



Severity Classification 2.9, 5.5

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Outline of presentation



- The Directive's requirements
- Definitions
- Assignment criteria
- Examples



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Directive 2010/63/EU par. 22, 24

- 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 levels*** of pain, suffering, distress and lasting harm that is inflicted on the animals.
- When developing a common format for **reporting** purposes, the **actual severity** of the pain, suffering, distress or lasting harm experienced by the animal should be taken into account rather than the ***predicted severity*** at the time of the project evaluation.

<https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF>



Article 15



Classification of severity of procedures

1. Member States shall ensure that all procedures are classified as '**non-recovery**', '**mild**', '**moderate**', or '**severe**' on a case-by-case basis using the assignment criteria set out in Annex VIII.
2. Subject to the use of the safeguard clause in Article 55(3), 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**.



Article 55(3)



- Where, for exceptional and **scientifically justifiable reasons**, a Member State deems it necessary to allow the use of a procedure involving **severe** pain, suffering or distress that is likely to be **long-lasting** and **cannot be ameliorated**, as referred to in Article 15(2), it **may adopt a provisional measure to allow** such procedure. Member States **may decide not to allow the use of NHP** in such procedures.



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- The Directive's requirements
- **Definitions**
- Assignment criteria
- Examples



ANNEX VIII



SEVERITY CLASSIFICATION OF PROCEDURES

Severity Categories:

- **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, as well as procedures with no significant impairment of the well-being or general condition of the animals



ANNEX VIII



SEVERITY CLASSIFICATION OF PROCEDURES

Severity Categories:

- **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 as well as procedures that are likely to cause **moderate impairment** of the well-being or general condition of the animals



ANNEX VIII



SEVERITY CLASSIFICATION OF PROCEDURES

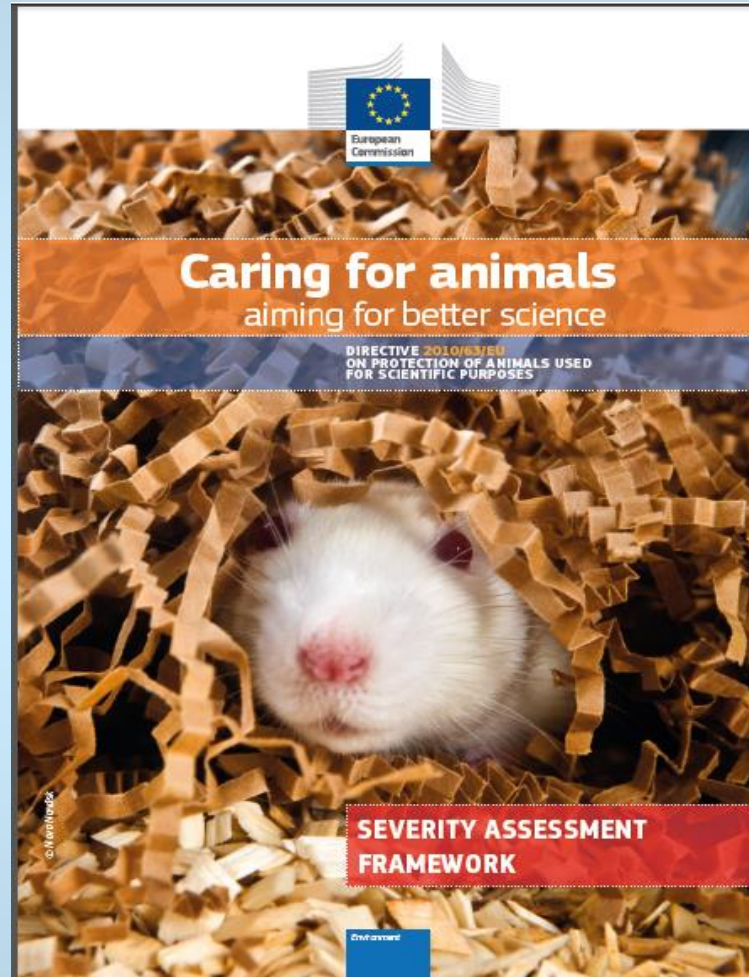
Severity Categories:

- **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 as well as procedures, that are likely to cause **severe impairment** of the well-being or general condition of the animals

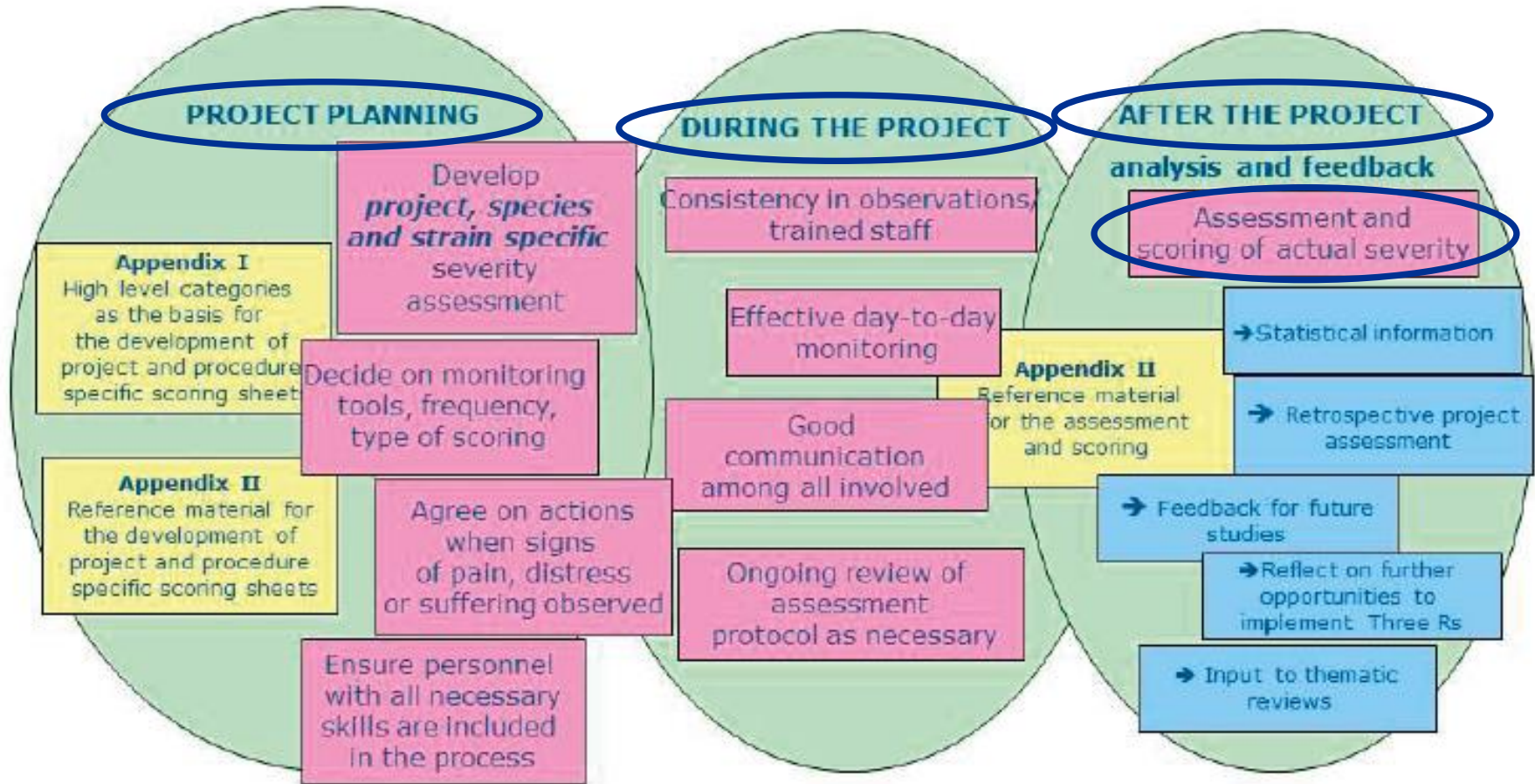


Severity Assessment Framework



<https://op.europa.eu/en/publication-detail/-/publication/fe448d22-282f-11e9-8d04-01aa75ed71a1/language-en>

SEVERITY ASSESSMENT – A CONTINUOUS PROCESS



Example(s) of project/procedure specific severity assessment process including the day-to-day assessment sheets, scoring tools, choices of monitoring methods and final assessment should be developed.

<https://op.europa.eu/en/publication-detail/-/publication/fe448d22-282f-11e9-8d04-01aa75ed71a1/language-en>



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Assignment Criteria



- The assignment of the severity category shall take into account any intervention or manipulation of an animal within a defined procedure
- It shall be based on the **most severe effects likely** to be experienced by an individual animal after applying all appropriate refinement techniques

Directive 2010/63/EU Annex VIII



Assignment Criteria



- For example: **many mild** procedures within a project may classify the project as “**moderate**” or “**severe**” due to **cumulative suffering**
- **Cumulative suffering** depends on the nature, number, duration and frequency of adverse and unexpected effects that appear during the course of a project



Assignment Criteria



Factors shall be considered on a **case-by-case** basis:

- type of manipulation, handling
- **nature** of pain, suffering, distress or lasting harm caused by the procedure, and its **intensity**, the **duration**, **frequency** and **multiplicity** of techniques employed
- **cumulative suffering** within a procedure
- prevention from expressing natural behaviour including **restrictions** on the housing, husbandry and care standards.

Directive 2010/63/EU Annex VIII



Assignment Criteria



Factors shall be considered on a **case-by-case** basis:

- type of species and genotype
- maturity, age and gender of the animal
- training experience of the animal with respect to the procedure
- if the animal is to be reused, 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.



Article 16

Reuse

1. Member States shall ensure that an animal already used in one or more procedures, when a different animal on which no procedure has previously been carried out could also be used, may only be reused in a new procedure provided that the following conditions are met:

- (a) the actual severity of the previous procedures was 'mild' or 'moderate';
- (b) it is demonstrated that the animal's general state of health and well-being has been fully restored;
- (c) the further procedure is classified as 'mild', 'moderate' or 'non-recovery'; and
- (d) it is in accordance with veterinary advice, taking into account the lifetime experience of the animal.



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“Mild” procedures (1)



- (a) administration of anaesthesia except for the sole purpose of killing;
- (b) 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;
- (c) non-invasive imaging of animals (e.g. MRI) with appropriate sedation or anaesthesia;
- (d) superficial procedures, e.g. ear and tail biopsies, non-surgical s.c. implantation of mini-pumps and transponders;

Directive 2010/63/EU Annex VIII



“Mild” procedures (2)



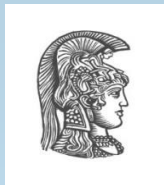
- (e) application of external telemetry devices that cause only **minor impairment** to the animals or **minor interference** with normal activity and behaviour;
- (f) administration of substances by s.c., i.m., i.p. routes, gavage and i.v. via superficial blood vessels, where the substance has no more than **mild impact** on the animal, and the volumes are within appropriate limits for the size and species of the animal;
- (g) induction of tumours, or spontaneous tumours, that cause **no detectable** clinical adverse effects (e.g. small, s.c., non-invasive nodules);



“Mild” procedures (3)



- (h) breeding of genetically altered animals, which is expected to result in a phenotype with **mild** effects;
- (i) 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;
- (j) short-term (< **24h**) restraint in **metabolic cages**;
- (k) studies involving **short-term** deprivation of social partners, **short-term** solitary caging of adult rats or mice of sociable strains.



Metabolic cages





“Moderate” procedures (1)



- a) **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;
- b) **acute** dose-range finding studies, **chronic** toxicity/carcinogenicity tests, with non-lethal end-points;
- c) **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.);



“Moderate” procedures (2)



- (d) models of induction of tumours, or spontaneous tumours, that are expected to cause moderate pain or distress or moderate interference with normal behaviour;
- (e) 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);
- (f) breeding of genetically altered animals which are expected to result in a phenotype with **moderate** effects;
- (g) creation of GA animals through surgical procedures;
- (h) use of **metabolic cages** involving **moderate restriction** of movement over a prolonged period (up to 5 days); ...
- (j) withdrawal of food for 48 hours in adult rats; ...



Swiss Tierversuch Severity



- Moderate Surgical examples:
- ovariectomy, hysterectomy, implantation of catheters in the abdominal aorta or bile duct, unilateral nephrectomy, splenectomy, establishment of a gastric fistula, implantation of minipumps intravenously, implantation of indwelling catheters in ventricles of the brain, or of electrodes in the brain, if the animals retain their freedom of movement; hypophysectomy with hormonal substitution.



“Severe” procedures (1)



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



“Severe” procedures (2)



- (d) irradiation or chemotherapy with a **lethal dose** without reconstitution of the immune system, or reconstitution with production of graft versus host disease;
- (e) 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;



“Severe” procedures (3)



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



“Severe” procedures (4)



- (i) use of **metabolic cages** involving **severe restriction** of movement over a prolonged period;
- (j) **inescapable** electric shock (e.g. to produce learned helplessness);
- (k) **complete isolation** for prolonged periods of social species e.g. dogs and non-human primates;
- (l) **immobilisation stress** to induce gastric ulcers or cardiac failure in rats;
- (m) **forced** swim or exercise tests with **exhaustion** as the end-point.



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- Severe Surgical examples:
- joint transplantations, transplantation of a functional internal organ; models with thoracotomy; intestinal resection;

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Severity Classification of Surgical Procedures and Application of Health Monitoring Strategies in Animal Research Proposals: A Retrospective Review

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Our prospective severity classification was based on the maximum severity that could be expected when the surgical procedure was conducted by a technically-skilled operator, including the use of all possible refinements and optimal care during and after surgery. Thus, we:

— categorised all thoracotomies as severe, as in the Swiss (16) and Berlin (17) guidance documents. This is a deviation from Annex VIII of the Directive (4), which only rates thoracotomies as 'severe' if analgesia is inadequate;

Background reading, guidelines and online resources on assessing the welfare of animals undergoing scientific procedures

American College of Laboratory Animal Medicine (ACLAM) (2006) *Guidelines for the Assessment and Management of Pain in Rodents and Rabbits*, download at <http://www.tinyurl.com/65ez5vh>

Assessing the Health and Welfare of Laboratory Animals (AHWLA) training resource. See <http://www.ahwla.org.uk/index.html>

Canadian Council on Animal Care (CCAC) *Welfare assessment*. See <http://www.ccac.ca/> and click on the Three Rs microsite, then search for 'welfare assessment' (English or French)

Categorising the severity of scientific procedures on animals - Summary and reports from three round-table discussions edited by Jane A. Smith and Maggy Jennings on behalf of the Boyd Group and the RSPCA, July 2004
Published by RSPCA Research Animals Department

FELASA Working Group on the Reporting of Clinical Signs in Laboratory Animals (2012) – (in press)

Institute for Laboratory Animal Research (ILAR) (2008) *Recognition and Alleviation of Distress in Laboratory Animals*. Washington, DC: National Academies Press
Institute for Laboratory Animal Research (ILAR) (2009) *Recognition and Alleviation in Laboratory Animals*. Washington, DC: National Academies Press
http://dels.nas.edu/animal_pain/

Johansen R, Needham JR, Colquhoun DJ, et al (2006) Guidelines for health monitoring of fish used in research. *Laboratory Animals* 40: 323–340

Joint Working Group on Refinement (2011) A guide to defining and implementing for the welfare assessment of laboratory animals. *Laboratory Animals* 45: 1-1

Leach MC et al. (2008) Identification of appropriate measures for the laboratory mouse welfare. *Animal Welfare* 17: 161-170

I. Dantas



Working Party Report

Classification and reporting of severity experienced by animals used in scientific procedures: FELASA/ECLAM/ESLAV Working Group report

David Smith¹, David Anderson², Anne-Dominique Degryse³, Carla Bol⁴, Ana Criado⁵, Alessia Ferrara⁶, Nuno Henrique Franco⁷, Istvan Gyertyan⁸, Jose M Orellana⁹, Grete Ostergaard¹⁰, Orsolya Varga¹¹ and Hanna-Marja Voipio¹²



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SAGE



Severity assessment score sheets



Example of a score sheet

Animal no.				
Date	01/06	02/06	03/06	04/06
Appearance				
Body weight				
Coat condition				
Body function				
Dyspnoea and/or tachypnoea				
Food intake				
Environment				
Loose stools or diarrhoea				
Blood in diarrhoea				
Behaviours				
Handling				
Aggression				
Abnormal gait				
Abnormal posture				
Reluctance to move				
Procedure-specific indicators				
Tumour size				
Ulceration of tumour				

Examples of clinical scores

Appearance	Score
Bodyweight	
5-10% weight loss	1
11-15 % weight loss	2
16-20% weight loss	3
20% + weight loss	HEP
Coat Condition	
Coat slightly unkempt	1
Slight piloerection	2
Marked piloerection	3
Body Function	
Tachypnoea (fast breathing)	1
Dyspnoea (difficulty breathing)	3
Environment	
Loose stools or diarrhoea	1
Blood in diarrhoea	HEP
Behaviour	
Tense and nervous on handling	1
Markedly distressed on handling, e.g. shaking, vocalizing, aggressive	3
Locomotion	
Slightly abnormal gait/posture	1
Markedly abnormal gait/posture	2

<https://op.europa.eu/en/publication-detail/-/publication/fe448d22-282f-11e9-8d04-01aa75ed71a1/language-en>

Example observation sheet (completed for hypothetical case)



Tumour Growth in Nude Mice – Procedure & Observation Sheet				
Cage 1 – Mouse numbers 1-5				
Date	Procedure	Tumour size (cm)	Weight (g)	Clinical Observations - check posture and gait carefully
28/02	s.c. injection		1- 21 2- 22 3- 21 4 -22 5- 22	No signs of welfare problems following injections
01/03				No Abnormality Detected (NAD)
02/03	Palpation			NAD
03/03				NAD
04/03	Palpation		1- 21 2- 22 3- 21 4 -22 5- 22	NAD
05/03				NAD
06/03	Palpation			NAD
07/03				Some aggressive behaviour; no wounds apparent
08/03	Tumour measurement	1 – 0.1 2 – 0.1	1- 21 2- 22	Mice 1 had bite wounds on tail and back – local treatment; moved to single housing. Nest box provided
	t	3 – 0.1 4 – no tumour 5 – 0.2	3- 21 4 -22 5- 22	for singly housed animal but removed from cage with remaining four mice in case this was triggering aggression
09/03				Wounds disinfected for mouse 1, healing well; no signs of aggression between remaining animals
10/03	Tumour measurement	1 – 0.2 2 – 0.1 3 – 0.1 4 – no tumour 5 – 0.2		Wounds disinfected for mouse 1
11/03				Wounds disinfected for mouse 1
12/03	Tumour measurement	1- 0.4 2 – 0.3 3 – 0.3 4 – no tumour 5 – 0.5	1- 22 2- 22 3 - 21 4 -21 5- 23	Wounds healed for mouse 1, disinfection discontinued.
13/03				NAD
14/03	Euthanase and harvest tumour.			



Please classify:



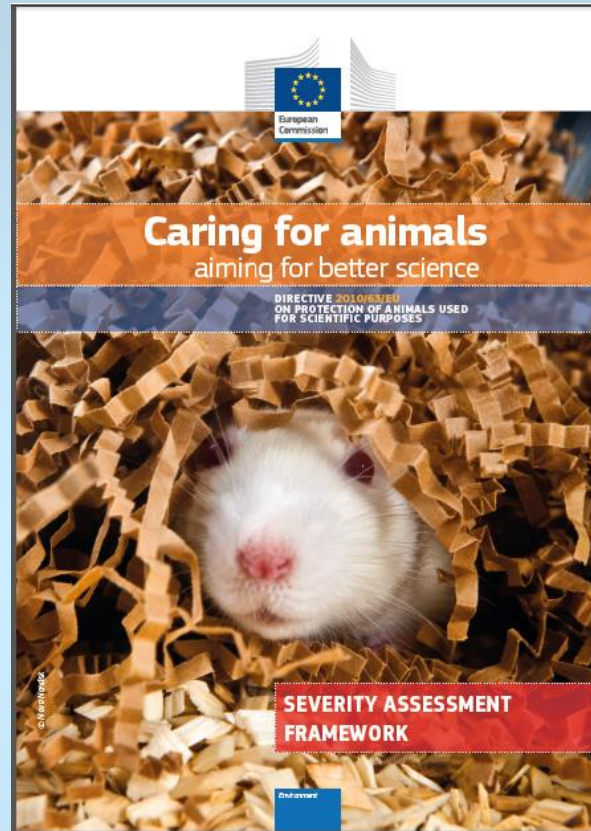
- Ovariectomy (for bone density decrease)
- Tail-suspension (for bone density decrease)
- Laparoscopic nephrectomy
- Experimental induction of diabetes (*via* streptozotocin i.p.)



“In a nutshell”



- Project application “**predicted**” severity
- “**Cumulative**” suffering must be calculated
- Re-evaluate “**actual**” severity in on-going study and retrospectively
- Include in statistical reporting of the use of animals
- Conditions for “Re-use”
- “*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.*”



Thank you for your attention!