Comparative Analysis of the Revised Directive 2010/63/EU for the Protection of Laboratory Animals with its Predecessor 86/609/EEC – a t⁴ Report

Thomas Hartung
Johns Hopkins University, CAAT, US, and CAAT-Europe, University of Konstanz, Germany

Summary
On 8th September 2010 the long process of revising the EU Directive for the protection of laboratory animals was concluded. Here a comparative evaluation of the new and old Directive is provided. While its ultimate goal is to replace the use of animals, the new Directive acknowledges that animals, including non-human primates, are still needed for scientific purposes today. Importantly, animals have an intrinsic value, which must be respected. There are some major advances for animal welfare, many of which had however already been common practice in the more progressive Member States. The new Directive prohibits new, more progressive legislation if not already in place and thus harmonises but also freezes the 27 Member States at a relatively high level. The revision was an important opportunity for the European Commission, on the one side to demonstrate its commitment to improve human health and safety by enabling animal testing and on the other side to improve animal health and welfare by setting minimum standards. By this Directive Europe is again taking a leading role in research and development for new non-animal tests and technologies by introducing a series of measures that strengthen the evaluation of the need of animal use in each case. It also represents a formal implementation of the 3Rs principle (Replacement, Reduction and Refinement of animal tests) put forward by Russel and Burch 1959.

Keywords: European legislation, 3Rs, animal testing, animal welfare

1 Introduction

In 1986 the European Council of Ministers adopted Directive 86/609/EEC (European Commission, 1986) on "the protection of animals used for experimental and other scientific purposes". At this time, the European institutions had no formal mandate for animal welfare, but the legislation was justified as harmonising product access to the common market. The Directive focused on improving the control of the use of laboratory animals, structuring minimum standards for housing and training of those responsible for animals and monitoring the experiments. The Directive also aimed to reduce the numbers of animals used for experiments by requiring that an animal experiment may not be performed when an alternative method exists, and by encouraging the development and validation of alternative methods to replace animal methods.

Why was it necessary to revise the Directive? First of all, Europe has evolved and animal welfare has become an integral part, enshrined for example in the Lisbon treaty on the Functioning of the EU (Article 13). Already the Amsterdam Treaty of 1997 included an Animal Welfare Protocol. In 1998, by adopting Decision 1999/575/EC of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes prepared by the Council of Europe, to which the EU is party, the EU acknowledged the international importance of this area. The European Centre for the Validation of Alternative Methods (ECVAM) was established in 1991 and helped shape the field. The European Commission committed to a Community Animal Welfare Action Plan in 2006. Beyond this, there is technical progress in laboratory animal sciences, animal-using research and industries and their regulation, all requiring adaptation of the Directive to technical progress (Recital 6 of the revision[1]). Thus, in 2002, the European Parliament called on the European Commission to revise the Directive. The process to revise the Directive thus started (Louhimies, 2002; Binder and Lengauer, 2006; Ruhdel, 2007). In the meantime, the

[1] *"New scientific knowledge is available in respect of factors influencing animal welfare as well as the capacity of animals to sense and express pain, suffering, distress and lasting harm. It is therefore necessary to improve the welfare of animals used in scientific procedures by raising the minimum standards for their protection in line with the latest scientific developments."*

Council of Europe in 2006 developed guidelines for the accommodation and care of laboratory animals, which were adopted as Commission Recommendation 2007/526/EC in 2007; they now form the basis of Annex III of the new legislation.

The European Commission made a proposal for the revision of the Directive in November 2008 to the European Council and the Parliament. This proposal, compounded under the lead of Directorate General (DG) Environment, was based on input from a Technical Expert Working Group (representing science/academia, industry, Member States, non-governmental organisations (NGOs) and other experts) and relevant EU committees, i.e. the Scientific Committee on Animal Health and Animal Welfare (SCAHAW) and Scientific Committee on Health and Environmental Risks (SCHER) of DG Health and Consumer, the Animal Health and Welfare panel (AHAW) of the European Food Safety Authority (EFSA), as well as an expert group on severity. The process also included two public internet consultations in which more than 12,000 comments from 283 individuals were received. Remarkably, an impact assessment was carried out (http://ec.europa.eu/environment/chemicals/lab_animals/ia_en.htm), which aimed at qualification, quantification and monetisation (financial quantification) of impacts, which is obviously not always possible when ethical or welfare considerations are at stake.

Following the respective readings, positions and a tripartite compromise of April 2010, the revised Directive was adopted at its second reading in the European Parliament on 8th September 2010 (European Commission, 2010). It enters into force (EiF) 20 days after its publication in the Official Journal on 20 October 2010. The new Directive will take effect on 1st January 2013. While its ultimate goal is to replace the use of animals, the Directive acknowledges that animals, including non-human primates, are still needed today (Recital 10)[2]. However, the revision clearly acknowledges the intrinsic value of animals (Recital 12)[3], an important concept to distinguish them from goods and other possessions. European Environment and former Research Commissioner Janez Potočnik said in the respective press release on 9th September 2010: "Today's vote ends a long negotiation process, which has shown how sensitive and important the issues at stake are. However, everyone agreed that it is vital to improve the situation for animals still needed in scientific research and safety testing, whilst maintaining a high standard of research and improving the focus on finding alternative methods to animal testing. The European Union will soon have the highest standards of experimental animal welfare in the world."

This systematic analysis demonstrates and interprets the differences between the old and the new Directive. The Directive is horizontal to the different regulations for products such as chemicals (Hartung, 2010a), nanoparticles (Hartung, 2010b), cosmetics (Hartung 2008b), food / pesticides (Hartung and Koëter, 2008) or drugs. The revision is promoting paradigm changes, e.g. in toxicology (Hartung and Leist, 2008, Leist et al. 2008, Hartung 2009), prompted by shortcomings of animal tests (Hartung 2008a). This will stimulate further support and progress towards novel *in vitro* (Hartung, 2007a) and *in silico* approaches (Hartung and Hoffmann, 2009) and their validation (Hartung, 2007b).

2 Analysis of changes

The new legislation is introduced with 56 recitals. Recitals, i.e. "whereas" clauses, are found in contracts and in legislation. The old Directive did not include recitals. There is a general discussion on how recitals should be interpreted in view of the operative provisions of the articles and on whether they have any legal consequences (Klimas and Vaiciukaite, 2008). Courts must choose to view recitals as subordinate to, dominant over, or even equal to operative provisions. Recitals in EC legislation are supposed to be general statements and must specify the reasons the operative provisions were adopted. They thus describe the situation before and at the time of the legal act and the discussion that led to the legislation or regulation. They thus mainly aid in the interpretation of the articles.

For the scope of this journal, especially Recital 47 is of interest: "*(47) The European Centre for the Validation of Alternative Methods, a policy action within the Joint Research Centre of the Commission, has coordinated the validation of alternative approaches in the Union since 1991. However, there is an increasing need for new methods to be developed and proposed for validation, which requires a reference laboratory of the Union for the validation of alternative methods to be established formally. This laboratory should be referred to as the European Centre for the Validation of Alternative Methods (ECVAM). It is necessary for the Commission to cooperate with the Member States when setting priorities for validation studies. The Member States should assist the Commission in identifying and nominating suitable laboratories to carry out such validation studies. For validation studies that are similar to previously validated methods and in respect of which a validation represents a significant competitive advantage, ECVAM should be able to collect charges from those who submit their methods for validation. Such charges should not be prohibitive of healthy competition in the testing industry.*"

Noteworthy, this is the only place ECVAM is explicitly mentioned, in line with the Commission's policy not to specify in

[2] "While it is desirable to replace the use of live animals in procedures by other methods not entailing the use of live animals, the use of live animals continues to be necessary to protect human and animal health and the environment. However, this Directive represents an important step towards achieving the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so. To that end, it seeks to facilitate and promote the advancement of alternative approaches. It also seeks to ensure a high level of protection for animals that still need to be used in procedures. This Directive should be reviewed regularly in light of evolving science and animal-protection measures."

[3] "Animals have an intrinsic value which must be respected. There are also the ethical concerns of the general public as regards the use of animals in procedures. Therefore, animals should always be treated as sentient creatures and their use in procedures should be restricted to areas which may ultimately benefit human or animal health, or the environment. The use of animals for scientific or educational purposes should therefore only be considered where a non-animal alternative is unavailable. Use of animals for scientific procedures in other areas under the competence of the Union should be prohibited."

legal acts which part of the Commission must execute an obligation. The only laws referring to ECVAM so far are the 7th amendment of the cosmetics directive (European Commission, 2003; Directive 2003/15/EC in Recitals 5 and 7 and Article 2) and the REACH regulation (European Commission, 2006; Regulation No. 1907/2006). ECVAM was established by a communication of the Commission to the Council and Parliament only, which is difficult to retrieve (Bottini et al., 2008) and of unclear binding legal status. The new Directive now introduces a Union Reference Laboratory and the role is assigned to the Joint Research Centre of the Commission, which includes ECVAM. Article 47 demands that both Commission and Member States "*shall contribute to the development and validation of alternative approaches*", which goes further than the requirement to "encourage research" in the old text. The Union Reference Laboratory is introduced in Article 48 and specified in Annex VII; a delegation clause allows the Commission alone to change its role and who is charged with this role (Articles 50 to 53, see below). The duties and tasks of the Union Reference Laboratory, beside that it shall "*participate in the validation of alternative approaches*", which implies an active role of ECVAM in the execution of studies, not only their peer-review as is the case in large part for the US and Japanese counterparts, but does not state whether it implies laboratory work, according to ANNEX VII are:

"(a) *coordinating and promoting the development and use of alternatives to procedures including in the areas of basic and applied research and regulatory testing;*
(b) coordinating the validation of alternative approaches at Union level;
(c) acting as a focal point for the exchange of information on the development of alternative approaches;
(d) setting up, maintaining and managing public databases and information systems on alternative approaches and their state of development;
(e) promoting dialogue between legislators, regulators, and all relevant stakeholders, in particular, industry, biomedical scientists, consumer organisations and animal welfare groups, with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches."

They are very similar to those defined in the communication establishing ECVAM 1991. Notably, the ECVAM Scientific Advisory Committee, introduced in the Communication from 1991 as the peer-review body, is not included, but a Member State role to establish priorities for validation is called for (Article 47). Interestingly, in future ECVAM can ask fees for services which do not "*directly contribute to the further advancement of replacement, reduction and refinement*". This most likely refers primarily to the validation of me-too developments, i.e. methods which copy a validated method.

The new legislation also includes eight Annexes. Articles 50 to 53 give the Commission the right to change these Annexes, which allows adapting the legislation to technical progress without necessitating a revision involving Parliament and Council. This shortcut reflects that it was very difficult to achieve agreement on the revision as a whole, a process that ran from the mid-Nineties to 2010. Noteworthy, Article 58 foresees a report by the Commission after seven years on the functioning of the Directive, another measure to achieve timely adaptation where appropriate. The Annexes detail:

- ANNEX I: List of animals referred to in Article 10 (species needed to be purpose-bred)
- ANNEX II: List of non-human primates and dates referred to in the second subparagraph of Article 10(1)
- ANNEX III: Requirements for establishments and for the care and accommodation of animals
- ANNEX IV: Methods of killing animals
- ANNEX V: List of elements referred to in Article 23(3) (minimum requirements with regard to education and training and the requirements for obtaining, maintaining and demonstrating requisite competence)
- ANNEX VI: List of elements referred to in Article 37(1)(c) (minimum elements to be included in an application for project authorisation)
- ANNEX VII: Duties and Tasks of the Union Reference Laboratory
- ANNEX VIII: Severity classification of procedures

The comparison of the legal texts from 1986 and 2010 was based on the articles of the body of the legislation. Recitals and annexes were considered where necessary. Table 1 confronts the new legislation with the respective wording of the old legislation. The shortened version in the print article displays only the articles most relevant to alternatives to animal experiments; the full table is available on the ALTEX (www.altex.ch) and AltWeb (http://altweb.jhsph.edu/) websites. Interpreting comments represent the understanding of the author.

At this moment, the laboratory animal welfare provisions in different Member States are very different. Since Directive 86/609/EEC is binding, it can be considered the common minimum standard. However, many aspects were not very detailed or explicit. Some Member States go considerable lengths beyond these standards, and in general the new Directive now harmonises all Member States on this higher level. Thus, in practice, little will change for the countries already applying high standards of animal welfare and many new demands of the revised Directive may long be in practice in a given country. A comparison of the relevant legislation of the different Member States is beyond the scope of this article.

The main elements of change are:

a) Significant increase in animal welfare

First, the scope of the Directive is expanded to include basic research and education (Article 1). In 1986, the European Economic Community (EEC), the predecessor of the EU, had no mandate for animal welfare other than regarding aspects related to trade: the Directive gives as a whereas clause "*there exist between the national laws at present in force for the protection of animals used for certain experimental purposes disparities which may affect the functioning of the common market*". The use of wild animals (Article 9), endangered species (Article 7)

Tab. 1: Comparison of the Directives of 2010 and 1986 – excerpt of the articles most relevant to alternatives to animal experiments (the full version of this table can be found at www.altex.ch)

DIRECTIVE 2010/63/EU of 8 August 2010 on the protection of animals used for scientific purposes	**COUNCIL DIRECTIVE of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86/609/EEC)**	**Comments**
Article 1 **Subject matter and scope**		
1. This Directive establishes measures for the protection of animals used for scientific or educational purposes. To that end, it lays down rules on the following: (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.	**Article 1** The aim of this Directive is to ensure that where animals are used for experimental or other scientific purposes the provisions laid down by law, regulation or administrative provisions in the Member States for their protection are approximated so as to avoid affecting the establishment and functioning of the common market, in particular by distorsions of competition or barriers to trade. Article 3 This Directive applies to the use of animals in experiments which are undertaken for one of the following purposes: (a) the development, manufacture, quality, effectiveness and safety testing of drugs, foodstuffs and other substances or products: (i) for the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in man, animals or plants; (ii) for the assessment, detection, regulation or modification of physiological conditions in man, animals or plants; (b) the protection of the natural environment in the interests of the health or welfare of man or animal.	New: - educational purposes - reference to 3Rs - inclusion of breeding and supply - no positive list, to which type of procedures the Directive applies. This is a fundamental difference in comparison to the old Directive, which defined 'the scope' with the positive list. Thus anything outside the scope was merely just not regulated. The new Directive uses the positive list to state the areas for which purposes animals ***can be used***. Thus any other use will be prohibited in the future (within the context of the area of competence of the Community e.g. excluding use of animals for the benefit of national security).
2. This Directive shall apply 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. This Directive shall apply until the animals referred to in the first subparagraph have been killed, rehomed or returned to a suitable habitat or husbandry system. The elimination of pain, suffering, distress or lasting harm by the successful use of anaesthesia, analgesia or other methods shall not exclude the use of an animal in procedures from the scope of this Directive.		New: - inclusion of "intended to be used" - inclusion of animals bred for their organs and tissue - redefinition of end of procedure
3. This Directive shall apply to the following animals: (a) live non-human vertebrate animals, including: i) independently feeding larval forms, and	Article 2 For the purposes of this Directive the following definitions shall apply: (a) 'animal' unless otherwise qualified, means any live non-human vertebrate,	New: - extension to foetal organisms and cephalopods

ii) foetal forms of mammals as from the last third of their normal development; (b) live cephalopods.	including free-living larval and/or reproducing larval forms, but excluding foetal or embryonic forms;	
4. This Directive shall apply to animals used in procedures, which are at an earlier stage of development than that referred to in point (a) of paragraph 3, if the animal is to be allowed to live beyond that stage of development and, as a result of the procedures performed, is likely to experience pain, suffering, distress or lasting harm after it has reached that stage of development.		Clarification for treatment of mothers or early life forms
5. This Directive shall not apply to the following: (a) non-experimental agricultural practices; (b) non-experimental clinical veterinary practices; (c) veterinary clinical trials required for the marketing authorisation of a veterinary medicinal product; (d) practices undertaken for the purposes of recognised animal husbandry; (e) practices undertaken for the primary purpose of identification of an animal; (f) practices not likely to cause pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice.	Article 2 (d) …Non experimental, agricultural or clinical veterinary practices are excluded;	New: - Exclusion of veterinary clinical trials required for the marketing authorisation of a veterinary medicinal product
6. This Directive shall apply without prejudice to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.		Referring to: Regulation (EC) No 1223/2009 of 30 November 2009 on cosmetic products, which applies as from 11 July 2013, which revised the 7th amendment of the cosmetics directive from 2003.
Article 2 **Stricter national measures**		
1. Member States may, while observing the general rules laid down in the Treaty, maintain provisions in force on [EiF], aimed at ensuring more extensive protection of animals falling within the scope of this Directive than those contained in this Directive. Before [1 January of the third year following the EiF] Member States shall inform the Commission about such national provisions. The Commission shall bring them to the attention of other Member States.	Article 24 This Directive shall not restrict the right of the Member States to apply or adopt stricter measures for the protection of animals used in experiments or for the control and restriction of the use of animals for experiments. In particular, Member States may require a prior authorization for experiments or programmes of work notified in accordance with the provisions of Article 12 (1).	Change in attitude, which led to strong concerns by animal welfare groups. *Compare to recital (7): "In the interests of the animals, and provided is does not affect the functioning of the internal market, it is appropriate to allow the Member States certain flexibility to maintain national rules aimed at more extensive protection of animals in so far as they are compatible with the treaty."*
2. When acting pursuant to paragraph 1, a Member State shall not prohibit or impede the supply or use of animals bred or kept in another Member State in accordance with this Directive, nor shall it prohibit or impede the placing on the market of products developed with the use of such animals in accordance with this Directive.		Consequence of Common Market

EiF = Entry into Force, i.e. 20 days after publication in the Official Journal on 20 October 2010.

Article 3 **Definitions#**		New: - broader definition of “procedure” and “project” instead of experiment, including education, organ donation, genetic modification and use of animals for routine production. - Often confused issues: Killing is not within the scope of a "procedure", however, it does not exclude those animals from the scope of this Directive, i.e. animals bred for the purpose of their organs and their tissue are within the scope throughout their lifetime (Article 33) and the killing has to be carried out as per Article 6.
Article 4 **Principle of replacement, reduction and refinement**		
1. 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 7 2. An experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practicably available.	This has led to enormous discussions about the legal difference between “wherever possible” and “reasonably and practicably available”. Most probably they are minor, but interpretation might be influenced by Article 13, especially because of Article 4 (4).
2. Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.		
3. Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.	[see also new Article 22, old Article 19]	
4. This Article shall, in the choice of methods, be implemented in accordance with Article 13.		See above (1).
Article 5 **Purposes of procedures**		
Procedures may be carried out for the following purposes only: (a) basic research; (b) translational or applied research with any of the following aims: (i) the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in human beings, animals or plants; (ii) the assessment, detection, regulation or modification of physiological conditions in human beings, animals or plants; or (iii) the welfare of animals and the improvement of the production conditions for animals reared for agricultural purposes. (c) for any of the aims in point (b) in the	[see also new Article 1, old Article 3]	New: - extension to basic research, welfare of animals / production conditions, preservation of the species, higher education / vocational training and forensic inquiries - restriction of development, manufacture, quality, effectiveness and safety testing to aims under (b) See also Article 1

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feed-stuffs and other substances or products; (d) protection of the natural environment in the interests of the health or welfare of human beings or animals; (e) research aimed at preservation of the species; (f) higher education, or training for the acquisition, maintenance or improvement of vocational skills; (g) forensic inquiries.		
Article 6 **Methods of killing#**		List in Annex IV
CHAPTER II **PROVISIONS ON THE USE OF CERTAIN ANIMALS IN PROCEDURES** **Article 7** **Endangered species#**		
Article 8 **Non-human primates#**		New: - restriction of non-human primate use, though “A debilitating clinical condition for the purposes of this Directive means a reduction in a person's normal physical or psychological ability to function.” - ban of great ape use, though with a safeguard clause
Article 9 **Animals taken from the wild#**		New: - stricter wording against use of wild animals
Article 10 **Animals bred for use in procedures#**		List in Annex I New: - requirement to move over to second or higher generation purpose-bred non-human primates subject to a feasibility study - explore self-sustaining colonies for non-human primate breeding
Article 11 **Stray and feral animals of domestic species#**		New: - stricter wording for exemptions for use of stray and feral animals
CHAPTER III **PROCEDURES** **Article 12** **Procedures#**		New: - no isolated experiments that are not part of a larger project shall be authorised
Article 13 **Choice of methods**		
1. Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognized under the legislation of the Union.	[see also new Article 4, old Article 7]	New: - accepted alternative methods have to be used This led to enormous discussion, whether this weakens the “alternative clause” of Article 4, since the requirement is only for methods accepted in legislation (validated

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

		or not). Common interpretation is that this only stresses in addition to Article 4 the need to use accepted alternative methods for regulatory testing.
2. In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected, that is to say those which: (a) use the minimum number of animals, (b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm, (c) cause the least pain, suffering, distress or lasting harm, and are most likely to provide satisfactory results.	Article 7 3. When an experiment has to be performed, the choice of species shall be carefully considered and, where necessary, explained to the authority. In a choice between experiments, those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm and which are most likely to provide satisfactory results shall be selected.	- reduce, refine and use of lower species, i.e. with lowest capacity to experience pain, suffering, distress or lasting harm
3. Death as the end-point of a procedure shall be avoided as far as possible and replaced by early and humane end-points. Where death as the end-point is unavoidable, the procedure shall be designed so as to: (a) result in the deaths of as few animals as possible; and (b) reduce the duration and intensity of suffering to the animal to the minimum possible and, as far as possible, ensure a painless death.		New: - avoidance of death as endpoint
Article 14 **Anaesthesia#**		New: - Neuromuscular blocking agents cannot be used without anaesthesia or analgesia. In addition, their use requires a scientific justification
Article 15 **Classification of severity of procedures#**		New: - concept of severity - ban of very severe procedures which are long lasting and cannot be ameliorated
Article 16 **Reuse#**		
Article 17 **End of the procedure#**		New: - Definition on until when the creation of a genetically modified line continues to be considered a “procedure”
Article 18 **Sharing organs and tissues**		
Member States shall facilitate, where appropriate, the establishment of programmes for the sharing of organs and tissues of animals killed.		New: - facilitate sharing of organs and tissues
Article 19 **Setting free of animals and rehoming#**		New: - rehoming explicitly allowed
CHAPTER IV **AUTHORISATION** **SECTION 1** **REQUIREMENTS FOR BREEDERS, SUPPLIERS AND USERS**		

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

Article 20 **Authorisation of breeders, suppliers and users#**		
Article 21 **Suspension and withdrawal of authorization#**		
Article 22 **Requirements for installations and equipment#**		New: - From housing and care guidance (legally not binding) to standards (legally binding), a key element to achieve good animal welfare
Article 23 **Competence of personnel#**		New: - requirement to work under supervision until competence has been demonstrated. - minimum requirements for curriculum in Annex V
Article 24 **Specific requirements for personnel#**		New: - requirement for a named person responsible for the competence of staff - explicit animal welfare obligations for person named responsible
Article 25 **Designated veterinarian#**		
Article 26 **Animal-welfare body#**		New: - institutional animal welfare body
Article 27 **Tasks of the animal-welfare body#**		
Article 28 **Breeding strategy for non-human primates#**		New: - requirement to decrease captured non-human primate use in experiments and as breeders
Article 29 **Scheme for rehoming or setting free of animals#**		
Article 30 **Animal records#**		
Article 31 **Information on dogs, cats and non-human primates#**		New: - more explicit definition of animal records to be kept for dogs, cats and non-human primates - individual history file also covering social information is introduced, not only for non-human primates but also for dogs and cats
Article 32 **Marking and identification of dogs, cats and non-human primates#**		
Article 33 **Care and accommodation#**		New: - detailed definition of standards of care in Annex III, which can be amended without revision of the entire legislation

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

SECTION 2 **INSPECTIONS** **Article 34** **Inspections by the Member States#**		New: - improved frequency of inspections - unannounced inspections and use of a risk based approach
Article 35 **Controls of Member State inspections#**		New: - Commission to inspect Member State inspection systems
SECTION 3 **REQUIREMENTS FOR PROJECTS** **Article 36** **Project authorization#**		
Article 37 **Application for project authorization#**		New: - detailed list of elements for applications for authorisation in Annex VI
Article 38 **Project evaluation#**		New: - strict minimum requirements for a systematic and comprehensive project evaluation covering ◦ criteria ◦ the steps (including a detailed list of minimum elements to cover the application of the Three Rs as specified in Annex VI) ◦ expertise that needs to inform the process ◦ impartiality and transparency
Article 39 **Retrospective assessment#**		New: - tailor-made retrospective evaluation of projects involving procedures with severe harm, projects involving non-human primates as well as those selected within the evaluation of applications
Article 40 **Granting of project authorization#**		New: - detailed requirements for authorisations
Article 41 **Authorisation decisions#**		New: - detailed requirements for authorisation process
Article 42 **Simplified administrative procedure#**		New: - option for simplified authorisation process
Article 43 **Non-technical project summaries#**		New: - publication of anonymous non-technical project summaries
Article 44 **Amendment, renewal and withdrawal of a project authorization#**		New: - further detailed requirements for authorisation process
Article 45 **Documentation#**		New: - further detailed requirements for authorisation process
CHAPTER V **AVOIDANCE OF DUPLICATION AND ALTERNATIVE APPROACHES** **Article 46** **Avoidance of duplication of procedures**		

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

Each Member State shall accept data from other Member States that are generated by procedures recognised by the legislation of the Union, unless further procedures need to be carried out regarding that data for the protection of public health, safety or the environment.	Article 22 1. In order to avoid unnecessary duplication of experiments for the purposes of satisfying national or Community health and safety legislation, Member States shall as far as possible recognize the validity of data generated by experiments carried out in the territory of another Member State unless further testing is necessary in order to protect public health and safety.	Mutual acceptance of data
Article 47 **Alternative approaches**		
1. The Commission and the Member States shall contribute to the development and validation of alternative approaches which could provide the same or higher levels of information as those obtained in procedures using animals, but which do not involve the use of animals or use fewer animals or which entail less painful procedures, and they shall take such other steps as they consider appropriate to encourage research in this field.	Article 23 1. The Commission and Member States should encourage research into the development and validation of alternative techniques which could provide the same level of information as that obtained in experiments using animals but which involve fewer animals or which entail less painful procedures, and shall take such other steps as they consider appropriate to encourage research in this field. The Commission and Member States shall monitor trends in experimental methods. …	The basis for funding of the development and validation of alternative methods
2. Member States shall assist the Commission in identifying and nominating suitable specialised and qualified laboratories to carry out such validation studies.		New: - nomination of national laboratories
3. After consulting the Member States, the Commission shall set the priorities for those validation studies and allocate the tasks between the laboratories for carrying out those studies.		New: - consultation of member states as to priorities for validation and sharing of work
4. Member States shall, at national level, ensure the promotion of alternative approaches and the dissemination of information thereon.		New: - Member State obligation to disseminate information on alternatives
5. Member States shall nominate a single point of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation.		New: - Member state obligation to create single point of contact for advice on regulatory relevance of alternatives
6. The Commission shall take appropriate action with a view to obtaining international acceptance of alternative approaches validated in the Union.		New: - Commission obligation to foster international acceptance of validated methods
Article 48 **Union Reference Laboratory**		
1. The Union Reference Laboratory and its duties and tasks shall be those referred to in Annex VII.		New: - anchoring of an EU reference laboratory (ECVAM) ANNEX VII Duties and Tasks of the Union Reference Laboratory

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

		1. The Union Reference Laboratory referred to in Article 48 is the Commission's Joint Research Centre. 2. The Union Reference Laboratory shall be responsible, in particular, for: (a) coordinating and promoting the development and use of alternatives to procedures including in the areas of basic and applied research and regulatory testing; (b) coordinating the validation of alternative approaches at Union level; (c) acting as a focal point for the exchange of information on the development of alternative approaches; (d) setting up, maintaining and managing public databases and information systems on alternative approaches and their state of development; (e) promoting dialogue between legislators, regulators, and all relevant stakeholders, in particular, industry, biomedical scientists, consumer organisations and animal welfare groups, with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches. 3. The Union Reference Laboratory shall participate in the validation of alternative approaches.
2. The Union Reference Laboratory may collect charges for the services it provides that do not directly contribute to the further advancement of replacement, reduction and refinement.		New: - ECVAM can ask for fees
3. Detailed rules necessary for the implementation of paragraph 2 of this Article and Annex VII may be adopted in accordance with the regulatory procedure referred to in Article 56(3).		
Article 49 **National committees for the protection of animals used for scientific purposes**		
1. Each Member State shall establish a national committee for the protection of animals used for scientific purposes. It shall advise the competent authorities and animal-welfare bodies on matters dealing with the acquisition, breeding, accommodation, care and use of animals in procedures and ensure sharing of best practice.		New: - Member State obligation to create national committees
2. The national committees referred to in paragraph 1 shall exchange information on the operation of animal-welfare bodies and project evaluation and share best practice within the Union.		New: - network of Member State committees

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

CHAPTER VI **FINAL PROVISIONS** **Article 50** **Adaptation of annexes to technical progress#**		
Article 51 **Exercise of the delegation#**		
Article 52 **Revocation of the delegation#**		
Article 53 **Objections to delegated acts#**		
Article 54 **Reporting#**		New: - reporting requirement for European Commission on implementation of Directive every 5 years - Member State obligation to provide annual statistical reports - reporting on actual severity Continuation of statistical reports. Content of statistical reports to be defined as part of the implementation.
Article 55 **Safeguard clauses#**		New: - an extremely cumbersome opportunity to overcome otherwise banned use of non-human primates, especially great apes and very severe procedures
Article 56 **Committee#**		Comitology committee required to adopt measures under adaptation to technical process
Article 57 **Commission report#**		New: - European Commission has to compile within one year the Member State reports received every five years on implementation and provide this to the European Parliament
Article 58 **Review#**		New: - after seven years the European Commission shall provide a review with suggested changes, if appropriate, to the Directive, especially with regard to alternative methods
Article 59 **Competent authorities#**		Obligation to nominate national competent authorities
Article 60 **Penalties#**		New: - obligation to Member States to enforce the Directive with penalties
Article 61 **Transposition#**		
Article 62 **Repeal#**		Repeal of the old Directive from 1st Jan 2014 onward

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

Article 63 **Amendment of Regulation (EC) No 1069/2009#**		Referring to: REGULATION (EC) No 1069/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21st October 2009 laying down health rules as regards animal by-products and derived products not intended for human consumption
Article 64 **Transitional provisions#**		Projects authorised before 2013 and not extending past 2018 do not fall under the new authorisation process until 1st January 2019
Article 65 **Entry into force#**		
Article 66 **Addressees#**		
ANNEX I List of animals referred to in Article 10		
ANNEX II List of non-human primates and dates referred to in the second subparagraph of Article 10(1)		
ANNEX III Requirements for establishments and for the care and accommodation of animals		New: - Status changed from guidelines into minimum standards
ANNEX IV Methods of killing animals		minimum requirements with regard to education and training and the requirements for obtaining, maintaining and demonstrating requisite competence
ANNEX V List of elements referred to in Article 23(3)		minimum elements to be included in an application for project authorisation
ANNEX VI List of elements referred to in Article 37 (1)(c)		
ANNEX VII Duties and Tasks of the Union Reference Laboratory		
ANNEX VIII Severity classification of procedures		

= details available in the complete table available at www.altex.ch or http://altweb.jhsph.edu/

and stray or feral animals (Article 11) is largely prohibited. Animals under protection now also include (Article 1) cephalopods and foetal forms of mammals in the last third of (uterine) development, as well as earlier treatments if the animals are allowed to survive until this stage of development. It is not clear yet what this will mean for statistics of animal use, especially due to the strong increase in the use of fish, especially zebrafish, in recent years. It sets a first time line for the developmental stages, defining from which point on procedures are to be counted as animal experiments. This will probably impact on experimental protocols, e.g. using fertilised fish eggs.

Second, experiments on great apes are practically banned ("*great apes shall not be used in procedures*"). The safeguard clauses of Article 55 represent strong hurdles, as the EU committee established in Article 56 has to agree on the need for the given project and objections from various Member States are likely) and those on other non-human primates are discouraged (Article 8, Recital 17)[4]. Non-human primate research is restricted to medical research and development, i.e. "*translational or applied research with … aims [of] the avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality or their effects in human beings, animals or plants*" or "*in the development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feed-stuffs and other substances or products*" and to "*basic research or preservation of the species*". The Directive further requires scientific justification that no other species can be used and that a debilitating clinical condition is being studied, i.e. a certain severity of the disease under study, though the definition of debilitating provided, i.e. "*a reduction in a person's normal physical or psychological ability to function*", is very open.

Third, a process is detailed that includes the application for compulsory authorisation of establishments and projects (Articles 22 to 33, 36 to 45), with detailed requirements for the establishments, including competence of personnel (Article 23 and 24, Annex V), animal welfare bodies (Article 26) and designated veterinarians (Article 25) for each place, their more transparent evaluation and reporting based also on severity of procedures (Article 15), under national inspection (Article 34) including EU control of the national inspection services (Article 35), and retrospective evaluation (Articles 38 to 40, 43, 45 and Recital 40). The latter introduces a type of control of success of projects, especially those with a certain severity or those which use non-human primates. Systematic project (the term "ethical" was dropped in the political discussion) evaluation as part of the authorisation addresses the aims and objectives of the project, the application of the 3Rs (Annex VI), the severity classification of the procedures (Annex VIII), the harm-benefit analysis of the project and determines the need for a retrospective assessment at the end of the project. Noteworthy, very severe procedures are banned (Recital 23[5] and Article 15: "*Member States shall ensure that a procedure is not performed if it involves severe pain, suffering or distress that is likely to be long-lasting and cannot be ameliorated*.") though this is under a safeguard clause. Death as end-point of an experiment "*shall be avoided as far as possible and replaced by early and humane end-points*." (Article 13) The mandatory humane killing of animals is regulated by Article 6 and Annex IV, which give specific guidance for different laboratory animal species. The transparency of the evaluation is improved by the publication of non-technical summaries (with full regard to confidentiality), a transparent project evaluation process, which may incorporate the opinion of independent parties, and improved reporting. Increased transparency and better enforcement shall re-enforce self-compliance and facilitate earlier detection of non-compliance. Annual inspections (Article 34) of one third of user establishments, all establishments housing/using non-human primates and an appropriate proportion of unannounced inspections are an important part of this control. The possibility for EU controls of national inspections systems (Article 35) further strengthens these provisions. Noteworthy, Member States also "*shall facilitate, where appropriate, the establishment of programmes for the sharing of organs and tissues of animals killed*" (Article 18).

Fourth, minimum, binding housing and care requirements are included (Article 22, Annex III). They represent the standards the European Commissions has signed under agreements of the Council of Europe in 2007 (Recital 5[6]) and are thus already incorporated in the EU legislative framework through a Commission Recommendation 2007/526/EC.

Fifth, animal welfare bodies (Article 26-27) must be created in each establishment to foster a climate of care and ensure incorporation of the 3Rs, advising the staff on welfare of animals, on the application of the 3Rs and especially on developments for their applications, establishing/reviewing internal operational processes, following the development and outcome of projects and advising on re-homing schemes. A named person responsible for ensuring the training/education and competence is required in each establishment as is a "designated veterinar-

4 "Having regard to the present state of scientific knowledge, the use of non-human primates in scientific procedures is still necessary in biomedical research. Due to their genetic proximity to human beings and to their highly developed social skills, the use of non-human primates in scientific procedures raises specific ethical and practical problems in terms of meeting their behavioural, environmental and social needs in a laboratory environment. Furthermore, the use of non-human primates is of the greatest concern to the public. Therefore the use of non-human primates should be permitted only in those biomedical areas essential for the benefit of human beings, for which no other alternative replacement methods are yet available. Their use should be permitted only for basic research, the preservation of the respective non-human primate species or when the work, including xenotransplantation, is carried out in relation to potentially life-threatening conditions in humans or in relation to cases having a substantial impact on a person's day-to-day functioning, i.e. debilitating conditions."

5 "From an ethical standpoint, there should be an upper limit of pain, suffering and distress above which animals should not be subjected in scientific procedures. To that end, the performance of procedures that result in severe pain, suffering or distress, which is likely to be long-lasting and cannot be ameliorated, should be prohibited."

6 "On 15 June 2006, the Fourth Multilateral Consultation of Parties to the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes adopted a revised Appendix A to that Convention, which set out guidelines for the accommodation and care of experimental animals. Commission Recommendation 2007/526/EC of 18 June 2007 on guidelines for the accommodation and care of animals used for experimental and other scientific purposes incorporated those guidelines."

ian" (Article 25). The provisions for qualification of staff are also more detailed now (Article 24).

Several aspects have not been changed but represent important animal welfare requirements, which will benefit from stronger reinforcement now, i.e. mandatory inspections (Article 35) and penalties (Article 60). These include mandatory anaesthesia (Article 14) if not "*inappropriate*", avoidance of reuse of animals for severe procedures (Article 16), mandatory use of alternatives (Article 4 and 13) and mutual acceptance of data between Member States (Article 46) to avoid duplicate procedures.

b) Active promotion and implementation of the principle of the 3Rs (Article 1, Article 13)

The Directive spells out the principle of the 3Rs: Replacement, Reduction and Refinement in Article 1. It is ensured that Refinement is not limited to scientific procedures but is also relevant in relation to care, accommodation and breeding of animals. Like the 1986 Directive, the 2010 Directive also calls on the Commission and the Member States to promote alternative methods, also referring to research funding in Recital 46[7] and Article 47. To promote this, an EU Reference Laboratory for the validation of alternative approaches shall be created (Article 48), which shall be ECVAM as part of the Joint Research Centre (see above). Member States shall, according to Article 47, assist by identifying and nominating suitable laboratories for validation studies (Article 47.2: "*Member States shall assist the Commission in identifying and nominating suitable specialised and qualified laboratories to carry out such validation studies*"), appointing a single point of contact for assessment of regulatory relevance of a method (Article 47.5: "*Member States shall nominate a single point of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation*.") and set up national committees for the protection of animals used for scientific purposes (Article 49). This is what remained from the original Commission proposal to establish National Reference Laboratories to participate in validations; they were meant to co-finance and execute validation studies, but the concept did not survive the political decision process. Member States shall also promote alternatives at national level (Article 47.4: "*Member States shall, at national level, ensure the promotion of alternative approaches and the dissemination of information thereon*.") and the Commission at international level, which is now a more explicit obligation (Article 47.6: "*The Commission shall take appropriate action with a view to obtaining international acceptance of alternative approaches validated in the Union*."). A single contact point in the Member States has to be established and national committees for the protection of animals used for scientific purposes shall support the Member States (Article 49). Member states also have the obligation to disseminate information on alternatives. This in the end still calls for the creation of national centres, as they exist as governmental institutions in Germany and the UK, formerly in Sweden and is currently established in the Netherlands. However, non-governmental 3Rs centres, as created in Austria, the Netherlands, Poland and Finland, might also be appointed. The development, validation and use of alternative approaches are thus more firmly anchored.

c) Administrative flexibility

Some flexibility for implementation is foreseen, aiming to be output- not process-driven. For example, Member States can allow group authorisation of multiple generic projects if they are for regulatory or production/diagnostic purposes with established methods and simplified administrative procedures (excl. severe procedures or those using non-human primates).

3 Implementation

The implementation of the Directive by 1st January 2013 requires a number of measures and the creation of institutions by the Commission and Member States:

Member States have to designate one or more competent authorities (Article 59), national inspections systems (Article 35), single points of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation (Article 47), national committees for the protection of animals used for scientific purposes (Article 49), nominate on a per case basis suitable specialised and qualified laboratories to carry out validation studies (Article 47), ensure the promotion of alternative approaches and the dissemination of information thereon (Article 47), revise their reporting scheme (Article 54), etc. It is obvious that many of these functions could be bundled in National Centres.

The European Commission has to transform ECVAM into a Union Reference Laboratory (Article 48), establish reporting systems on the implementation of the Directive and animal use statistics (Article 57), set up an advisory Committee (Article 56), review the Directive (Article 58) and adapt the annexes to technical progress (Articles 50 and 51).

4 Criticism and conclusions

The new Directive is a compromise between different stakeholder groups. It has earned criticism from all sides, though all-together the compromise appears to be acceptable to most parties.

Animal welfare organisations (e.g. Dr. Hadwen Trust, Four Paws and Humane Society, 2009), while recognising the advances, have lobbied for stronger animal welfare requirements. They especially criticise the fact that individual Member States can no longer promote more rigorous animal welfare laws.

7 "The availability of alternative methods is highly dependent on the progress of the research into the development of alternatives. The Community Framework Programmes for Research and Technological Development provided increasing funding for projects which aim to replace, reduce and refine the use of animals in procedures. In order to increase competitiveness of research and industry in the Union and to replace, reduce and refine the use of animals in procedures, the Commission and the Member States should contribute through research and by other means to the development and validation of alternative approaches."

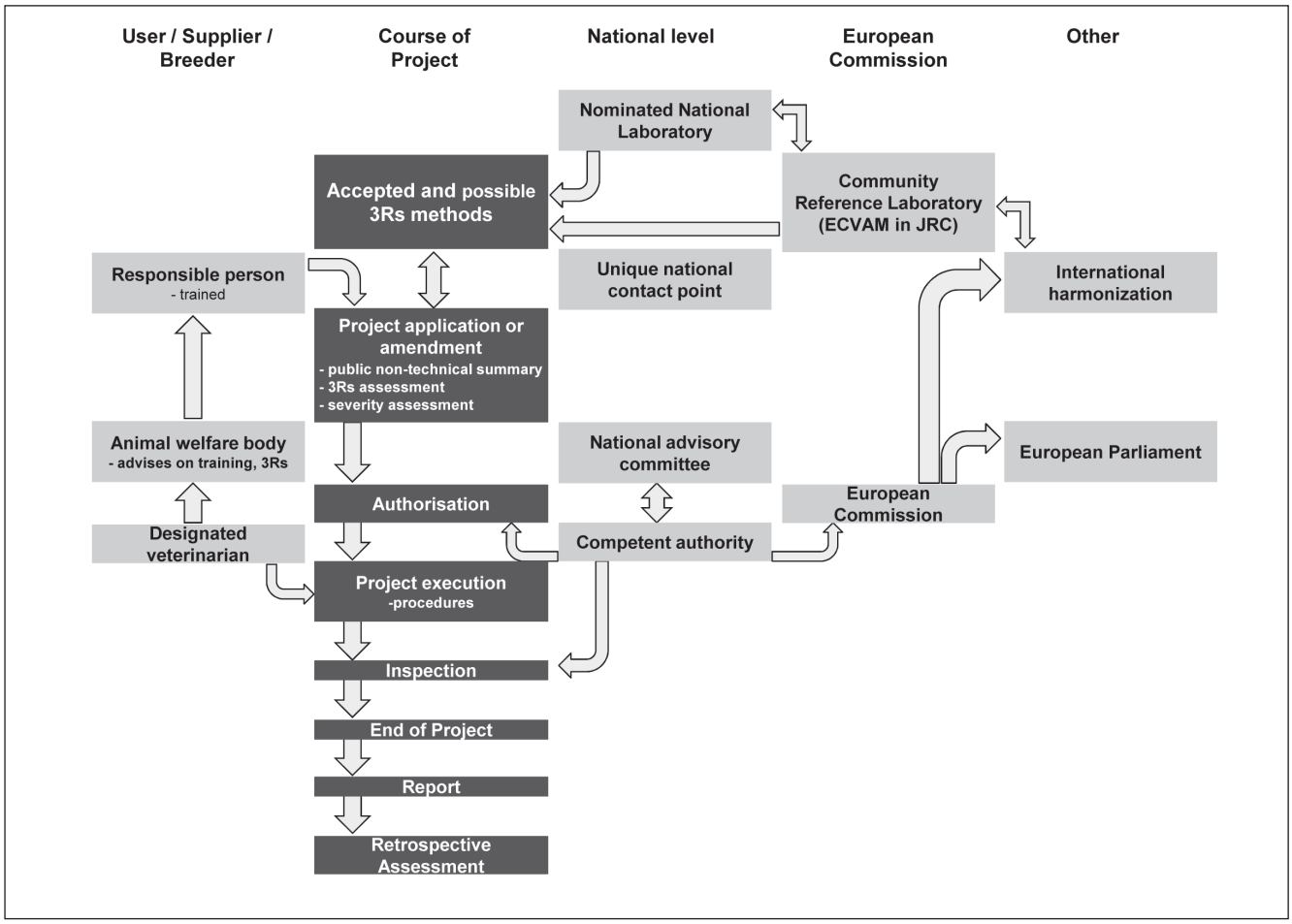

Fig. 1: Schematic diagramme of processes and interactions of the 2010 EU Directive on the protection of animals used for scientific purposes

There is a certain discrepancy that Recital 7 recognises the need that individual Member States pursue more progressive approaches[8], while Article 2 explicitly excludes this. There has been enormous discussion about the rephrasing of the animal welfare clause (new Article 4 versus old Article 13), i.e. the mandatory use of alternatives and the legal difference between "wherever possible" (new) and "reasonably and practicably available" (old). Most probably they are minor, but interpretation might especially because of Article 4.4 be influenced by Article 13: "*Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognized under the legislation of the Union*." This refers explicitly only to methods accepted by regulatory authorities after successful validation, i.e. currently only relatively few methods. The common interpretation, however, is that this only stresses next to the general provision to use alternatives in general (Article 4) the need to apply accepted alternatives in the field of regulatory testing.

The criticism made by animal welfare organisations is exemplified by the response of the European Coalition to End Animal Experiments (ECEAE, http://www.eceae.org/a1_directive.php):

"For example, the Directive will not include:

- *A ban on the use of wild-caught animals within short deadlines*
- *Clear restrictions on the use of non-human primates*
- *Strong restrictions on the repeated use of animals*
- *A complete ban on experiments which involve severe and prolonged suffering*

And many important issues that received strong public support were not addressed during the revision process:

- *A strategy to reduce and ultimately replace animal experiments*

[8] "Attitudes towards animals also depend on national perceptions, and there is a demand in certain Member States to maintain more extensive animal-welfare rules than those agreed upon at the level of the Union. In the interests of the animals, and provided it does not affect the functioning of the internal market, it is appropriate to allow the Member States certain flexibility to maintain national rules aimed at more extensive protection of animals in so far as they are compatible with the Treaty."

– *Funding to develop non-animal alternative methods*
– *An immediate ban on certain experiments such as those which do not relate to serious or life-threatening human conditions*
– *The inclusion of a system of data-sharing to avoid the duplication of animal experiments"*

Industry has brought forward concerns for competitiveness: the revision would create in many areas an enormous workload, excessive costs and also restrictions to research, without positive and clear benefits to animal welfare. This will make it very difficult to create international scientific collaborations with countries outside the EU. In this context it might result in market distortions and consequences will include being unable to face a global market and render the EU globally uncompetitive. However, we should be clear that most of the provisions, which are now going to be implemented in all Member States, are currently common practice and law in some of the more economically successful Member States. It is not clear whether animal studies and projects will now increasingly take place outside the EU under lower standards of welfare. The level of bureaucracy and increase of costs has to be considered: The revision of the Directive is complex (Fig. 1) and several levels of authorisations and review prior and during the project of research are introduced. Again, most of this is already done in some countries without major distortion of markets.

The research community was concerned during the discussion toward the revision mainly about the following aspects (EUROHORC, 2009; i.e. by the organisation of European Heads of Research Councils), which were considered to limit research:

1. Restriction of use of Non-Human Primates (Article 8)
2. Severity Levels (Article 15)
3. Restrictions on reuse (Article 16)
4. Extension of scope of Directive to cover invertebrates and larval forms (Article 2)
5. Care and accommodation (Article 33 and Annex IV)

Similar concerns were voiced by the European Coalition for Biomedical Research (http://www.ecbr.eu/).

For alternative methods, the Commission proposal from 2008 had suggested the creation of National Reference Laboratories to collaborate with the Commission (ECVAM) on validation. This proposal was abandoned during the decision process. The nominated national laboratories and national contact points represent a start, but not necessarily a financial commitment to further the case.

All together, the new Directive harmonises the Member States on a high animal welfare level. It further enhances the European legislation's pilot role in advancing these standards world-wide.

References

Binder, R. and Lengauer, E. (2006). The current revision of Directive 86/609/EWG from the perspective of animal welfare legislation. *ALTEX 23*,179-185.

Bottini, A. A., Alepee, N., de Silva, O. et al. (2008). Optimization of the post-validation process. The report and recommendations of ECVAM workshop 67. *ATLA 36*, 353-366.

Dr. Hadwen Trust, Four Paws and Humane Society (2009). Response to the European Commission's proposal to revise Directive 86/609 on the protection of animals used for scientific purposes [COM(2008)543/5]. Available at: http://www.makeanimaltestinghistory.org/resources/reports/Joint%20response%20to%20the%2086_609%20proposals.pdf

EUROHORC (2009). European Directive 86/609 on the protection of animals used in scientific procedures: Summary of the opinions of the members of EUROHORCs on the main areas of concern on the revised draft of the Directive. 6 April 2009. Available at: http://www.eurohorcs.org/SiteCollectionDocuments/EU_animals_Directive_revision_0904.pdf

European Commission (2010). Directive 2010/63/EU of the European Parliament and of the council of 22 September 2010 and of the council of 22 September 2010 on the protection of animals used for scientific purposes. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:EN:PDF

European Commission (2006). 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). *Official Journal 136*. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:EN:PDF

European Commission (2003). Directive 2003/15/EC of the European Parliament and of the council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. *Official Journal L66*, 26-35. Available at http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/200315/200315_en.pdf

European Commission (1986). Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes. *Official Journal L 358*, 1-28. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31986L0609:EN:HTML

Hartung, T. (2010a). Food for thought … on alternative methods for chemical safety testing. *ALTEX 27*, 3-14.

Hartung, T. (2010b). Food for thought … on alternative methods for nanoparticle safety testing. *ALTEX 27*, 87-95.

Hartung, T. (2009). Toxicology for the twenty-first century. *Nature 460*, 208-212.

Hartung, T. and Hoffmann, S. (2009). Food for thought on ... in silico methods in toxicology. *ALTEX 26*, 155-166.

Hartung, T. (2008a). Food for thought … on animal tests. *ALTEX 25*, 3-9.

Hartung, T. (2008b). Food for thought ... on alternative methods for cosmetics safety testing. *ALTEX 25*, 147-162.

Hartung, T. and Koëter, H. (2008). Food for thought ... on food safety testing. *ALTEX 25*, 259-264.

Hartung, T. and Leist, M. (2008). Food for thought … on the evolution of toxicology and phasing out of animal testing. *ALTEX 25*, 91-96.

Hartung, T. (2007a). Food for thought … on cell culture. *ALTEX 24*, 143-147.
Hartung, T. (2007b). Food for thought … on validation. *ALTEX 24*, 67-72.
Klimas, T. and Vaiciukaite, T. (2008). The law of recitals in European Community Legislation. *ILSA Journal of International & Comparative Law 15*. Electronic copy available at: http://ssrn.com/abstract=1159604
Leist, M., Hartung,T. and Nicotera, P. (2008). The dawning of a new age of toxicology. *ALTEX 25*, 103-114.
Louhimies, S. (2002). Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes. *ATLA 30, Suppl. 2*, 217-219.
Ruhdel, I. (2007). Revision of the EU Directive 86/609/EEC: results of the Internet consultations of the European Commission. *ALTEX 24*, 41-45.

Acknowledgement
The most valuable contribution from Annamaria A. Bottini and the discussion with the ECVAM legal taskforce over the years and especially Susanna Louhimies, DG Environment, who was the driving force behind this revision, is gratefully appreciated.

Correspondence to
Prof. Thomas Hartung, MD, PhD
Johns Hopkins Bloomberg School of Public Health
Dept. Environmental Health Sciences
Center for Alternatives to Animal Testing
615 N. Wolfe St.
Baltimore, MD, 21205, USA
e-mail: THartung@jhsph.edu

Calendar of Events

» t[4] Workshop: Critical evaluation of the use of dogs in biomedical research & testing: an information day and workshop
January 12-13, 2011
Johns Hopkins University, CAAT
Baltimore, USA
http://caat.jhsph.edu

» t[4] Workshop: In-depth exploration of the possibilities of using *in vitro* biomarkers for organ toxicity in the risk assessment process
January 17-19, 2011
Utrecht University
Utrecht, The Netherlands
http://caat.jhsph.edu

» ICCVAM Workshop Series on Best Practices for Regulatory Safety Testing
January 19-20, 2011
William H. Natcher Conference Center
Bethesda, MD, USA
http://iccvam.niehs.nih.gov/meetings/schedule.htm

» Workshop on *in vitro* toxicology
January 21-24, 2011
Department of Endocrinology, Taramani (University of Madras)
Chennai, India
Information: Mahatma Gandhi Doerenkamp Center, mgdcaua@yahoo.in

» International Conference on Ecosystem Conservation and Sustainable Development. Workshop Animal Alternatives and Sustainable Development
February 10-12, 2011
Ambo University
West Shoa, Ethiopia
Information: drpnatarajan123@gmail.com

» Society of Toxicology 50[th] Annual Meeting
March 6-10, 2011
Walter E. Washington Convention Center
Washington DC, USA
http://www.toxicology.org/ai/meet/am2011/

» Norecopa Consensus Meeting: Harmonization of the care and use of agricultural animals in research
May 10-12, 2011
Oslo, Norway
http://wwwnorecopa.no/sider/tekst.asp?side=21

» UFAW International Symposium 2011
June 28-29 2011
Portsmouth, UK
www.ufaw.org.uk

» Third International Conference on Alternatives for Developmental Neurotoxicity Testing (DNT)
May 11-13, 2011
Ispra, Italy
http://ihcp.jrc.ec.europa.eu/docs/flyer/dn3_first_brochure.pdf

» International course in Laboratory Animal Science
July 4-15, 2011
Utrecht, The Netherlands
http://www.uu.nl/lascourse

» 8[th] World Congress on Alternatives & Animal Use in the Life Sciences
August 21-25, 2011
Montréal, Canada
http://www.wc8.ccac.ca/

» 47[th] Congress of the European Societies of Toxicology
August 28-31, 2011
Palais de Congrès de Paris
Paris, France
http://www.eurotox2011.com/site/-Homepage,1551-

» Sens-it-iv End Congress: The Sens-it-iv Tool Box and Scientific Spin-offs
November 24-25, 2011
Crowne Plaza Airport Hotel
Brussels, Belgium
http://www.sens-it-iv.eu/index.php?id=1100