Expert working group on severity classification of scientific procedures performed on animals

FINAL REPORT

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Conducted in support of the revision of Directive 86/609/EEC on the protection of animals used for scientific purposes

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This report is the result of the work undertaken by the Expert Working Group on Severity Classification Criteria, which was tasked to provide scientific-technical background information in support of the revision of Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes.

The views expressed in this report do not necessarily reflect those of the organisations and Member States having nominated the participating experts.

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SEVERITY CLASSIFICATION OF PROCEDURES

A severity category is to be assigned to each procedure. This will assist the harm-benefit analysis of the project.

The severity of a procedure is determined by the degree of pain, suffering, distress or lasting harm expected to be experienced by the animal during the course of the procedure. The procedure consists of a combination of one or more technical acts carried out on an animal which may cause that animal pain, suffering, distress or lasting harm. The assignment of the severity category takes into account any intervention or manipulation of an animal within a defined procedure. The severity category shall be assigned based on the most severe effects likely to be experienced by an individual animal after applying all appropriate refinement techniques.

Definitions

The proposal has 4 severity categories; non-recovery, mild, moderate and severe. These should be defined as follows:

Non-recovery:
Procedures, which are performed entirely under general anaesthesia from which the animal shall not recover consciousness.

Mild:
Procedures on animals as a result of which the animals are likely to experience short term mild pain, suffering or distress. Procedures with no significant impairment of the wellbeing or general condition of the animals.

Moderate:
Procedures on animals as a result of which the animals are likely to experience short term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress. Procedures that are likely to cause moderate impairment of the wellbeing or general condition of the animals.

Severe:
Procedures on animals as a result of which the animals are likely to experience severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress. Procedures, that are likely to cause severe impairment of the wellbeing or general condition of the animals.

Lower threshold[1]

The lower threshold is exceeded if the animals may experience a level of pain, suffering or distress equivalent to, or higher than that caused by the introduction of a needle.

Furthermore, the administration of anaesthesia for scientific purposes (excluding euthanasia) will bring a procedure above the lower threshold.

Other types of lower thresholds are necessary for determining equivalence for specific research procedures.

A number of examples are given of procedures that are considered below the threshold for regulation. It is important to note that applying several such ("below threshold") techniques together in one animal may require the procedure to be classified as mild or higher.

Upper threshold

The upper threshold is exceeded if the animals may experience severe pain, suffering or distress which is likely to be long-lasting and cannot be ameliorated.

Death as the end-point should be avoided by adopting appropriate monitoring strategies and early humane end-points wherever possible. Consideration should be given to the balance of the total number of animals used versus severity on the individual animal where by increasing the number of animals, the severity experienced by the individual animal may be reduced.

There may be exceptional and scientifically justifiable needs that can only be achieved by exceeding the upper threshold. Therefore consideration to a safeguard clause should be given.

Assignment criteria and elements

Assigning a procedure to a particular category does not only depend on the type of procedure but on a number of other factors. When assigning procedures to one of these four categories these additional various factors need to be considered on a case by case basis. The factors include:

- type of manipulation, handling
- nature of pain, suffering, distress or lasting harm caused by (all elements of) the procedure, and its intensity, duration, frequency and multiplicity of techniques employed
- cumulative suffering within a procedure

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[1] **Derived from the Council of Europe Resolution under ETS 123 "The use of animals for other research purposes, for example, on nutrition and feeding, when they may experience a level of pain, suffering or distress equivalent to, or higher than, that caused by the introduction of a needle [for example, blood sampling, deprivation of food]" (1992)**

- prevention from expressing natural behaviour including restrictions on the housing, husbandry and care standards

The above factors are related to the procedure itself. However, for the classification the following factors also need to be taken into account as these can significantly influence the final classification.

- type of species and genotype
- maturity, age and gender of the animal
- training experience of the animal to the procedure
- if the animal is to be re-used, the actual severity of the previous procedures
- the methods used to reduce or eliminate pain, suffering and distress, including refinement of housing, husbandry and care conditions
- humane end-points

For example, a procedure considered to be in the severe category due to the type of procedures to be applied, could be assigned to a lower category by the application of appropriate humane end-points.

Careful monitoring of animals during procedures, the use of clinical assessments and objective indicators can be of value in minimising the impact on the animals, and can therefore impact on severity classification.

These assessments will also be of value during the retrospective assessment of the actual severity.

It is important to appreciate that an objective assessment of pain, suffering and distress in animals is frequently not possible. Therefore, many aspects of the assessment will require professional judgment to be exercised.

Examples of different types of procedure

It is imperative to note that the examples given below are only indicative. The final severity categorisation can only be made as a consequence of a critical case-by-case assessment of all factors likely to have an impact on the severity of a procedure in a given situation. The presumption is that all procedures are carried out by competent persons according to best practice.

Mild

Pharmacokinetic study where a single dose is administered and a limited number of blood samples are taken (totalling < 10% of circulating volume) and the substance is not expected to cause any detectable adverse effect;

Non-invasive imaging of animals (eg MRI) with appropriate sedation or anaesthesia;

Superficial procedures, e.g. ear and tail biopsies, non surgical subcutaneous implantation of mini-pumps and transponders;

Application of external telemetry devices that cause only minor impairment to the animals or minor interference with normal activity and behaviour;

Administration of substances by subcutaneous, intramuscular, intraperitoneal routes, gavage and intravenously via superficial blood vessels, where the substance has no more than mild impact on the animal, and the volumes are within appropriate limits for the size and species of the animal;

Induction of tumours, or spontaneous tumours, that cause no detectable clinical adverse effects (e.g. small, subcutaneous, non-invasive nodules);

Breeding of genetically altered animals which is expected to result in a phenotype with mild effects;

Feeding of modified diets, that do not meet all of the animals' nutritional needs and are expected to cause mild clinical abnormality within the time-scale of the study;

Short term (<24h) restraint in metabolic cages;

Studies involving short-term deprivation of social partners, short-term solitary caging of adult rats or mice of sociable strains;

Models which expose animals to noxious stimuli which are briefly associated with mild pain, suffering or distress, and which the animals can successfully avoid.

Moderate

Frequent application of test substances which produce moderate clinical effects, and withdrawal of blood samples (>10% of circulating volume) in a conscious animal within a few days without volume replacement;

Acute dose-range finding studies, chronic toxicity / carcinogenicity tests, with non-lethal endpoints;

Surgery under general anaesthesia and appropriate analgesia, associated with post-surgical pain, suffering or impairment of general condition. Examples include: thoracotomy, craniotomy, laparotomy, orchidectomy, lymphadenectomy, thyroidectomy, orthopaedic surgery with effective stabilisation and wound management, organ transplantation with effective management of rejection, surgical implantation of catheters, or biomedical devices (e.g. telemetry transmitters, minipumps, etc.);

Models of induction of tumours, or spontaneous tumours, that are expected to cause moderate pain or distress or moderate interference with normal behaviour;

Irradiation or chemotherapy with a sublethal dose, or with an otherwise lethal dose but with reconstitution of the immune system. Adverse effects would be expected to be mild or moderate and would be short-lived (<5 days);

Breeding of genetically altered animals which are expected to result in a phenotype with moderate effects;

Creation of genetically altered animals through surgical procedures;

Use of metabolic cages involving moderate restriction of movement over a prolonged period (up to 5 days);

Studies with modified diets that do not meet all of the animals' nutritional needs and are expected to cause moderate clinical abnormality within the time-scale of the study;

Withdrawal of food for 48 hours in adult rats;

Evoking escape and avoidance reactions where the animal is unable to escape or avoid the stimulus, and are expected to result in moderate distress.

Severe

Toxicity testing where death is the end-point, or fatalities are to be expected and severe pathophysiological states are induced. For example, single dose acute toxicity testing (see OECD testing guidelines);

Testing of a device where failure may cause severe pain, distress or death of the animal (e.g. cardiac assist devices);

Vaccine potency testing characterised by persistent impairment of the animal's condition, progressive disease leading to death, associated with long-lasting moderate pain, distress or suffering;

Irradiation or chemotherapy with a lethal dose without reconstitution of the immune system, or reconstitution with production of graft versus host disease;

Models with induction of tumours, or with spontaneous tumours, that are expected to cause progressive lethal disease associated with long-lasting moderate pain, distress or suffering. For example tumours causing cachexia, invasive bone tumours, tumours resulting in metastatic spread, and tumours that are allowed to ulcerate;

Surgical and other interventions in animals under general anaesthesia which are expected to result in severe or persistent moderate postoperative pain, suffering or distress or severe and persistent impairment of the general condition of the animals. Production of

unstable fractures, thoracotomy without adequate analgesia, or trauma to produce multiple organ failure;

Organ transplantation where organ rejection is likely to lead to severe distress or impairment of the general condition of the animals (e.g. xenotransplantation);

Breeding animals with genetic disorders that are expected to experience severe and persistent impairment of general condition, for example Huntington's disease, Muscular dystrophy, chronic relapsing neuritis models;

Use of metabolic cages involving severe restriction of movement over a prolonged period;

Inescapable electric shock (e.g. to produce learned helplessness);

Complete isolation for prolonged periods of social species e.g. dogs and non-human primates;

Immobilisation stress to induce gastric ulcers or cardiac failure in rats;

Forced swim or exercise tests with exhaustion as the end point.

Examples of procedures below the lower threshold

Assessing body composition by non-invasive measures and minimal restraint;

Monitoring ECG with non-invasive techniques with minimal or no restraint of habituated animals;

Application of external telemetry devices that are expected to cause no impairment to socially adapted animals and do not interfere with normal activity and behaviour;

Breeding genetically altered animals which are expected to have no clinically detectable adverse phenotype;

Feeding a diet that meets the full nutritional needs of the animals.

Adding inert markers in the diet to follow passage of digesta;

Withdrawal of food for <24h in adult rats;

Non-invasive observation of normal behaviour without disturbing the animal;

Open field testing.

Participating experts

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Expert Working Group to develop criteria for a severity classification for the use of animals for scientific purposes

BACKGROUND

The Commission proposal to revise Directive 86/609/EEC foresees the establishment of a severity classification based on 4 categories. The fine-tuning of the criteria was proposed to take place after the adoption of the core text. However, due to the fact that a number of Articles and their implementation are dependent on the final severity classification criteria, it would be beneficial to have these criteria agreed concurrently with the core text.

The Commission recognises this urgency and will convene an Exert Working Group, EWG, on 9-10 July 2009 to that effect. The criteria should be developed on the basis of the current existing schemes in the EU and consideration should be given to all available information and best practice including that existing outside the EU. To facilitate achieving the objectives set for the EWG, the experts are requested to study all background documents prior to the meeting.

THE COMMISSION PROPOSAL AND EP AMENDMENTS

Recitals

Recital 21 states that to *"enhance transparency, facilitate the project authorisation and provide tools for monitoring compliance, a severity classification of procedures should be introduced on the basis of estimated level of pain, suffering, distress and lasting harm that is inflicted on the animals".*

And continues: "*To give precision how severity classes should be assigned, the Commission should develop criteria with stakeholder input using existing severity classification schemes in place in Member States as well as those promoted by international organisations as basis."*

Recital 22 states that *"...When developing a common format for reporting purposes, instead of the predicted severity at the time of the ethical evaluation, the actual severity experienced by the animal should be taken into account."*

Enacting terms

Article 15 of the Draft Directive requires that all procedures are classified as 'up to mild', 'moderate', 'severe' or 'non-recovery' on the basis of the duration and intensity of potential pain, suffering, distress and lasting harm, the frequency of intervention, the deprivation of ethological needs and the use of anaesthesia or analgesia or both.

In addition, Member States shall ensure that the procedures classified as "severe" are not performed if the pain, suffering or distress is likely to be prolonged.

Article 16 - Re-use

The restrictions on re-use are determined by the severity of procedures applied to the animals.

Article 38 – Retrospective Assessment

Exemption from the requirement to conduct retrospective assessment is determined by the severity classification. Projects involving only procedures classified as "up to mild" shall be exempted from the requirement for a retrospective assessment.

Article 43 – Authorisation decisions

Where the project concerned involves only procedures classified as “up to mild” and does not require the use of non-human primates, authorisation will be deemed to have been granted if the Member State fails to take a decision on a project application within 30 days of submission.

European Parliament amendments

The European Parliament, EP, adopted in their first reading report a number of amendments; some of whose interpretation is significantly impacted by the final criteria for the Severity Classification. Amendment 69 introduces a new Annex to the Directive covering the severity classification criteria. Ideally the outcome of the EWG would provide an agreed severity classification criteria for the EU to be considered under this new Annex.

It is important to note that at this stage all EP amendments are still to be discussed and negotiated with the Member States and the Commission. EP amendments include:

Amendment 69 – Article 15

Member States shall ensure that all procedures are classified as "up to mild", "moderate" ***or*** "severe" ***in conformity with Annex VII*** *(*which provides general definitions of degrees of severity)**.**

Amendment 73/74 – Article 16 – Re-use

Criteria for permission for re-use severity have been changed to permit routine re-use of "***moderate***" – "***moderate***" procedures.

Amendment 167 – Article 35 – Authorisation of Projects

Member States shall ensure that **projects** *classified as “moderate" or "severe” or any projects involving non-human primates* are not carried out without a prior authorisation by the competent authority. *All other projects shall be* ***notified*** *in advance to the competent authority following ethical review by the institution's permanent ethical review body.*

Amendment 120 – Article 38

All projects involving only procedures classified as "up to ***moderate***" shall be exempted from the requirement for a retrospective assessment.

Amendment 128 - Article 42

Amendments to "up to mild" or "moderate" procedures that do not increase the severity of the procedure may be made by the permanent ethical review body of the establishment but must be communicated to the competent authority within one week of such change.

THE BASIS AND THE OBJECTIVES FOR THE WORK OF THE EWG

The development of the criteria should be based on the follow 4 principles:

1. Severity classification will be ***applied to procedures***, not projects. Similarly, projects should be subject to harm-benefit analysis, not procedures.

2. Classification should include ***4 categories*** of severity:

    a. Up to (and including) mild[2]

    b. Moderate

    c. Severe

    d. Non-recovery[3]

3. The classification is to be used ***prospectively*** for determining e.g. the type of authorisation required and requirements for a retrospective assessment.

4. The classification should be used ***retrospectively*** for the purposes

    a. Re-use to determine the classification of the previous procedure

    b. Statistical reporting.

The objectives of the two days are to:

1. ***Develop general criteria*** that should be considered when determining severity, e.g. duration, intensity and frequency of intervention, the deprivation of ethological needs and the use of anaesthesia or other pain relieving methods;

[2] The use of terms "*up to mild"* is to cater for the inclusion in the statistics the animals for which no actual harm was inflicted during the procedures, but which during the prospective assessment were considered potentially to be inflicted with mild pain, suffering, distress or lasting harm.

[3] Non-recovery means a procedure performed under general anaesthesia, at the end of which and without a possibility to recover consciousness, the animal is killed.

2. Determine a ***lower threshold***[4] below which the Directive should not apply and an ***upper threshold*** beyond which no animal use should be allowed;

3. Develop ***definitions for the 4 categories*** of severity;

4. Prepare a set of ***examples for each category***;

5. Should time allow, consider how to ***determine retrospective assessment*** for purposes of statistical returns.

ADDITIONAL CONSIDERATIONS

In addition to reflecting on the points raised above prior to the meeting, the participants are requested to consider other relevant issues to facilitate the discussions. These include:

– Method of assigning severity class: should the severity of the procedure be linked to the experience of a "single" animal, or that of an "average" animal? If time allows, would the same apply to retrospective assessment?

– To facilitate project authorisation and provide tools for monitoring compliance with severity, it would seem that an estimate of the overall suffering will be needed for each procedure (for the project harm/benefit assessment) and a maximum permitted severity for each procedure (to assist compliance and set a limit suffering). This would suggest a "band" and "limit" approach for each procedure. What experience exists and how does this approach work in practice?

– Do other approaches exist? How these would work in practice?

Finally, experts who have experience of an existing severity classification system should be prepared to provide a brief summary to the EWG on the principles of the classification system and what (s)he considers as the strengths and the weaknesses of the given system.

[4] Council of Europe Resolution on ETS123 1992: "The Parties to the Convention consider the amount of pain, suffering or distress caused by the introduction of a needle into the body of an animal as illustrating the level at which the use of an animal becomes a "**procedure**". Some studies on the behaviour of animals may result in sufficient suffering or distress for the study to be considered as a procedure, even if it does not imply physical interference incl. the use of animals as control animals when they may experience a level of pain, suffering or distress equivalent to, or higher than, that caused by the introduction of a needle; the use of animals in research on nutrition and feeding, when they may experience a level of pain, suffering or distress equivalent to, or higher than, that caused by the introduction of a needle [for example, blood sampling, deprivation of food]; the use of animals for the production of serum.