How to improve scientific validity and animal welfare:

guidelines for animal research

norecopa.no/copenhagen2019

Adrian Smith
adrian.smith@norecopa.no

https://norecopa.no


© Alamy
Colourbox.com

Carol M. Newton (1925-2014)

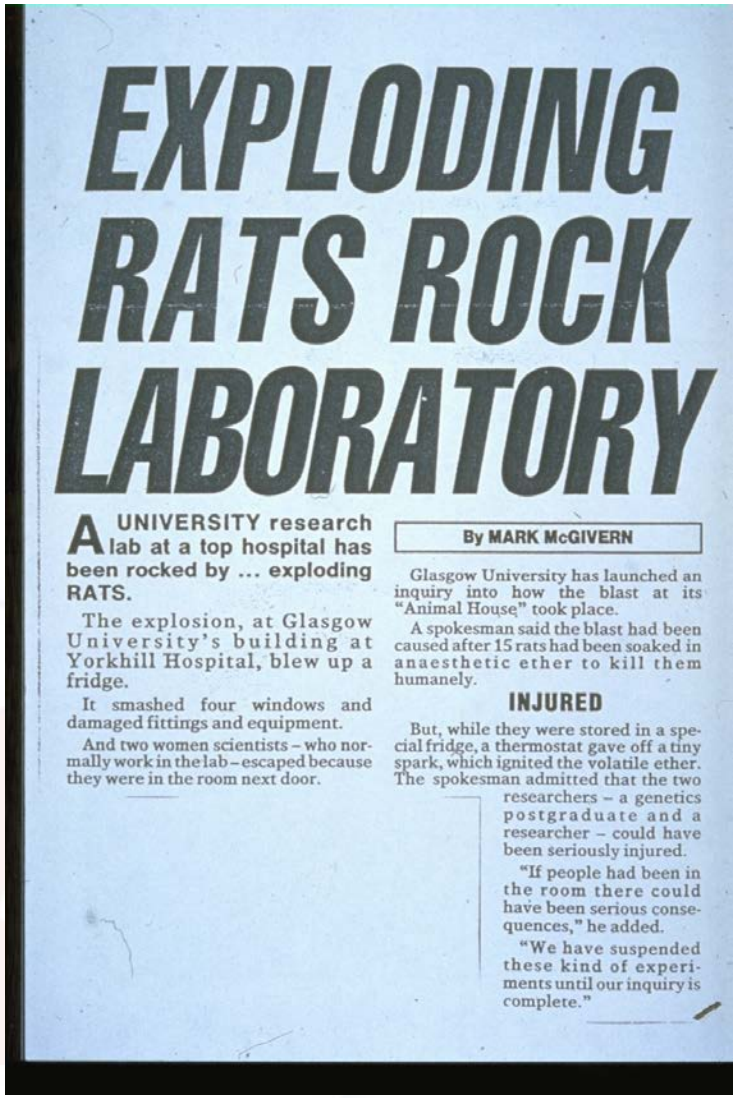
National Library of Medicine

The three S's

- *Good Science*
- *Good Sense*
- *Good Sensibilities*

norecopa.no/3S

Carol M Newton, quoted in Rowsell HC (1977): The Ethics of Biomedical Experimentation in The Future of Animals, Cells, Models, and Systems in Research, Development, Education, and Testing pp. 267-281, National Academy of Sciences, Washington, D.C., ISBN 0-309-02603-2.



EXPLODING RATS ROCK LABORATORY

A UNIVERSITY research lab at a top hospital has been rocked by ... exploding RATS.

The explosion, at Glasgow University's building at Yorkhill Hospital, blew up a fridge.

It smashed four windows and damaged fittings and equipment.

And two women scientists – who normally work in the lab – escaped because they were in the room next door.

By MARK McGIVERN

Glasgow University has launched an inquiry into how the blast at its "Animal House" took place.

A spokesman said the blast had been caused after 15 rats had been soaked in anaesthetic ether to kill them humanely.

INJURED

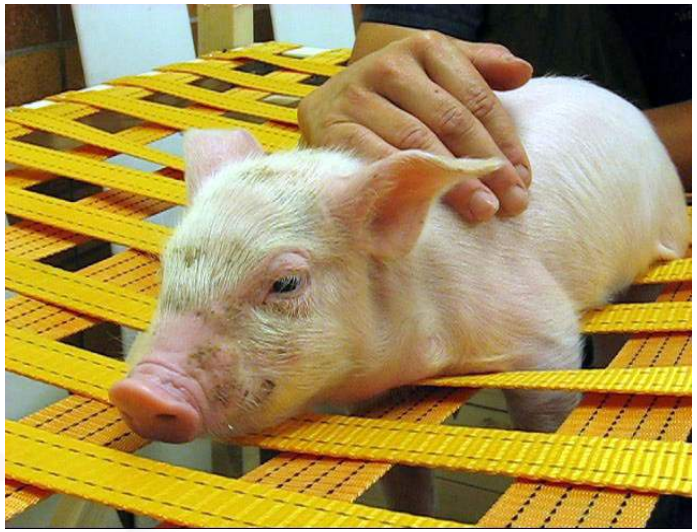
But, while they were stored in a special fridge, a thermostat gave off a tiny spark, which ignited the volatile ether. The spokesman admitted that the two researchers – a genetics postgraduate and a researcher – could have been seriously injured.

"If people had been in the room there could have been serious consequences," he added.

"We have suspended these kind of experiments until our inquiry is complete."

thewolfmountainnaturecenter.org

Bakken, Morten; Moe, Randi Oppermann; Smith, Adrian; Selle, Gunn-Marit Eriksrød.
Effects of enviromental stressors on deep body temperature and activity levels in silver fox vixens (Vulpes vulpes). *Applied Animal Behaviour Science* 1999 s. 141-151

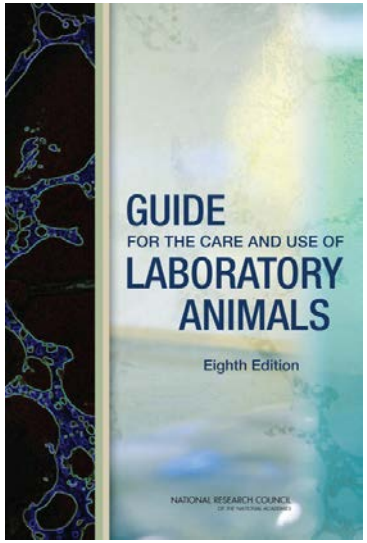


photos: NMBU

The AAALAC Program

- Animal care and use policies, and responsibilities
- Animal environment, housing and management
- Veterinary care
- The physical plant (buildings)

A complete description of the facility's structure and functions

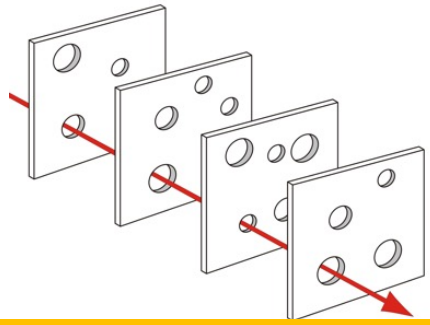


Work at least *in the spirit of* AAALAC and GLP even if you don't apply for accreditation!

https://norecopa.no/textbase/guide-for-the-care-and-use-of-laboratory-animals-8th-ed

A Contingency Plan, based upon risk assessment

- Access to emergency services (police, fire, medical and veterinary help, security guards, personnel transport in cases of acute illness)
- Means of communication with staff members at all levels
- SOPs for acute illness, including
  - serious haemorrhages
  - fainting
  - allergic and anaphylactic reactions
  - burns
  - head injuries
  - bites
  - corrosive injuries
  - and forms for reporting such injuries
- Firefighting, evacuation of personnel and animals
- Access to specialist services (e.g. ventilation system, plumbing, electrical installations, suppliers of equipment)
- Routines in cases of power failure, water leaks and (if applicable) natural disasters such as flooding
- Routines for emergency killing of animals
- Routines in cases of threats to the facility or personnel



Temporary staff at weekends and holidays

https://norecopa.no/prepare/6-facility-evaluation/master-plan-and-sops/contingency-plan

Contingency and redundancy

Anything that can go wrong, will go wrong (Murphy's Law)
when it's least convenient *(Sod's Law)*

Photo: NMBU

A simple contract between the animal facility and the research group

- Is it feasible, in the given time frame?
- On a large number of animals?
- In the facility's space?
- With the facility's equipment?
- Do all the staff have the time to attain competence?
- Cost of staff out of hours, 7 days a week
- Time to order, breed, import, acclimate and group the animals?
- Total length of project – including preparation (change in buildings, purchase of equipment or new cages/tanks, approval of these plans by authorities + lab animal standards)?
- Cleaning up costs

	Animal facility	Researcher	Not applicable
Animal:			
Arrival date			
Species			
Strain/stock and substrain			
Supplier (full name and address) or bred on the premises			
Number and sex			
Age, weight, stage of life cycle on arrival			
Pre-treatment (surgical or medical) from supplier			
Quality (e.g. SPF, germ-free, gnotobiotic, conventional)			
Acclimation time before the start of the experiment			
Time and duration of fasting (with/without water and bedding)			
Environment:			
Type of housing: barrier/conventional			
Temperature (mean ± variation)			
Light schedule			
Relative humidity (mean ± variation)			
Number of air changes in the animal room/cabinet per hour			
Environmental enrichment			
Housing:			
Free-range, shelf, cabinet, isolator			
Cage type and size			
Number and method of distribution of animals per cage			

https://norecopa.no/prepare/5-objectives-and-timescale-funding-and-division-of-labour/division-of-labour-costs-and-responsibility


MASTER PLAN 2012
Januar
Februar
Mars
April
Mai
Juni
Juli
August
September
Oktober
November
Desember
Bevegelige helligdager med unntak av søndager er merket med rødt.
A Master Plan to help everyone remember what has to be done

NASA

cbsnews.com

no.wikipedia.org

- Complex machines (animals) create *known or unknown unknown interactions* that are impossible to foresee

- Design weaknesses (*which the engineers knew about!)*

- External pressure to launch (political, media) - Publish or perish.

- Management decisions (pushing the safety envelope):
  "We've got away with it before"
  "We've managed to publish the experiments before"

- A combination of many factors, each of which may be harmless until they occur simultaneously

We need guidelines for *reporting* animal studies, and we have been trying to solve the reproducibility problem for a long time!

- Guidelines for specification of animals and husbandry methods when reporting the results of animal experiments (GV-SOLAS, 1985)
- Reporting animal use in scientific papers (Jane Smith *et al.)*, 1997
- Öbrink & Rehbinder: Animal definition: a necessity for the validity of animal experiments? *Laboratory Animals,* 2000
- Guidelines for reporting the results of experiments on fish (2000)
- ARRIVE Guidelines, 2010 (Kilkenny *et al.*, NC3Rs)
- Gold Standard Publication Checklist, 2010 (SYRCLE)
- Institute for Laboratory Animal Research, NRC, 2011
- Instructions to authors, in many journals

  e.g. Nature's Reporting Checklist

Why is it taking so long to improve reproducibility?

Berti & Cima 1955, quoted in Öbrink and Rehbinder

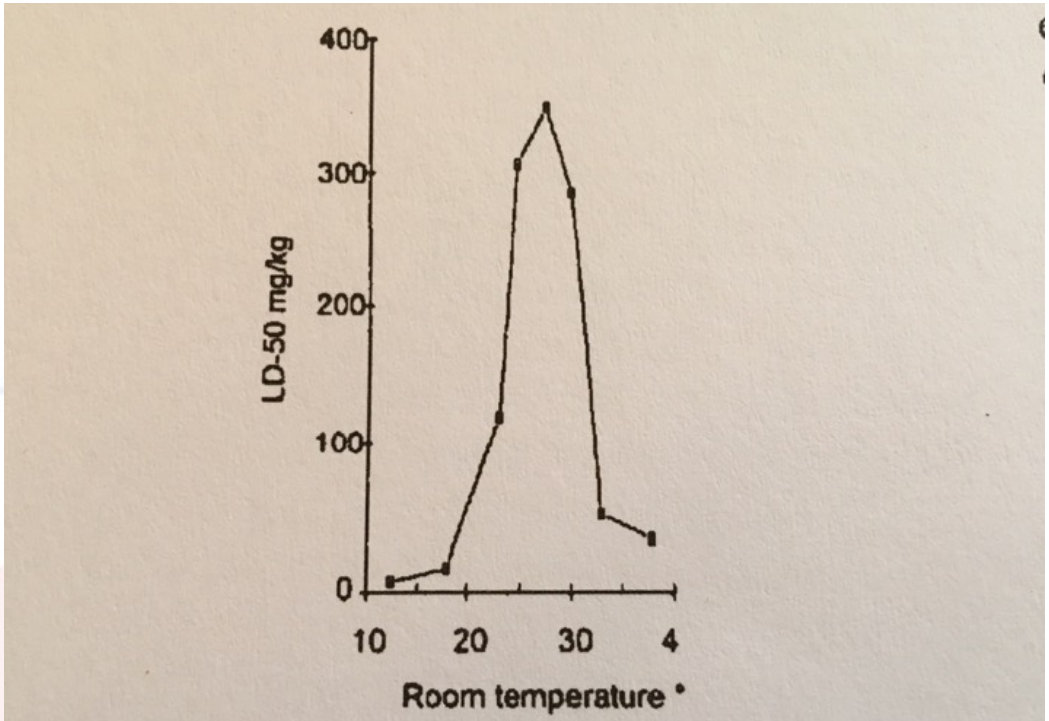


Fig 7 Influence of room temperature on LD-50 of the drug Chlorpromazine in mouse

Hurni 1969, quoted in Öbrink and Rehbinder

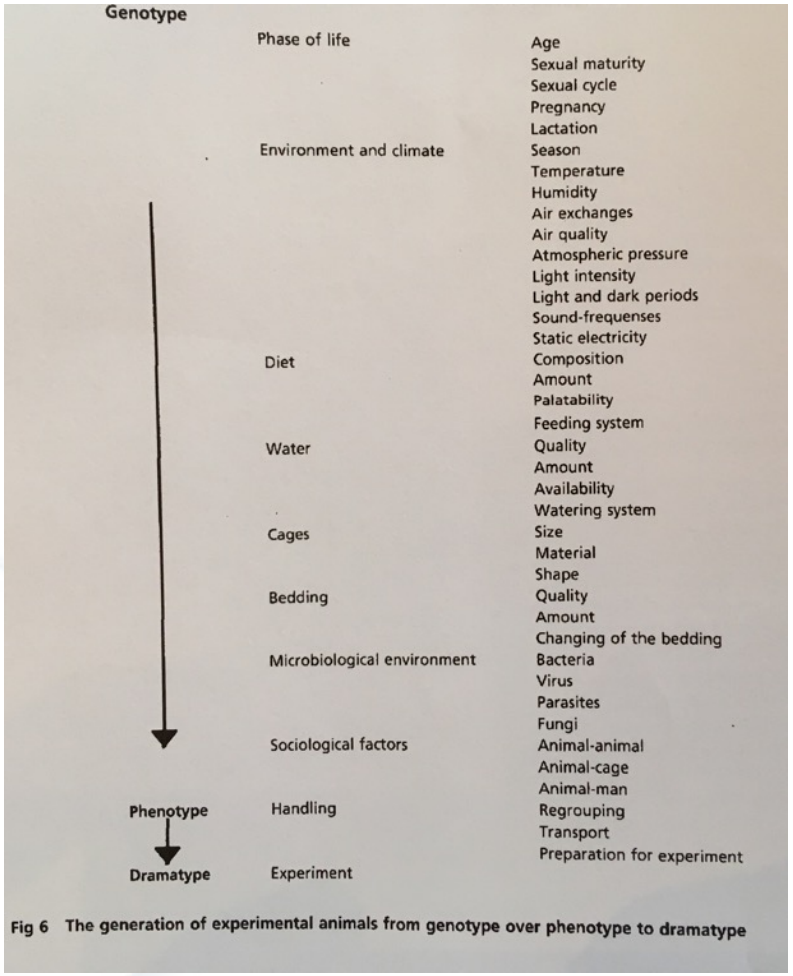
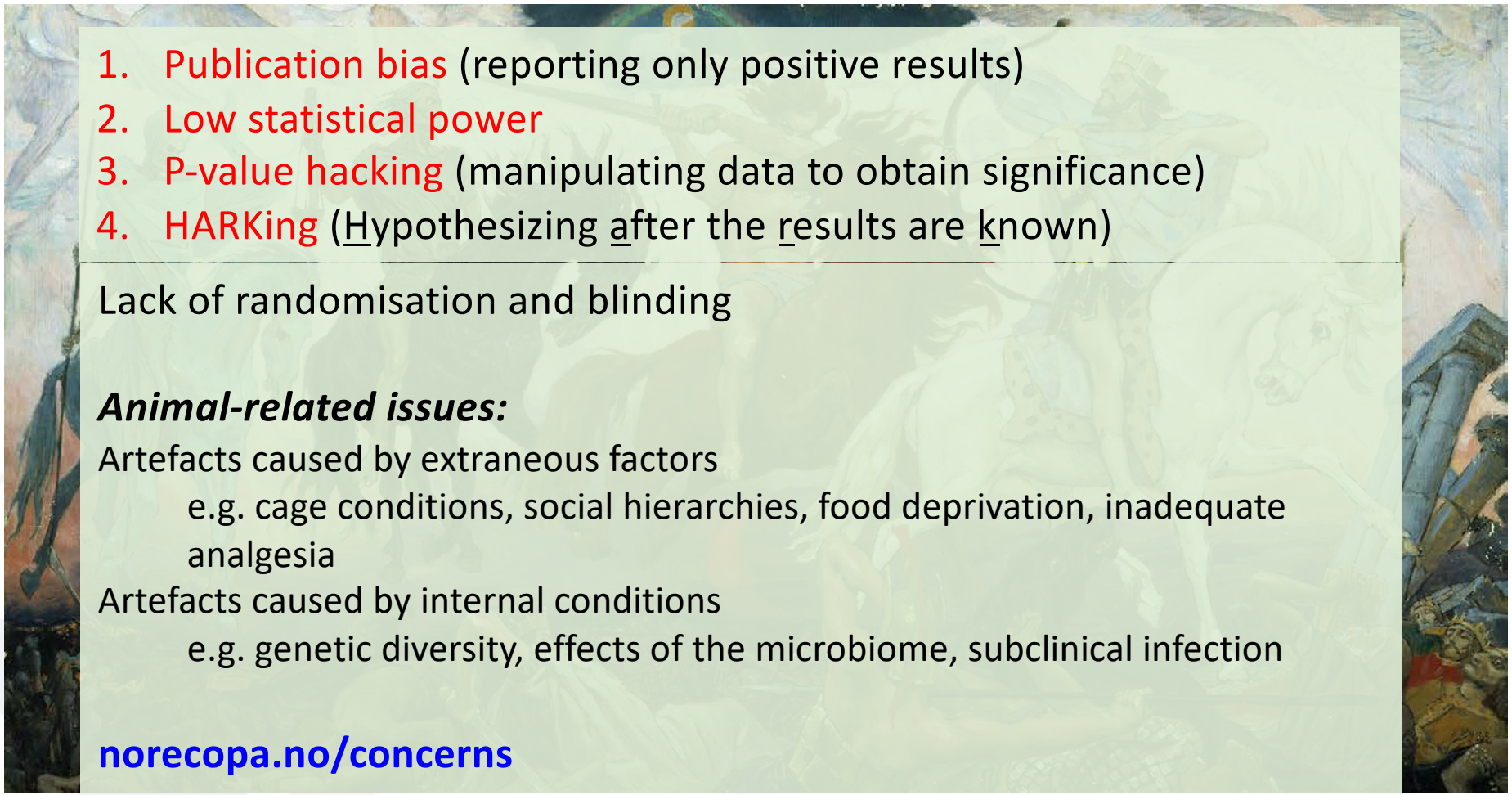


Fig 6 The generation of experimental animals from genotype over phenotype to dramatype



1. Publication bias (reporting only positive results)
2. Low statistical power
3. P-value hacking (manipulating data to obtain significance)
4. HARKing (Hypothesizing after the results are known)

Lack of randomisation and blinding

Animal-related issues:

Artefacts caused by extraneous factors

e.g. cage conditions, social hierarchies, food deprivation, inadequate analgesia

Artefacts caused by internal conditions

e.g. genetic diversity, effects of the microbiome, subclinical infection

norecopa.no/concerns

nature human behaviour

Perspective | Open Access | Published: 10 January 2017

A manifesto for reproducible science

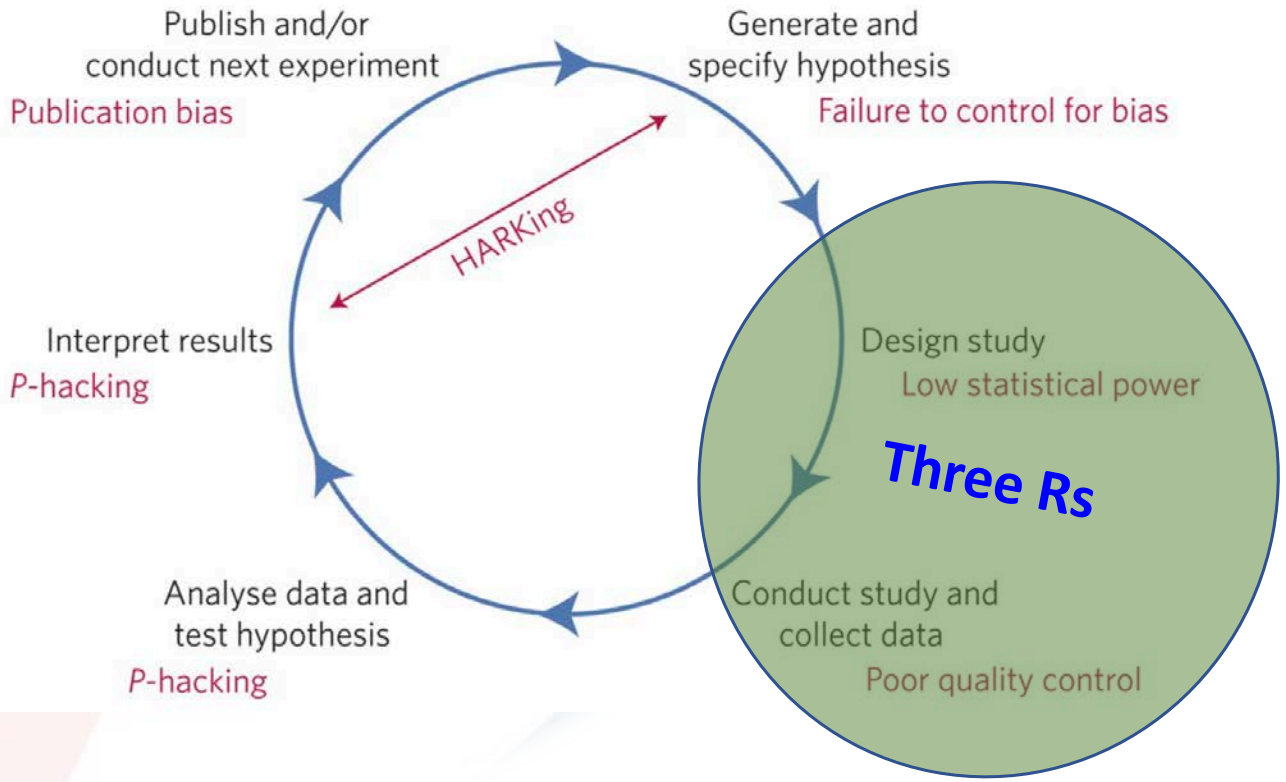
Marcus R. Munafò, Brian A. No
Button, Christopher D. Chambers,
Jan Wagenmakers, Jennifer J. Wa

Nature Human Behaviour 1, Artic

33k Accesses | **518** Citations |

Figure 1: Threats to reproducible science.

From: A manifesto for reproducible science



Pain management in pigs undergoing experimental surgery; a literature review (2012–4)

A. G. Bradbury, M. Eddleston, R. E. Clutton

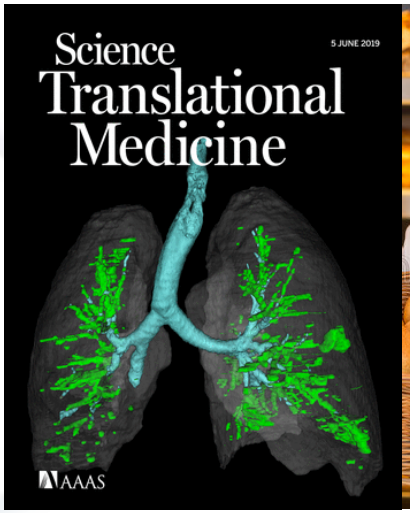
Br J Anaesth (2016) 116 (1): 37-45. **DOI:** https://doi.org/10.1093/bja/aev301
Published: 03 October 2015

selection criteria. Most articles (193/233, 83%) described use of drugs with analgesic properties, but only 87/233 (37%) described postoperative analgesia. No article provided justification for the analgesic chosen, despite the lack of guidelines for analgesia in porcine surgical models and the lack of formal studies on this subject. Postoperative pain assessment was reported in only 23/233 (10%) articles. It was found that the reporting of postoperative pain management in the studies was remarkably low, reflecting either under-reporting or under-use. Analgesic description, when given, was frequently too limited to enable reproducibility. Development of a

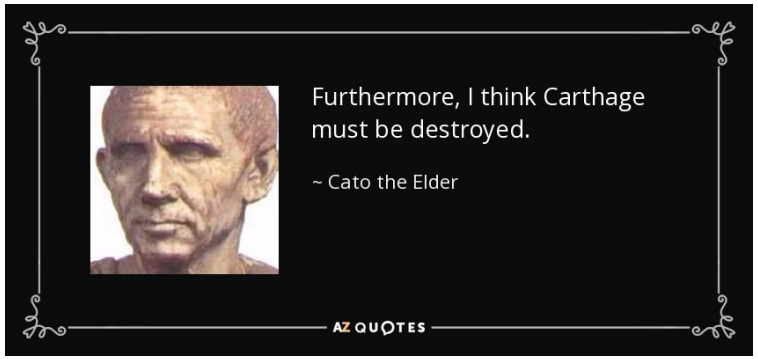
https://www.bls.gov/ooh/images/3077.jpg

PREPARE *from day 1*

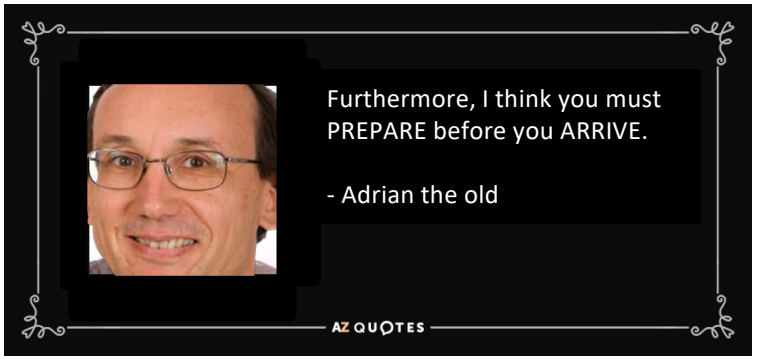
ARRIVE

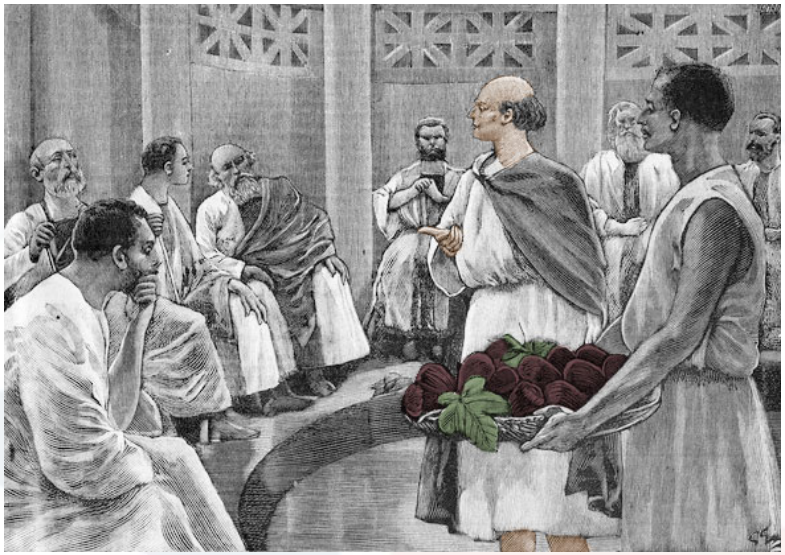


https://www.dreamstime.com



azquotes.com





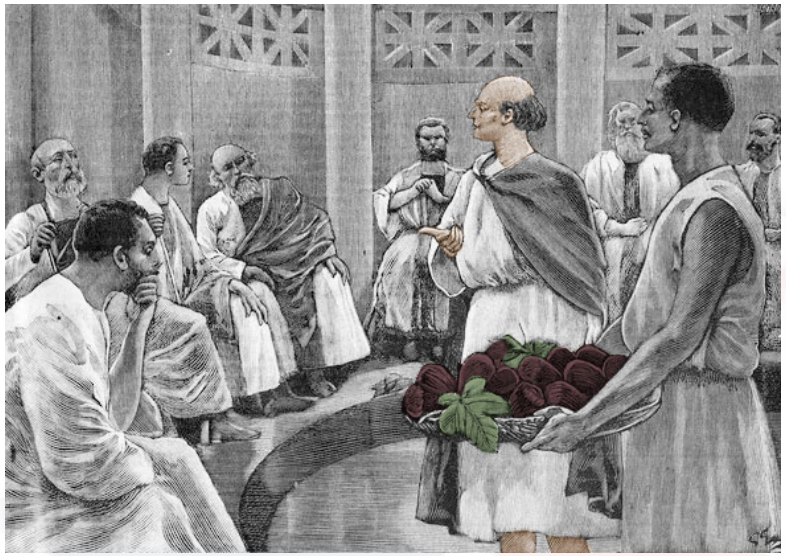
pass-the-garum.blogspot.com

with thanks to senator Otto Kalliokoski

Two frustrations:

"We can solve the reproducibility crisis by:"

- better reporting (of burnt cakes)
- courses in Experimental Design that only cover the "mathematical" elements (e.g. group size, randomisation, blinding, bias, statistical analysis) and ignore the animal/human-related issues



pass-the-garum.blogspot.com

pinterest.com

The ARRIVE guidelines

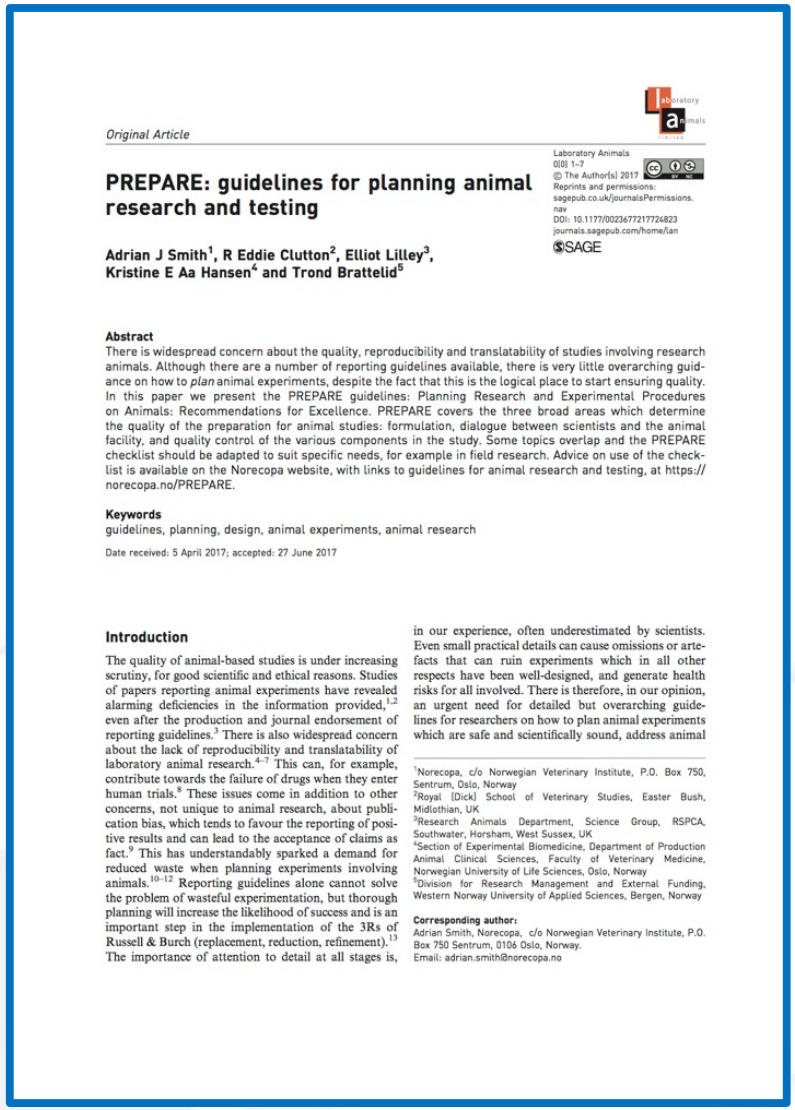
The ARRIVE guidelines claim that they 'provide a logical checklist with all the things that need to be considered when designing an experiment'. ***Disagree!***

In our experience when planning animal research, **a number of additional points need to be addressed at the planning stage**.

These items **improve**

- **study quality**
- **animal welfare**
- **reproducibility**

- and also the **safety of humans and animals** affected directly or indirectly by the work



Original Article

PREPARE: guidelines for planning animal research and testing

Adrian J Smith[1], R Eddie Clutton[2], Elliot Lilley[3], Kristine E Aa Hansen[4] and Trond Brattelid[5]

Laboratory Animals
0(0) 1–7

DOI: 10.1177/0023677217724823
journals.sagepub.com/home/lan
SAGE

Abstract

There is widespread concern about the quality, reproducibility and translatability of studies involving research animals. Although there are a number of reporting guidelines available, there is very little overarching guidance on how to *plan* animal experiments, despite the fact that this is the logical place to start ensuring quality. In this paper we present the PREPARE guidelines: Planning Research and Experimental Procedures on Animals: Recommendations for Excellence. PREPARE covers the three broad areas which determine the quality of the preparation for animal studies: formulation, dialogue between scientists and the animal facility, and quality control of the various components in the study. Some topics overlap and the PREPARE checklist should be adapted to suit specific needs, for example in field research. Advice on use of the checklist is available on the Norecopa website, with links to guidelines for animal research and testing, at https://norecopa.no/PREPARE.

Keywords

guidelines, planning, design, animal experiments, animal research

Date received: 5 April 2017; accepted: 27 June 2017

Introduction

The quality of animal-based studies is under increasing scrutiny, for good scientific and ethical reasons. Studies of papers reporting animal experiments have revealed alarming deficiencies in the information provided,[1,2] even after the production and journal endorsement of reporting guidelines.[3] There is also widespread concern about the lack of reproducibility and translatability of laboratory animal research.[4–7] This can, for example, contribute towards the failure of drugs when they enter human trials.[8] These issues come in addition to other concerns, not unique to animal research, about publication bias, which tends to favour the reporting of positive results and can lead to the acceptance of claims as fact.[9] This has understandably sparked a demand for reduced waste when planning experiments involving animals.[10–12] Reporting guidelines alone cannot solve the problem of wasteful experimentation, but thorough planning will increase the likelihood of success and is an important step in the implementation of the 3Rs of Russell & Burch (replacement, reduction, refinement).[13] The importance of attention to detail at all stages is, in our experience, often underestimated by scientists. Even small practical details can cause omissions or artefacts that can ruin experiments which in all other respects have been well-designed, and generate health risks for all involved. There is therefore, in our opinion, an urgent need for detailed but overarching guidelines for researchers on how to plan animal experiments which are safe and scientifically sound, address animal

[1]Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750, Sentrum, Oslo, Norway
[2]Royal (Dick) School of Veterinary Studies, Easter Bush, Midlothian, UK
[3]Research Animals Department, Science Group, RSPCA, Southwater, Horsham, West Sussex, UK
[4]Section of Experimental Biomedicine, Department of Production Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, Oslo, Norway
[5]Division for Research Management and External Funding, Western Norway University of Applied Sciences, Bergen, Norway

Corresponding author:
Adrian Smith, Norecopa, c/o Norwegian Veterinary Institute, P.O. Box 750 Sentrum, 0106 Oslo, Norway.
Email: adrian.smith@norecopa.no

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https://doi.org/10.1177/0023677217724823

Over 11,000 downloads from the journal website so far

Also downloadable from
norecopa.no/PREPARE

PREPARE:

Planning **R**esearch and **E**xperimental **P**rocedures on **A**nimals: **R**ecommendations for **E**xcellence

PREPARE covers 15 topics:

Formulation of the study

1. Literature searches
2. Legal issues
3. Ethical issues, harm-benefit assessment and humane endpoints
4. Experimental design and statistical analysis

Dialogue between scientists and the animal facility

5. Objectives and timescale, funding and division of labour
6. Facility evaluation
7. Education and training
8. Health risks, waste disposal and decontamination

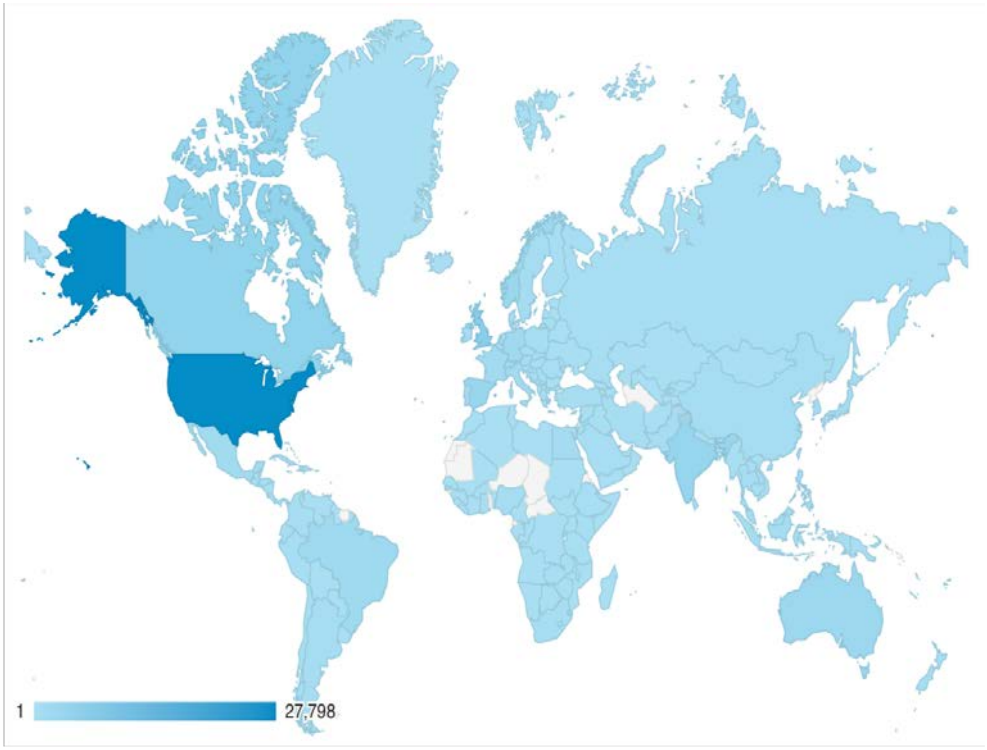
Methods

9. Test substances and procedures
10. Experimental animals
11. Quarantine and health monitoring
12. Housing and husbandry
13. Experimental procedures
14. Humane killing, release, reuse or rehoming
15. Necropsy

norecopa.no/PREPARE/prepare-checklist

norecopa.no : constructed for those involved in animal research and testing

8,600 webpages
80,000 links



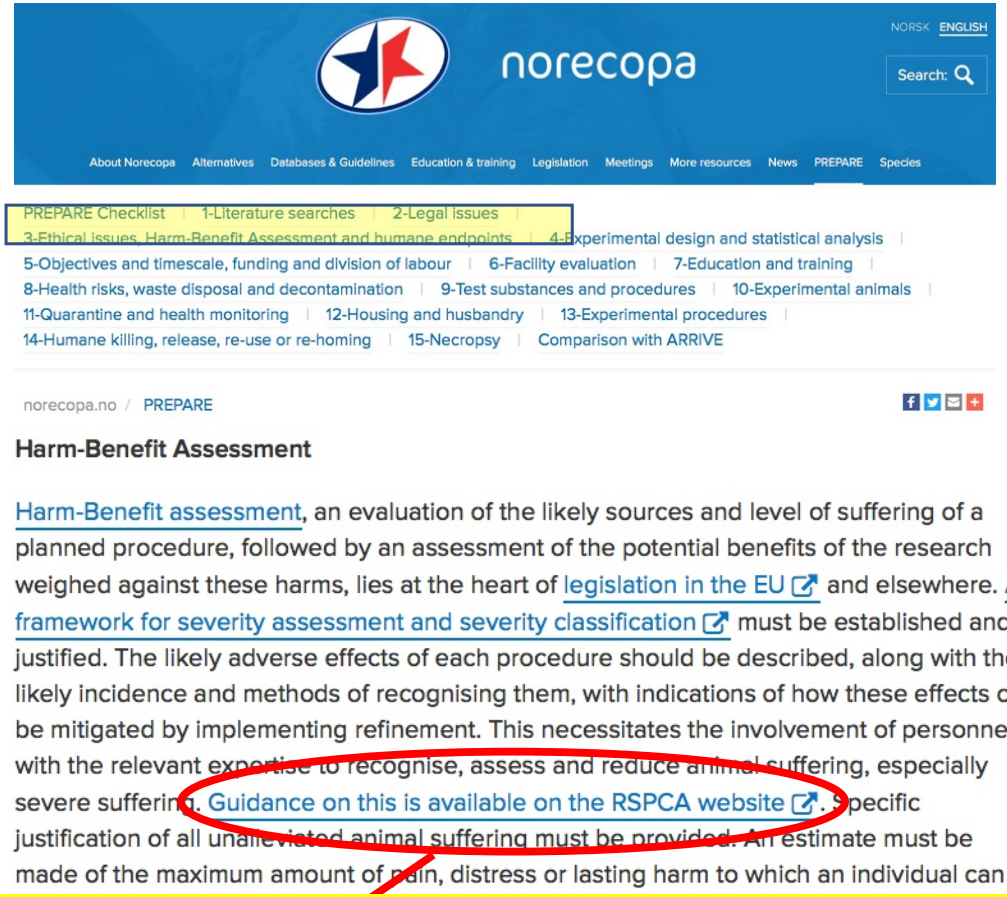
1.	United States
2.	United Kingdom
3.	Canada
4.	India
5.	Spain
6.	Norway
7.	Australia
8.	Brazil
9.	Germany
10.	Mexico

250,000 page views in 2019

In addition to the PREPARE checklist, much more information is available on:

norecopa.no/PREPARE

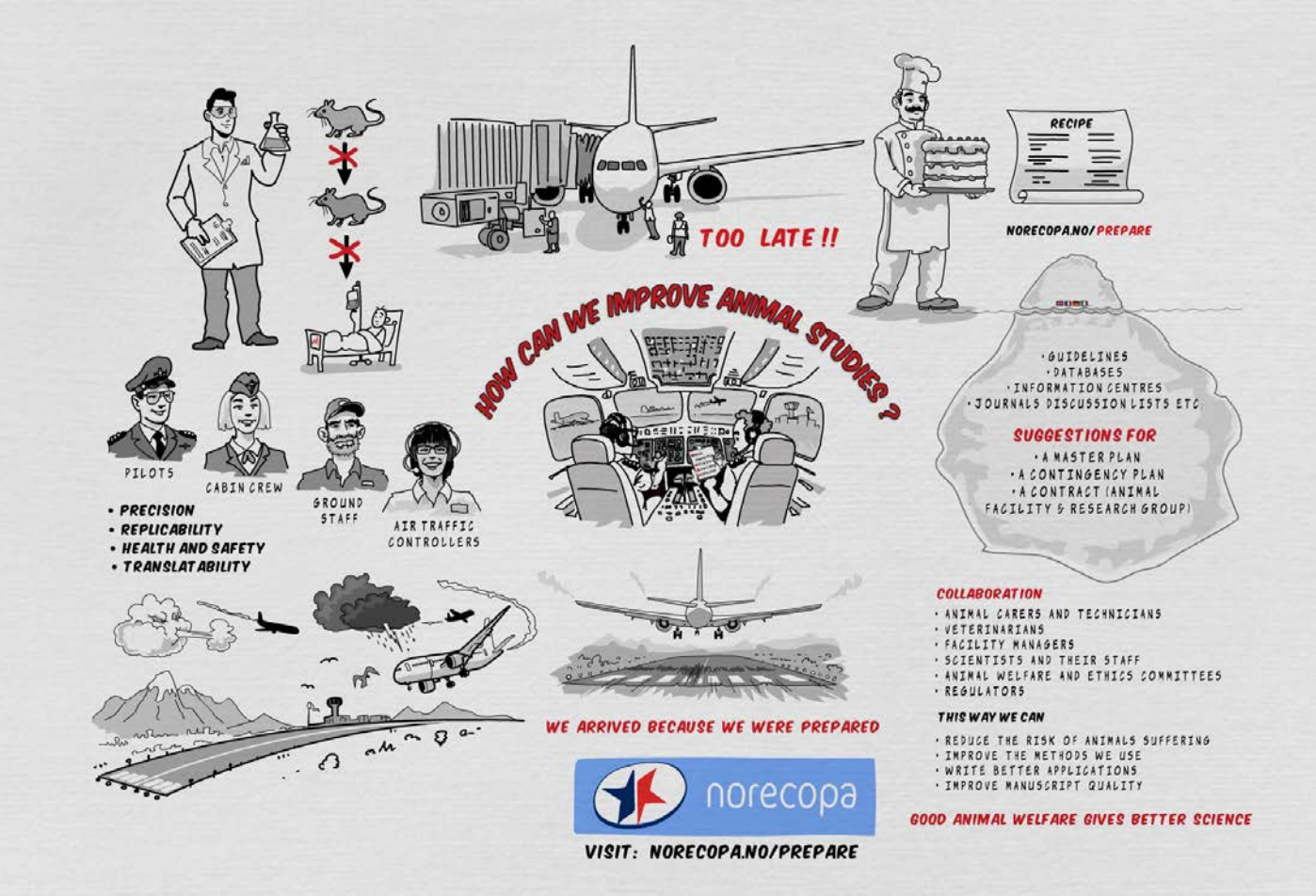
norecopa.no/PREPARE



Links to quality guidelines worldwide on e.g. blood sampling, injection volumes, housing and husbandry, analgesia, humane endpoints, experimental design

vimeo.com/358069203 or norecopa.no/PREPARE

3-minute cartoon film

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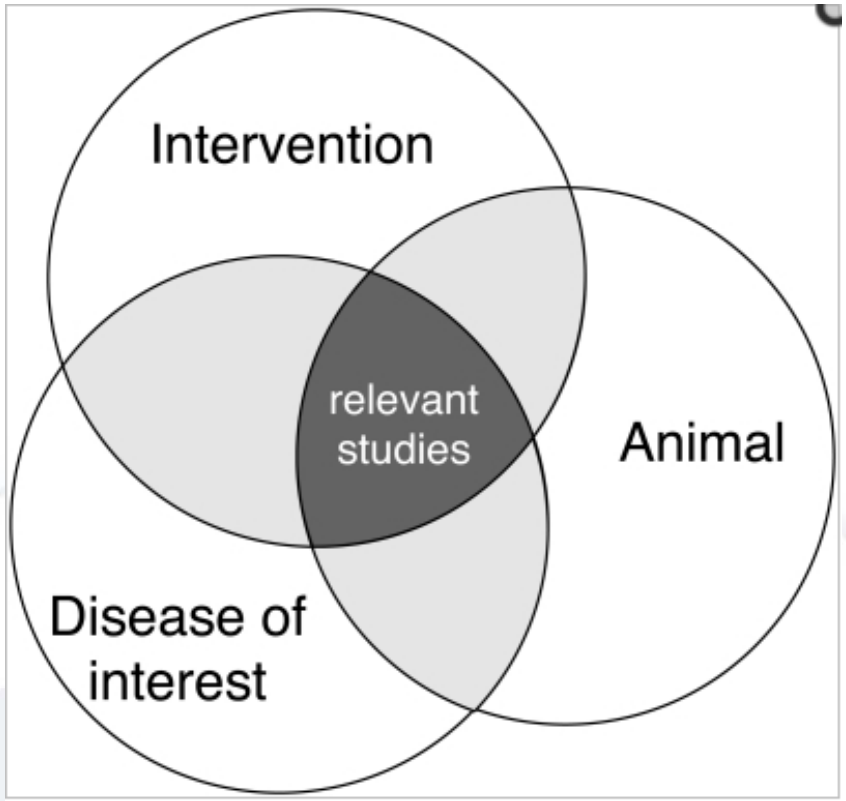
Norecopa: PREPARE for better Science
3R Symposium, Copenhagen, 12-13 November 2019



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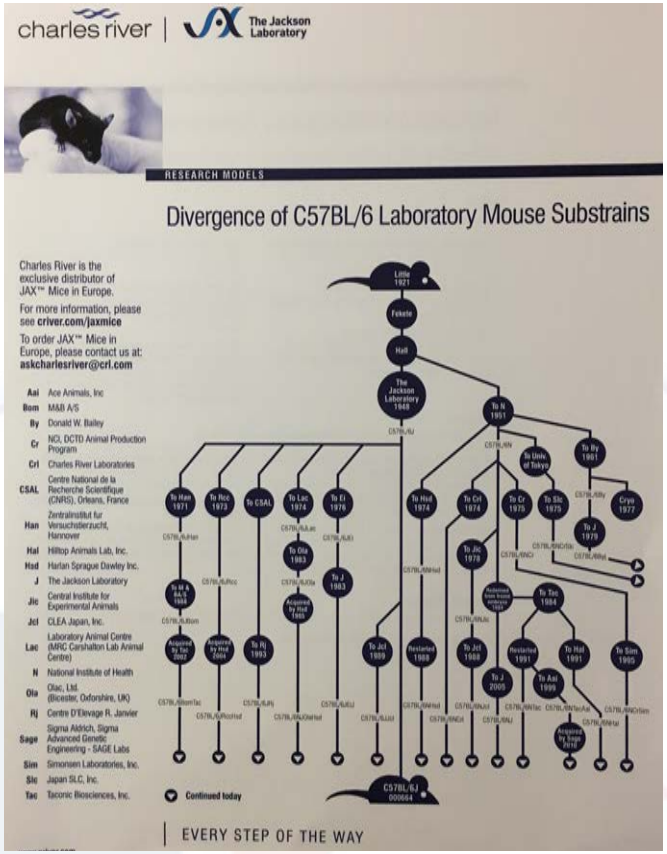
Literature searches and Systematic Reviews of published animal studies

Good literature searches are an integral part of planning animal research and testing, as indicated in the PREPARE guidelines. Some core resources are cited here. The section of the Norecopa website on databases and guidelines will also be helpful.

The EURL ECVAM Search Guide
How to conduct a literature search by Alice Tillema, Radboud University
Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed
A search filter for increasing the retrieval of animal studies in Embase
Alternatives Search: Demonstrating Compliance (UC Davis website)
Finding 3Rs information: a needle in a haystack? (practical advice from Utrecht University)
Database searches and resources for non-animal methods (a presentation by Michelle Hudson-Shore, FRAME)

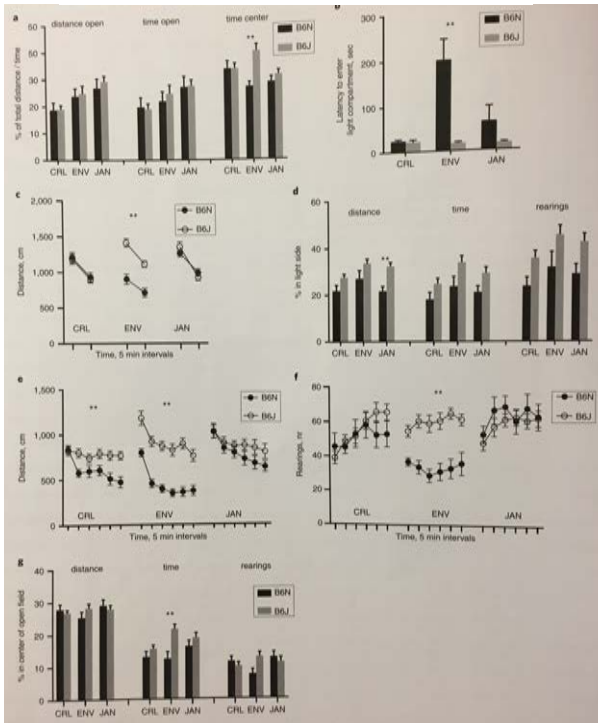
A step-by-step guide to systematically identify all relevant animal studies
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3265183

C57BL/6 mice



Åhlgren & Voikar (2019): Behavioural differences between /6J and /6N mice

nature.com/articles/s41684-019-0288-8



We are what we eat...

Find a researcher

Axel Kornerup Hansen

Professor

Experimental Animal Models

Ridebanevej 9, 2. sal, 1870 Frederiksberg C, 1-62,
Building: 413

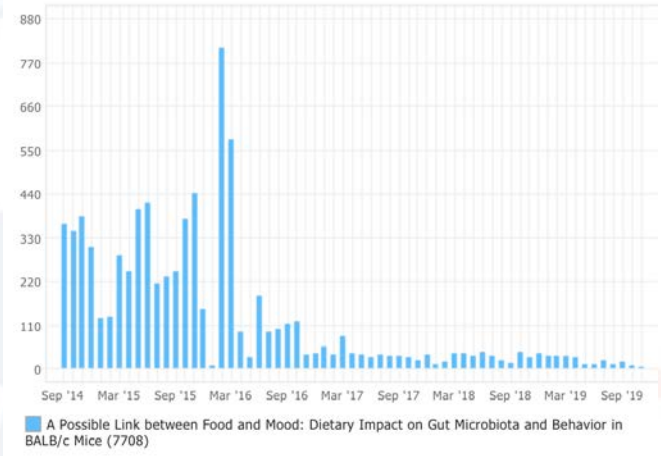
akh@sund.ku.dk

Most downloads

A possible link between food and mood: dietary impact on gut microbiota and behavior in BALB/c mice

7708 downloads

Contribution to journal › Journal article › Research › peer-review



no longer FELASA guidelines on nutrition...

we are what we eat...

norecopa

Diet-Induced Metabolic Syndrome in Rodent Models

A discussion of how diets made from purified ingredients influence the phenotypes of the MS in commonly used rodent models.

Angela M. Gajda, MS, Michael A. Pellizzon, Ph.D., Matthew R. Ricci, Ph.D. and Edward A. Ulman, Ph.D.

Pellizzon and Ricci *Nutrition & Metabolism* (2018) 15:3
DOI 10.1186/s12986-018-0243-5

Nutrition & Metabolism

Laboratory Animal Diets:

A Critical Part of Your In Vivo Research

Most all of us are aware that certain dietary choices can increase or decrease the likelihood of developing certain diseases. Our diets can also change our metabolism as well the levels of circulating factors (hormones, lipids, etc.) which may be markers for disease risk. What is often overlooked is the fact that these concepts also apply to laboratory animals, making diet a critical part of study design.

Matthew R. Ricci, Ph.D. and Edward A. Ulman, Ph.D.

PERSPECTIVE Open Access

The common use of improper control diets in diet-induced metabolic disease research confounds data interpretation: the fiber factor

Michael A. Pellizzon* and Matthew R. Ricci

Currently no FELASA guidance on nutrition (a working group has been convened)

Contingent suffering

animalcaresystems.com

(not just the direct suffering caused by the procedure)

Fear, boredom and discomfort

Caused by, for example:

Transport, or changes in housing, husbandry and social groups

Single-housed male mice show symptoms of what in humans would be characterised as depression

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0111065

photo: colourbox.com

Stress caused by capture and handling

INDEPENDENT

News › Science

Scores of scientific studies based on mice thrown into doubt because they wer

Mice pic
naturall

't act

Ian Johnstor

https://www.nc3rs.org.uk/how-to-pick-up-a-mouse

Stress caused by capture and handling

http://bitly.com/scruff-technique

Artefacts caused by poor administration techniques

Photo: NMBU

- *Variations in placement from time to time, and therefore absorption rate*
- *Pain on injection*
- *Realistic?*

Disposable needles are designed to be used only once!

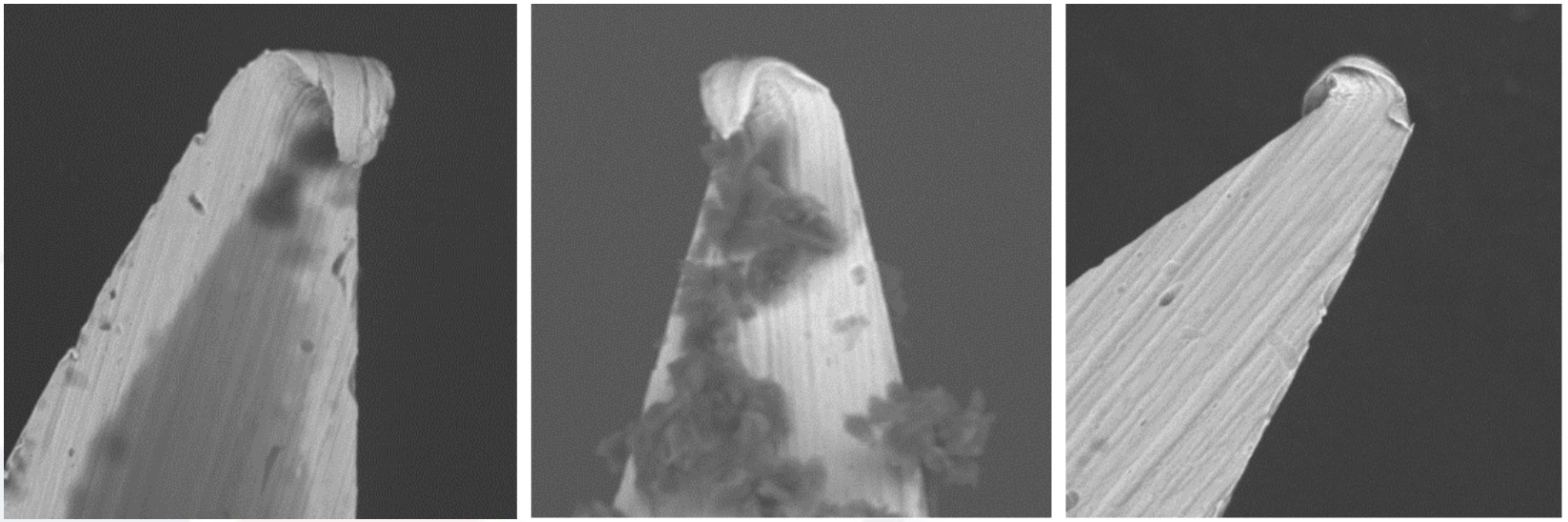


Photo: AstraZeneca

https://www.nc3rs.org.uk/news/re-use-needles-indicator-culture-care

'Simple' blood sampling techniques?

medipoint.com/html/for_use_on_mice.html

The best blood sampling techniques are those where you can:

- ✓ see the blood vessel
- ✓ regulate the amount of blood you remove
- ✓ stop the bleeding easily
- ✓ not damage the surrounding tissue
- ✓ collect samples rapidly to avoid artefacts due to mechanical stress, temperature changes, length of sampling

http://blogs.discovermagazine.com/notrocketscience/2011/01/12/flipper-bands-impair-penguin-survival-and-breeding-success/#.VLU6_8Y7_wo

Photo: T. Poppe, NMBU

Enorm isklump festet seg til reinsdyrets radiohalsbånd

SMERTER: Denne villreinen måtte avlives i Nordfjella. En isklump på GPS halsbåndet hadde vokst seg større enn hodet på reinen.

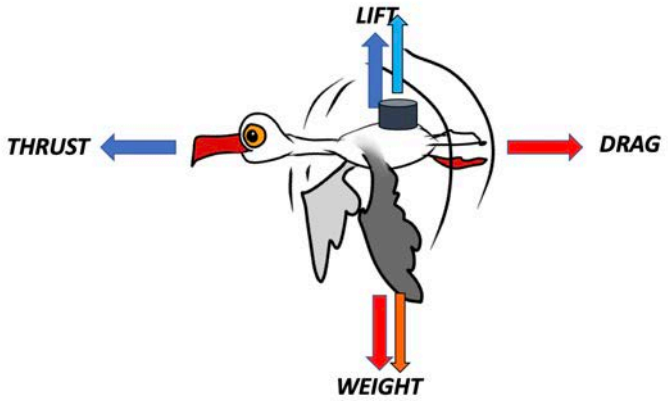
Av TOR-HARTVIG BONDØ og LINN K. YTTERVIK
(VG) 22.01.2016 20:27

49

annonse

Primary effects

The increased lift balances the extra force from the tag weight



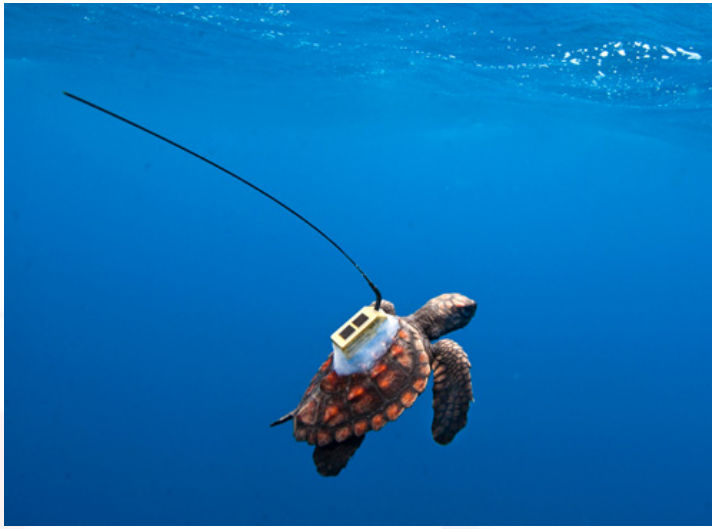
From Rory Wilson: norecopa.no/media/8018/rory-wilson.pdf

Double the speed and the drag quadruples.

This requires 8 times the power to maintain flight...

plus G-forces...

Drag occurs in water as well as in the air...



From Rory Wilson: norecopa.no/media/8018/rory-wilson.pdf

Consult the animal carers and technicians from Day 1:

- they have a right to know and will be more motivated
- they know the possibilities (and limitations) in the animal facility
- they often possess a large range of practical skills and are good at lateral thinking
- they know the animals best
- the animals know them best
- lack of involvement creates anxiety, depression and opposition to animal research, as well as limiting creativity which might improve the experiments

Closely related to a culture of care is the concept of a **Culture of Challenge** (Louhimies, 2015)**.**
Look for the acceptable, rather than choosing the accepted.

"as often as necessary"

"because we've always done it that way"

Don't forget to highlight 3R methods in the scientific literature!

http://www.theodora.com/rodent_laboratory/blood_collection.html

photo:NMBU

SCID-Hu mice immunized with a pneumococcal vaccine produce specific human antibodies and show increased resistance to infection.

Saphenous vein puncture for

blood sampling of the mouse, rat, hamster,

gerbil, guinea-pig,

ferret and mink

and it does not have to be in a high-impact journal.

Working Party Report

Guidance on the severity classification of scientific procedures involving fish: report of a Working Group appointed by the Norwegian Consensus-Platform for the Replacement, Reduction and Refinement of animal experiments (Norecopa)

P Hawkins (Convenor)[1], N Dennison[2], G Goodman[3], S Hetherington[4], S Llywelyn-Jones[5], K Ryder[2] and A J Smith[6]

[1]Research Animals Department, RSPCA, Wilberforce Way, Southwater, West Sussex RH13 9RS, UK; [2]Animals (Scientific Procedures) Inspectorate, Home Office, PO Box 6775, Dundee DD1 9WW, UK; [3]Biological Services, The University of Edinburgh, Chancellor Building, 49, Little France Crescent, Edinburgh EH16 4SB, UK; [4]CEMAS, Pakefield Road, Lowestoft, NR33 0HT, UK; [5]King's College London, Biological Services Unit, 4th floor, Hodgkin Building, Guy's Campus, London SE1 1UL, UK; [6]Norecopa, c/o Norwegian Veterinary Institute, PO Box 750 Sentrum, N-0106 Oslo, Norway
Corresponding author: P Hawkins. Email: phawkins@rspca.org.uk

Abstract

The severity classification of procedures using animals is an important tool to help focus the implementation of refinement and to assist in reporting the application of the 3Rs (replacement, reduction and refinement). The recently revised Directive that regulates animal research and testing within the European Union requires Member States to ensure that all procedures are classified as 'non-recovery', 'mild', 'moderate' or 'severe', using assignment criteria set out by the European Commission (EC). However, these are focused upon terrestrial species, so are of limited relevance to fish users. A Working Group set up by the Norwegian Consensus-Platform for the 3Rs (Norecopa) has produced guidance on the classification of severity in scientific procedures involving fish, including examples of 'subthreshold', 'mild', 'moderate', 'severe' and 'upper threshold' procedures. The aim is to complement the EC guidelines and help to ensure that suffering in fish is effectively predicted and minimized. Norecopa has established a website (www.norecopa.no/categories) where more information on severity classification for procedures using fish, including field research, will be made available.

Keywords: Fish, harm–benefit assessment, humane endpoints, refinement, severity

Laboratory Animals 2011; 1–6. DOI: 10.1258/la.2011.010181

Background

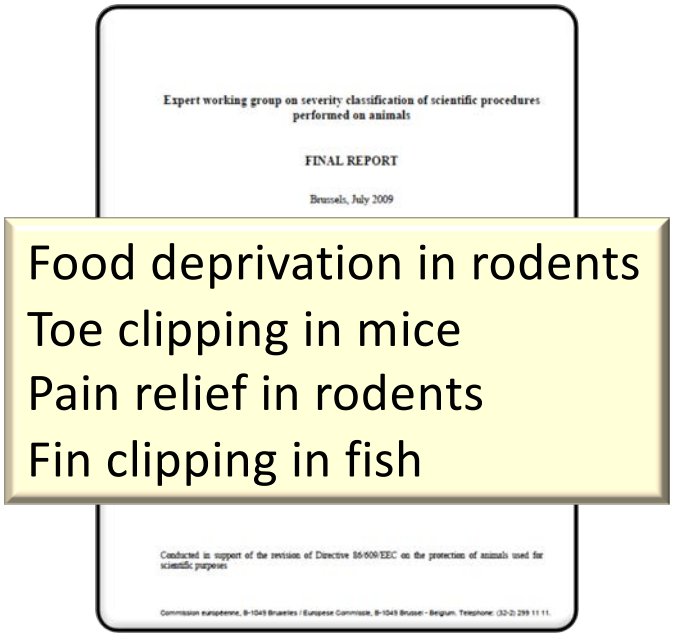
An effective prediction of the effects of a research protocol on the animals concerned helps to ensure that any pain, suffering or distress they may experience will be effectively anticipated, recognized and alleviated. This is essential not only for animal welfare but also for scientific validity, because physiological and behavioural responses to suffering can significantly affect data quality. Severity classification is thus an important tool to help focus the implementation of refinement, including monitoring its progress, and to assist in reporting the application of the 3Rs (replacement, reduction and refinement) of Russell and Burch,[1] which is now an integral part of the legislation on animal research and testing in many countries. Predictions of severity are also fundamental to the harm–benefit assessments undertaken by bodies such as regulatory authorities and ethical committees when deciding whether or not a project should be licensed or funded.

There may also be a legal requirement to predict and classify severity. For example, the new Directive regulating animal use within the European Union, which must be implemented within all Member States by January 2013, requires the severity of each procedure to be classified on the basis of the 'degree of pain, suffering, distress or lasting harm expected to be experienced by an individual animal during the course of the procedure', with the aim of enhancing transparency, facilitating the project authorization process and providing tools for monitoring compliance.[2] Member States will have to ensure that all procedures are classified as 'non-recovery', 'mild', 'moderate' or 'severe' on a case-by-case basis, using the assignment

Laboratory Animals 2011; 1–6

Guidance on the severity classification of procedures involving fish

Report from a Working Group
convened by Norecopa



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

FINAL REPORT

Brussels, July 2009

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

Commission européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel - Belgium. Telephone: (32-2) 299 11 11.

Food deprivation in rodents
Toe clipping in mice
Pain relief in rodents
Fin clipping in fish

http://ec.europa.eu/environment/chemicals/lab_animals/pdf/report_ewg.pdf

P Hawkins, N Dennison, G Goodman, S Hetherington,
S Llywelyn-Jones, K Ryder and AJ Smith

Laboratory Animals, 45: 219-224, 2011

norecopa.no/categories

norecopa.no/education-training/homemade-educational-materials

+ the NORINA database of 3,100 audiovisual aids for use in education and training
Established in 1991, updated weekly. norecopa.no/NORINA

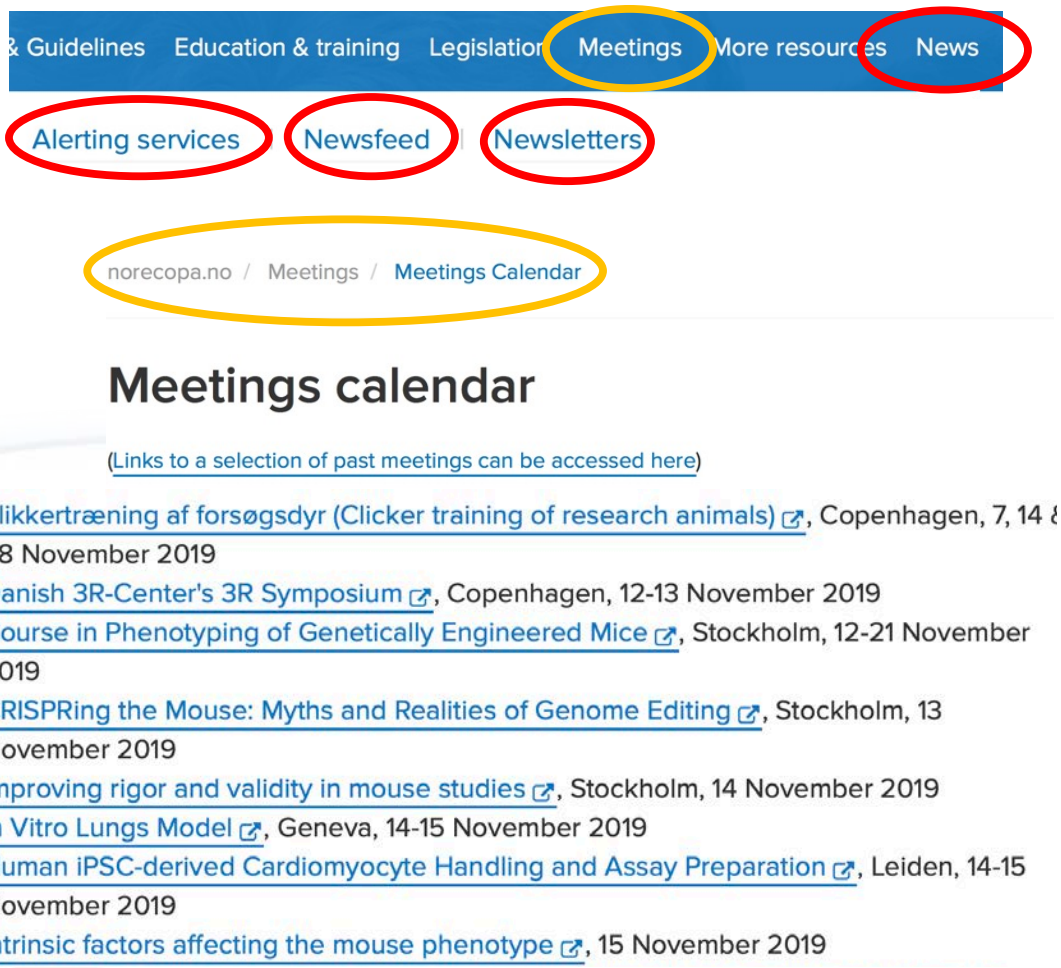
International consensus meetings

Harmonisation of the Care and Use of:

- *Fish (2005)*
- *Wildlife (2008)*
- *Fish (2009)*
- *Agricultural animals (2012)*
- *Wildlife (2017)*

https://norecopa.no/meetings

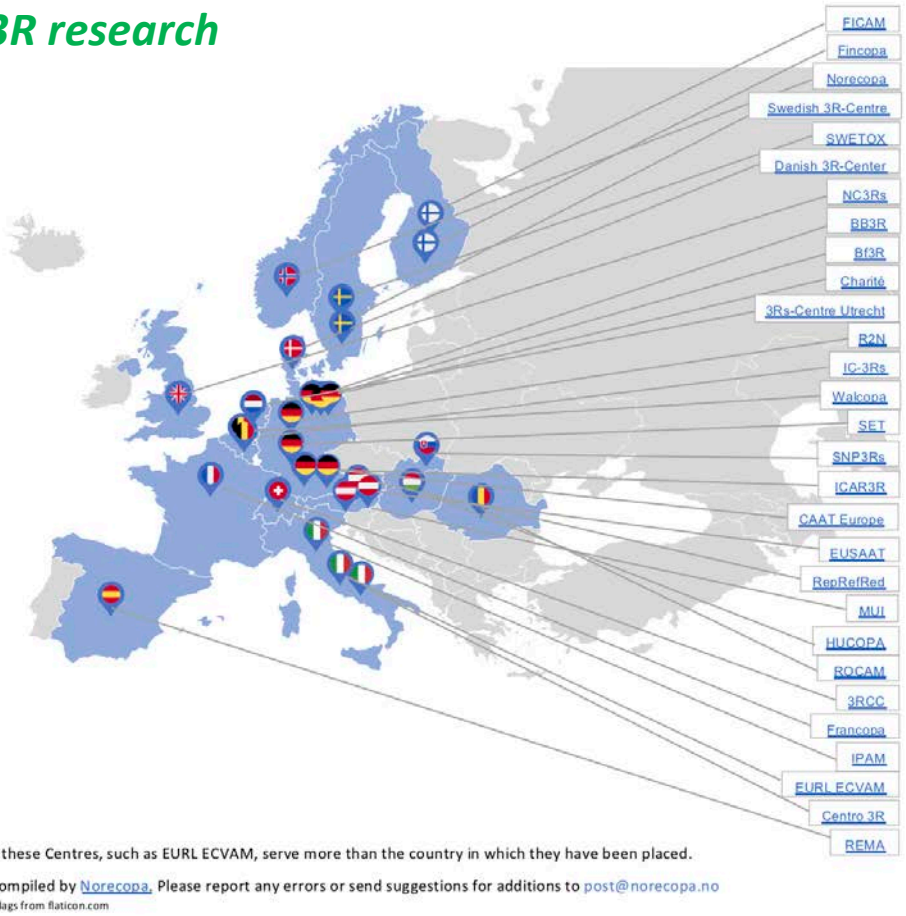
All presentations and consensus statements are on the internet: ***a lasting resource***


& Guidelines
Education & training
Legislation
Meetings
More resources
News
Alerting services
Newsfeed
Newsletters
norecopa.no / Meetings / Meetings Calendar
Meetings calendar
(Links to a selection of past meetings can be accessed here)
Klikkertræning af forsøgsdyr (Clicker training of research animals), Copenhagen, 7, 14 & 28 November 2019
Danish 3R-Center's 3R Symposium, Copenhagen, 12-13 November 2019
Course in Phenotyping of Genetically Engineered Mice, Stockholm, 12-21 November 2019
CRISPRing the Mouse: Myths and Realities of Genome Editing, Stockholm, 13 November 2019
Improving rigor and validity in mouse studies, Stockholm, 14 November 2019
In Vitro Lungs Model, Geneva, 14-15 November 2019
Human iPSC-derived Cardiomyocyte Handling and Assay Preparation, Leiden, 14-15 November 2019
Intrinsic factors affecting the mouse phenotype, 15 November 2019

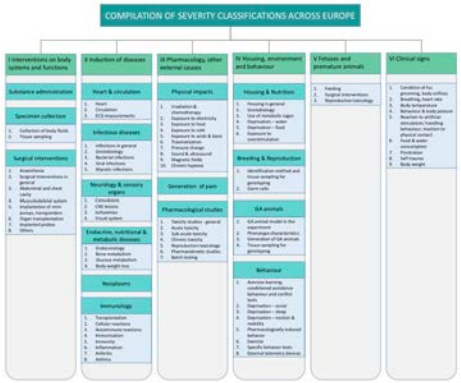
European network of 3R Centres established in 2018 - many with money earmarked for 3R research

Interactive map:
norecopa.no/3REuropeOverview

List of 3R centres:
norecopa.no/3REurope



Mild, Moderate or Severe? A compilation of severity classification



norecopa.no/severity

The compilation covers

- Interventions on body systems and functions
  - Substance administration
  - Specimen collection
  - Surgical interventions
- Induction of diseases
  - Heart and circulation
  - Infectious diseases
  - Neurology and sensory organs
  - Endocrine, nutritional and metabolic diseases
  - Neoplasms
  - Immunology
- Pharmacology and other external causes
  - Physical impacts
  - Generation of pain
  - Pharmacological studies
- Housing, environment and behaviour
  - Housing and nutrition
  - Breeding and Reproduction
  - GA animals
  - Behaviour
- Foetuses and premature animals
- Clinical signs

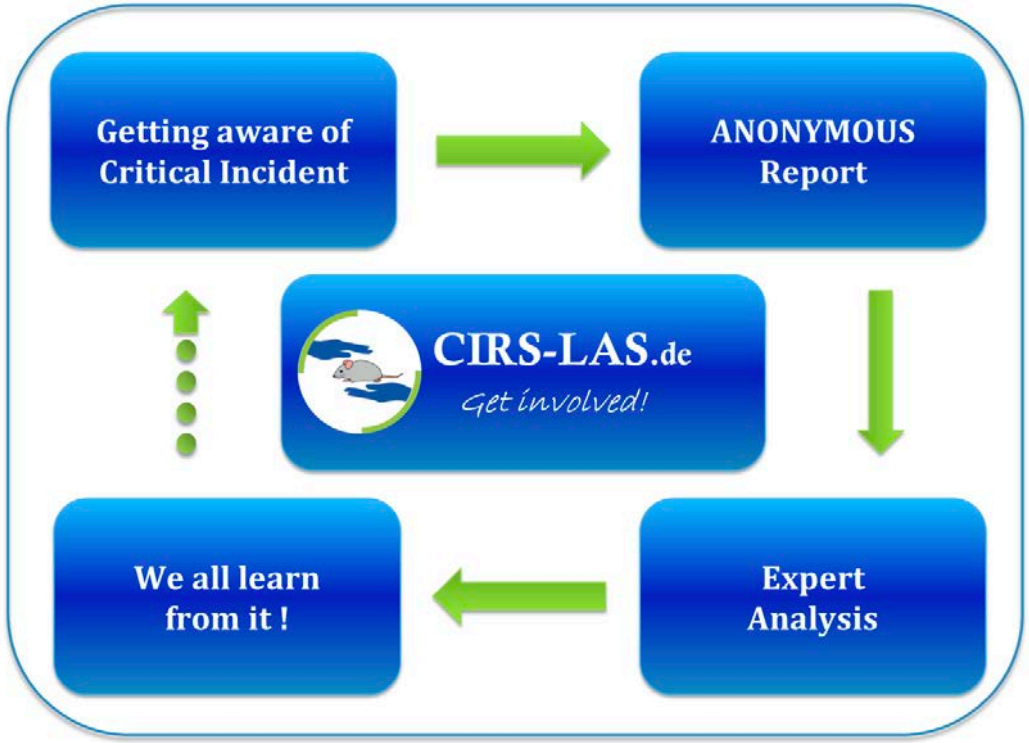
Source	Non-harmful / below threshold / severity degree 0	Mild / severity degree 1	Moderate / severity degree 2	Severe / severity degree 3
Directive 2010/63/EU, Annex VIII		Administration of substances by subcutaneous, intramuscular, intraperitoneal routes, gavage and intravenously via superficial blood 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.	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.	
Home Office (2014 a)		Injection by conventional routes, i.e. subcutaneous, intravenous, intraperitoneal or intramuscular (assuming competence of the person performing the procedure and that best practice guidelines for volume, pH, needle size, etc. are followed). Multiple injections by these routes may remain in the mild category if there are no cumulative effects.		
Federal Food Safety and Veterinary Office FSVO (2018)	Single injection of small volumes s.c. and i.v. (species-specific), including repeated injections at long intervals (at least 24 hours).	i.v. or i.p. injections in sedated animals by catheter or tube and substances introduced into the body such as enemas. Implants and permanent accesses that can be created and used by means of a minimally invasive (superficial) procedure. Examples: Repeated iv or sc injection of small volumes (species-specific). Insertion of cannulae into peripheral blood vessels. Subcutaneous injection of tumour tissue. Single subcutaneous implantations of osmotic minipumps and transponders. Subcutaneously channelled venous catheters.	Repeated injections at short intervals (several times within 24 hours). Implants and permanent accesses that have to be created by means of a deep surgical procedure or causing mild long-term constraint on an animal. Examples: Chronic iv catheters. Duodenal infusion cannula. Hepatic portal vein catheter. Gastric tube or chronic intragastric infusion cannula. Intraperitoneal or intravenous osmotic minipumps. Gavage. Telemetry transmitters. Implanted iv catheters with pumps in a jacket worn by dogs. Implantation of indwelling catheters in	Implants and permanent accesses that have to be created by means of a deep surgical procedure and causing severe long-term strain on an animal. Examples: Attachment of implants on the locomotor apparatus or other large implants that restrict movement (e.g. dorsal skinfold chamber in mice). Implantation of catheters in the abdominal aorta or bile duct. Implantation of an arterial blood-pressure catheter in the aortic arch via the left carotid artery or in the abdominal aorta via the femoral artery. Implantation of a combination of a venous and arterial catheter.

CIRS-LAS Portal

Critical incident reporting system in laboratory animal science

Refine
Reduce
Replace

Operating principles



Recent incidents

Injury of the mesentery by vertebral kyphoplasty

Mouse neonates exposed to CO2

Animal escapes during transportation

Kidney damage in mouse after surgery on heating mat

Soft tissue implant in rabbit

https://kmonadollaraday.files.wordpress.com/2011/03/information-silos.jpg

There are lots of platforms...

...but are there enough trains?

http://www.london-gifts.co.uk

Norecopa aims to be a fast train to global 3R resources

Photo: http://www.bbc.com/news/uk-england-london-35882068

Some of the challenges

- Greater use of pre-registration sites to avoid publication bias
- Journals must publish negative results and replication studies
- Financial constraints preventing attempts to replicate studies
- Pressure by PIs on PhD students to publish in high impact journals
- Peer pressure to use methods because "we have always done it that way"
- Pressure of time to complete projects
- Culture of care and culture of integrity
- Uncertainty about severity classification and lack of knowledge about refinements
- The huge cleft and knowledge gap between *in vitro* experts (who are not necessarily developing replacement techniques *per se*) and lab animal specialists
- Perpetuation of this gap by lack of crosstalk (and need?) between the specialties
- Few interspeciality meetings, animal welfare more as an exotic curiosity than true integration

Emerging Topics in Life Sciences (2019)
https://doi.org/10.1042/ETLS20190061

PORTLAND PRESS

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Perspective

Animal experimentation: implementation and application of the 3Rs

David I. Lewis

School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, U.K.

Correspondence: David I Lewis (d.i.lewis@leeds.ac.uk)

Despite the development of powerful molecular biological techniques and technologies, studies involving research animals remain a key component of discovery biology, and in the discovery and development of new medicines. In 1959, *The Principles of Humane Experimental Technique*, the 3Rs (**R**eplacement, **R**eduction and **R**efinement) were developed to provide a framework to ensure animal research was undertaken as humanely as possible. Sixty years since their inception, the extent to which the 3Rs have been adopted and implemented by the global scientific and medical research communities has unfortunately been slow and patchy. However, this situation is changing rapidly as awareness increases, not only of the 3Rs themselves, but of the impact of animal welfare on the reproducibility, reliability and translatability of data from animal studies.

Emerging Topics in Life Sciences (2019)
https://doi.org/10.1042/ETLS20190061

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Perspective

Animal experimentation: implementation and application of the 3Rs

David I. Lewis

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Correspondence: David I Lewis (d.i.lewis@leeds.ac.uk)

There has to be far greater raising of awareness, globally, of the 3Rs and their impact, mandatory education, training and continuing professional development, and increased collaboration between all involved students, early career and established researchers, vets, animal caretakers and technologists, animal welfare experts and animal ethics committee members. There needs to be more funding for 3Rs interventions, greater sharing and promotion of 3Rs resources including those developed by other agencies or bodies,

Hair *et al. Research Integrity and Peer Review* (2019) 4:12
https://doi.org/10.1186/s41073-019-0069-3

Research Integrity and Peer Review

RESEARCH Open Access

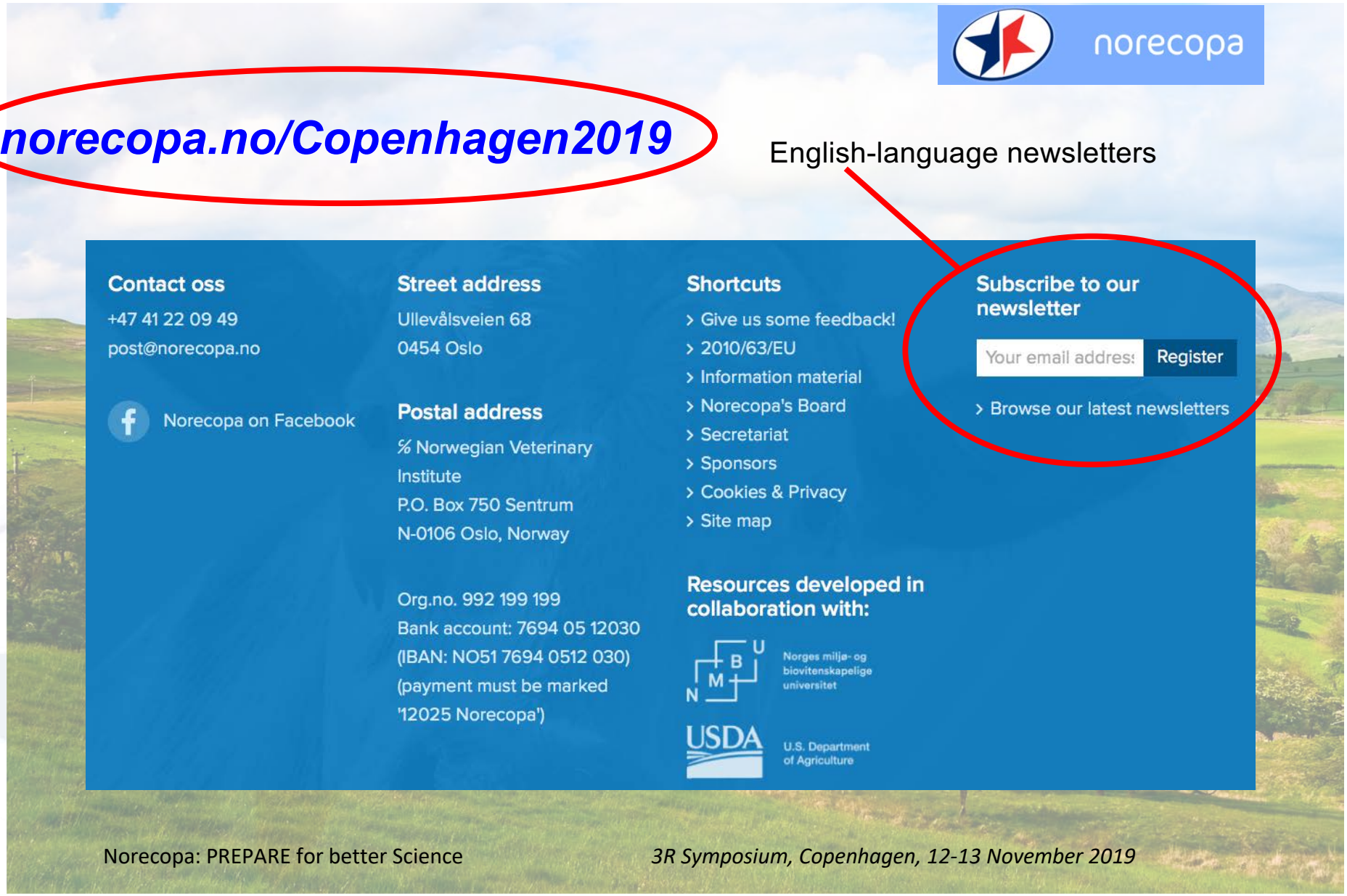
A randomised controlled trial of an Intervention to Improve Compliance with the ARRIVE guidelines (IICARus)

Kaitlyn Hair, Malcolm R. Macleod, and Emily S. Sena*, on behalf of the IICARus Collaboration

Our findings are in line with prior reports that endorsement by editors and reviewers has not significantly improved reporting of ARRIVE quality items. We need therefore a better understanding of the barriers to implementing quality checklists for animal experiments. It has been suggested that requesting checklist adherence at the submission stage may be too late, given the observed correlation between reporting at the planning application stage and at the publication stage. The PREPARE (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence) guidelines were published recently and may be a useful tool, in combination with the ARRIVE checklist, to promote a greater focus on experimental rigour at all stages of the research cycle.

Thanks to Norecopa's main sponsors:

- Standing Committee on Business Affairs, Norwegian Parliament
- Norwegian Ministries of Agriculture and Fisheries
- Research Council of Norway
- Laboratory Animals Ltd.
- Architect Finn Rahns Legacy
- Nordic Society Against Painful Experiments (NSMSD)
- Norwegian Animal Protection Alliance's Fund
- Norwegian Society for the Protection of Animals
- Novo Nordisk
- Scottish Accreditation Board
- Stiansen Foundation
- Universities Federation for Animal Welfare (UFAW)
- US Department of Agriculture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Contact oss
+47 41 22 09 49
post@norecopa.no
Norecopa on Facebook
Street address
Ullevålsveien 68
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Postal address
% Norwegian Veterinary Institute
P.O. Box 750 Sentrum
N-0106 Oslo, Norway
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