Trials (Amendment) Rules, 2023*, available at https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=OTk1Ng== (23.01.2024).

224 *Ibid*, section 2.

225 It may be noted that beyond the legal framework, EFSA has launched various initiatives to facilitate the integration of NAMs for regulatory risk assessment as an alternative to animal studies, including the launch of a new platform for modelling and predicting the toxicity of chemicals. See: EFSA, *Introducing TKPlate – food safety without animal testing?*, 14th November 2023, available at https://www.efsa.europa.eu/en/news/introducing-tkplate-food-safety-without-animal-testing (18.01.2024). See also Cattaneo, Irene and others, Implementing New Approach Methodologies (NAMs) in food safety assessments: Strategic objectives and actions taken by the European Food Safety Authority, *op. cit.*

sector specific laws, such as REACH and pesticide laws, are drafted in a way which **renders *in vivo* testing mandatory in practice**.

With regard to food- and feed-specific laws, it is reported[226] that new *in vivo* testing is not mandatory, for example, in EU Regulations concerning food additives, food contaminants or novel foods. But for the **assessment and authorisation of (animal) feed additives**, *Commission Regulation (EC) No. 429/2008*[227] **does ask for *in vivo* testing in relation to tolerance studies and safety assessments**. Moreover, safety assessments cannot be based on NAMs because minimum requirements include 90-day animal feeding studies to detect possible toxicological effects.[228]

4. Transparency of research and data

4.1. Reporting requirements

There is **no evidence, among the European and non-European countries studied, of legal measures requiring the results of research involving animal testing to be published** or for technical data to be made accessible for scientific purposes. Legal duties with regard to transparency rather concern the **recording and publication of animal testing statistics** as well as, among European Union Member States, **non-technical information** about scientific projects involving animals.

Beyond the legal framework, however, it should be noted that reporting guidelines increasingly play a key role in promoting transparency and consistency of reporting of preclinical and clinical research among the scientific community.[229] With regard to *in vivo* testing, arguably the most important guidelines are those developed by the UK's NC3Rs (see section 2.2. above) in 2010, known as the ***Animal Research: Reporting of in vivo Experiments* ("ARRIVE") guidelines**. Aimed at bringing uniformity in the reporting of animal studies and thereby facilitating the reuse of collected information,[230] they are primarily targeted at researchers, reviewers and journal editors of studies involving animals. They have been **endorsed by more than a thousand journals** from across the life sciences, being incorporated into their instructions to authors and reviewers.[231] Like the consolidated standards of reporting trials (CONSORT) statement which applies to clinical trials,[232] the ARRIVE guidelines consist of a **checklist of the items that should be included in publications describing *in vivo***

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226 For a comprehensive overview, see Cattaneo, Irene and others, Implementing New Approach Methodologies (NAMs) in food safety assessments: Strategic objectives and actions taken by the European Food Safety Authority, *op. cit.*, in particular, Table 1, p. 279.

227 *Consolidated text: Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R0429-20210327 (18.01.2024).

228 See various examples in *Commission Regulation (EC) No. 429/2008, op. cit.,* Annex II, Section III.

229 Although it may be noted that a large number of animal studies are not published: about one-third of all animal experiments in two German university medical centres were not published: Wieschowski, S. and others (2019), Publication rates in animal research. Extent and characteristics of published and non-published animal studies followed up at two German university medical centres, *PloS ONE* 14(11).

230 See ARRIVE, *About*, available at https://arriveguidelines.org/about (23.01.2024).

231 See Percie du Sert, N. and others, The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, *BMC Veterinary Research* (2020) 16:242.

232 See Equator Network, *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials*, available at https://www.equator-network.org/reporting-guidelines/consort/ (23.01.2024).

experiments to enable others to scrutinise work adequately, assess its methodology and reproduce methods and results.[233]

Although widely referred to by those conducting animal experiments for scientific research purposes, **concerns surrounding the enforcement of reporting standards and a lack of understanding** around the consequences of incomplete reporting have led to the guidelines being **updated in 2020** to facilitate their use in practice; they are now referred to as 'ARRIVE 2.0'.

4.1.1. Europe

For those subject to **ETS 123**,[234] Articles 27 and 28 establish **requirements on parties to collect and report on statistical information** on the use of animals in procedures, specifically: the numbers and kinds of animals used in procedures; the numbers of animals in selected categories used in procedures directly concerned with medicine and in education and training; the number of animals in selected categories used in procedures for the protection of man and the environment; the numbers of animals in selected categories used in procedures required by law.

For EU Member States, the **2010 Directive imposes two main reporting duties** (in addition to the requirement[235] for periodic reporting by Member States of information relating to implementation of the 2010 Directive):

- **Statistical information** on the use of animals in procedures and the origin and species of nonhuman primates used in procedures;[236]
- **Non-technical project summaries** ("NTS") of authorised projects to provide further understanding of why and how animals are still needed in research and testing.[237]

Statistical information on the use of animals is collected by EU Member States and submitted to the European Commission annually. It is contained in the public, open access **ALURES Statistical EU Database**.[238] Launched in 2021, this allows for statistical data mining at the Union level, and from 2023, has also permitted access to national data. The **Database consists of 3 sections**: section 1 gives the number of animals used for the first time for various scientific purposes, showing the species and origins of the animals; section 2 gives numbers of all uses of animals for scientific purposes, also providing the reason for use, the severity (mild, moderate, severe) experience by animals, their genetic status and animals used for meeting regulatory requirements; and section 3 gives the numbers of genetically altered animals to support scientific research.

NTSs are available in the open access ALURES NTS EU Database and provide anonymised information on the objectives of projects, the predicted harm and benefits, the number and types of animals to be used and a statement of compliance with the requirement of the 3Rs.[239] NTSs are described by

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233 See Percie du Sert, N. and others, The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, *op. cit.* at p.1.

234 *Op. cit.*, see section 1 of the present study.

235 2010 Directive, Article 54(1).

236 2010 Directive, Articles 54(2) and 54(3).

237 2010 Directive, Article 43.

238 European Commission, *Alures-Animal Use Reporting*, available at https://webgate.ec.europa.eu/envdataportal/content/alures/section1_number-of-animals.html# (22.01.2024).

239 Key components to be included in the NTS are set out in Article 43 of the 2010 Directive, with sub-components detailed in Annex I of *Commission Implementing Decision 2020/569/EU*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32020D0569#d1e32-19-1 (22.01.2024).

European Commission as having proven to be a useful tool in promoting transparency, contributing to the sharing of good practices in relation to the 3Rs and helping to avoid duplication of animal testing. They are, however, not specifically aimed at the scientific community, and are required to use language and terminology which will be easily understood by the public.[240] Member States have the **option of requiring NTSs to specify whether a project is to undergo a retrospective assessment**. At present, this requirement is reported as having been transposed into national legislation by 17 Member States.[241]

The European Commission stated in its most recent statistical report that one of the main aims of the ALURES databases is to:

> "[…] *facilitate initiatives by stakeholders, including public and private research organisations, and funding bodies, to strategically progress towards the ultimate goal of full replacement by focusing the development of alternatives on areas that will have the greatest impact*."[242]

In 2019, as part of the only amendment to the 2010 Directive since its inception, *Regulation (EU) 2019/1010*[243] **modified those Articles of the 2010 Directive concerning statistical information and NTSs** in a number of respects, principally: that from 2021, the publication of NTSs and corresponding updates (as well as retrospective assessments for those participating) be **submitted for publication by Member States within 6 months of the date of project authorisation**; and providing for the European Commission to harmonise reporting obligations and improve transparency and accuracy by improving reporting categorisation and specifying in greater detail how information in NTSs and retrospective assessments should be set out.[244]

It should be recalled that one area of EU law not specifically aimed at animal testing, but which concerns transparency and contributes to reducing the number of tests carried out on animals, is **data sharing requirements applied as part of the registration process under REACH** for substances manufactured or imported into the EU (see section 2.1.2. above). As discussed, the ECHA requires **companies producing or importing the same substance to share information** about the properties of their substance, and companies registering the same substances must jointly submit any results on the testing of vertebrate animals.[245]

At the national level, our non-exhaustive enquiries have **not uncovered any domestic obligations** requiring the publication, specifically for scientific purposes, of research involving animal testing. However, it would appear that many EU Member States already required, even prior to the

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240 See European Commission, *Caring for animals – aiming for better science – Non-technical project summaries*, Publications Office, 2022, available at https://op.europa.eu/en/publication-detail/-/publication/fca9ae7f-2554-11e9-8d04-01aa75ed71a1 (22.01.2024), pp. 6-7.

241 See European Commission, *Environment – Statistics and non-technical project summaries*, available at https://environment.ec.europa.eu/topics/chemicals/animals-science/statistics-and-non-technical-project-summaries_en (22.01.2024).

242 European Commission, *Commission Staff Working Document – Summary Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union and Norway in 2020*, *op. cit.*, p.13.

243 *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 (22.01.2024), Article 6.

244 Implemented under *Commission Implementing Decision (EU) 2020/569 of 16 April 2020 establishing a common format and information content for the submission of the information to be reported by Member States pursuant to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes and repealing Commission Implementing Decision 2012/707/EU*, available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32020D0569 (22.01.2024).

245 Pursuant to provisions principally contained in Chapter III of REACH, *op. cit.*

implementation of the 2010 Directive, the publication of statistics concerning the use of animals for scientific purposes. **The introduction of the 2010 Directive, in many cases, extended existing requirements**. Transposition into German law, for example, necessitated a revision of its VersTierMeldV (see section 1.2.3.) to include those vertebrates and other organisms covered by the Directive and statistics on genetically modified animals.[246] Retrospective reporting on the severity of pain, suffering or harm to which animals are subjected was also required, adding a new item of reporting for countries like Germany; and for the Netherlands, changes to its classification system (which had a six-scale system rather than the Directive's four).[247]

The UK, whose statistics are, since Brexit, no longer included in the EU's databases, continues to collect data on animal testing under national law. **In some respects, the UK's data goes further than that required by the EU**: the UK publishes information on all procedures, whereas EU-wide statistics capture only the number of animals used (which can make overall numbers slightly lower, as several procedures are sometimes performed on the same animal); moreover, the UK publishes information on an additional sub-threshold severity category which the EU does not require. On the other hand, it is **no longer subject to EU requirements** for authorised projects to produce NTSs, nor does it now have access to the EU's REACH database, potentially increasing the risk of duplicate experiments on animals.[248]

4.1.2. Other jurisdictions

In other jurisdictions examined, there are, like the EU, **no known legal requirements on those engaged in regulated experiments on animals to make research results publicly available for scientific purposes**. Evidence from jurisdictions outside of Europe indicates that any legal duties to publish information with regard to animal testing go no further than providing statistical data.

In **the US**, the AWRs[249] require that each USDA-registered research facility and federal research facility submit an annual report documenting its use of animals for research, testing, teaching, experimentation and/or surgery.[250] Data in the summary reports are categorised with reference to the number or animals held by a facility but not used, those used in research but with no pain involved, those used in research with pain involved and where pain drugs have been administered, those used in research with pain involved and where pain drugs were not administered and the total number of animals used in research. It will be recalled, however, that most purpose-bred birds, mice and rats are not covered by the AWA.

In **Australia**, duties to keep records and provide reports of animal use are conducted on a state or territory basis, according to local animal welfare laws. Although an exhaustive review of state and territory laws is beyond the scope of this study,[251] it appears that reports are to be submitted on an

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246 Bundesinstitut für Risikobewertung, *Questions and answers on animal experiments, alternative methods and animal experiment numbers, op. cit.*, p.3.

247 See Javier Guillén and others, *The European Framework on Research Animal Welfare Regulations and Guidelines*, in Javier Guillén (ed.), *Laboratory Animals – Regulations and Recommendations for the Care and Use of Animals in Research, op. cit.,* pp.134-5.

248 See Dunn, R., Brexit: A Boon or a Curse for Animals Used in Scientific Procedures?, *op. cit.*, at p. 11.

249 AWRs, *op. cit.*, section 2.36.

250 See USDA, *Research Facility Annual Usage Summary Report*, last modified 25 October 2022, available at https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_obtain_research_facility_annual_report/ct_research_facility_annual_summary_reports (22.01.2024).

251 See for example Queensland Government, *Animal use statistics report*, available at https://www.business.qld.gov.au/industries/farms-fishing-forestry/agriculture/animal/health/welfare/science/record/statistics (22.01.2024); New South Wales

annual basis and concern general data about animal use for statistical purposes rather than information about animal experimentation for scientific purposes.

In **New Zealand**, annual numbers of animals have been collected since 1987, with all 'code holders' (being holders of a code of ethical conduct ("CEC") or those having an arrangement to use another organisation's CEC) being required to keep records.[252] According to the *Animal Welfare (Records and Statistics) Regulations 1999,*[253] records must be retained for a period of five years after the year to which they relate, and an annual return of the figures[254] for the previous calendar year must be submitted to the Ministry for Primary Industries by the end of February each year. Beyond the publication of statistics, there is no indication that involved in animal testing are generally required by law to make their research accessible for scientific purposes.

There are no known legal requirements in **India** applying to the reporting of research for scientific and/or statistical purposes.

4.2. Preregistration of research involving animal experiments

The preregistration of animal research refers to **scientists depositing their study plan involving animal research in an open registry**, normally prior to starting any experiments. The original idea for the study design, chosen methods and statistical analysis is stored and is retraceable for other researchers and reviewers and can no longer be altered.[255] This encourages the publication of all results obtained regardless of their outcome and permits retrospective comparison between the original study plan and the final outcome,; it supports planning of studies from the outset, may prevent questionable research practices, renders it nearly impossible to deliberately manipulate study results to achieve more attractive outcomes and can improve the reporting of data.[256]

The **preregistration of clinical research** – that is, research carried out on humans – is already subject to legal regulation in both the US and the EU and is **mandatory by law for most regulated clinical trials**. In 1997, the **US Congress** passed the first federal law requiring clinical trial registration,[257] with the first online registry for clinical trials being launched by the NIH[258] in 2000. An **EU Directive**[259] initiated the

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Government, *NSW Animal Use in Research Statistics*, available at https://www.dpi.nsw.gov.au/dpi/animals/animal-ethics-infolink/nsw-animal-use-statistics (22.01.2024); Animal Welfare Victoria, *Animal use statistics*, available at https://agriculture.vic.gov.au/livestock-and-animals/animal-welfare-victoria/animals-used-in-research-and-teaching/animal-use-statistics (22.01.2024).

252 See Ministry for Primary Industries, *2021 Statistics on the Use of Animals in Research, Testing and Teaching in New Zealand*, MPT Information Paper 2023/05, May 2023, available at https://www.mpi.govt.nz/dmsdocument/56998-Statistics-on-the-Use-of-Animals-in-Research-Testing-and-Teaching-in-New-Zealand-in-2021 (23.01.2024).

253 *Animal Welfare (Records and Statistics) Regulations 1999*, available at https://www.legislation.govt.nz/regulation/public/1999/0392/latest/whole.html (22.01.2024).

254 *Ibid*, regulation 5.

255 Heinl, C. and others (2022), Preregistration in Animal Research, in Faintuch, J., Faintuch, S. (eds), *Integrity of Scientific Research*, Springer., section 3. See also Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *PNAS Nexus*, 2022, 1, 1-6.

256 *Ibid*.

257 *Ibid*, Fig. 37.1

258 See section 1.3.1. of the present study, above.

259 *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*, available at https://eur-lex.europa.eu/eli/dir/2001/20/2022-01-01 (23.01.2024).

establishment of an EU database for the registration of clinical trials in 2001, and this was **expanded further in 2014** when *Clinical Trial Regulation No. 536/2014*[260] required the dissemination of results within one year of completion of a clinical trial, and **again in 2022** when a portal named *Clinical Trials Information System* ("CTIS") became the single point of entry for the submission of data and information relating to clinical trials required by the Regulation.

However, the **preregistration of preclinical research** – that is, research that begins prior to testing on humans, and which frequently relies on animal experiments – is, according to our research, **currently not mandated by law anywhere in the world**. That is not to say that preregistration is not available to scientists:[261] in recent years, publishers have started to include preregistration of animal studies in their publication guidelines,[262] funders are requiring preregistration for grant applications[263] and policy makers are discussing preregistration in animal research.[264] It is reported that an advisory committee advising the US's NIH on enhancing the transparency, rigour and translatability of animal research has recommended that a pilot study be launched to promote and evaluate the benefits of preregistration of animal research.[265]

Arguably the most significant development in recent years is the **launch of several online platforms, enabling the preregistration of animal research on an autonomous basis**. Participation is purely voluntary, but there is evidence that **publishers are starting to integrate registration into their editorial policies**. Submissions are subject to common minimum standards, including: free public access, transparency on ownership and financial resources, the possibility to track changes occurring after registration, data security, sustainability of data storage to prevent corruption or loss of data, citability of preregistration, the possibility to compare the planned study with its outcome and minimal defined content.[266] There are **three online platforms for the preregistration of animal research**, open to all scientific studies involving animals conducted around the world, and which are commonly referred to in scientific literature:

- ***Open Science Framework* ("OSF") *registry***:[267] the first platform to allow preregistration of studies from different disciplines, the *OSF registry* is built and maintained by the *Center for Open Science*, a non-profit technology organisation founded in 2013.[268]

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260 *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, available at https://eur-lex.europa.eu/eli/reg/2014/536/2022-12-05 (23.01.2024).

261 The following developments are cited in Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *op. cit.*, p. 2.

262 See American Association for Cancer Research, *Editorial Policies*, available at https://aacrjournals.org/pages/editorial-policies (24.01.2024).

263 German Federal Ministry of Education and Research, *Richtlinie zur Förderung von konfirmatorischen präklinischen Studien – Qualität in der Gesundheitsforschung*, 27th December 2018, available at https://www.gesundheitsforschung-bmbf.de/de/8344.php (24.01.2024).

264 De Groot TD-F, Dik-Faver RK, Von Martles MRHM, *Motie van het lid De Groot c.s. over het registreren van alle individuele dierproeven*, 28th June 2018, Tweede Kamer der Staten-Generaal, available at https://www.tweedekamer.nl/kamerstukken/detail?id=2018Z12717&did=2018D36726 (24.01.2024).

265 Wold B., Tabak, L., *ACD working group on enhancing rigor, transparency and translatability in animal research – final report*, 11th June 2021, available at https://acd.od.nih.gov/documents/presentations/06112021_RR-AR%20Report.pdf (24.01.2024).

266 Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *op. cit.*, p. 3.

267 See OSF homepage, available at https://osf.io/ (24.01.2024).

268 Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *op. cit.*, p. 3.

- ***Preclinicaltrials.eu***:[269] launched in 2018, this platform is hosted by Utrecht University and is specifically dedicated to animal studies. It is partly funded by the Dutch Government, following a motion accepted by the Dutch Parliament in 2018 stimulating preregistration for all animal research in the Netherlands.[270]
- ***Animalstudyregistry.org***:[271] launched in 2019 and also aimed specifically at animal research, this platform is operated by the German Bf3R.

The **options for the preregistration of studies differs between the three registries**. In particular, the embargo period, during which details of the study will remain hidden from the public, varies across the registries; whereas *OSF registry* is not restricted to any language, *Preclinicaltrials.eu* and *animalstudyregistry.org* ask for entries only in English; after final registration, studies cannot be withdrawn from *preclinicaltrials.eu*, whereas researchers can do so in the *OSF registry* and also in *animalstudyregistry.org* where done so with good reason.[272] Moreover, the information to preregister a study varies between the registries.

Although a scan of literature referring to these registries indicates the rising attention of preregistration in preclinical research involving animals, it also suggests slow uptake in the participation of the voluntary registries.[273] There are however **limited calls for preregistration of preclinical research to become a legal requirement**, as is the currently the case for clinical research conducting human trials;[274] instead, the focus generally remains on encouraging publishers, funders and other institutions to require or recommend preregistration as a condition of engagement.[275]

5. Latest developments

The following lists some of the most important recent legal developments in Europe and beyond concerning the regulation of animal testing for scientific purposes.

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269 Home page of *preclinicaltrials.eu*, available at https://preclinicaltrials.eu/ (24.01.2024).

270 Van der Naald M., Chamuleau SAJ, Menon JML *et al.*, Preregistration of animal research protocols: development and 3-year overview of preclinicaltrials.eu, *BMJ Open Science*, 2022, 6, at p. 4.

271 *Animalstudyregistry.org* home page, available at https://www.animalstudyregistry.org/asr_web/index.action (24.01.2024).

272 Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *op. cit.*, p. 3.

273 For example, see Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *op. cit.*, and Van der Naald M., Chamuleau SAJ, Menon JML *et al.*, Preregistration of animal research protocols: development and 3-year overview of preclinicaltrials.eu, *BMJ Open Science*, 2022, 6, at p. 5.

274 Although, note Grimm, D., *Q&A: Should all animal experiments be listed in a public registry?*, Science.Org, 29th November 2016, available at https://www.science.org/content/article/qa-should-all-animal-experiments-be-listed-public-registry (24.01.2024), in which bioethicist, Daniel Strech, says, "*if we want these registries to become a reality, we need a government agency like the FDA to mandate them.* […]"

275 See Heinl, C. and others, Declaration of common standards for preregistration of animal research – speeding up the scientific progress, *op. cit.*, p. 5; van der Naald M., Wenker, S., Doevendans, P.A., *et al*, Publication rate in preclinical research: a plea for preregistration, *BMJ Open Science*, 2020; 4; Van der Naald M., Chamuleau SAJ, Menon JML *et al.*, Preregistration of animal research protocols: development and 3-year overview of preclinicaltrials.eu, *op. cit.*

5.1. Europe

- **European Commission response to European Citizens' Initiative on animal testing**: on 25th July 2023, the European Commission responded to the European Citizens' Initiative ("ECI"),[276] '*Save Cruelty-free Cosmetics – Commit to a Europe without Animal Testing*'. Three specific objectives of the ECI were addressed by the Commission:
    - Protect and strengthen the cosmetics animal testing ban: The Commission recognises that the ban on the placing on the market of cosmetic products under the EU Cosmetics Regulation does not extend to safety tests required to assess risks from chemicals to workers and the environment under REACH. However, it proposes to await the outcome of two cases before the ECJ[277] with regard to the interface between these two pieces of legislation before considering potential legislative changes.
    - Transform EU chemicals legislation: in response to calls for concrete steps to test the risk of chemicals without the use of animals, the Commission responded that it will work with all relevant parties on a roadmap towards chemical safety assessments that are free from animal testing.
    - Modernise science in the EU: in response to organisers' calls for animal experiments to go beyond the formulated goal of the 2010 Directive (to replace all animal experiments *as soon as it is scientifically possible*) is not sufficient and that animal experiments should be abolished even without suitable replacement methods, the Commission says that it does not share the view that a legislative proposal is required to reach such a goal, and that it is rather proposing to take action to develop alternative approaches and to take action to accelerate the reduction of animal testing in research, education and training.[278]

- **European Court of Justice ruling on animal testing for ingredients used solely in cosmetics**: on 22nd November 2023, in the case of *Symrise AG v ECHA (Case T-655/20)*,[279] the Court of Justice of the European Union ("ECJ") ruled against German chemicals company *Symrise AG*, who had challenged a ECHA request in 2018 to perform animal testing on two cosmetic ingredients, ultraviolet light filters solely used as ingredients in sunscreens. The toxicity testing required by the ECHA would involve over 5,500 animals. The decision means that ingredients used exclusively in cosmetics may still be tested on animals under REACH to assess the safety risks of workers who may be exposed to the ingredients.[280] Animal welfare organisations argue that this represents a loophole in the EU Cosmetics Regulation which undermines the ban on animal testing for cosmetics.[281]

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276 Since April 2012, European citizens' initiatives (ECI) provide a tool for citizens to invite the European Commission to propose legal action in areas where the Commission has the power to do so. For the Commission to consider an ECI, signatures from at least one million citizens from at least seven EU Member States are required. The Commission registered the ECI, '*Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing*' on 30 June 2021. Its organisers collected 1.2 million statements of support between 31 August 2021 and 31 August 2022: see European Commission, *Press Release – Commission acts to accelerate phasing out of animal testing in response to a European Citizens' Initiative,* 25th July 2023, available at https://ec.europa.eu/commission/presscorner/detail/en/ip_23_3993 (24.01.2024).

277 See next point below.

278 See European Commission, *Press Release – Commission acts to accelerate phasing out of animal testing in response to a European Citizens' Initiative, op. cit.*

279 *Symrise AG v ECHA (Case T-655/20), op. cit.*

280 See further reference to the case in section 3.3. of the present study, above.

281 See Eurogroup for Animals, *Court of Justice of the European Union ruling exposes limitations of cosmetics animal testing ban*, 24th November 2023, available at https://www.eurogroupforanimals.org/news/court-justice-european-union-ruling-exposes-limitations-

- **Revision of CLP Regulation to contain wording aimed at alternatives to animal testing:** on 5th December 2023, it was announced that the European Parliament and the Council had reached provisional agreement on the revision of the CLP Regulation, following a proposal by the European Commission back in December 2022.[282] The revision package consists of a legislative proposal for the amendment of the CLP Regulation and a delegated act[283] as a complement to the legislative proposal. The delegated act already entered into force in April 2023, but the new Regulation must now be formally adopted by the European Parliament and the Council. It is reported that measures include newly improved wording agreed earlier in September at a vote by the Parliament's Environment, Public Health and Food Safety Committee ("ENVI") with regard to the use of non-animal methods and to allow the CLP Regulation to take into account future advances in animal-free science.[284]

- **Proposal to replace existing pharmaceutical legislation with new Directive and Regulation containing provisions aimed at promoting 3Rs and decreasing animal testing:** on 26th April 2023, the European Commission adopted a proposal for a new Directive and a new Regulation to revise and replace the current pharmaceutical legislation.[285] This will include provisions designed to strengthen the 3Rs principle and place obligations on marketing authorisation applicants and holders to comply with various conditions aimed at reducing animal testing. Express reference to the protection of animals is contained in the recitals or the proposed legislation, and Recitals to the Regulation[286] and the Directive[287] emphasise the importance of the 3Rs principles, with explicit reference to the need for applicants and the relevant regulators to take into account NAMs as an

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cosmetics-animal-testing-ban (25.01.2024) and Margarita Sachkova, *Court of Justice of the European Union's Ruling Destroys Ban on Animal Testing for Cosmetics*, Peta UK, 22nd November 2023, available at https://www.peta.org.uk/blog/reach-sunscreen/ (25.01.2024).

282 European Commission, *Press Release - Commission welcomes provisional agreement on improving classification, labelling and packaging of hazardous chemicals*, available at https://ec.europa.eu/commission/presscorner/detail/en/ip_23_6381 (24.01.2024).

283 European Commission, *Delegated Regulation amending Regulation 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures,* 19th December 2022, available at https://environment.ec.europa.eu/publications/clp-delegated-act_en (24.01.2024).

284 See Eurogroup for Animals, *European Parliament debates and votes on CLP revision*, 6th October 2023, available at https://www.eurogroupforanimals.org/news/european-parliament-debates-and-votes-clp-revision (24.01.2024): this states that, "[…] *Article 7 has been amended to read "non-animal, animal, and human testing", along with a newly added paragraph clearly stating "tests using new approach methodologies shall also be considered". In addition, Article 53 has been amended to include "the promotion of alternative methods for assessment of hazards of substances and mixtures", expressly addressing it as a priority for future adaptations to the regulation.*"

285 European Commission – Public Health, *Reform of the EU pharmaceutical legislation*, 26th April 2023, available at https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en (25.01.2024).

286 *Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, available at* https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0193 (25.01.2024).

287 *Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC,* available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0192 (25.02.2024).

alternative to animal testing as well as the establishment of procedures to avoid unnecessary duplication of animal studies.[288] Some of the proposed Articles are worth setting out here:

- Article 6(5) of the Regulation and 6(7) of the Directive states:

  "*The marketing authorisation applicant shall demonstrate that the principle of replacement, reduction and refinement of animal testing for scientific purposes has been applied in compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application.*

  The marketing authorisation applicant shall not carry out animal tests in case scientifically satisfactory non-animal testing methods are available."

- Where an opinion of the EMA is favourable to granting relevant marketing authorisation, Article 44(1)(j) of the Directive (with a corresponding provision at Article 12(4)(m) of the Regulation) subjects the granting of national marketing authorisation to a number of possible conditions, including a requirement:

  "*where appropriate, to carry out medicinal product-specific validation studies to replace animal-based control methods with non-animal based control methods."*

- **European Parliament adopts resolution "*on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education*"**: on 16th September 2021, the European Parliament voted almost unanimously to request the European Commission to develop an EU action plan to abolish animal research more quickly.[289] In its response, the EU Commission welcomed the intention to abolish animal experiments in the long term, but reiterated that the 2010 Directive already sets such a goal.[290]

- **UK ban on animal testing for chemicals exclusively intended as ingredients in cosmetic products**: on 22nd November 2023, the UK's department for home affairs, the Home Office, confirmed an announcement made in May 2023 that no animal testing is authorised in relation to chemicals exclusively intended to be used as ingredients in chemical products. Although such testing is permitted under the EU's REACH as a last resort for the purpose of worker and environmental safety (see *Symrise AG v ECHA* case above), the UK is, since Brexit, no longer bound by REACH. The UK Government will consider whether changes to the legal framework will be appropriate in the long term, but the ban will come into immediate effect through the refusal to issue new licences for animal testing of chemicals that are exclusively intended to be used as ingredients in cosmetic products. It says it will also engage with the small number of companies benefiting from existing licences (referred to as 'legacy licences') which permit such testing.[291]

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288 See proposed Regulation, Recitals 46 and 47 and proposed Directive, Recitals 31 and 32.

289 See Legislative Observatory, *2021/2784 (RSP) Resolution on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education*, available at https://oeil.secure.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2021/2784(RSP) (25.01.2024).

290 See European Commission, *Follow-up to the European Parliament non-legislative resolution on plans and actions to accelerate a transition to innovation without the use of animals in research, regulatory testing and education*, undated, available at https://oeil.secure.europarl.europa.eu/oeil/spdoc.do?i=57777&j=0&l=en (25.01.2024).

291 See Theyworkforyou.com, *Animal Experiments: Cosmetics – Home Office written question,* 22nd November 2023, available at https://www.theyworkforyou.com/wrans/?id=2023-11-15.2108.h&s=chemicals (25.01.2024); and Parliament UK website, *Regulation Update – Statement made on 17th May 2023*, 17th May 2023, available at https://questions-statements.parliament.uk/written-statements/detail/2023-05-17/hcws779 (25.01.2024).

- **Dutch Government strategy to phase out regulatory animal testing by 2025 is scaled back**: it was confirmed on 11th December 2018 that plans by the Dutch Government, announced in 2016 for developing animal-free research and a schedule for phasing out animal procedures by 2025,[292] were no longer being pursued.[293] Although the Netherlands still intends to be a forerunner in the international transition to animal-free innovation, the target date is no longer defined, indicated the Minister of Agriculture, Nature and Food Quality.

5.2. Beyond Europe

- **US passes law removing a requirement for drugs to be tested on animals**: on 29th December 2022, the Food and Drug Administration Modernisation Act 2.0 was signed by President Biden as part of a large spending package removing an obligation, dating back to 1938, for potential drugs to be tested for safety and efficacy on animals and allowing human trials to begin after either animal or non-animal tests.[294] The non-exhaustive list of non-animal tests specifically identified alongside animal testing in the new legislation are cell-based assays, organ chips and microphysiological systems, computer modelling and other nonhuman or human biology-based test methods, such as bioprinting.

- **India amends pharmaceutical legislation to include non-animal methods for drug development**: in March 2023, India's *Drugs and Cosmetics Rules, 2019* were amended – similar to reforms in the US - to permit researchers to use non-animal methods alongside animal studies in the assessment of the safety and efficacy of new drugs or investigational new drugs. Previously, only animal tests had been permitted.[295]

- **Academic and industry experts in South Korea urge the passing of legislation to promote alternative approaches to animal testing**: in November 2023, 346 South Korean academic and industry experts wrote to the chair of the National Assembly's Health and Welfare Committee to urge the Korean Government to pass into law draft legislation already introduced at the National Assembly in recent years. The *Act on the Promotion of Development, Dissemination and Use of Alternatives to Animal Testing Methods* ("PAAM Act") in 2020 and the *Act on the Vitalization of Development, Dissemination and use of Alternatives to Animal Testing Methods* ("VAAM Act") in 2022. Described as promoting state-of-the-art science to replace animal testing, the proposed laws require collaborative work between authorities through a basic plan every 5 years and establish a committee of experts in alternative approaches to animal testing.[296]

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292 See Nationaal Comité advies dierproevenbeleid, *NCad opinion Transition to non-animal research*, 15th December 2016, available at https://www.ncadierproevenbeleid.nl/documenten/rapport/2016/12/15/ncad-opinion-transition-to-non-animal-research (25.01.2024).

293 Tweede Kamer der Staten-Generaal, *Brief van de Minister van Landbouw, Natuu ren Voedselkwaliteit,* Dierproeven, Nr. 86, Vergaderhaar 2018-2019, 11th December 2018, available at https://eara.us10.list-manage.com/track/click?u=f06d4e3bcff1a29b0eb102c6f&id=80deb1626f&e=6bde7eb6c3 (25.01.2024).

294 For more information, see section 3.3. of the present study, above. See also Meredith Wadman, *FDA no longer needs to require animal tests before human drug trials,* Science.org, 10th January 2023, available at https://www.science.org/content/article/fda-no-longer-needs-require-animal-tests-human-drug-trials (25.01.2024).

295 See section 3.3. of the present study, above.

296 See Human Society International, *Over 300 South Korean academic and industry experts urge the passage of bills promoting better science without the use of animals*, 21st November 2023, available at https://www.hsi.org/news-resources/south-korean-experts-urge-replacement-of-animal-testing/ (25.01.2024).

- **Canada amends environmental protection legislation to promote 3Rs in toxicity testing and bans the testing of cosmetics on animals**: in June 2023, the *Canadian Environmental Protection Act, 1999* ("CEPA") was, for the first time in over 20 years, amended by *Bill S-5 (Strengthening Environmental Protection for a Healthier Canada Act)*[297] to explicitly promote 3Rs principles in relation to the toxicity testing of chemicals and to support their implementation by regulators, *Health Canada* and *environment and Climate Change Canada*. It requires Ministers to publish, within two years, a timetabled plan – to be updated and reported on annually - setting out activities or initiatives to promote the development and implementation of such methods and strategies.[298] A public consultation on the development of the strategy for the promotion of the 3Rs when addressing chemical assessment data needs under CEPA closed on 29th January 2024.[299]

  Moreover, it has amended its *Food and Drugs Act*[300] to join other countries in banning the testing of cosmetics on animals and the sale of cosmetics that rely on new animal testing data as well as prohibiting the use of false or misleading labelling in relation to the testing of cosmetics on animals.[301]

297 *Bill S-5*, available at https://www.parl.ca/DocumentViewer/en/44-1/bill/S-5/royal-assent (25.01.2025).

298 See Eurogroup for Animals, *Canada takes two steps to reduce reliance on animal testing*, 7th July 2023, available at https://www.eurogroupforanimals.org/news/canada-takes-two-steps-reduce-reliance-animal-testing (25.01.2024).

299 See Government of Canada, *Notice of intent on the development of a strategy to guide the replacement, reduction, or refinement of vertebrate animal testing under the Canadian Environmental Protection Act, 1999 (CEPA)*, available at https://www.canada.ca/en/health-canada/programs/consultation-strategy-replace-reduce-refine-vertebrate-animal-testing/notice-intent.html (25.01.2024).

300 *Food and Drugs Act, F-27*, available at https://laws-lois.justice.gc.ca/eng/acts/F-27/index.html (25.01.2024)

301 Pursuant to *Bill C-47*, available at https://www.parl.ca/documentviewer/en/44-1/bill/C-47/royal-assent (25.01.2024), Division 28, sections 505 and 506, amending section 16 of *Food and Drugs Act*

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