Protecting animals and enabling research in the European Union: an overview of development and implementation of Directive 2010/63/EU

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Abstract

In 1986, European Directive 86/609/EEC, regulating the use of animals in research, was one of the first examples of common legislation to set standards for animal protection across the Member States of the former European Economic Community (EEC), now the European Union (EU), with the aim of securing a level European playing field. Starting in 2002, a process of revising European animal experimentation legislation was undertaken with one of its key aims being to ensure high standards of welfare for laboratory animals across Europe. This resulted in Directive 2010/63/EU, which has regulated this activity in Europe since 2013. Since this is an EU Directive, transposition into national legislation is a necessary and important part of the implementation of the new legislation. This paper gives an overview of the transposition process followed by an analysis of the potential to reach the different objectives of the Directive, particularly with a focus on securing the same high standards of animal protection across member countries. The analysis focuses on three separate issues: (a) minimum standards for laboratory animal housing and care, (b) restrictions on the use of certain animal species and (c) project review and authorization.

Keywords: animal experimentation; research ethics; European Union; laboratory animals; legislation;

Introduction

Europe has a long history of animal protection legislation; the first national legislation in the world to regulate the use of research animals was developed in a European country (Orlans 2002). In 1986, European Directive 86/609/EEC, regulating the use of animals in research (Council of the European Communities 1986), was one of the first examples of common legislation to set standards for animal protection across the Member States of the former European Economic Community (EEC), now the European Union (EU). This Directive became the entire basis for legislation in some European Member States, whereas other countries developed more extensive and far-reaching national legislation, resulting in substantial differences across European countries regarding the conditions for research and the protection for animals.

Starting in 2002, a process of revising European animal experimentation legislation was undertaken, resulting in Directive 2010/63/EU (European Union 2010). This revision aimed to "strengthen the protection of animals still used in scientific procedures (...) and ensure a level playing field throughout the EU for industry and the research community" (European Commission 2008). In this paper, we aim to present and discuss the development of recent European legislation regarding animal experimentation with a focus on how far the revised legislation has succeeded in eliminating disparities between countries and how the tension between the different aims of the revision can be handled in actual practice.

We begin with an overview of the political and administrative process of revising and implementing this legislation and with the changes that the revision introduced. We then focus on three different issues regulated by the Directive: minimum standards for housing and care, restrictions on the use of different animal species and project review for authorization. Finally, we discuss to which extend regarding these issues the aims of the Directive can be said to have been achieved by the Directive.

From Directive 86/609/EEC to Directive 2010/63/EU

European Legislation Regulating Animal Experimentation From 1986 to 2010

Two Europe-wide legal instruments regulating the use of animals in research came into effect in 1986 (for an overview of European governance, see Table 1). The first of these was the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS123), published by the Council of Europe (Council of Europe 1986). With the primary aim of reducing the number of animals used in research and encouraging signing parties to use animals only where alternatives do not exist, this document laid down general principles for when and how experiments with animals were to be carried out, and also provided technical details on how to house animals. Later in the year, the European Economic Community (now the European Union) published Directive 86/609/EEC. The Convention and the Directive overlap considerably in content, but are two different documents and have different legal status. Conventions are only legally binding to the parties which ratify them, whereas directives must be implemented by all Member States. The functioning of the former European Communities per definition limited the scope of Directive 86/609/EEC to areas of economic activity (thus excluding animal use within academic research and teaching, see (European Parliament 2002) p11), whereas Convention ETS123 covered all uses of animals for experimental and other scientific purposes. This discrepancy was

partly overcome in 1999 when the European Union became party to Convention ETS123 ((European Union 1999).

Directive 86/609/EEC remained in place with no plans for changes until 2002 when the revision process was initiated. During these more than 15 years, considerable technical and scientific progress was made, and significant changes had also affected the political and legislative context. The European Economic Community had become the European Union with a wider political mandate. Legislation going beyond mere economic activity was seen as necessary to harmonise Member State Law to facilitate the functioning of the Single Market (Treaty on the Functioning of the European Union, Article 114). Any obstacles to the free movement of people, goods, services and capital were increasingly addressed through Directives and Regulations; the interpretation of the single market was broad, covering a wide range of activities relating to the economy. This included the strengthening of the European Research Area.

An important driver in the legislation on animal use for scientific purposes concerns ensuring that no Member State derives an advantage over another by allowing weaker standards than the agreed minimum when it comes to protecting animal welfare. Animal welfare has gained a stronger status with the mandate of political as well as economic integration that has come with the formation of the European Union (Table 1). This strengthening was first established in 1997 through a protocol annexed to the Treaty of Amsterdam requiring that animal welfare was to be considered in the development of European legislation (European Union 1997). Thus, when revision started in 2002, the 1986 Directive was seen as unsuccessful in creating an adequate minimum standard because the regulation of animal experimentation had become very uneven across the EU as a result of the fact that some Member States had more extensive national legislation while others had merely transposed the 1986 Directive.

The revision was requested by the European Parliament, explicitly motivated by the changes in science and in public attitudes that had occurred since Directive 86/609/EEC came into force; specifically, it was motivated by the limited coverage excluding animals in education and basic research, by the differing standards between countries and by insufficient attention to the 3Rs and animal welfare. The Parliament furthermore argued that given increased public concern over animal welfare, it was inappropriate that legislation protecting experimental animals would have “as its original basis, not the welfare of such animals, but undistorted trade between Member States” (European Parliament 2002). In asking for animal welfare to be given stronger status within this legislation, the European Parliament, which is the only directly democratically elected body of the key EU institutions, also politically challenged the moral basis for the previous legislation.

The revision process was initiated through the establishment of a Technical Expert Working Group (TEWG), which brought together national authorities as well as stakeholder organizations to provide scientific and technical advice in response to specific questions raised by the European Commission. The response was published in 2003 in final reports of the four respective subgroups on 1) Scope; 2) Authorization; 3) Ethical review and 4) Cost-benefit (European Commission 2003). The Commission further sought scientific expert input in regard to animal sentience, origin of experimental animals and euthanasia methods (European Food Safety Authority: Scientific Panel on Animal Health and

Welfare 2005). The TEWG work was followed by a period of internal Commission consultation and drafting leading up to the presentation of the first draft proposal in the autumn of 2008.

The scientific community, industry and NGOs followed the revision process closely. During the revision period, hearings were organized and policy briefings and statements published by several important European research organizations. The first public draft version of the revised Directive was met with considerable criticism by the research community, which feared limitations to research which they argued would interfere with the possibilities for scientists and industry to operate within the European Research Area (e.g. (FELASA 2007) (Anonymous 2008)). This debate was coupled with an intense political battle over the new draft version of the Directive in the European Institutions (European Parliament Legislative Observatory 2010). The turbulent process leading up to the finally accepted Directive agreed upon by the European Commission, the European Parliament and the European Council on 7 April, 2010 was aptly described by the scientific journal Nature as "more than a decade of pitched battles between research advocates and animal-rights campaigners" (Abbott 2010).

Directive 2010/63/EU introduces substantial changes compared to 86/609/EEC. Setting the standard according to the most extensive and demanding national legislations may not have been explicitly established as the goal for the revision, but considering the aim to provide a level playing field, and the political impossibility of lowering standards in countries where extensive national legislation was in place, it was an unavoidable outcome. In his comparative analysis of the 1986 and the 2010 Directives, Thomas Hartung concluded that little would change for the countries with more demanding legislation, whereas for countries where legislation had been based mainly on Directive 86/609/EEC, a number of new demands would arise. Some of the most important features introduced by Directive 2010/63/EU are extended scope, enhanced focus on the 3Rs and alternative methods, mandatory project evaluation, severity classification and retrospective assessment, institutional animal welfare bodies as well as revised guidelines for accommodation and care, which are now mandatory. For a detailed, article by article, comparison of the two Directives, the reader is referred to Hartung (2010) and for a general overview of European legislation regulating animal research to (Guillen and others 2014).

Table 1. Overview of European governance and the status of animal welfare within the European Union

Brief overview of European governance	There are many different Europes in terms of Governance. Following World War II, two separate European governance projects were installed. The first, the Council of Europe, related to human rights and culture; the second is what is now the European Union, related to ensuring peace through free trade. The Council of Europe, with its current membership of 47 states, operates in International Law to produce various Conventions, particularly the European Convention on Human Rights (and the European Court of Human Rights). The European Union started its life as a Community of 6 Member States focused on coal and

	steel production. It has grown in two dimensions: geographically, from 6 to currently 28 Member States; and, in the depth and scope of the Union (from coal and steel, through a European Economic Community, to a single market and a more related social union, including foreign policy, for example. The 'operating software' of the European Union, where the extent of the delegation of authority and the competence of the union is found, are the two Treaties on European Union, and on the Functioning of European Union (TEU and TFEU), which have been amended over time by further Treaties (e.g. Maastricht, 1993 and Lisbon, 2009). Whereas the Council of Europe operates in International Law (whereby, having joined the Council, States negotiate each action - e.g. convention - and then decide individually whether to adopt it in their domestic Law), the European Union operates as a 'Supranational' State, whereby each participant Member State accepts the competence of the EU in defined matters - particularly the creation of a single market. The EU produces, through its democratic processes, legislation - particularly Regulations and Directives - that are binding on the Member States of the European Union. Whereas a Regulation has direct effect in Member State Law, a Directive must be implemented by Member State, giving rise to (slightly) different interpretations, and the use of some discretions found in the Directive.
Legal status of animal welfare in the European Union	The status of animal welfare within the European Union was first established in 1997 through a protocol annexed to the Treaty of Amsterdam requiring that animal welfare was to be considered in the development of European legislation Animal welfare as a set value of the European Union was further strengthened through the Treaty of Lisbon (2007), where it is now an independent Article requiring that "In formulating and implementing the Union's agriculture, fisheries, transport, internal market, research and technological development and space policies, the Union and the Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals, while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage." Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community, signed at Lisbon, 13 December 2007. Official Journal, C306, 17 December 2007.

Directive 2010/63/EU and Its Transposition

Since the legislation is by way of a Directive, transposition into national legislation is an important part of the implementation of the new law. Whereas an EU Regulation applies directly into member state law, a Directive must be 'transposed' - implemented - into member state law within a defined timescale to gain its effect. This generally gives some space for Member State discretion in the implementation: the Directive must be implemented into Member States' domestic Law, but first, there is formal discretion as a Directive will contain specific choices that a Member State can take, under specific conditions (perhaps requiring alternative safeguards), or second, because the act of transposition requires an interpretation of the language of the Directive's text, and that is essentially a political act. Therefore, whereas the aim of a Directive is harmonisation, there are limits to the level of harmonisation that can be achieved compared to the direct effect of a Regulation (that does not require the transposition). It is the role of the European Commission and the Court of Justice of the European Union (ECJ) to ensure that those differences resulting from the various ways of applying these discretions are not too wide to prevent the intended harmonisation.

Directive 2010/63/EU entered into force in the autumn of 2010 and required Member States to transpose it into national legislation by 1 January 2013. Transposition progressed at a very different pace within the different Member States. Only a minority complied within the deadline; most countries completed transposition during 2013. In two cases – The Netherlands and Italy – delays in transposing the Directive led to the European Commission referring the countries to the European Court of Justice for failure to enact EU legislation; however both countries eventually completed the transposition.

To help Member States in the implementation and to ensure a common understanding, the European Commission produced a number of guidance documents. These include a 'Questions and Answers' document on the legal understanding, and a series of guidance documents on different aspects of the Directive. These guidance documents were produced by expert working groups with representatives from different stakeholder organizations (e.g. industry, academia, NGOs, professional organizations) at meetings in Brussels, and the resulting documents were thereafter endorsed by the National Contact Points, i.e. the person in each Member State responsible for the implementation of the Directive. A list of the different aspects covered and a brief description of the content of the guidance documents is presented in Table 2. The content of the documents corresponds well to the most important new demands introduced by Directive 2010/63/EU, but does not give an exhaustive picture of the changes.

Table 2. The different aspects covered in guidance produced by expert working groups under the European Commission to support implementation of the Directive. Each of these topics corresponds to one (two for Severity assessment) guidance document available at http://ec.europa.eu/environment/chemicals/lab_animals/interpretation_en.htm.

Animal Welfare Bodies and National Committees: Guidance and principles of good practise on the design and functioning of Animal Welfare Bodies and National Committees for the protection of animals used for scientific purposes

Education and training: Education and training framework with a modular Learning Outcome-based training structure, principles and criteria for supervision, competence assessment, continued professional development and a mutual approval and accreditation of courses

Genetically altered animals: The principles of creation, establishment and maintenance of genetically altered animal lines and how these are considered within project authorisation and statistical reporting

Inspections and enforcement: Guidance and principles of good practice on the planning and execution of an effective inspection and enforcement programme

Non-technical project summaries: Guidance on the drafting and publication of non-technical project summaries including a template and an illustrative example

Project Evaluation/Retrospective Assessment: Guidance for performance of Project Evaluation including harm-benefit assessment and Retrospective Assessment of projects

Severity assessment: The severity assessment framework from project planning, monitoring and assessing the severity through to final assignment of actual severity. Severity assessment – illustrative examples

Other: Practices that are exempted from the scope; understanding of definitions for a procedure and project; use, re-use and continued use; multiple generic projects and complex or multi-disciplinary projects

Some transnational infrastructures have also being created to support implementation. Several of these have been instituted by the European Commission, whereas others were initiatives born out of practitioners' perceived need to network. The European Education and Training Platform in Laboratory Animal Science facilitates exchange of information on laboratory animal science education and training provided in different countries and by different providers in order to promote mutual recognition of training courses between countries. The PARERE Network (Preliminary Assessment of Regulatory Relevance) serves as the "single point of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation." (Article 47). There is an on-going discussion of the need for networks of animal welfare bodies and of animal ethics committees.

Directive 2010/63/EU goes beyond the general requirements for transposition of EU directives by also explicitly hindering Member States from developing national measures which are more restrictive than those set in the Directive. A Member State is only allowed to maintain more restrictive national measures provided these were in force in November, 2010 and the European Commission had been informed before 1 January, 2013. In 2016 the European Commission initiated an infringement process against Italy for imposing greater restrictions on animal research than what is mandated by the Directive (European Animal Research Association 2016).

Directive 2010/63/EU – Harmonization and Room for Interpretation

Directive 2010/63/EU is organized into three main sections: 56 Recitals, 66 Articles and seven Annexes. The Recitals form a structured narrative text which presents the reasons for the legal act and guidance for the implementation of the Articles, whereas the Articles and the Annexes, which complement them, provide the actual norms or rules introduced by the act. The Articles are organized into six chapters.

Chapter I, General provisions, establishes the situations in which the Directive applies and for what purposes animals can be used, defines key terms, and establishes the 3Rs principle as the guidance for animal experimentation. *Chapter II, Provision on the use of certain animals for procedures,* establishes the limitations for the use of endangered species, non-human primates, animals taken from the wild and stray and feral animals of domestic species and defines purpose-bred animals as the standard approach for animals of the typical laboratory species. *Chapter III, Procedures,* includes more specific provisions for implementing the 3Rs through methods, anaesthesia, severity classification, reuse of animals, endpoints, sharing organs and tissues and rehoming animals. *Chapter IV, Authorization,* establishes requirements for breeders, suppliers and users of animals in terms of conditions of care, responsibilities and training of personnel and advisory bodies. It further addresses inspections and requirements for project evaluation and authorization. *Chapter V, Avoidance of duplication and alternative approaches,* focuses on the recognition and development of non-animal alternatives and *Chapter VI, Final provisions* sets the rules for implementation, adaptation, reporting and the role of different entities. Finally, the seven annexes provide more detailed information complementing some of the articles.

The new Directive is in many respects a significant development from previous law. It is comprehensive, in as much as it seeks to regulate all aspects of the use of animals in scientific experiments. Thus, it has an increased scope in terms of the types of animals (now including not only vertebrates but also cephalopods and later fetal and larval stages of vertebrate animals) and the forms of animal use that are covered (research, testing and teaching). Furthermore, it regulates

(primarily through licensing) each aspect of the chain of animal involvement: the breeding of animals for use in science, the scientists engaged in research and testing, those who have welfare responsibilities for the animals during that period, and the institutions in which research takes place.

Thus, on the face of it, the new Directive produces a high degree of structural harmonization. Whether this is translated into harmonized practice depends upon how much underlying room for interpretation there is. In the following, we will look at three different issues which, as we will see, represent three different degrees of harmonization potential in practice: minimum standards for housing and care, restrictions on the use of different animal species and project evaluation and authorization.

Minimum Standards for Laboratory Animal Housing and Care

The standards for housing and caring for laboratory animals are laid down in Annex III of the Directive: Requirements for establishments and for the care and accommodation of animals. This approach, with an annex to the main text containing extensive technical detail, is the same as was used for Directive 86/609/EEC as well as for the European Convention ETS123. In fact, the standards used in the present Directive come from the revised version of the ETS123 Appendix A.

This text has been undergoing a very thorough revision since 1998. The revised version, published in 2006, was the result of more than five years of work of more than 50 experts on animal behavior, health and welfare. In addition to revising the existing technical standards, standards for a number of less common but still important animal species groups were developed. The standards now include rodents, rabbits, cats, dogs, ferrets, non-human primates, birds, reptiles and amphibians. (Forbes 2004) (Council of Europe 2006).

Annex III has a section which addresses general aspects of the oorganization of the animal facility (functions, general design and rooms of different types), environmental control (climate, lighting, noise and alarm systems) and animal care (health, housing environment, feeding/watering and handling). This is followed by a species-specific section that provides technical details and measures for minimum space requirements for animal enclosures of different species. Whereas Annex III is based on the ETS123 Appendix A, it incorporates only the engineering standards, thus leaving out the performance standards of Appendix A.

In the Directive itself, there is reference to Annex III in Articles 22 (Requirement for installations and equipment) and 33 (Care and accommodation). Article 22 requires that the standard set in Annex III is complied with in order for establishments to “have installations and equipment suited to the species of animals housed” and allows no exemption. Article 33, on the other hand, allows exemptions from Annex III “for scientific, animal-welfare or animal-health reasons”.

All in all, this part of the Directive sets a very clear minimum standard, for which there is little room for exemptions. That Article 22 does not allow exemptions means that an establishment must definitely have the capacity to comply with Annex III. The exemptions in Article 33 most likely only cover individual experiments or management situations, as it is unlikely that a justifiable reason can be presented for general exemptions from the minimum housing and care requirements defined in Annex III. Here, there is a potential for a high degree of harmonisation.

Restrictions on the Use of Certain Animal Species

In a number of Articles, the Directive restricts the use of particular animals: animals of endangered species, non-human primates, animals taken from the wild and stray/feral animals of domestic species. Each of these Articles starts by stating that animals of the type in question "shall not be used in procedures". However, for each case, there are also a number of foreseen exemptions, as illustrated in Table 3.

In all cases except for great apes, the foreseen exemptions are listed immediately after the statement that these animals shall not be used in procedures. For endangered species and non-human primates which are not great apes, the only limitation, in effect, is that the use of these animals may only be accepted for certain research purposes (see Table 3 for which purposes are allowed and for which species). The strongest restriction is on great apes: their use requires activation of the general safeguard clause Article 55. This permits a Member State to provisionally allow otherwise banned experiments if essential "for the preservation of the species or in relation to an unexpected outbreak of a life-threatening or debilitating clinical condition in human beings".

In terms of harmonisation, and strong animal welfare, the Directive appears very strong regarding the restriction of the use of particular animals. This creates a presumption that such animals should not be used, but there is still no absolute restriction. This opens the possibility for different interpretations at the national level – in fact, it explicitly gives competent authorities and Member States authority to determine when the conditions for exemptions are fulfilled. Thereby, room is created for different interpretations of what is required for exemption to the general rule.

Table 3. Overview of restrictions and associated exemptions on the use of different types of animals. The information is the authors' summary of the relevant Articles.

Type of animal	**Exceptions listed in the Article in question**	**Safeguard clauses (Art55)**
Endangered species (Article 7)	a) the procedure is for the purpose of - translational or applied research into human, animal or plant health - testing substances or products for the purposes of human, animal or plant health - research for preservation of the species and b) there is scientific justification that the purpose cannot be achieved using another species	-

Non-human primates (Article 8.1)	a) the procedure is for the purpose of - basic research - translational or applied research into debilitating or potentially life-threatening clinical conditions in humans - testing substances or products for the purposes of addressing debilitating or potentially life-threatening clinical conditions in humans - research for preservation of the species and b) there is scientific justification that the purpose cannot be achieved using another species	When a Member State has scientifically justifiable grounds for believing it is essential to use non-human primates for translational or applied research into human health, it may provisionally allow such use, provided the purpose cannot be obtained using another species.
Non-human primates of endangered species (Article 8.2)	a) the procedure is for the purpose of - translational or applied research into debilitating or potentially life-threatening clinical conditions in humans - testing substances or products for the purposes of addressing debilitating or potentially life-threatening clinical conditions in humans - research for preservation of the species and b) there is scientific justification that the purpose cannot be achieved using another species	-

Great apes (Article 8.3)	-	When a Member State has justifiable grounds for believing that action is essential for the preservation of the species or in relation to an unexpected outbreak of a life-threatening or debilitating clinical condition in human beings, it may provisionally allow the use of great apes in procedures, provided the purpose cannot be obtained using another species.
Animals taken from the wild (Article 9)	Competent authorities may grant exemptions on the basis of scientific justification that the purpose cannot be achieved using an animal that has been bred for use in procedures	
Stray and feral animals of domestic species (Article 11)	Competent authorities may grant exemptions only if a) there is an essential need to study the health and welfare of the animals or serious threats to the environment or human or animal health and b) there is scientific justification that the purpose can be achieved only by using a stray or feral animal	-

Project Evaluation and Authorization

The framework for evaluating and authorizing projects is an aspect which is substantially affected by the transposition of the Directive, in that an evaluation and subsequent authorization is now required before any experiment with animals is initiated. Furthermore, Member States are required to set up a competent authority to regulate and administer the evaluation and authorization of projects involving animal experiments.

As shown in Table 4, the Directive defines a number of criteria that should be satisfied for authorization to take place - articles 36, 37 and 38 establish the requirement for authorization, the

information which should be provided in applications and the aspects and expertise to be considered in evaluation - but the specific way in which authorization process is organized is not defined. In fact, Article 59 opens for the delegation of different tasks (including project authorization) to bodies other than the competent authority. The way project authorizations are handled plays a crucial regulatory role in that this is the mechanism which determines what research can take place and under what conditions. This is the reason why, in the ANIMPACT project, on which the present paper is largely based, we have mapped the systems for project evaluation and authorization across the EU in detail.

Table 4. Requirements for project authorization set in Directive 2010/63/EU. To increase readability, references to other articles have been simplified (text in square brackets)

Article 36 - Project authorisation 1. Member States shall ensure [except for when authorized under the simplified procedure established for routine testing] that projects are not carried out without prior authorization from the competent authority, and that projects are carried out in accordance with the authorization […] 2. Member States shall ensure that no project is carried out unless a favourable project evaluation by the competent authority has been received in accordance with Article 38.
Article 37 - Application for project authorization 1. Member States shall ensure that an application for project authorisation is submitted by the user or the person responsible for the project. The application shall include at least the following: (a) the project proposal; (b) a non-technical project summary; and (c) information on the elements set out in Annex VI. (…)
Article 38 - Project evaluation 1. The project evaluation shall be performed with a degree of detail appropriate for the type of project and shall verify that the project meets the following criteria: (a) the project is justified from a scientific or educational point of view or required by law; (b) the purposes of the project justify the use of animals; and (c) the project is designed so as to enable procedures to be carried out in the most humane and environmentally sensitive manner possible. 2. The project evaluation shall consist, in particular, of the following:

(a) an evaluation of the objectives of the project, the predicted scientific benefits or educational value; (b) an assessment of the compliance of the project with the requirement of replacement, reduction and refinement; (c) an assessment and assignment of the classification of the severity of procedures; (d) a harm-benefit analysis of the project to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment; (e) an assessment of any justification [required for a number of predefined exceptions]; and (f) a determination as to whether and when the project should be assessed retrospectively.

3. The competent authority carrying out the project evaluation shall consider expertise, in particular, in the following areas:

(a) the areas of scientific use for which animals will be used including replacement, reduction and refinement in the respective areas; (b) experimental design, including statistics where appropriate; (c) veterinary practice in laboratory animal science or wildlife veterinary practice where appropriate; (d) animal husbandry and care, in relation to the species that are intended to be used.

4. The project evaluation process shall be transparent. Subject to safeguarding intellectual property and confidential information, the project evaluation shall be performed in an impartial manner and may integrate the opinion of independent parties

When Directive 2010/63/EU entered into force, most if not all European Member States already had a system in place for evaluating and authorizing animal experiments. As can be seen in Table 4, the Directive gives detailed guidelines on *what is to be covered* in the evaluation, whereas it does not specify *how* it should be undertaken, e.g. regarding *the composition of reviewing body* and regarding on *what level* the evaluation is to take place.

As a result, the regulation is sufficiently general on project evaluation to allow an array of rather diverse previously established systems to continue to operate. Based on the information we have collected from Member State competent authorities (Silva and others 2015), it is evident that there is considerable diversity between Member States as regards the approach to evaluation and authorization, in terms of administrative/geographical organization as well as committee composition and expertise.

The geographic or administrative level organization includes a range of approaches: national, regional and institutional evaluation committees as well as combinations of these, as illustrated in Figure 1.

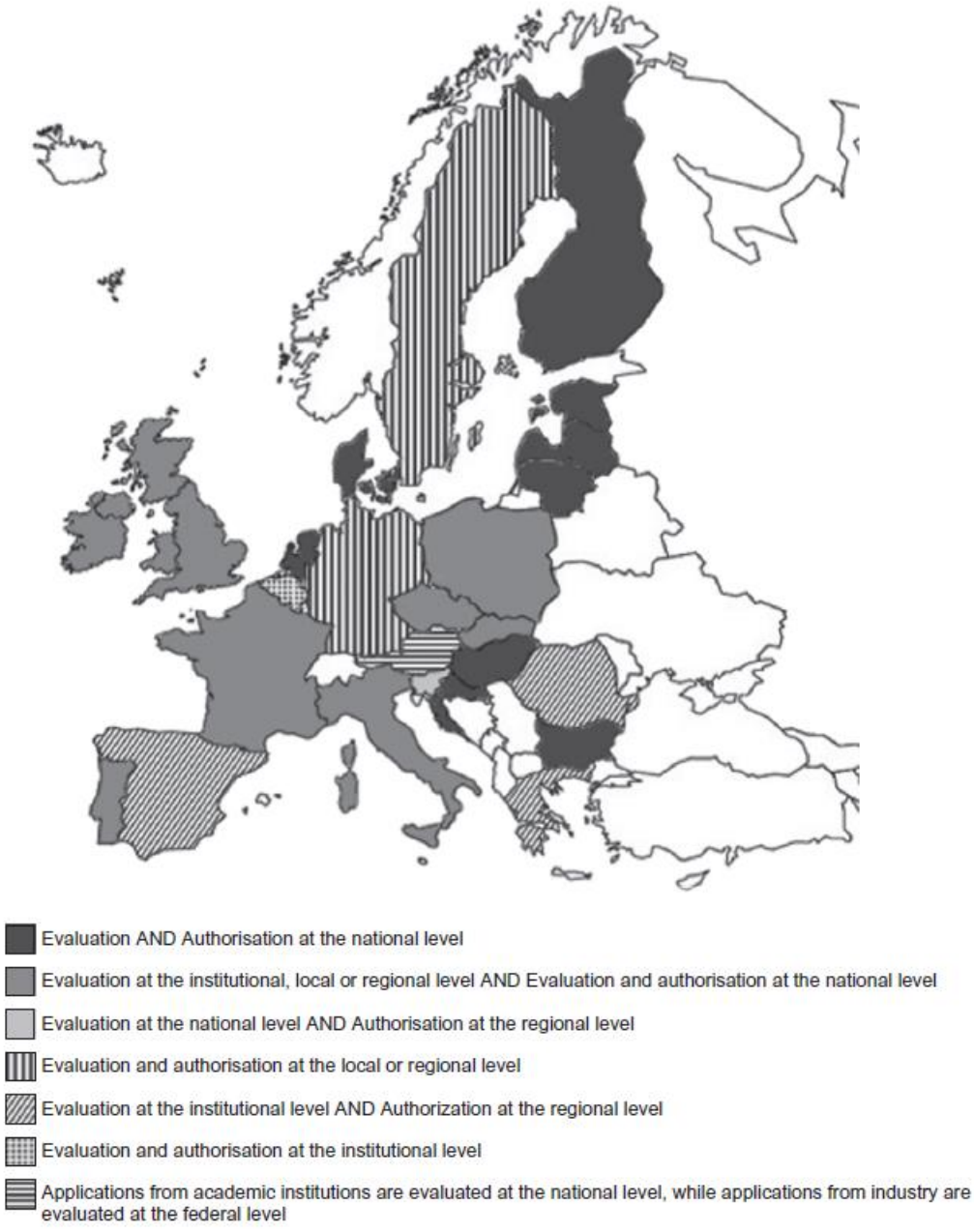

Figure 1 Diversity in administrative and geographical organization of project review for authorization of animal experiments in different EU Member States under Directive 2010/63/EU as of August 2015. Cyprus, Luxembourg and Malta were excluded from this mapping due to marginal relevance of animal research. Information confirmed by the respective Member State competent authority with the exception for Austria, Bulgaria and France.

Authorization may be granted by a single person at a governmental agency, but evaluation in all EU Member States is now carried out by a group of people with relative diversity in background and expertise. Even though the word “ethics” is actively avoided in the text of the Directive, in most countries these groups are referred to as animal ethics committees or variations of that term. In terms of composition, the committees vary in areas of expertise represented and in whether only technical expertise is included or is combined with

representatives of society and of special interest groups. S*cientific research* and *veterinary/animal welfare* expertise is required for nearly all countries where committee composition is regulated. *Legal, ethics* and *alternatives to animal experiments* are other types of recommended expertise in some countries, although less frequent. Of non-technical representation, animal protection NGOs is the most frequently included, whereas one country has patient representation. True lay representation without association to any special interest is less common. The balance in composition also varies. In all Member States, except for one, there is a majority of experts. Only Sweden has committees which are fully balanced between experts and non-experts. In the majority of Member States, the committees, in fact, *only* include experts. This variation in committee composition is probably still compatible with the Directive, which defines the areas of expertise which should be consulted in the evaluation as the areas of scientific use in question, experimental design, veterinary practice for the relevant species and animal husbandry and care (Article 38(3)).

How the variation in composition will affect the variation in outcome is not yet known - and it will not be simple to evaluate. But, it is known from an experimental study from the USA that even committees operating within the same national legislation and with similar composition evaluate projects differently, especially on aspects for which there are no detailed criteria (Plous and Herzog 2001).

Furthermore, European committees evaluating projects with animals are required to address a number of elements which are not clearly defined. An attempt to provide a comprehensive and standardized framework for harm-benefit analysis was recently proposed by an AALAS-FELASA working group (Bronstad and others 2016; Laber and others 2016); however this proposed framework has no legal status and is less than clear on a number of points.

Thus the "harm-benefit analysis of a project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations" is especially challenging (Olsson and others 2015), but also the assessment of whether the '3Rs' have been fully taken into account involve value judgements which allow for a huge element of discretion (Sandoe and others 2015). This gives reason to believe that there will not be a fully harmonised, level playing field when it comes to the crucial issue of how planned experiments are reviewed and under which conditions they will be authorized.

Criticism and Monitoring of the Directive and Its Implementation

Since its implementation, Directive 2010/63/EU has been publicly criticized primarily by groups arguing for increased protection of animals. In March 2015, the Citizen's Initiative (an instrument allowing EU citizens to participate directly in the legislative process) Stop Vivisection was submitted to the European Commission. The 1.17 million signees to this initiative asked for an abrogation of Directive 2010/63/EU and the adoption of legislation that would fully phase out animal experiments by 2020 (Stop Vivisection 2015).

The comparatively strong support this represents is clear when considering that since the Citizen's Initiatives instrument was introduced in 2010, only three initiatives have managed to gather the required number of signatures (a million citizens in total and a minimum number of

signatories in at least seven EU countries) to be received by the EC. However, the direct political consequences were minor or negligible.

In response, the European Commission clearly stated that the ultimate aim is full replacement of animal experiments but that this is presently not possible and that "a premature ban of research using animals in the EU would likely export the biomedical research and testing outside the EU to countries where welfare standards may be lower and more animals may be needed to achieve the same scientific results"(European Commission 2015).
The Commission further committed itself to actions to "accelerate the development and uptake of non-animal approaches in research and testing". However, these actions were presented in general terms rather than as measurable concrete activities.

Various mechanisms are in place to monitor how well the Directive and its implementation function. The Directive itself requires the European Commission to review legislation by November 2017 (approximately five years after its transposition into national legislation) "taking into account advancements in the development of alternative methods not entailing the use of animals, in particular of non-human primates, and shall propose amendments, where appropriate" and in addition "where appropriate, and in consultation with the Member States and stakeholders, conduct periodic thematic reviews of the replacement, reduction and refinement of the use of animals in procedures, paying specific attention to non-human primates, technological developments, and new scientific and animal-welfare knowledge" (Article 58). In June 2016, when this paper was written, the review procedure only just started through an online stakeholder consultation.

Funded under the European Seventh Framework Program for Research and Technological Development, the project ANIMPACT - *An ethical, legal and practical perspective on the impact of a new regulatory framework for the scientific use of animals on research and innovation* - has addressed the interaction between legislation and research under Directive 2010/63/EU. The present paper is the first to be published from the project. In-depth analyses of project review systems and of stakeholders' perception of European legislation regulating animal experimentation are underway.

In 2015 and 2016, The European Federation of Pharmaceutical Industries and Associations (EFPIA) organized workshops in which the functioning of different aspects of the legislation was discussed within a group of invited industry and public research representatives. Each workshop was preceded by a survey which produced input on how implementation worked in different member states. Following up on this, EFPIA together with FELASA (Federation of European Laboratory Animal Science Associations) and ESLAV (European Society for Laboratory Animal Veterinarians) set up a joint task force. With focus on "provisions which set new requirements, where experience is still limited or in areas where provisions can be interpreted in different manners", this group of experts will cover project review and authorization, genetically modified animals, severity classification (including animal reuse) and new functions and competences (Smith and Bonaparte 2016).

Discussion

Regulation of animal research in the European Union changed substantially when Directive 2010/63/EU replaced the much older and much less extensive Directive 86/609/EEC. Individual Member States had to transpose the new rules into their respective national legislation by

January of 2013, but in practice this is a process of change which actually started as early as 2010 when agreement was reached on the Directive and which is still ongoing. Besides the delay in formal transposition in many Member States, it takes time to implement the new measures in practice, in particular when these require the creation of new organisms, such as institutional animal welfare bodies. Faced with the challenge of analyzing an ongoing process, we focus in this paper on three different issues covered in the Directive and discuss how well the different objectives of the revised legislation are met through the manner in which each of these issues are regulated.

Two of the main objectives are clear from the two first recitals of the Directive (the part of an EU legislative instrument which sets out the reasons for the contents of the instrument): to create a level playing field for research and to increase the protection of animal welfare. The first of these two objectives derives from the widened notion of which activities fall within the scope of EU legislation. A level playing field is needed not only for industry but also for academic research; thus, all Member States within the EU need to have similar standards for research with animals.

The second objective arises with animal welfare having become part of the political scope of the EU through the Treaty of Lisbon, which makes it a legitimate and indeed mandated issue to consider in legislation. This is also related to the third objective, the promotion of the the 3Rs (Recital 11). We propose that a fourth objective exists, perhaps partly emanating from the previous objectives, and that is to ensure that research with animals will remain possible within the European Union. This has to do with making sure that not only does a potentially critical public view research with animals as a properly regulated activity (social license), but also that it does so without making demands which would negatively affect European research competitiveness internationally. The extent to which these four objectives are met vary considerably for the different issues under regulation, as we will see in the following discussion of the three cases chosen for analysis in this paper.

The objective of setting a level playing field and of harmonizing the regulation across the different European Member States is well covered through the *minimum standards for laboratory animal housing and care*, which are set forth in Annex III of the Directive. This annex sets detailed standards which must be followed in each Member State after the date on which they become active (1 January, 2017).

These standards also meet the objective of improving animal welfare considering that they have been developed through substantial work by experts on the behavior, welfare and health of the different animal species. Exemptions are allowed for animal health, animal welfare or scientific reasons, meaning that, for instance, fighting male mice can be separated and housed individually if they risk injuring each other, that an animal recovering from surgery may be kept individually and in a more confined space and, lastly, that individual housing in, for example, metabolic cages can be used to collect specific scientific data. However, there is no room for a general exemption which would allow an animal facility to run with substandard housing or care.

Above all, a potential effect on competitiveness could arise from the need to invest in new equipment to meet the standards. However, the time given before new measures become

mandatory should mitigate that by allowing the establishment to replace equipment gradually; since the requirements are formulated based on input from scientists in the field who collaborate on a global level, it is likely that standards for housing or care will not differ dramatically from other parts of the world, notably North America and Australia/New Zealand.

The *restriction on the use of certain species* for research is less straightforward. It seems on the face of it to have a substantial impact; the starting point is to exclude a number of animal groups from use in research, but for several of the groups in practice this impact is mitigated by the rather permissive exemptions built into the very same articles which intend to restrict animal use. In particular, when the exemptions are to be given by the competent authorities (such as for great apes, stray and feral domestic animals and animals taken from the wild), the practical implementation is likely to vary between countries, interfering with the objective of creating a level playing field.

From the perspective of improving animal welfare, the impact will depend on how much animal use is actually restricted. In addition, interestingly, restrictions are based on research purposes and not on the suffering of animals. This is in contrast with the Treaty's basis of protecting "the welfare of animals as sentient beings".

There will be an effect on competitiveness if the restrictions in practice stops European researchers from doing experiments that can be done in other parts of the world. The consequences of primate research increasingly being done in China rather than in Europe are being discussed in the scientific community but the discussion is based on the effects of a critical European public rather than restrictive legislation (Anonymous 2016).

The third issue, *project review and authorization*, is probably the most complex of the three. Individual Member States have to set up the infrastructure for review and authorization, without any direct guidance in the Directive, and have come up with highly varying approaches in terms of expertise involved and balance of committee composition. These highly variable committees are then asked to base their decisions on a less than well-defined mechanism – the harm-benefit analysis - and the outcome of these decisions will have a huge impact on research.

It seems obvious that the objective of creating a level playing field is poorly met here because the system is so variable across Member States. Given this variation, the impact on animal welfare will also vary across Member States. This variation may negatively affect competitiveness, particularly for international research projects when we take into consideration the uncertainty of what will be required for a project to be approved in the different countries.

In addition to the Directive itself, however, there are other mechanisms to support the implementation. On the initiative of the European Commission, as mentioned above, a series of guidance documents have been produced by expert working groups assembled for the purpose. These documents expand the reasoning on a number of various issues covered by the Directive, but despite the fact that they are often referred to as "consensus documents", they are not legally binding and they have been produced with less time and fewer resources than the official legal documents.

The Directive and its implementation is also a high priority issue of discussion for the professional organizations in the field. Working groups, workshops and an ongoing discussion of how to implement different issues have contributed to creating a view of a shared community under a shared legislation. In this context, it is also important to note that Directive 2010/63/EU was developed in EU27 – that is all current member states except Croatia, which only joined the EU in 2013, and have all been able to contribute actively to its development. This is very different from the 1986 Directive, which was developed by the much smaller EEC in 1986 and gradually imposed on a number of member states as the EU expanded.

Conclusion

Overall, when an issue is clearly described in sufficient detail in the Directive, with little room for different interpretations, transposition is likely to produce similar standards across the different Member States. Harmonization, on the other hand, is likely to be less successful when the Directive is less specific and when implementation relies on infrastructures which are highly variable and for which little common regulation exists.

We have shown three examples of varying degrees of expected harmonization. Furthermore, we argue that even though full harmonization may neither be possible nor wholly desirable, there is great value in the ongoing discussion and increased interaction and attention to the issue which the revision has generated. Irrespective of discrepancies in legislation, this process may contribute to creating a shared view of the purpose and scope of animal research legislation.

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