New Tools for Assessing the Welfare of Animals Used in Research

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WORLD ORGANISATION FOR ANIMAL HEALTH
Protecting animals, preserving our future

- Regulations governing the care and use of laboratory animals
- Available tools for assessing and/or improving laboratory animal welfare

No Global Regulatory Standard-1

◆ **1876 Cruelty to Animals Act, UK**

    ○ 2014 The UK Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes

◆ **1963 Guide for the Care and Use of Laboratory Animals, ILAR, USA**

    ○ 2010 8th edition

◆ **1966 Animal Welfare Act, USA**

    ○ 1985 Health Research Extension Act → Public Health Service Policy on Humane Care and Use of Laboratory Animals

◆ **1985 International Guiding Principles for Biomedical Research Involving Animals, CIOMS**

    ○ 2012 revised jointly by CIOMS and ICLAS

No Global Regulatory Standard-2

◆ **1986 Council of Europe, ETS123** European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes

    o   2007 Revised Appendix A

◆ **1986 Directive 86/609,** European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes

    o   2010 Directive 2010/63/EU

◆ **2010/2011 OIE, Terrestrial Animal Health Code, Chapter 7.8,** Use of Animals in Research and Education

- Absent in many parts of the world
- Strain between investigators and AW-centric procedures
  - compliance (regulatory burden)
  - ethical precepts (sentience; utilitarianism; animal rights; harm/benefit analysis; 3Rs)
- Societal pressures

Regulatory Elements

- Submission of experimental protocols
- Committee of experts
- Institutional animal committee
- Ethics committee
- National committee
- National veterinary office
- The Three Rs
- Laboratory staff, veterinarians, animal care personnel
- Licensure of researchers and users

What is achieved

- Protect animal welfare
- Attend to bioethical principles and societal concerns
- Ensure proper training
- Ensure proper use of animals
- Empower users
- Protect human safety
- Standardize procedures to produce reproducible results
- Minimize pain and distress
- Help keep numbers of animals to scientifically and statistically minimum needed
- Improve animal care
- Ensure correct euthanasia procedures

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Improving Animal Welfare of Laboratory Animals

- Implement the Three Rs in a <u>deliberate manner</u>

- Assess severity using scoring sheets and share your knowledge

- Establish protocol-appropriate surrogate and humane endpoints

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Implement the 3Rs in a deliberate manner

o **Replacement:**
  - o Using non-animal methods, e.g. *in silico, human data* (absolute)
  - o Using cells, tissues, organs of animals *in vitro* (relative)

o **Reduction:**
  - o Using fewer animals, always guided by statistics
  - o Obtain same information from fewer animals or more information from the same number of animals

o **Refinement:**
  - o Using methods which minimise pain or distress
  - o Using species with less capacity to feel pain
  - o Includes improvements in housing and care, e.g., social housing, enrichment

o Continue to apply the 3Rs throughout the project

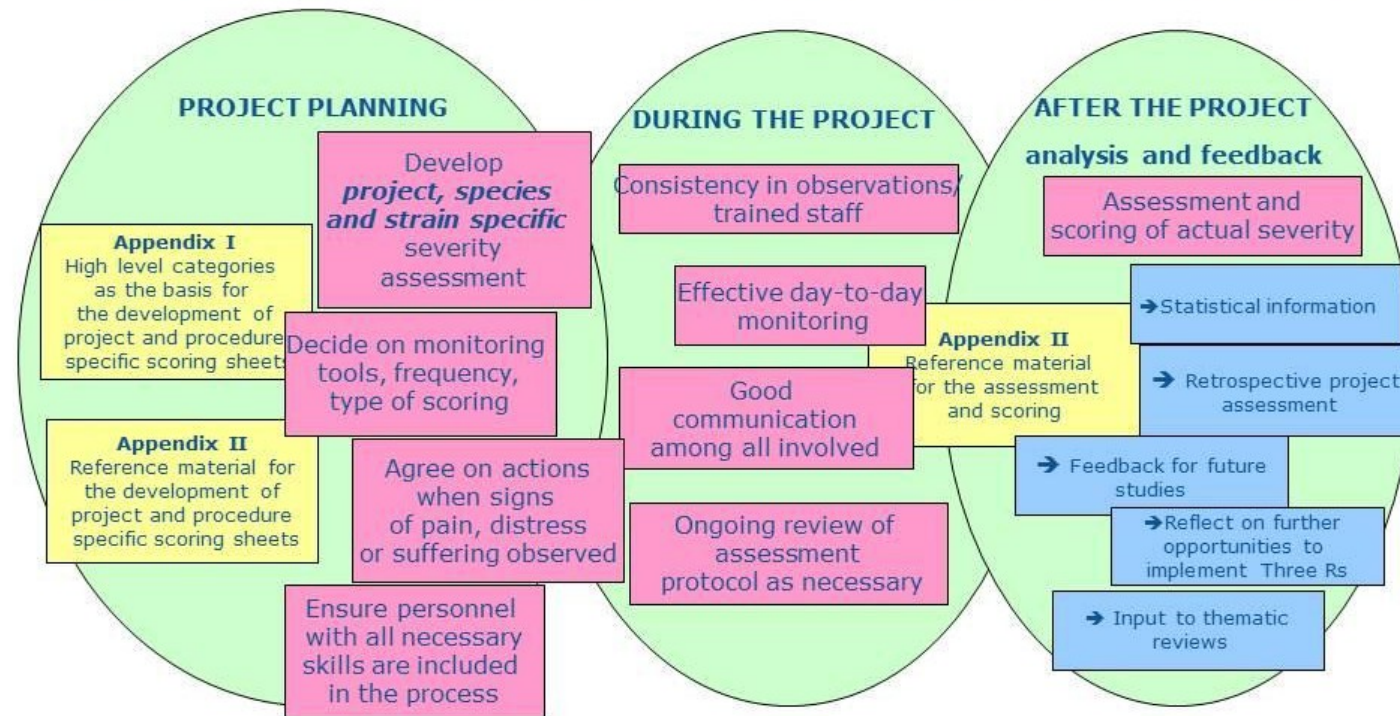o Reproducibility and systematic reviews

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Prospective and Retrospective Severity Assessment

SEVERITY ASSESSMENT – A CONTINUOUS PROCESS

PROJECT PLANNING

Appendix I
High level categories as the basis for the development of project and procedure specific scoring sheets

Develop *project, species and strain specific* severity assessment

Decide on monitoring tools, frequency, type of scoring

Appendix II
Reference material for the development of project and procedure specific scoring sheets

Agree on actions when signs of pain, distress or suffering observed

Ensure personnel with all necessary skills are included in the process

DURING THE PROJECT

Consistency in observations/ trained staff

Effective day-to-day monitoring

Good communication among all involved

Ongoing review of assessment protocol as necessary

AFTER THE PROJECT

analysis and feedback

Assessment and scoring of actual severity

Appendix II
Reference material for the assessment and scoring

→ Statistical information

→ Retrospective project assessment

→ Feedback for future studies

→ Reflect on further opportunities to implement Three Rs

→ Input to thematic reviews

Working Document on a Severity Assessment Framework, EWG-EC 2012
http://ec.europa.eu/environment/chemicals/lab_animals/pdf/Endorsed_Severity_Assessment.pdf

2.1.2   Prospective assessment

What does this study involve doing to the animals?	What will the animals experience? How much suffering might it cause? What might make it worse?	How will suffering be reduced to a minimum?	
	Adverse effects	Methodology and interventions	Endpoints
Baseline effects of genetic alteration	Genetic modification may lead to clinical adverse effects In cases where these are unpredictable, any indication that animals with the mutation have moved away from normal physical or behavioural parameters (i.e. those that are known occur in genetic background related phenotypes and/or wild type controls) could denote a welfare problem	On-going cage side monitoring Welfare assessment at defined developmental time points; birth, weaning and sexual maturity Depending on the nature of any detected adverse effect, appropriate ameliorating factors will be applied where possible such as altered breeding strategies or husbandry refinements (e.g. increased nesting material to assist impaired thermoregulation	Animals will be killed if moderate severity is exceeded
Tissue sampling for genotyping	Potential pain and/or distress caused by tissue sampling methodology, e.g. ear punching/notching or tail 'tipping' Tail biopsy is commonly used when larger quantities of DNA are required, but may cause both short and long term pain (the latter due to neuroma formation)	Where identifying individual animals using ear notching, it is good practice to use the ear tissue for genotyping where possible For tail 'tipping', the minimum amount of tail should be taken (bearing in mind that repeat sampling is highly undesirable), anaesthesia and analgesia should be used as	Not applicable, as the procedure should be a 'one off' and it is unlikely that pain or distress would be caused to a level where humane killing would be necessary
		appropriate and excessive bleeding should be dealt with promptly Developments in less invasive techniques should be monitored, evaluated locally and implemented wherever feasible	
Phenotyping	Stress induced by handling or application of the phenotypic assay, e.g. stress of being placed into an unfamiliar environment, administration of experimental compounds to induce a response, infection monitoring, anaesthesia and restraint for imaging etc.	Training of staff conducting phenotyping in competent, empathetic and standardised handling and observations Use of anaesthesia during imaging or painful procedures. Structuring of phenotypic tests to move from the least invasive (e.g. observation of behaviour in an open arena), to the most invasive (e.g. procedures requiring anaesthesia)	Where the mutation elicits a severe response to a phenotypic assay, humane endpoints will be reached and animals humanely killed

Examples to illustrate the process of severity classification, day-to-day assessment and actual severity assessment. European Commission, http://ec.europa.eu/environment/chemicals/lab_animals/pdf/examples.pdf

Improving Animal Welfare: Scoring sheet for assessing tumor size

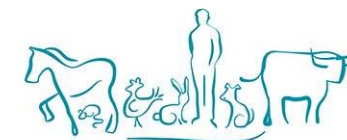## TABLE 5A-1 Sample Tumor Scoring Sheet

SECTION A	LESION/TUMOR CHARACTERISTICS		Score					MOUSE ID	Study No.	Group No.
				Calendar days						
	Dry scab/crust forming coherent covering with skin		0							
	Acute burst releasing fluid/pus OR acute split at border		1							
	Chronically wet/weeping scab/crust OR solid yellow matter exposed		2							
	Bleeding or raw tissue exposed or white basal layer exposed		3							
	BEHAVIORAL CHANGES									
	No changes (i.e., normal)		0							
	Repeated grooming (tumor may not be easily visible or quite small)		1							
	Abnormal gait (tumor may not be easily visible or quite small)		1							
	Locomotion impeded (tumor is pronounced)		2							
	Recurrent scratching/biting of tumor		3							
	Nociception (struggling/sqeaking) on touching tumor		3							
IF YOU HAVE SCORED ANY 3s IN SECTION A, CULL TODAY.										
IF YOU HAVE SCORED ANY 2s IN SECTION A, REFER TO SECTION B, ELSE GO TO SECTION C.										
SECTION B	SIZE/PROGRESSION OF LESION (expressed in orthogonal diameters**)	# D1/D2**								
	Shrinking		0							
	Static		1							
	2-3 mm growing		2							
	3-5 mm growing		3							
	5+ mm growing		4							
	SIZE/PROGRESSION OF TUMOR									
	Shrinking		0							
	Static		1							
	10-12 mm growing		2							
	12-14 mm growing		4							
	14+ mm growing (mean D1/D2 or D1 or either > 17 mm)		6							
	TOTAL FOR SECTION A + SECTION B									
	**# D1 and D2 are orthogonal diameters									
IF THE TOTAL FOR SECTIONS A + B IS 6, CULL WITHIN 1 DAY. IF 4-5 MONITOR DAILY, CULL WITHIN 1 WEEK IF NO IMPROVEMENT.										
ELSE GO TO SECTION C										
SECTION C	KEEP MONITORING AS REQUIRED (DAILY)									
		Date								

Adapted with permission from a scoring sheet developed by Fraser Darling, The Institute of Cancer Research, London, UK.

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Implement Performance (and Engineering) Standards

- **Engineering standard: a defined, measurable parameter**
  - E.g., cage size, temperature range, humidity range
  - Ensures the baseline welfare considerations
  - Easy to verify and comply with
- **Performance standard: an outcomes-based parameter**
  - E.g., enriched housing
  - Depends on literature reviews and scientific evidence
  - Can be driven by welfare considerations

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Develop Principles Guiding the Use of Species x for Research y

From the report *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*, National Research Council 2011

o The knowledge gained must be necessary to advance the public's health

o There must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects

o The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats.

https://www.nap.edu/catalog/13257/chimpanzees-in-biomedical-and-behavioral-research-assessing-the-necessity

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Thank you

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