International Trend in 3Rs

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Today’s Talk

• Alternatives=3Rs in Animal Experimentation
• Brief History of World Congress of Alternatives
• International Trend in 3Rs since 2010
  • OIE Research Animal Welfare Code
  • CIOMS Guiding principles
  • EU laboratory animal protection Directive
  • ILAR Guide
  • OECD revised Draize’s test
Alternatives to Animal Experiment = 3Rs

• Replacement
  • replacement refers to the use of methods utilizing cells, tissues or organs of animals (relative replacement), as well as those that do not require the use of animals to achieve the scientific aims (absolute replacement);

• Reduction
  • reduction refers to the use of methods that enable researchers to obtain comparable levels of information from fewer animals or to obtain more information from the same number of animals;

• Refinement
  • refinement refers to the use of methods that prevent, alleviate or minimise pain, suffering, distress or lasting harm and/or enhance welfare for the animals used. Refinement includes the appropriate selection of relevant species with a lesser degree of structural and functional complexity in their nervous systems and a lesser apparent capacity for experiences that derive from this complexity. Opportunities for refinement should be considered and implemented throughout the lifetime of the animal and include, for example, housing and transportation as well as procedures and euthanasia.
International Advancement in 3Rs: World Congress

• 1993 1st World Congress on Alternatives and Animal Use in the Life Sciences, Baltimore, USA
• 1996 2nd World Congress on Alternatives and Animal Use in the Life Sciences, Utrecht, The Netherlands
• 1999 3rd World Congress on Alternatives and Animal Use in the Life Sciences, Bologna, Italy
• 2002 4th World Congress on Alternatives and Animal Use in the Life Sciences, New Orleans, USA,
• 2005 5th World Congress on Alternatives and Animal Use in the Life Sciences, Berlin, Germany
• 2007 6th World Congress on Alternatives and Animal Use in the Life Sciences, Tokyo, Japan
• 2009 7th World Congress on Alternatives and Animal Use in the Life Sciences, Rome, Italy
• 2011 8th World Congress on Alternatives and Animal Use in the Life Sciences, Montreal, Canada
• 2014 9th World Congress on Alternatives and Animal Use in the Life Sciences, Prague, Czech Republic
• 2017 10th World Congress on Alternatives and Animal Use in the Life Sciences, USA
• 2020 11th
• 2023 12th
International Trend in Laboratory Animal Welfare since 2010

• Relevant International Standards, Regulations and Guides
  • OIE Standard 2010
  • CIOMS Guiding Principle 2012

• Relevant National and Regional Laws, Standards and Guidelines
  • EU Directive of Research Animal Protection revised 2010
  • ILAR Guide revised to 8th Ed. 2011
    • AAALAC International main reference

- The transport of animals by land
- The transport of animals by sea
- The transport of animals by air
- The slaughter of animals for human consumption
- The killing of animals for disease control purposes
- The control of stray dog populations
- The use of animals in research and education
- Animal welfare and beef cattle production systems
- Animal welfare and broiler chicken production systems
- The welfare of farmed fish during transport
- The welfare aspects of stunning and killing of farmed fish for human consumption
- Killing of farmed fish for disease control purposes.
Chapter 7.8. Use of animals in research and education

• Article 7.8.2. Scope

• This chapter applies to animals as defined in the Terrestrial Code (excluding bees) bred, supplied and/or used in research (including testing) and higher education. Animals to be used for production of biologicals and/or humanely killed for harvesting their cells, tissues and organs for scientific purposes are also covered. Member Countries should consider both the species and the developmental stage of the animal in implementing these standards.

• Article 7.8.3. The Three Rs

• The internationally accepted tenet, the ‘Three Rs’, comprises the following alternatives:
INTERNATIONAL GUIDING PRINCIPLES

FOR

BIOMEDICAL RESEARCH INVOLVING ANIMALS

DECEMBER 2012
CIOMS Guiding Principles

- Initially published in 1985
- Influence to International and national regulations for laboratory animal welfare
  - UK Scientific (Animal Procedure) Act revised in 1986
  - US Animal Welfare Act revised in 1985
  - ILAR Guide revised in 1985
- Proposed by biomedical Scientists
CIOMS: Article 3

• The principles of the Three Rs—Replacement, Reduction and Refinement—should be incorporated into the design and conduct of scientific and/or educational activities that involve animals.

• Cost and convenience must not take precedence over these principles.
Biological evaluation of medical devices —
Part 2: Animal welfare requirements

Évaluation biologique des dispositifs médicaux —
Partie 2: Exigences relatives à la protection des animaux
ISO10993-2

3Rs

• **3.10 reduction**
  reducing to the essential minimum the number of animals used in an animal test to meet a defined scientific objective

• **3.11 refinement**
  sum total of measures taken to safeguard the welfare of the test animals by minimizing any resulting pain, suffering, distress or lasting harm to the animals that are used

• **3.12 replacement**
  any scientifically valid and reasonably and practically available test method that either completely or partially replaces the use of living vertebrate animals with test methods that have not the potential to cause pain or distress to animals
Date: 2015-06-12

**BRIEF MINUTES AND PROGRESS ACHIEVED AT THE MEETING**

**on 9 and 10 JUNE 2015 IN LUND, SWEDEN**

The meeting was chaired by Prof. Tsutomu Kurosawa, Japan, and attended by 13 delegates from 8 countries.

ISO 10993-2 was discussed and the following identified:

- The scope should be changed to:
  
  "This standard is intended to be applied to medical devices. Users of other standards for animal tests should consider whether this part of ISO 10993 can be used in other application area."

- The normative reference should be changed to the current version of ISO 10993-1.

- For terms and definitions, new terms such as "ethical oversight committee, laboratory animal veterinarian (qualified) and veterinary care" should be added. The definitions of several terms should be changed.
Changes are made as indicated in the document revised at the meeting. Major revision includes:

- Addition of *veterinary care*,
- Laboratory animal veterinarian and their responsibilities and authority,
- Trained veterinary care staff,
- Addition of ILAR Guide, IACLAM and AAALAC International in NOTES.
- For surgery, aseptic methods, monitoring, pharmaceutical grade of chemical usage are added.
- Usage of other analgesics than NSAIDs.
- Annex A should be revised. Procedural training in surgery is added in details. *Veterinary authority* for humane endpoint in emergency case is noticed. Ethical review committee is described.
- Several outdated original articles should be deleted from Bibliography.
- Considering the items above, WG 3 agreed that a major revision is needed.
DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 22 September 2010
on the protection of animals used for scientific purposes
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 thereof,

Having regard to the proposal from the European Commission,

Having regard to the opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

and other scientific purposes (4). By becoming party to that Convention, the Community acknowledged the importance of the protection and welfare of animals used for scientific purposes at international level.

EU Directive (56 Articles)
Chapter 1 GENERAL PROVISIONS

• 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.
• The “Three Rs” in EU legislative framework

• Directive 2010/63/EU on the protection of animals used for scientific purposes, for the first time in EU legislation spells out the principle of the “Three Rs” and makes it a firm legal requirement in all aspects of care and use of animals in the field.

• Furthermore, the Directive ensures that its application goes beyond that of the original interpretation also to cover animal breeding and care – that is, to ensure refinement during housing, breeding and care even if the animal is not undergoing a scientific procedure.
ILAR Guide
The latest version of the Guide has been (or will be) translated into a number of different languages including (8 languages).
ILAR Guide: Key Concepts

• Applicability and Goals
• Intended Audiences and Uses of the Guide
• Ethics and Animal Use
• The Three Rs
• Key Terms Used in the Guide
• Humane Care
• Animal Care and Use Program
• Engineering, Performance, and Practice Standards
• Policies, Principles, and Procedures
Revised

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Acute Eye Irritation/Corrosion

INTRODUCTION

1. OECD Guidelines for Testing of Chemicals are periodically reviewed to ensure that they reflect the best available science. In previous reviews of this Test Guideline, special attention was given to possible improvements through the evaluation of all existing information on the test substance in order to avoid unnecessary testing in laboratory animals and thereby address animal welfare concerns. This Test Guideline (adopted in 1981 and updated in 1987, 2002, and 2012) includes the recommendation that prior to undertaking the described in vivo test for acute eye irritation/corrosion, a weight-of-the-evidence analysis be performed (1) on the existing relevant data. Where insufficient data are available, it is recommended that they be developed through application of sequential testing (2) (3). The testing strategy
OECD TG405: Acute Eye Irritation/Corrosion

• **Draize test** developed in 1940s in US.
• Well known as **rabbit eye test**.
• US FDA suggested to use this test for cosmetics.
• A symbol of anti animal experiment movement.
• Many alternative methods were developed.
• TG405 was revised several times.
Photos used by anti animal experiment groups
Revision of TG405 in 2012

• The testing strategy includes the performance of validated and accepted **in vitro tests** and is provided as a Supplement to the Guideline.

• Testing in animals should only be conducted if determined to be necessary **after consideration of available alternative methods**, and use of those determined to be appropriate.

• There are instances where using this Test Guideline is **still necessary or required** by some regulatory authorities.
• Balanced preemptive pain management should include:
  • (i) \textit{routine pretreatment} with a topical anesthetic and a systemic analgesic
  • (ii) \textit{routine post-treatment} schedule of systemic analgesia
  • (iii) scheduled observation, monitoring, and recording of animals \textit{for clinical signs of pain and/or distress}, and
  • (iv) scheduled observation, \textit{monitoring, and recording of the nature, severity, and progression of all eye injuries}. 
Revised OECD TG405; Article 26

• Once severe ocular effects have been identified, an attending or qualified laboratory animal veterinarian or personnel trained to identify the clinical lesions should be consulted for a clinical examination to determine if the combination of these effects warrants early study termination.
Summary of International Trends in 3Rs

• Alternatives to Animal Experiments = 3Rs
• International Standards define 3Rs
• Regional regulations and guidelines emphasize 3Rs
• 3Rs is a minimal requirement for animal experiments
• We alternative scientists should explain the necessity of further advancement of 3Rs to Biomedical communities such as academia, industries, funding agencies and regulators