EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

ESF-EMRC Position on the Proposal for a Directive on the Protection of Animals used for Scientific Purposes

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The aim of this paper of the European Medical Research Councils (EMRC), the Standing Committee for Medical Sciences at the European Science Foundation (ESF), is to provide an input into the discussions on the revision of the EC Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes.

This paper summarises the current scientific and technical positions on eight elements of the proposed revision of the Directive of those medical research councils in Europe that are ESF Member Organisations (MOs). It builds on previous work of the ESF[1,2] and draws on documents produced by ESF MOs at the various stages of the consultation process for the revision of this Directive.

The two key reference documents for this paper are the public version of the European Commission proposal for a directive of the European Parliament and of the Council on the protection of animals used for scientific purposes (5/11/2008) and the European Parliament Draft report on the proposal for a directive of the European Parliament and of the Council on the protection of animals used for scientific purposes (18/02/2009).

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Introduction

The high-level pan-European Expert Group (EG) of scientists, representing 11 EU nations and including several physicians and veterinarians met recently in Berlin to consider the two key reference documents mentioned above and to try, even at this late stage, to make sure that the new Directive reinforces some of the fundamental principles that should be applied to the use of animals in scientific research. Three main themes run through the conclusions of the Expert Group.

- First, the overarching importance of the 3Rs (refinement, reduction and replacement), which actually provide a comprehensive set of guiding principles for many areas of the Directive and avoid complications in many areas (e.g. re-use, different regulations for different species, alternative approaches, etc.)
- Second, the importance of the harm-benefit analysis for each prospective project involving animals in research and coupling this to the improvement of animal welfare to the highest level compatible with the scientific objectives of the project. The Directive should allow sufficient flexibility to allow further improvement in animal welfare over and above that set by the Directive and its technical annexes.
- Third, that in order to improve animal welfare, the Directive must promote efficient decision making with defined time limits and the minimum of bureaucracy.

The comments expressed in this paper fall under eight key areas of the Directive, and they are discussed in the numerical order of the relevant Articles.

'Scope of the Directive' (Art. 2) and 'Definitions' (Art. 3)

It is important the Directive defines its scope. For example, that research involving farm and wild animals is not hindered by applying the same rules as those intended for laboratory-based animals. There must be good scientific evidence as to why a particular species should be included under the Directive, and precise definition of the developmental stages of the species that are covered by the Directive. For mammals, the EG supports the view that foetal forms in the last third of gestation should fall under the Directive. While the EG supports the view of a number of invertebrates, in this case only the adult form should be included. Otherwise enormous numbers of planktonic forms would be covered. There is no evidence as to why they should be included, and inclusion of these forms would make it impossible to reduce the numbers of animals used in experimental research.

1. ESF SPB N°9 "Use of Animals in Research", September 2000 & ESF SPB N°15 "Use of Animals in Research", August 2001 (2nd Edition)
2. ESF-EMRC "Position on the Proposed Revision of the Directive on the Protection of Animals Used for Experimental and Other Scientific Purposes (86/609/EEC)", September 2008

‘Non-Human Primates’ (Art. 8)

Both the Recitals and Articles of the revised Directive must recognise the major contribution made by current research in non-human primates (NHPs). This contribution has been outlined in very considerable detail in both the recent EU-SCHER report (2009) and the UK Weatherall Report (2006). This applies not only to devastating diseases such as AIDS, chronic conditions such as spinal cord injury and Parkinson’s disease, but is of equal importance to our understanding of basic science. The EG wish to emphasise that it is translation of this basic knowledge that leads to all improvements in both human and veterinary welfare.

The revised Directive should make clear why all research proposals involving NHPs need to be looked at with such care. Whether or not a species needs special protection should not be based solely on its phylogenetic relations to humans, but on its potential for suffering. NHPs are distinguished by the very advanced nature of their social, cognitive, sensory and motor functions. It should also be made clear that these same characteristics, which help to define them as a separate group under the Directive, also make them the best available model for invasive study of such functions in humans. The EG is of the view that blocking basic research will, in fact, prevent the translation of progress from the basic laboratory to the understanding of diseases which target these particular functions and which are therefore so debilitating for human patients.

Critically, the EG is firmly of the opinion that Article 8, paragraph 1 must be revised to continue to allow basic research in NHPs.

The EG agrees that a strong ethical and scientific case must be made before such research can be permitted and proposes amending the Directive to clarify that the scientist applying to the permanent ethical review body must provide this justification (Article 8, paragraph 1).

The EG also feels that the special place of the great apes needs further explanation (Article 8, Article 50). The EG felt strongly that research in great apes can only be justified for research aimed at “the avoidance, prevention, diagnosis or treatment of life-threatening or debilitating clinical conditions in human beings”, and requiring the highest level of justification and review. However, the Commission should recognise that a total ban on great ape research, as set out in Article 8 paragraph 2, will terminate all prospects of such research in the EU in the future, with a potentially disastrous outcome for the ability to tackle diseases that might be particularly targeted at humans and other advanced primates.

A total ban would also logically and ethically require that the EU bars its citizens from any medical advances achieved outside the EU, based on research on great apes. For example, a Hepatitis C vaccine is being currently developed in the USA in chimpanzees, the only non-human species susceptible to this disease.

The Expert Group’s proposed rewording of Article 8 guarantees a special protection for great apes because it restricts their use to very special circumstances. This ensures that the demand, of the declaration 0040/2007 that, making ending the use of apes in scientific experiments an urgent priority’ is fulfilled.[3]

Banding of procedures according to Severity -‘Anesthesia’ (Art. 14) and ‘Classification of Severity Procedures’ (Art. 15)

The EG believes it very important that the banding of procedures is properly and precisely defined, and Annex VIIa provides guidelines to definitions of banding using the Swiss system. Explicit examples are provided. The Group would also like to stress that many projects involving NHPs involve procedures that are rated as ‘mild’, including, for example, the training of animals for food or fluid reinforcement.

The Group proposes that Article 15 paragraph 2 be amended to make sure projects requiring ‘severe’ procedures should be exceptional, and should be licensed in response to the provision of a sound scientific and ethical justification by the applicant to the permanent ethical review body.

Re-Use’ (Art. 16) and ‘General Definitions of Degrees of Severity’ (Annex VIIa) referred to in Article 15(1)

This is an area where the Directive should be amended using the 3Rs as key guiding principles. The revised Directive should clarify the important distinction between “continued use” of pre-prepared animals that can and (in the interests of the 3Rs) should be used multiple times, and “re-use” in an entirely new procedure. This is a sufficiently important point to warrant absolute clarity. The EG also views that, for 3Rs reasons, it should be possible to use animals, including those in a ‘severe’ procedure, in terminal, non-recovery procedures carried out under general anaesthesia. Thus it is important that ‘non-recovery’ remains in a separate band in the new Annex VIIa.

3. While we believe that there are reasons why NHPs should be considered separately, as a principle it is unhelpful and unworkable to draw up different regulations for different species. The regulations must be based on the harm-benefit analysis and the 3Rs. Therefore the EG believes that no specific reference should be made to cats and dogs in the revised Directive.

Final Report and 'Retrospective Assessment' (Art. 38)

The EG believes it is important to provide clarification in this area. A final report should be required from every licensed project and this should be submitted to the permanent ethical review body. Having received this report, the competent authority may decide to carry out a retrospective assessment (Article 38, paragraph 1). The 3Rs should provide the major rationale for both final reports and retrospective assessments. That is, what has been learned from the project than contributes to further refinement, reduction and replacement? The EG also felt it was important to make sure that the Directive makes it explicit that retrospective assessment does not require re-evaluation of the ethical arguments, since these must have been dealt with already when the permanent ethical review body agreed to license the project.

Timetable of 'Authorisations Decisions' (Art. 43)

The EG insists that the bureaucratic implementation of the Directive must be clear and well-defined, including the timetable for licensing of research by the permanent ethical review body and the competent authority. The Group suggests that, after the applicant has submitted an application for a licence, a 90-day upper limit be set for reaching a decision for applications involving non-human primates, and that a similar limit for projects whose overall banding is rated as 'severe'.

Avoiding duplication and sharing of data –'Unnecessary duplication of procedures' (Art. 44)

The Expert Group strongly supported the overall concept of data sharing to improve the quality of the science and avoid unnecessary duplication of animal experiments. The avoidance of duplication is already an issue routinely considered both by funding agencies and by ethical review bodies, and is a requirement of the Directive (see Annex VII). However, the revised Directive must recognise the major practical differences between procedures performed to generate data required by law (which have to follow strict and uniform protocols) *versus* those of basic research where every project and almost every protocol is different, and where the procedures and the data generated with them are, by the very nature of fundamental research, not yet validated. It is therefore not appropriate to demand acceptance of non-validated data; indeed it may be necessary to validate them with some repetition of related, if not identical, procedures. Promoting the sharing of data is uniformly accepted as desirable. It happens extensively in basic research via collaborations, conferences and formal publications. Most recently there have been worldwide efforts to place all published results within the public domain by research funders insisting that articles are published on an 'open-access' basis. These activities and other more formal structures (such as sharing of genomic information from mouse strains) are already promoted and actively funded by research agencies and charities. The bioscience sector believes that it has already delivered very significant progress on data sharing.

Turning to some of the specific requirements of the Directive, the requirement that those working in fundamental bioscience research should contribute financially towards work that had already been executed and published (Article 44, paragraph 2a) is unworkable. Funding strategies are already highly constrained in both scope and quantity, and it is inconceivable that funding agencies would pay for access to such data. Moreover, restricting such an arrangement to EU partners would likely violate international trade rules; but sharing data outside the EU would be a one way loss of data that would radically compromise EU competitiveness.

Checking for existing, published data relevant to proposed research projects is already a central part both of funding agencies' evaluation of projects submitted to them, and of the local ethical review process. No Member State or other licensing authority, can "verify whether such data exists" (Article 44, paragraph 2b); approximating to that requires expert scientific input best provided by the applicants themselves in their application to the permanent ethical review body.

Promoting the 3Rs throughout the EU as an alternative to 'National reference laboratories' (Art. 46)

The draft revised Directive ensures that the principle of the 3Rs (reduction, replacement and refinement) – notably absent from many areas of the current Directive – is rigorously applied. *Article 45* states that *"The Commission and Member States shall contribute to the development and validation of alternative approaches that could provide the same or higher level of information as that obtained in procedures using animals but that do not involve the use of animals or use fewer animals or which entail less painful procedures, and shall take such other steps as they consider appropriate to encourage research in this field"*.

It is important for the welfare of animals and for the maintenance of public trust that there is a continued and increased funding for research aimed at the development

and validation of all 3Rs including alternatives to the use of animals in fundamental research and regulatory testing. Because at present alternative methods obviously are lacking, especially research on the development of new methods and truly innovative approaches should be supported. For this purpose 3Rs research programmes should be initiated or enhanced by the Member States as well as by the Commission. A further measure to promote alternative approaches can be the establishment of National Centres for 3Rs in Member States that have the capacity to do this.

Alternative methods for replacement, and in addition, refinement and reduction in animal experiments should only be accepted after peer review of the scientific quality of the work and, where necessary, after formal validation. The scientific community takes seriously its responsibility to progress and implement up-to-date knowledge on the 3Rs. If a revision of the Directive is to result in stronger constraints on the use of animals, this will not necessarily encourage the development of alternative methods, which are currently limited. This applies to nearly all species used in animal experiments. With respect to non-human primates the comment in the working mandate of the EC's Scientific Committee on Health and Environmental Risks (SCHER) supports this stating *"not enough alternative methods are yet available to replace the use of non-human primates in all areas of biomedical research today."*
Article 46, is entitled *"National reference laboratories for alternative methods"* and states *"Each Member State shall, within, one year after entry into force of this Directive, designate a national reference laboratory for the validation of alternative methods replacing, reducing and refining the use of animals."* The ESF Expert Group does not support this article, as it is neither necessary nor feasible to have a national reference laboratory in each EU Member State for the validation of alternative methods. We should prefer to see the emphasis placed on properly funded 3Rs led-research. For a formal validation only a few (2-3) laboratories are necessary in Europe, selected on the basis of their expertise. Member States should cooperate and jointly designate reference laboratories that could perform validation studies in cooperation with the European Centre for the Validation of Alternative Methods (ECVAM). Therefore, *Article 46* should be amended by deleting the word "national" wherever it occurs in the text.

It is surprising that ECVAM is not even mentioned in *Article 46* (or other *Articles*). As the Commission created ECVAM in 1991 specifically for the validation of alternative methods this institution should be mentioned in the text and its principle tasks should be described. Therefore, a new paragraph should be inserted as *Article 46.1*: *"The role of the European Centre for the Validation of Alternative Methods shall be strengthened so that it includes the co-ordination and promotion of the validation and use of alternatives to animal procedures including applied and basic biomedical and veterinary research and regulatory testing. Furthermore, ECVAM shall communicate information on the availability and application of alternative methods to the relevant authorities of the Member States"*. Then *Article 46.4(c)* should be deleted because communication of information is one of the main tasks of ECVAM.

Summary

At their meeting in the last week of February 2009, the high level pan-European Expert Group (EG) concluded that the new EU Directive requires amendments to be sure that it reinforces some of the fundamental principles that should be applied to the use of animals in scientific research i.e.:
– The overarching importance of the 3Rs (refinement, reduction and replacement).
– The importance of the harm-benefit analysis for each prospective project involving animals in research and coupling this to the improvement of animal welfare to the highest level compatible with the scientific objectives of the project.
– The need to promote efficient decision making with defined time limits and the minimum of bureaucracy so as to further improve animal welfare.

Among the eight key areas of the Directive that are still causing concerns three continue to have a major impact on the future of human health in Europe:
– Basic research in non-human primates.
– Sharing data to prevent unnecessary duplication of procedures.
– Promotion of the 3Rs.

Progress in medical research in such important fields as chronic neurologic diseases (for instance Parkinson's and Alzheimer's disease, spinal cord injury, behavioural and emotional disorders), cardiovascular, rheumatologic, endocrine and metabolic diseases still requires the use of animals in experimental research.

We hope the consensus reached within the medical research community at the pan-European level as reported in this position paper will contribute to protecting animals used for scientific purposes while at the same time allow the continuous advancement of medical research with the aim of improving health and well being of the European citizens.

Proposed amendments

Articles proposed by the European Commission for which concerns still exist	**Priority Topics**	**Proposed Amendments**
Article 2 § 1 sub § 2 § 2 point (a) § 3 § 4 introductory part § 4 point (d)	*Scope*	**Where there is any pain**, suffering, distress or lasting harm, **its elimination** 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. (a) live non-human vertebrate animals, including independently feeding larval forms and foetal forms **of mammal species** as from the last third of **gestation**. delete 4. **Other than the general controls over breeding facilities**, this Directive shall not apply to the following: (d) practices that **do not cause pain, suffering, distress, or lasting harm**.
Article 3 (1)	*Definitions*	'procedure' means any use of an animal **subjected to one or more techniques to address a predetermined experimental or other scientific objective**, with known or unknown outcome, which may cause the **living** animal pain, suffering distress or lasting harm, including any course of action intended, or liable, to result in the birth of an animal in any such condition or in the creation of a new genetically modified animal line.
Article 8 § 1 and 2	*Non-human primates*	1. Non-human primates **because of their highly evolved sensory and cognitive capacities** shall not be used in procedures, with the exception of those procedures meeting the following conditions: (a) the procedure has one of the purposes referred to in points (1), (2)(a), (3) and (5) of Article 5; (b) **that the applicant provides** a scientific justification, that the purpose of the procedure cannot be achieved by the use of other species than non-human primates. 2. Notwithstanding paragraph 1, great apes, **because of their very highly evolved sensory and cognitive capacities** shall only be used in procedures, **undertaken with a view to the avoidance, prevention, diagnosis or treatment of clinical conditions in humans or these species that are life-threatening, debilitating or endanger the survival of the species. To ensure that great apes are only used under exceptional circumstances any project involving these species would require the highest level of justification and review.**

Article 14 § 1 § 2 point ca § 3 § 5	*Anaesthesia*	1. Member States shall ensure that, **wherever appropriate**, all procedures are carried out under general or local anaesthesia **or using other methods that may alleviate pain**. *[New]* (ca) **where analgesics are used to prevent or control potential severe pain**. delete 5. An animal, which may suffer pain once anaesthesia has worn off, shall be treated with **appropriate** pre-emptive **or** post-operative analgesics or other appropriate pain-relieving methods. **Any derogation from this obligation on scientific grounds shall require justification and approval at ethical evaluation**.
Article 15 § 1 § 2	*Classification of severity procedures*	1. Member States shall ensure that all procedures are classified as 'up to mild', 'moderate', 'severe' **or 'non recovery', in conformity with annex VIIa**. 2. Member States shall ensure that the procedures classified as "severe" are **scientifically justified, and ethically monitored** if the pain, suffering or distress is likely to be prolonged. **These procedures shall be subject to particular harm: benefit analysis and scrutiny by the competent authority**.
Article 16	*Re-Use*	Member States shall ensure that an animal **that has** already **completed** a procedure, when a different animal on which no **preparatory or other procedure** has previously been carried out could **instead** be used, may be re-used in **subsequent** new **procedures when it demonstrably serves the 3Rs principles**.
Article 38 § 1 § 2 § 3 § 4	*Retrospective Assessment*	1. **Based on a final project report all projects shall undergo a retrospective review by the permanent ethical review body which will submit the results of such review to the competent authority. With a view to promotion of the 3Rs, the competent authority may, in the light of the report from the permanent ethical review body, in addition, perform a retrospective assessment of those projects classified as severe.** 2. Retrospective assessment shall evaluate the following: (a) whether the objectives of the project were achieved; (b) harm inflicted on animals including the numbers and species of animals used and the severity of the procedures; (c) elements that may contribute to the further implementation of the requirement of replacement, reduction and refinement. delete 4. sub§ 1 delete **4. sub§ 2 *[New]* Retrospective assessment by the competent authority shall not delay or hinder the granting of subsequent project authorisations as determined in Article 41.**
Article 43 § 1 and 2	*Authorisation decisions (time limit)*	Member States shall ensure that the decision to grant an authorisation is taken and communicated to the user establishment at the latest within **90 days** from the submission of the application. Should the Member State fail to take a decision within that period, the authorisation shall be deemed to have been granted.

Article 44 § 1	*Unnecessary duplication of procedures*	Each Member State shall accept data that are **required by law** and generated by procedures recognised by Community legislation **from another Member State, unless further procedures need to be carried out regarding that data for the protection of public health, safety or the environment**.
§ 2		2. Outside the area of testing required by law, subject to safeguarding confidential information, the Member States shall **promote** the sharing of data generated by procedures.
§ 2a (new)		**2a. *[New]* Subject to safeguarding confidential information, Member States shall promote the sharing of data generated by procedures as soon as is reasonably practicable, including those which have taken place in the European Union prior to the Directive coming into force.**
§ 2b (new)		**2b. *[New]* Before applying for a project authorisation, a person intending to carry out a procedure must take all reasonable steps to ascertain whether data relevant to his proposed project already exists and, if it does, to access it.**
§ 2c (new)		**2c. *[New]* Member States shall not authorise a procedure where a person has not taken the reasonable steps required by paragraph (3).**
§ 2d (new)		**2d. *[New]* Where relevant data is reasonably available, Member States shall only grant authorisation for a project where this is demonstrated at ethical evaluation to be necessary.**
Article 45	*Alternative approaches*	The Commission and Member States shall contribute to the development and validation of alternative approaches that could provide the same or higher level of information as that obtained in procedures using animals but that do not involve the use of animals or use fewer animals or that entail less painful procedures and shall take such other steps as they consider appropriate to encourage research in this field. **One measure to promote alternative approaches can be the nomination of National Centres for Alternatives in Member States having the capacity to do this**.
Article 46	*National **Centers** for **Alternatives***	**1. *[New]* The role of the European Centre for the Validation of Alternative Methods shall be strengthened so that it includes the co-ordination and promotion of the validation, and use of alternatives to animal procedures including applied and basic biomedical and veterinary research and regulatory testing. Furthermore, ECVAM shall communicate information on the availability and application of alternative methods to the relevant authorities of the Member States.**

Annex VIIa (new)	*General Definitions of degrees of severity*	**Guidelines for a National Set of Definitions** of Degrees of Severity referred to in Article 15(1) In general: Unless the contrary is known or established it should be assumed that procedures that cause pain in humans also cause pain in animals. **When assessing the severity of a procedure that is frequently repeated in a given animal (such as taking blood samples), the possibility to reduce the severity by acquainting and habituating the animal to the procedure and by encouraging cooperative behavior needs to be taken into account.** **Non-recovery: Severity Grade 0** **– experiments under general anaesthesia without recovery** **– humane killing of animals for their tissues** **No pain or mild pain: Severity Grade 1** Interventions and manipulations in animals for experimental purposes as a result of which the animals experience no pain or short term mild pain, suffering, injury, or mild distress with no significant impairment of their general condition. Examples: – studies with differing feed compositions or with unphysiological diet, with minor clinical signs or symptoms – **keeping and training non-human primates under food- and/or fluid-controlled diets and with regular monitoring of the animals health** – withdrawal of blood samples or injection (s.c., i.m., i.p., i.v.) of a drug – **repeated recordings of brain activity using transdural microelectrodes with appropriate habituation to the procedures** – superficial tissue biopsy **and minimally invasive surgery** under anaesthesia – non-invasive scanning techniques, with or without sedation or anaesthesia of the animals – tolerability studies which give cause to expect short term, minor, local or systemic reactions – ECG recordings in conscious animals – observational studies such as open-field test, labyrinth tests, or staircase test – experiments under general anaesthesia without recovery. **Moderate: Severity Grade 2** Interventions and manipulations in animals for experimental purposes which subject the animals to short term moderate distress, or a moderately long to long-lasting episode of mild distress, pain, suffering, or injury, **which accumulate over time, or prolonged suffering**, or significant **and persistant** impairment of general condition. Examples: – surgery under anaesthesia and appropriate analgesia – implantation of devices such as catheters, telemetry transmitters, minipumps under general anaesthesia – studies with unphysiological diet, with clinical signs or symptoms untreated diabetes mellitus – frequent repeated blood sampling or administration of substances – induction of anxiety in animal models – acute toxicity tests, acute tolerability studies; range-finding studies, chronic toxicity/carcinogenicity tests with non-lethal endpoints – seizure models e.g. epilepsy studies – non-lethal animal models of cancer e.g. xenograft studies

		Severe: Severity Grade 3 Interventions and manipulations in animals for experimental purposes which cause the animals severe to very severe distress, or subject them to a moderately long to long-lasting episode of moderate distress, severe pain **or severe injury**, **which accumulate over time**, **or** prolonged **severe** suffering or severe and persistent impairment of general condition. Examples: – bacterial or viral lethal infections, when studies include the symptomatic period of infection – chronic models of rheumatoid arthritis – genetically modified animals with lethal phenotypes (e.g. oncogenes), without early termination of the experiment – organ transplantation (e.g. kidney, pancreas) – chronic models of severe neurological diseases, e.g. Parkinson's disease.

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