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3Rs in the European landscape
Adrian Smith
adrian.smith@norecopa.no
Slides at: norecopa.no/240625
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Bulgaria
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Russell and Burch's original definition of the 3Rs:

- **Replacement**: *any scientific method employing non-sentient material which may in the history of animal experimentation replace methods which use conscious living vertebrates*
- **Reduction**: *means of minimising, other than by Replacement, the number of animals used to obtain information of a given amount and precision*
- **Refinement**: *measures leading to a decrease in the incidence or severity of inhumane procedures applied to those animals which have to be used*.

Some contemporary descriptions emphasise **welfare benefit** and **knowledge gain** as well as minimising inhumanity

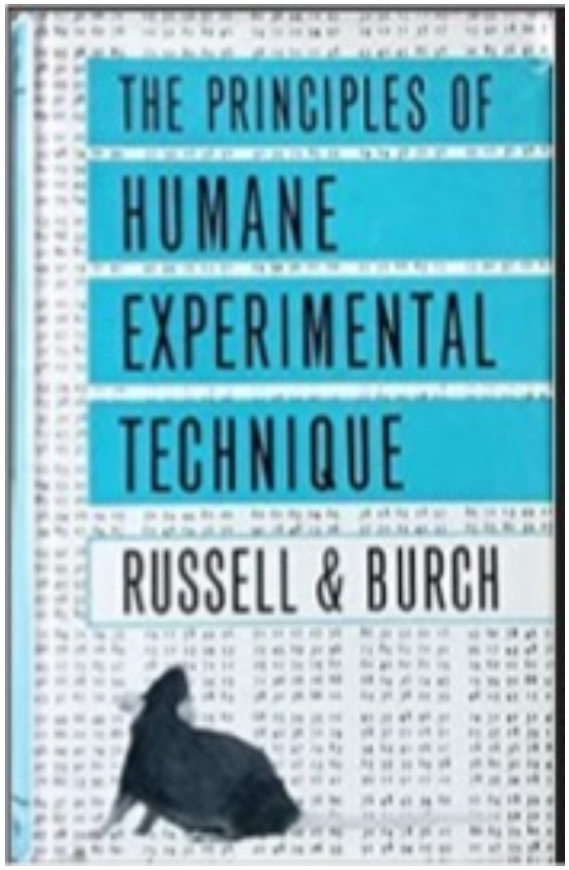
	Basic	Updated
Replacement	Avoiding or replacing the use of animals in areas where they otherwise would have been used.	Accelerating the development and use of predictive and robust models and tools, based on the latest science and technologies, to address important scientific questions without the use of animals.
Reduction	Minimising the number of animals used consistent with scientific aims.	Appropriately designed and analysed animal experiments that are robust and reproducible, and truly add to the knowledge base.
Refinement	Minimising the pain, suffering, distress or lasting harm that research animals might experience.	Advancing research animal welfare by exploiting the latest *in vivo* technologies and by improving understanding of the impact of welfare on scientific outcomes.

nc3rs.org.uk/who-we-are/3rs

Tannenbaum & Bennett (2015)

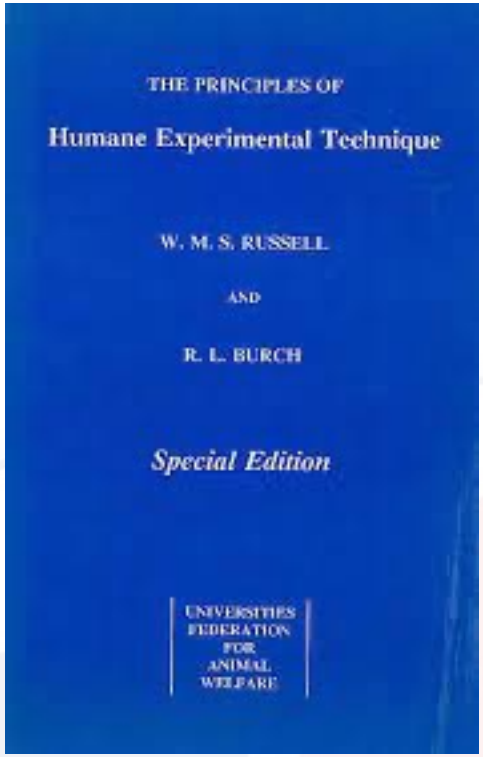
Timeline for the 3Rs: Replacement, Reduction, Refinement

- By 1955, the concept of the 3Rs was essentially present in a paper published by Russell
- The explicit term "The 3Rs" evolved sometime between 1955 and 1957 (Russell, 2005)
- The 3Rs were formally presented at a UFAW Symposium in May 1957 on *Humane Technique in the Laboratory*
- Russell and Burch published ***The Principles of Humane Experimental Technique*** in 1959



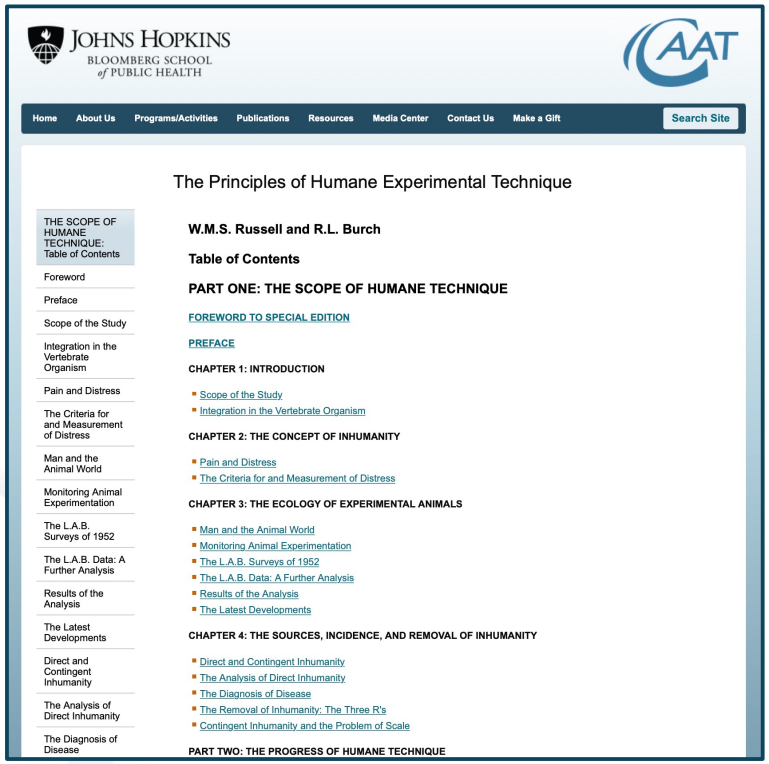
Russell WMS & Burch RL (1959)

Reprinted by UFAW in 1992



norecopa.no/textbase/the-principles-of-humane-experimental-technique

The text of the book is available online



caat.jhsph.edu/principles/the-principles-of-humane-experimental-technique

Much more information at norecopa.no/3R

Norecopa: PREPARE for better Science

Interest in the 3RS

- *A largely unknown concept for the first 20 years*
- *1969: The UK organisation FRAME (Fund for Replacement of Medical Experiments) was established, and also worked (independently of UFAW/Russell & Burch) on alternatives*
- *1991: The HSUS (Humane Society of the United States) instigated a Russell and Burch Award*
- *1995: Russell and Burch met at Sheringham (the first time since 1959 except for a brief meeting in 1991)*
- *2000: The European Science Foundation 'strongly endorses the principles of the Three Rs'*

FRAME

Rex Burch & William Russell at a workshop in Sheringham, UK, in 1995 organised by ECVAM, CAAT and FRAME

journals.sagepub.com/doi/abs/10.1177/026119299502300614

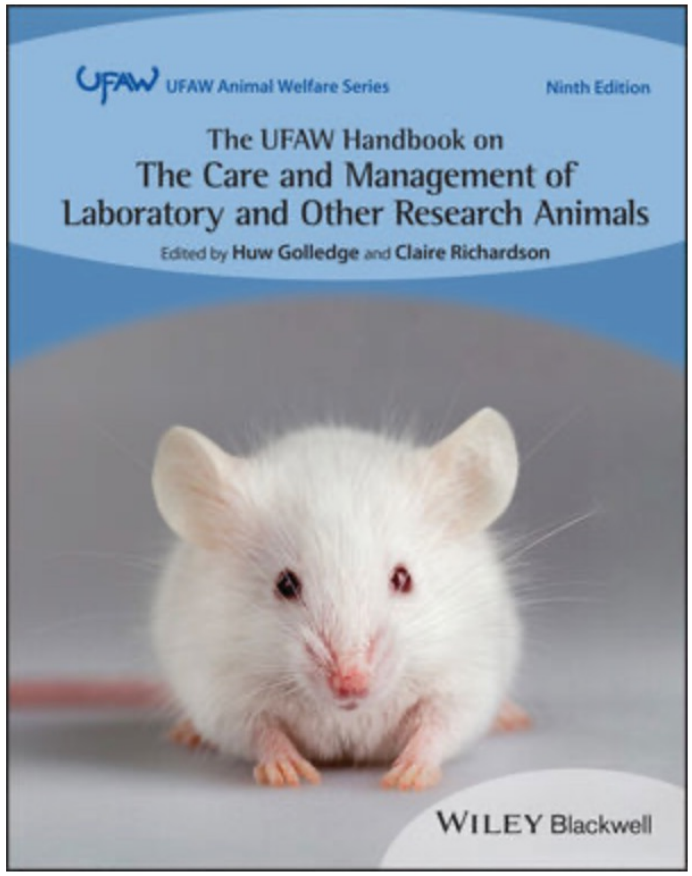
Interest in the 3RS

UFAW continued to update its *Handbook on the Care and Management of Laboratory and Other Research animals* (first published in 1947, 9th edition in 2024)

1986: The European Directive 86/609/EEC did not explicitly mention the 3Rs but it required member states to implement national legislation which effectively implemented them. It also led to the establishment of ECVAM (*European Centre for the Validation of Alternative Methods*) in 1991.

1993: A series of *World Congresses on Alternatives and Animal Use in the Life Sciences* was started in Baltimore (Rio in August 2025)

2010: EU legislation mentioned the 3Rs specifically for the first time in Directive 2010/63/EU



This concept actually predates Russell & Burch:

Marshal Hall: Seven principles of physiology (1831 & 1847)

en.wikipedia.org/wiki/Marshall_Hall_(physiologist)

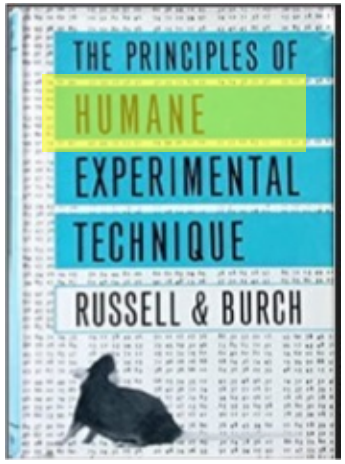
1. *We should never have recourse to experiment in cases which observation can afford us the information required.*
2. *No experiment should be performed without a distinct and definite object, and without the persuasion, after the maturest consideration, that that object will be attained by that experiment, in the form of a real and uncomplicated result.*
3. *We should not needlessly repeat experiments which have already been performed by physiologists of reputation.*
4. *After due consideration that a given experiment is, at once, essential and adequate to the discovery of a truth, it should be instituted with the least possible infliction of suffering.*
5. *Every physiological experiment should be performed under such circumstances as will secure due observation and attestation of its results, and so obviate, as much as possible, the necessity for its repetition.*
6. *Facts should be laid before the public in the simplest, plainest terms. If there be a difference of opinion: '…add such views as may seem nearest the truth. These are neither wholly in accord with one opinion nor another, nor exceedingly at variance with both, … a thing which may be observed in most controversies, when men seek impartially for truth'. (Celsus, translated from Latin)*
7. *In quoting the opinions of other authors, it should always be in their own words.*

ahajournals.org/doi/epdf/10.1161/01.CIR.48.3.651

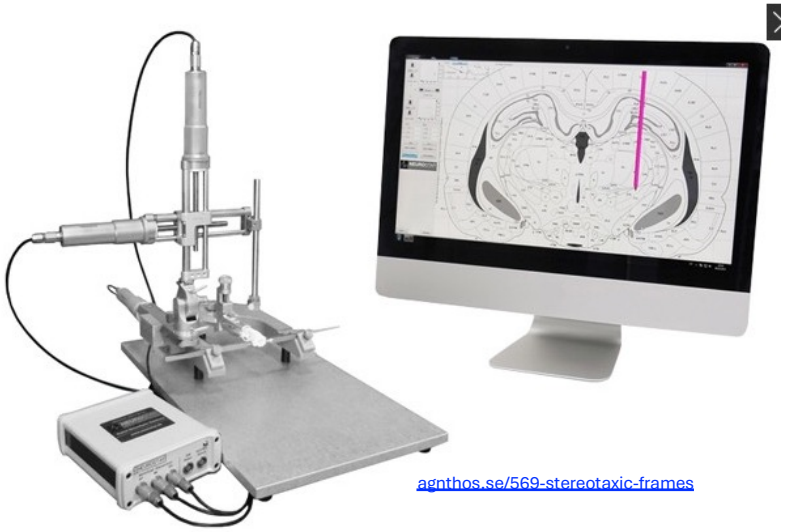
The background for the 3Rs landscape

peta.org

https://filipinofreethinkers.org/wp-content/uploads/2011/09/vivisection11.jpg



Russell WMS & Burch RL (1959)

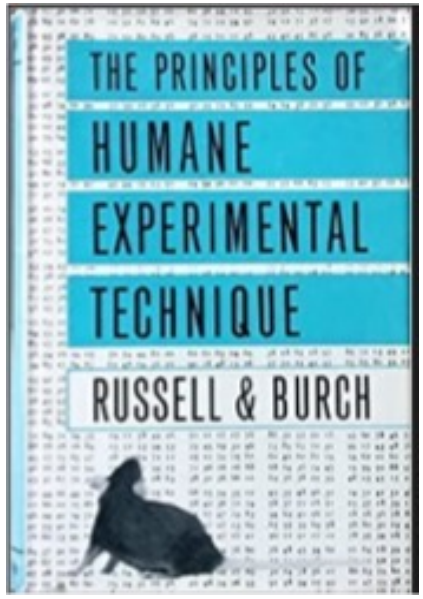


agnthos.se/569-stereotaxic-frames

Replacement → Reduction → Refinement

'Suppose, for a particular purpose, we cannot use replacing techniques. Suppose it is agreed that we shall be using every device of theory and practice to reduce to a minimum the number of animals we have to employ. It is at this point that refinement starts, and its object is simply to reduce to an absolute minimum the amount of distress imposed on those animals that are still used.'

Chapter 7



Russell WMS & Burch RL (1959)

peta.org

PETA Donate

ANIMALS ARE NOT OURS

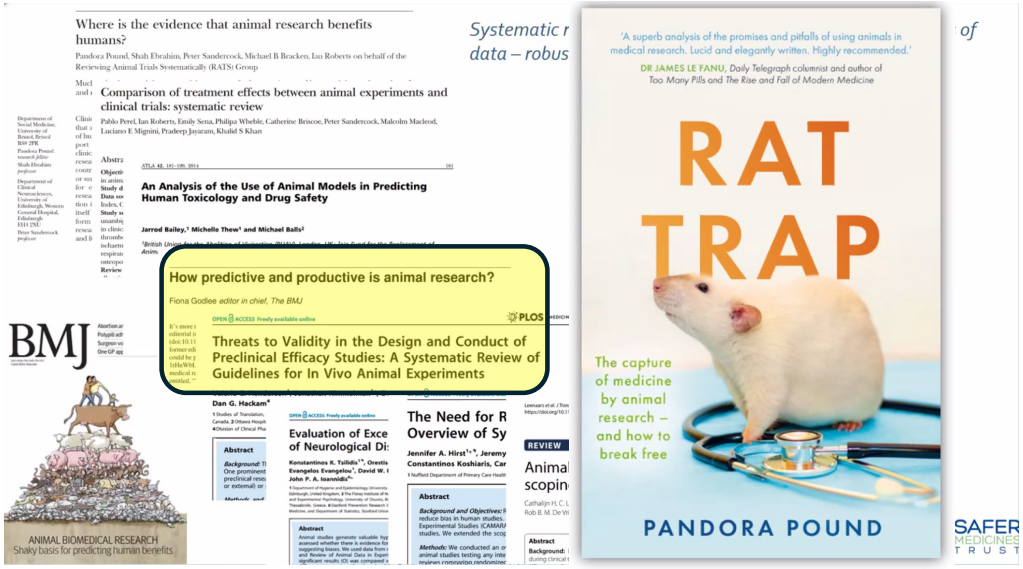
to experiment on, eat, wear, use for entertainment, or abuse in any other way.

Features | Videos | Adoptable Animals | Rescue Stories

... / News / Experiments on Animals Fail 90% of the Time. Why Are They Still Done?

Experiments on Animals Fail 90% of the Time. Why Are They Still Done?

https://www.peta.org/news/experiments-on-animals-fail-90-of-the-time-why-are-they-still-done



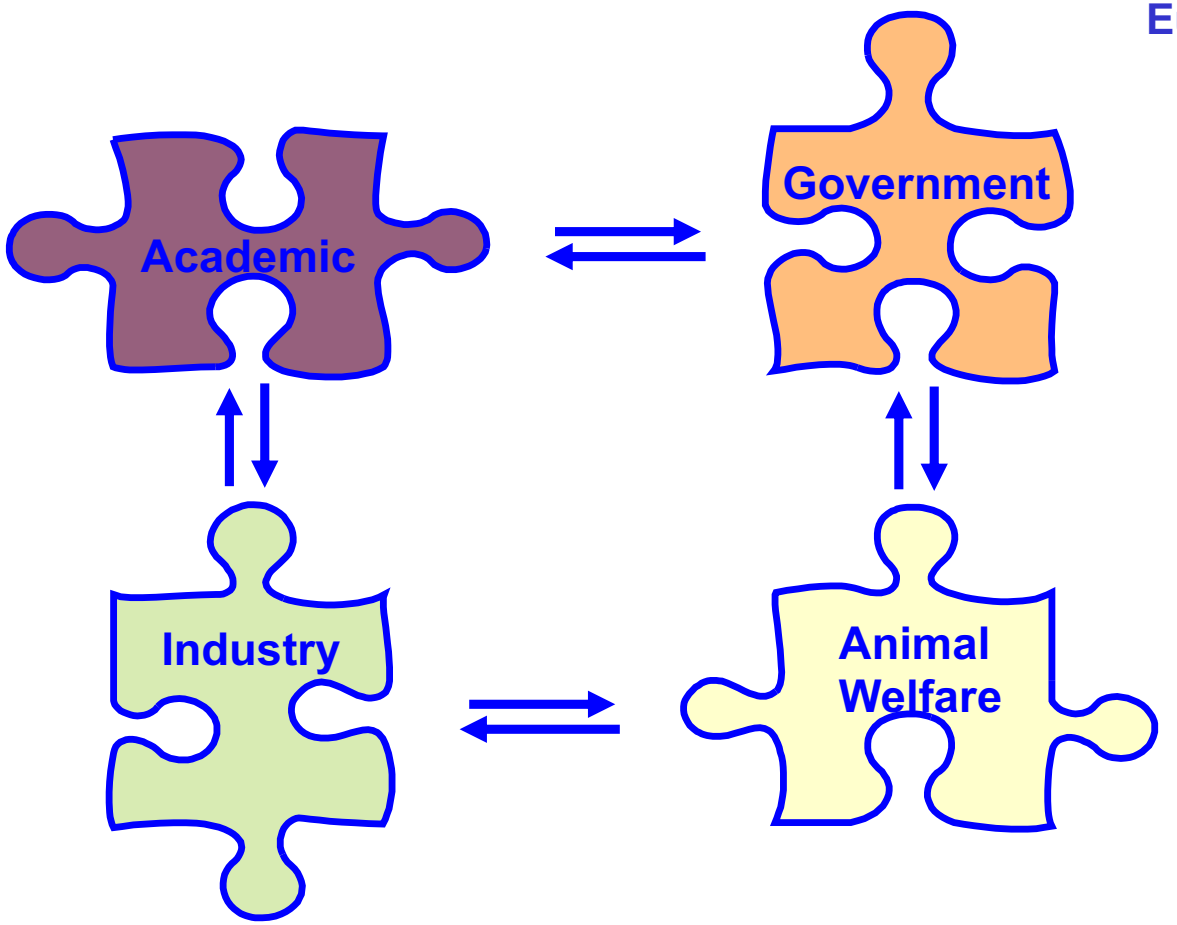
webinar 31 Juy 2023 by Pandora Pound

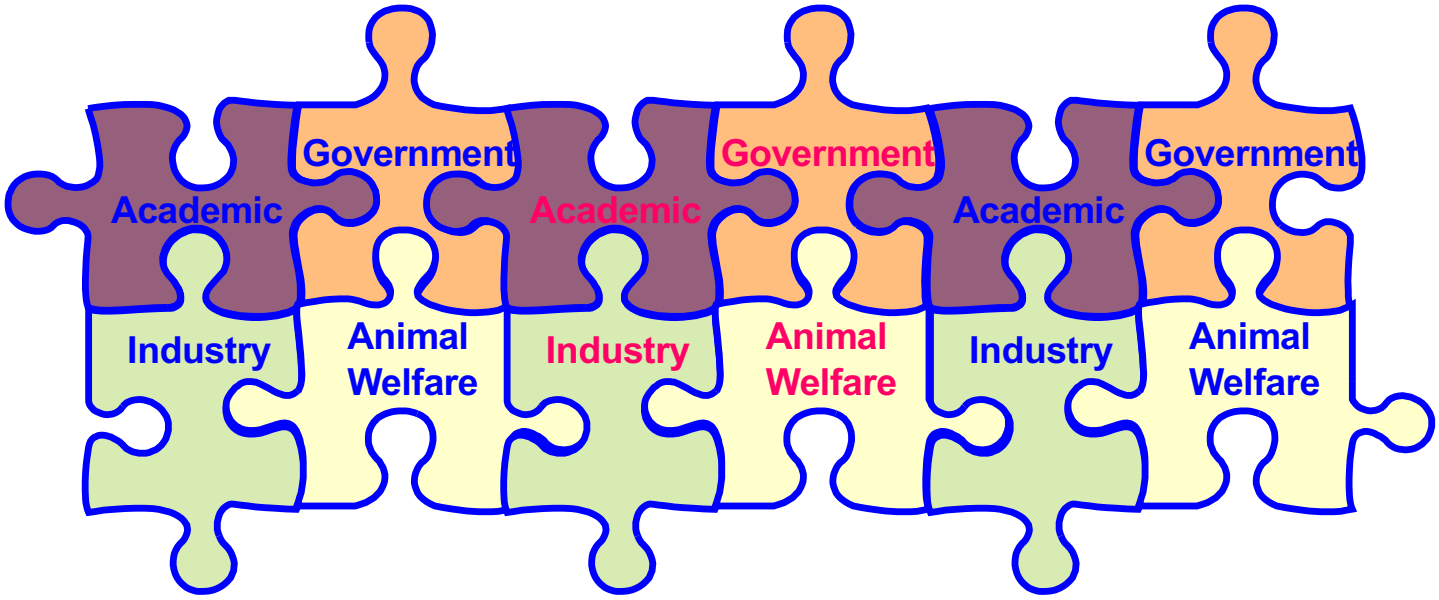
https://www.understandinganimalresearch.org.uk/news/the-90-myth

National Consensus Platforms

ecopa

European Consensus Platform for Alternatives





Relatively low uptake:

currently 7 countries: Finland, France, Germany, Italy, Norway, Spain, Switzerland

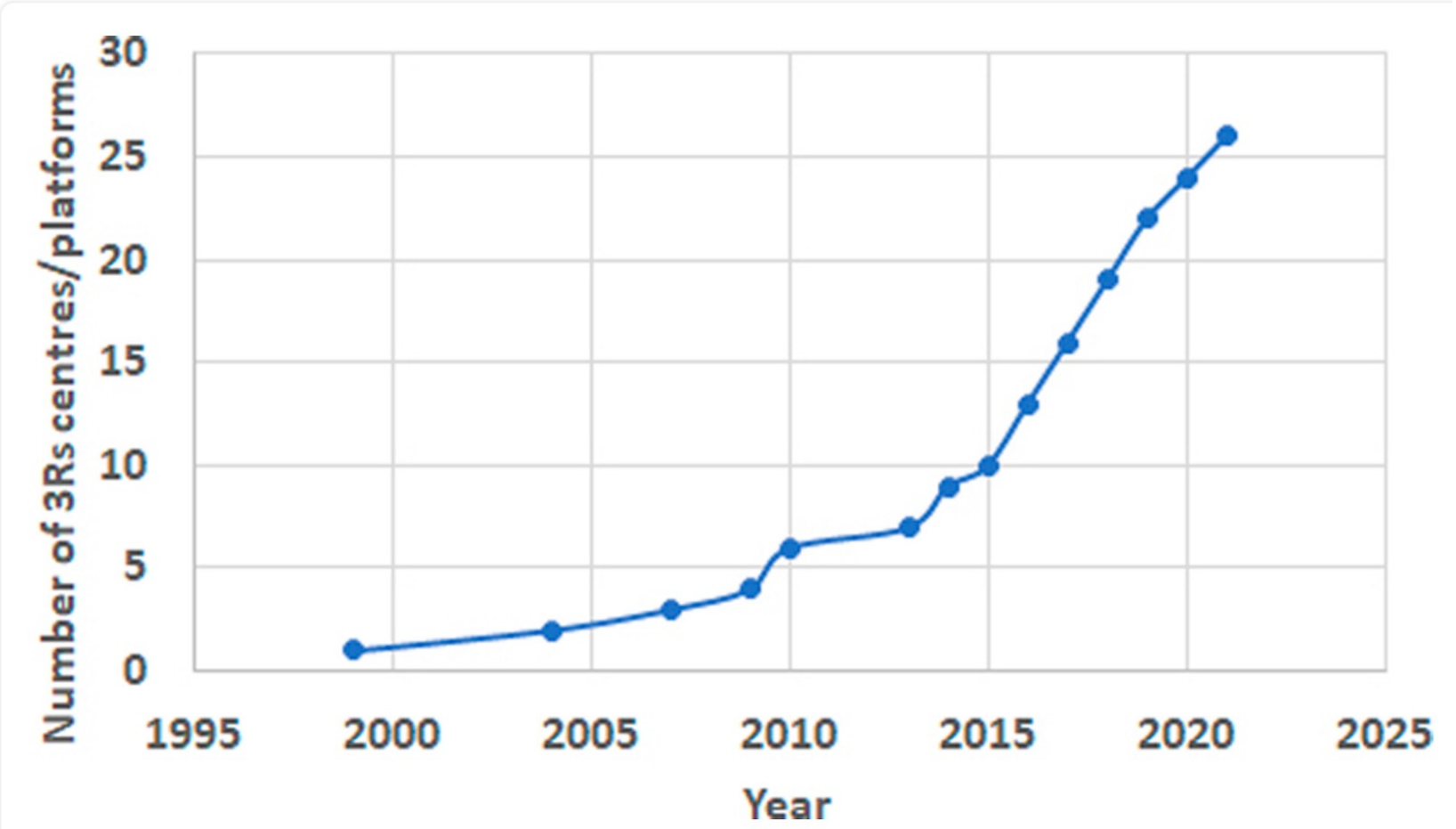
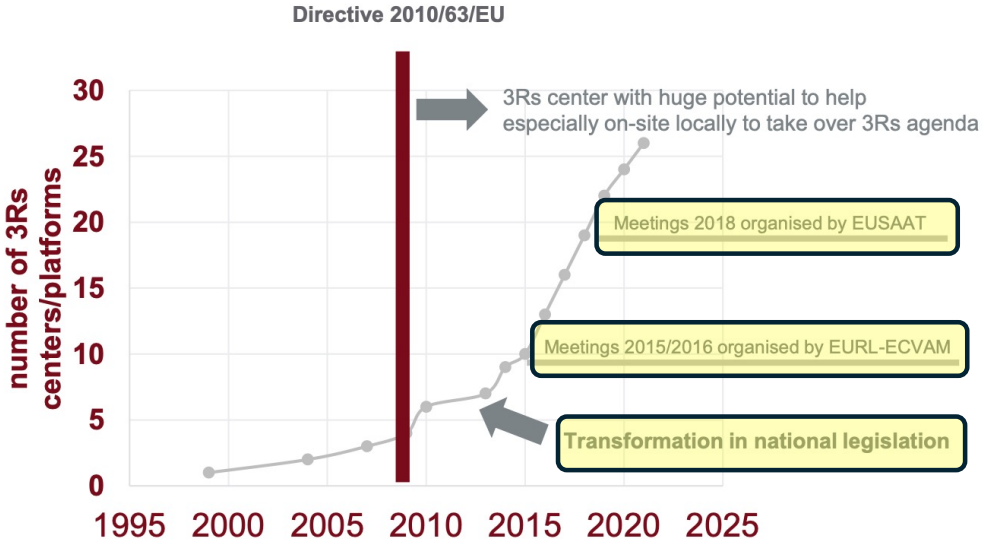


Figure 1. The cumulative increase in the number of Three Rs centres and platforms in Europe over recent years.

Neuhaus *et al*., 2022
https://journals.sagepub.com/doi/10.1177/02611929221099165

Power of Politics: The Rise of 3Rs centres and platforms in Europe

Further increase in 2022/2023:
Finish 3R centre
French 3R centre
Portuguese 3R centre (i3S)

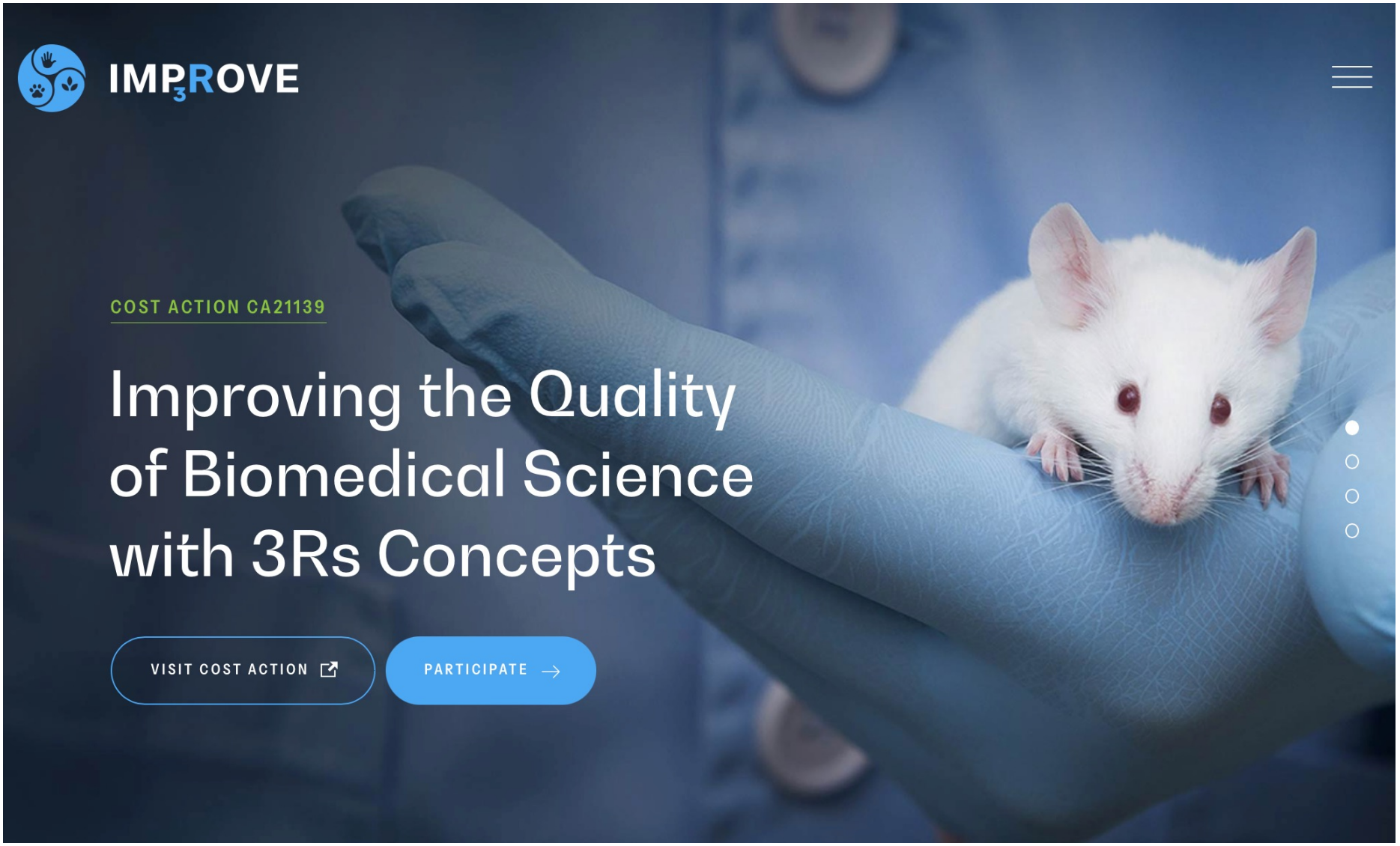


Data in table obtained from 26 3Rs centres and platforms participated in a survey of EU3Rnet (Neuhaus *et al.*, ATLA, 2022)

European Centre for Validation of Alternative Methods at the EU Research Centre in Ispra (Italy)

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

Winfried Neuhaus, presentation to Norecopa, 20 May 2025
https://norecopa.no/media/biujsjxu/eu3rnet.pdf


IMP3ROVE
COST ACTION CA21139
Improving the Quality of Biomedical Science with 3Rs Concepts
VISIT COST ACTION
PARTICIPATE

Main topics → Four working groups

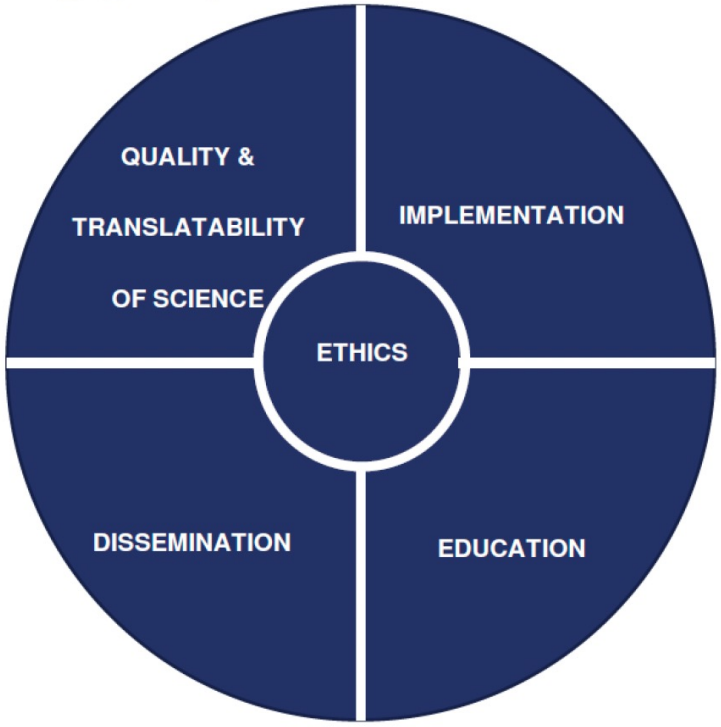
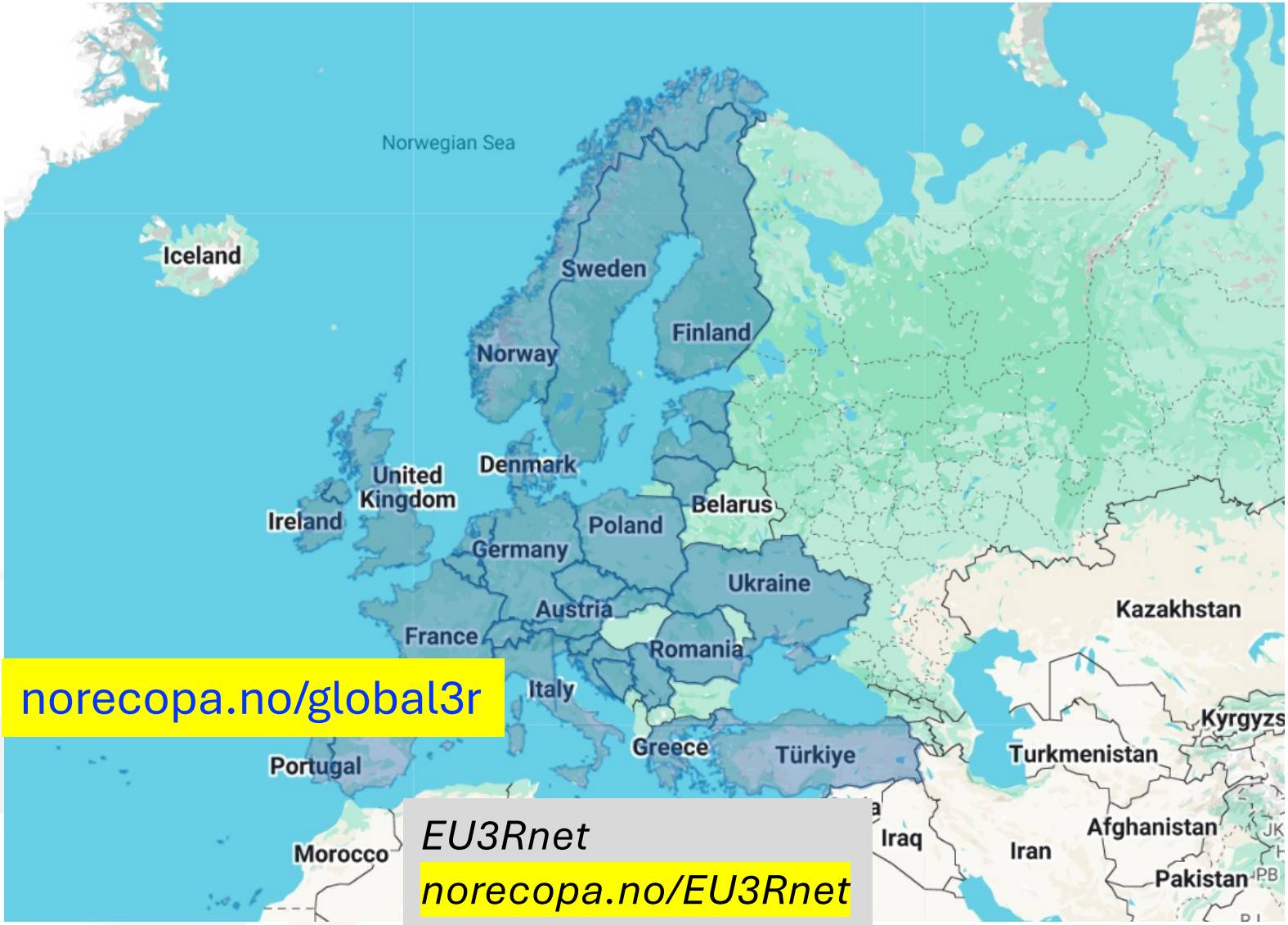


Figure 1: Main topics of the COST Action IMPROVE



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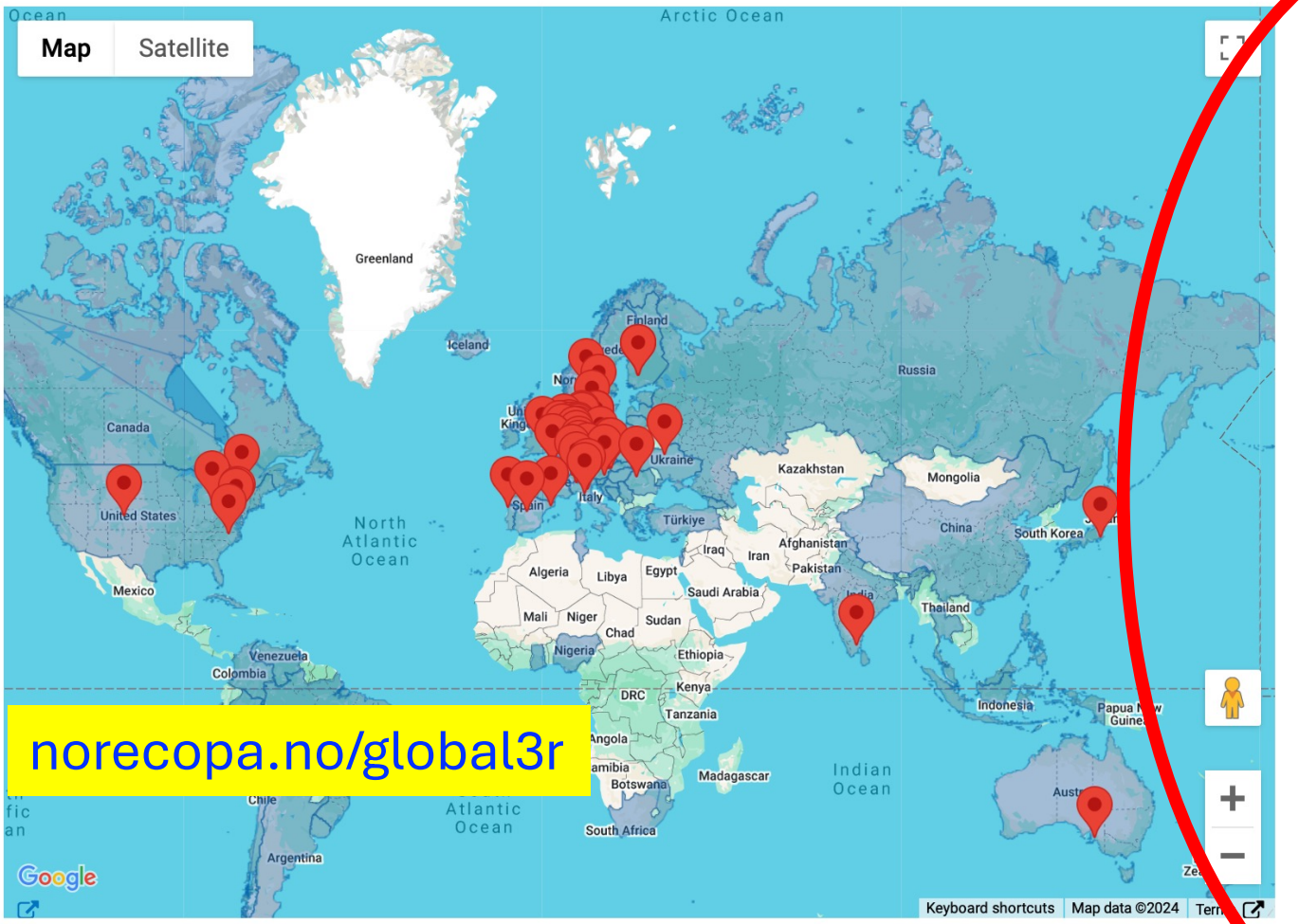
Search Centres



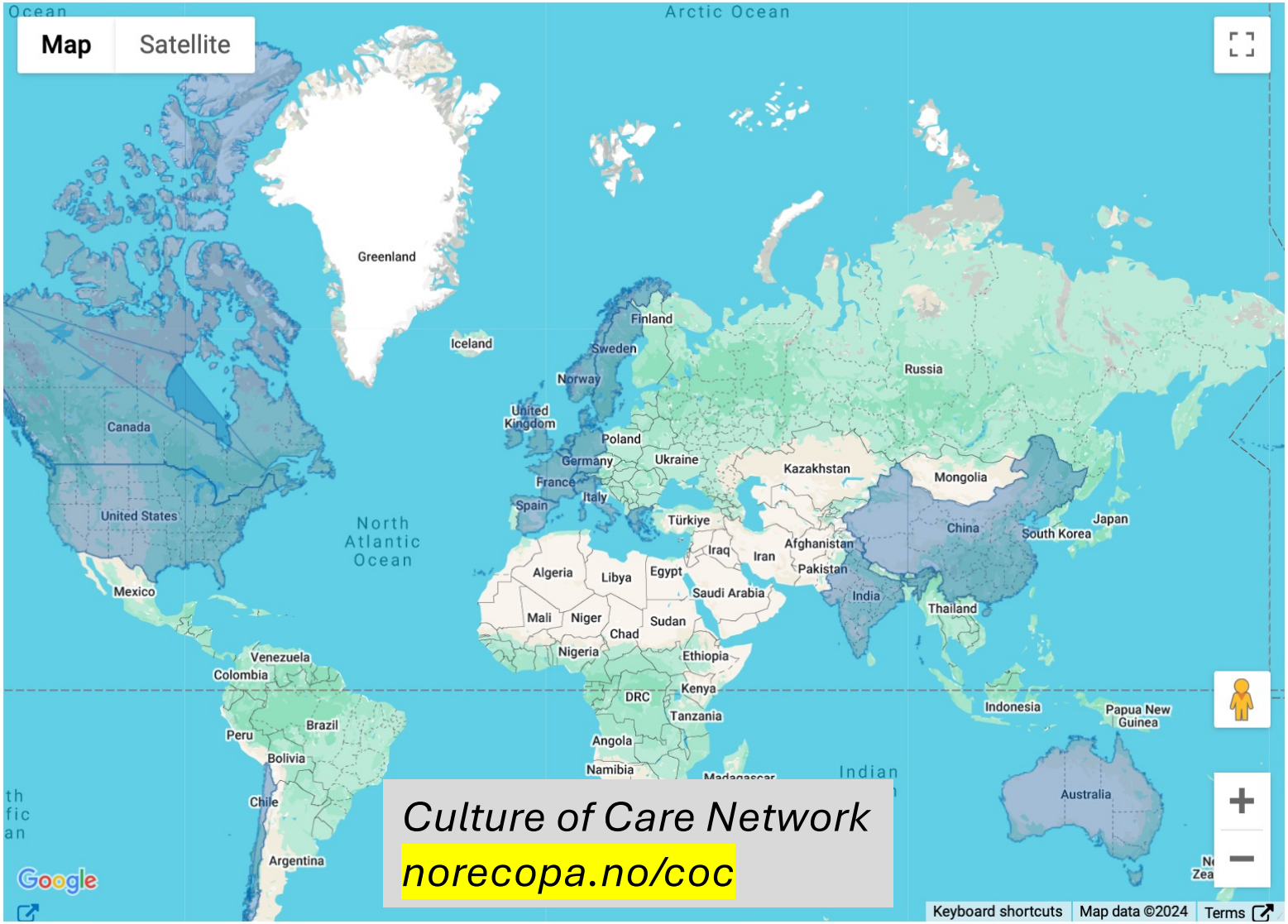
norecopa.no/global3r

Centres

- [x] Replacement
- [x] Reduction
- [x] Refinement
- [x] ecopa

Associations

- [x] ACURET
- [x] AFLAS (includes South Korea)
- [x] Concordat on Openness
- [x] Culture of Care Network
- [x] ecopa
- [x] ENAWB
- [x] EU-NETVAL
- [x] EU3Rnet
- [x] FELASA
- [x] FESSACAL
- [x] ICLAS (includes South Korea)
- [x] Scand-LAS



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Culture of Care

The International Culture of Care Network

norecopa.no/coc

A demonstrable commitment, throughout the establishment, to improving:

- animal welfare
- scientific quality
- care of staff
- transparency for all stakeholders, including the public

ENAWB: European Network of National Networks of Animal Welfare Bodies

norecopa.no/ENAWB

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The excitement over NAMs (& NATs)

NAMs: New Approach Methodologies

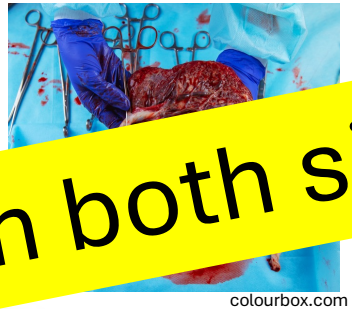
Avoidance (methods which don't directly replace animal experimer

e.g. studies on the human placenta
"Read-Across"

NATs: Non-Animal Technologies

Alternatives to ani

e.g. organoids
organs-on-
experiments on fruit flies



colourbox.com

	Chemical 1	Chemical 2	Chemical 3	Chemical 4
Structure	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx
Property 1	● ⇨ ○		● ⇨ ○	
Propert	⇨ ○		○ ⇦ ●	
	⇦ ●		● ⇨ ○	
	⇨ ○		● ⇨ ○	
	● ⇨ ○		○ ⇦ ●	
Activity 3	○ ⇦ ●		● ⇨ ○	

● Existing data point ○ Missing data point

Oversell from both sides?!

norecopa.no/nams-and-nats

NB. Those who work with NAMs may not even be aware that they use a method that can reduce animal use.
It is therefore important to build bridges between the lab animal community and the NAMs/NATs-communities !

https://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm

https://nc3rs.org.uk/sites/default/files/documents/NonAnimalTechCO082_RYE_4_nrfinal2.pdf

Three Rs and Welfare – beyond ”our bubble”

Vootele Voikar
@VVoikar

After #FELASA2022 preparing for #FENS2022 two largest conferences of European societies close to my work on the same year. Collaboration and dialogue between two is crucial for the success in #animalresearch

Käännä julkaisu

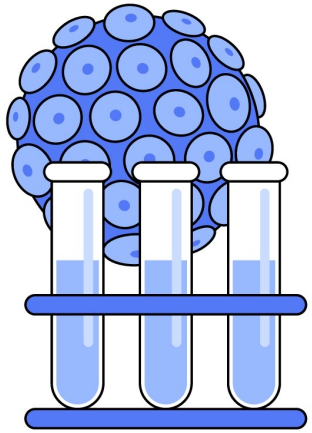
	FELASA-2022	FENS-2022
Attendees	2208	>7500
Count of some key words in abstract books:		
Mice	433	8716
Rats	112	3346
Welfare	399	28
3Rs	122	5

10.54 ap. · 8. heinäk. 2022

“Alternatives” – a threat to established research?

The word ”alternatives”, suggested by Rex Burch, was deliberately not used in the invitations to interviews, to avoid the risk of researchers declining to participate.

Instead, they wrote:
‘a review of progress in the development of humane techniques’.



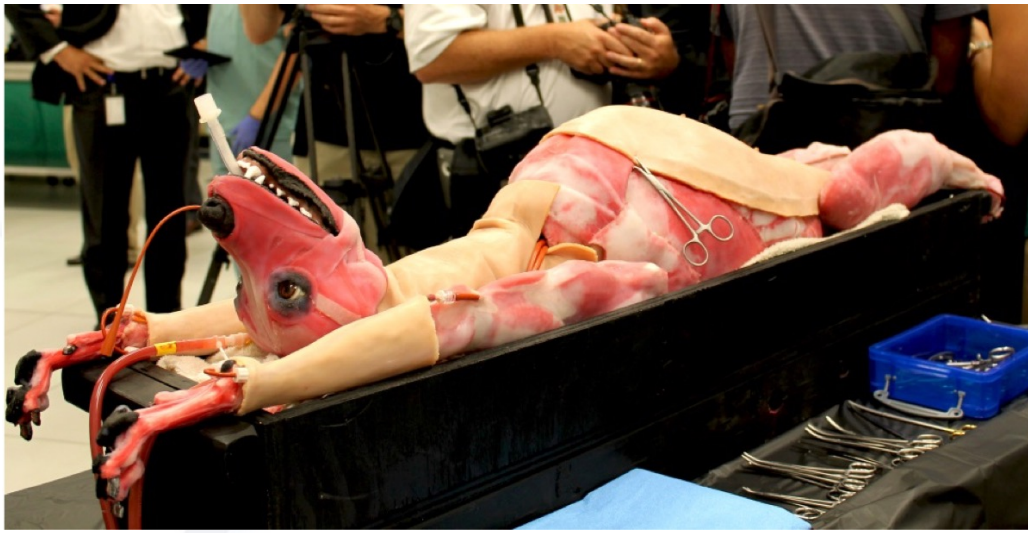
colourbox.com

Stephens (2009) in norecopa.no/3R

“They don’t even look like the animal model!”

Discrimination and fidelity

Rikke Langebæk



syndaver.com

High discrimination

High fidelity

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norecopa.no/media/8099/langebæk.pdf

"...better science?" In the spirit of the 3Rs

- Replacement if possible
- Reduction and Refinement if not possible to replace
- Valid data (a true treatment effect)
- Reproducible and Translatable experiments
- Best possible animal welfare
- Health & Safety (of animals and people)
- Culture of Care at the animal facility
- Communication of best practice to others

colourbox.com

Norecopa: PREPARE for better Science

The Path to Better Science:

Norecopa: PREPARE for better Science

https://nrkbeta.no/2010/09/28/mediebransjens-svar-paa-elg-i-solnedgang

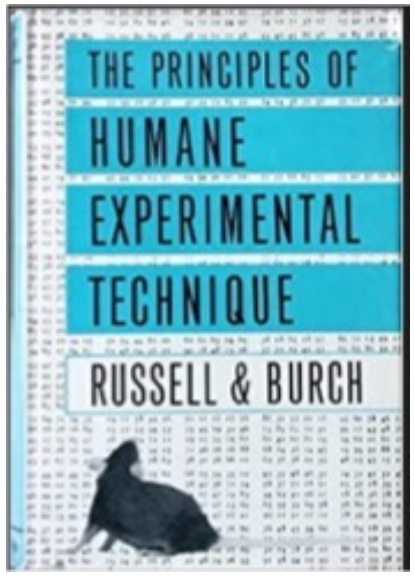
Bad habits have been around for a long time…

Russell & Burch (1959) quote Visscher (1951):

"In general, methodology is usually relegated to a place of smaller type and sharply abbreviated importance in journal publication of research.

Numerous essential details are customarily omitted, either because they are considered to be common knowledge, or simply for lack of space."

…or is it because they didn't do good science?



Russell WMS & Burch RL (1959)

Scientists themselves are becoming increasingly concerned about the validity of animal experiments

NATURE | NEWS

Swiss survey highlights potential flaws in animal studies

Poor experimental design and statistical analysis could contribute to widespread problems in reproducing preclinical animal experiments

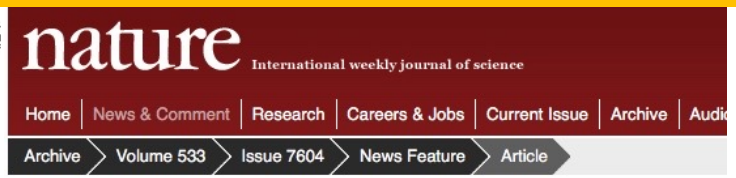
Pain management in pigs undergoing experimental surgery; a literature review (2012–4)

FREE

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



NATURE | NEWS FEATURE

1,500 scientists lift the lid on reproducibility

Survey sheds light on the 'crisis' rocking research.

Monya Baker

25 May 2016 | Corrected: 28 July 2016

More than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments. Those are some of the telling figures that emerged from *Nature*'s survey of 1,576 researchers who took a brief online questionnaire on reproducibility in research.

nature human behaviour

Perspective | Open Access | Published: 10 January 2017

A manifesto for reproducible science

Marcus R. Munafò ✉, Brian A. Nosek, Dorothy V. M. Bishop, Katherine S. Button, Christopher D. Chambers, Nathalie Percie du Sert, Uri Simonsohn, Eric-Jan Wagenmakers, Jennifer J. Ware & John P. A. Ioannidis

Nature Human Behaviour **1**, Article number: 0021 (2017) | Cite this article

33k Accesses | **518** Citations | **2593** Altmetric | Metrics

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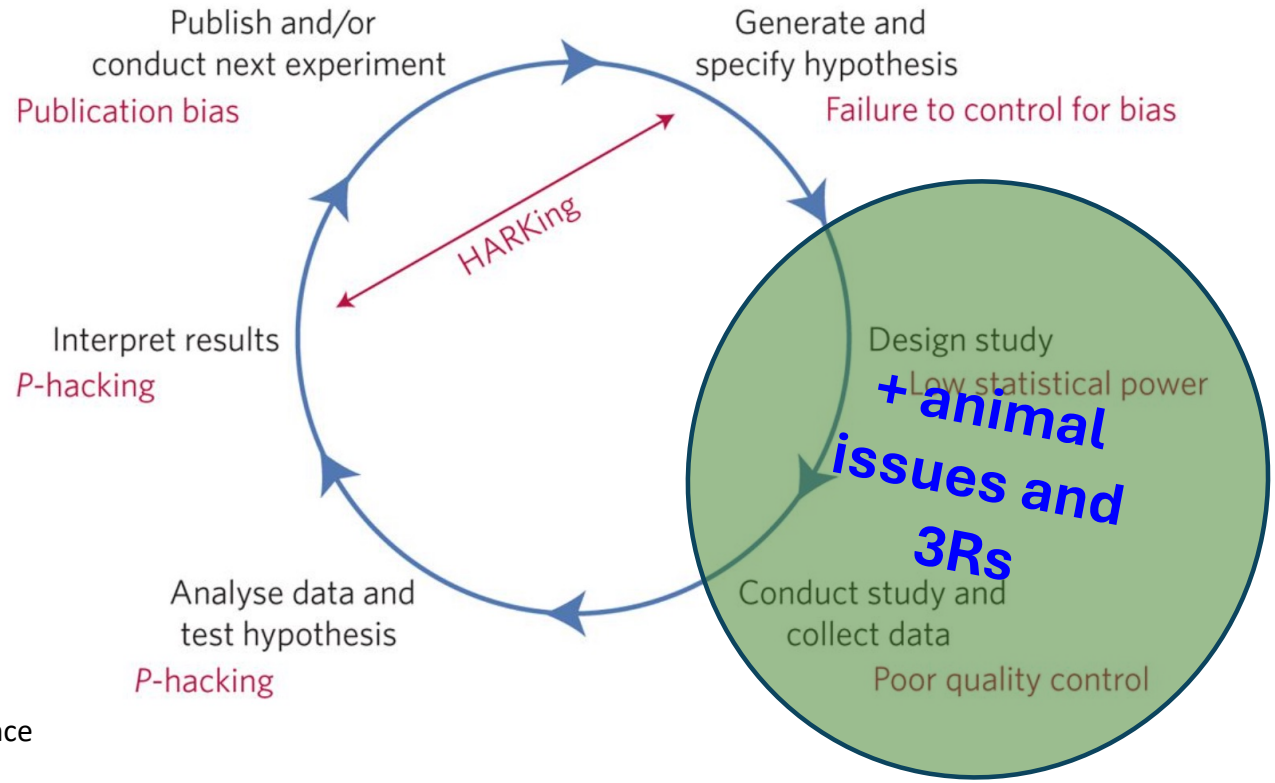
Figure 1: Threats to reproducible science.

From: A manifesto for reproducible science



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So we need more than the 3Rs...

***The 3 Rs* to minimise the harm:**

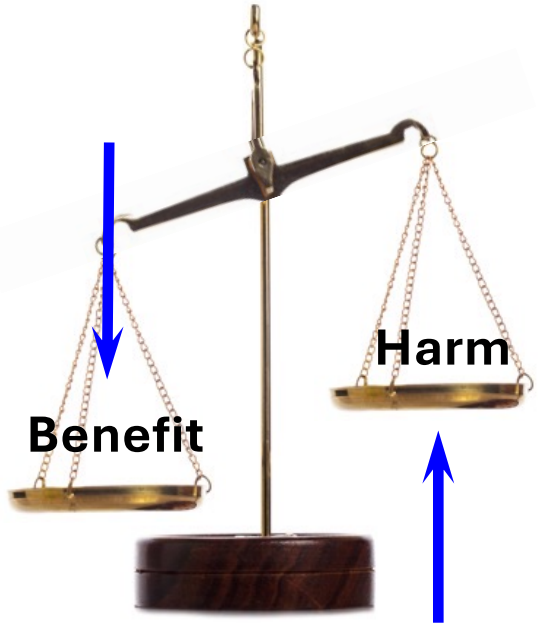
- *Replace the unnecessary experiments*
- *Reduce the number of animals used*
- *Refine the conditions for the animals*

***The 3 Ss* - your commonsense and your heart**

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

***The 3 Vs* to increase the validity of the experiment:**

- *Construct Validity (can the model answer the question?*
- *Internal Validity (has the experiment been correctly designed?)*
- *External Validity (are the results translatable to the target group?)*



norecopa.no/3R
norecopa.no/3S
norecopa.no/3V

The Path to Better Science:

norecopa.no/PREPARE *and*
https://riojournal.com/article/105198

Norecopa: PREPARE for better Science

The Path to Better Science:

We cannot improve our research by

better reporting alone...

This may not be sufficiently obvious to scientists who are not familiar with the challenges of running an animal facility ... or they assume that we have thought of everything...

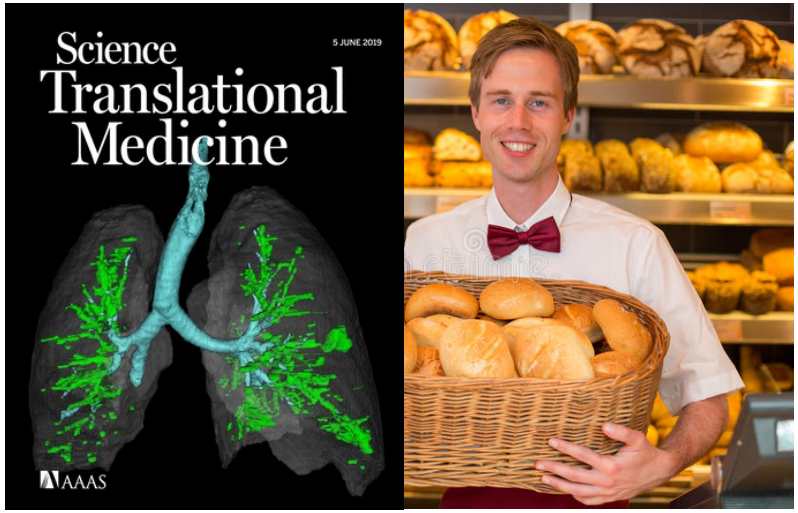
The reproducibility/translatability devil is often in the practical details...

reddit.com

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

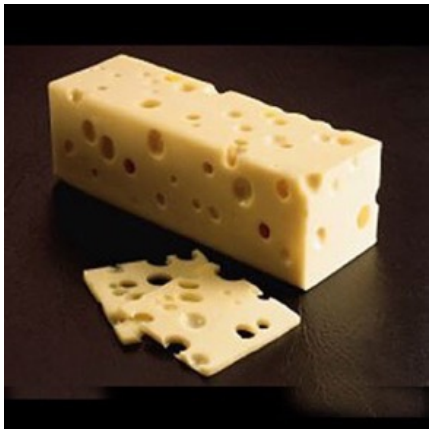
PREPARE *from day 1*

ARRIVE



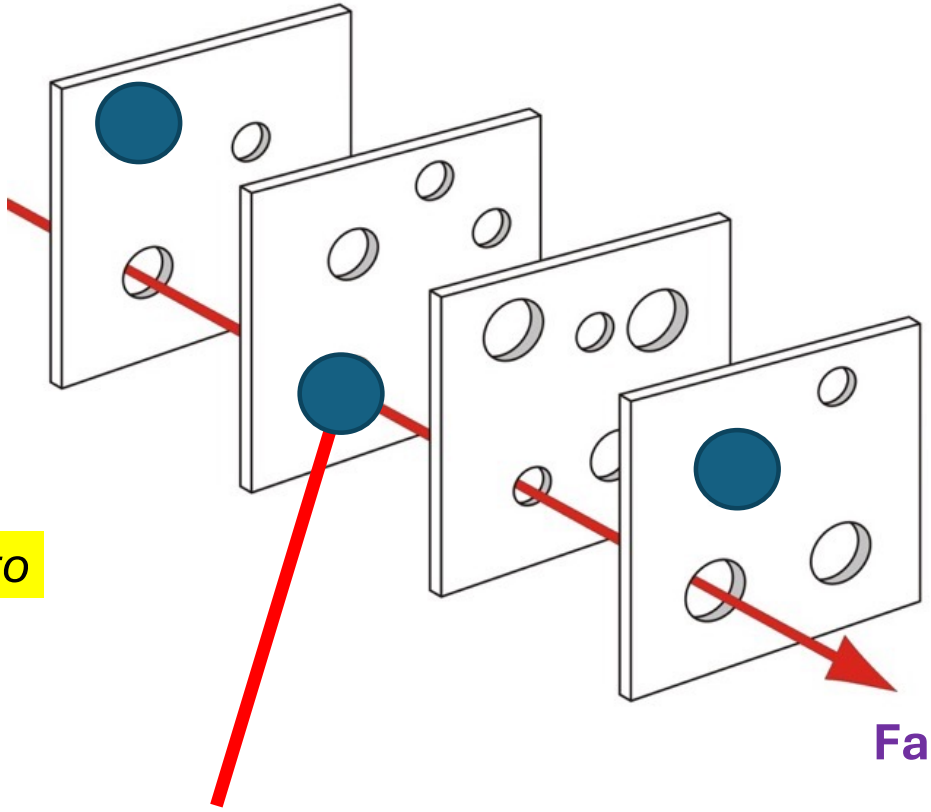
https://www.dreamstime.com

Responsibility: Threat and Error Management



eaugallecheese.com/Swiss-Cheese

Embrace these as opportunities to improve the quality of our work!



wikipedia.org/wiki/Swiss_cheese_model

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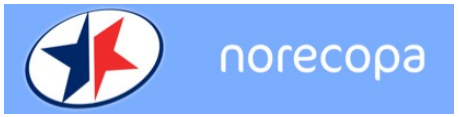

PREPARE:

***P**lanning **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

Items in pink are not typically highlighted in reporting guidelines

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The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

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PREPARE[1] consists of planning guidelines which are complementary to reporting guidelines such as ARRIVE[2].

Topic	Recommendation
	(B) Dialogue between scientists and the animal facility
5. Objectives and timescale, funding and division of labour	☐ Arrange meetings with all relevant staff when early plans for the project exist. ☐ Construct an approximate timescale for the project, indicating the need for assistance with preparation, animal care, procedures and waste disposal/decontamination. ☐ Discuss and disclose all expected and potential costs. ☐ Construct a detailed plan for division of labour and expenses at all stages of the study.
6. Facility evaluation	☐ Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. ☐ Discuss staffing levels at times of extra risk.
7. Education and	☐ Assess the current competence of staff members and the need for further education or training prior

Fillable Word file that can be used to write a Study Plan

1. Literature searches	☐ Form a clear hypothesis, with primary and secondary outcomes. ☐ Consider the use of systematic reviews. ☐ Decide upon databases and information specialists to be consulted, and construct search terms. ☐ Assess the relevance of the species to be used, its biology and suitability to answer the experimental questions with the least suffering, and its welfare needs. ☐ Assess the reproducibility and translatability of the project.
2. Legal issues	☐ Consider how the research is affected by relevant legislation for animal research and other areas, e.g. animal transport, occupational health and safety. ☐ Locate relevant guidance documents (e.g. EU guidance on project evaluation).
3. Ethical issues, harm-benefit assessment and humane endpoints	☐ Construct a lay summary. ☐ In dialogue with ethics committees, consider whether statements about this type of research have already been produced. ☐ Address the 3Rs (replacement, reduction, refinement) and the 3Ss (good science, good sense, good sensibilities). ☐ Consider pre-registration and the publication of negative results. ☐ Perform a harm-benefit assessment and justify any likely animal harm. ☐ Discuss the learning objectives, if the animal use is for educational or training purposes. ☐ Allocate a severity classification to the project. ☐ Define objective, easily measurable and unequivocal humane endpoints. ☐ Discuss the justification, if any, for death as an end-point.
4. Experimental design and statistical analysis	☐ Consider pilot studies, statistical power and significance levels. ☐ Define the experimental unit and decide upon animal numbers. ☐ Choose methods of randomisation, prevent observer bias, and decide upon inclusion and exclusion criteria.
10. Experimental animals	☐ Decide upon the characteristics of the animals that are essential for the study and for reporting. ☐ Avoid generation of surplus animals.
11. Quarantine and health monitoring	☐ Discuss the animals' likely health status, any needs for transport, quarantine and isolation, health monitoring and consequences for the personnel.
12. Housing and husbandry	☐ Attend to the animals' specific instincts and needs, in collaboration with expert staff. ☐ Discuss acclimatization, optimal housing conditions and procedures, environmental factors and any experimental limitations on these (e.g. food deprivation, solitary housing).
13. Experimental procedures	☐ Develop refined procedures for capture, immobilisation, marking, and release or rehoming. ☐ Develop refined procedures for substance administration, sampling, sedation and anaesthesia, surgery and other techniques.
14. Humane killing, release, reuse or rehoming	☐ Consult relevant legislation and guidelines well in advance of the study. ☐ Define primary and emergency methods for humane killing. ☐ Assess the competence of those who may have to perform these tasks.
15. Necropsy	☐ Construct a systematic plan for all stages of necropsy, including location, and identification of all animals and samples.

References

1. Smith AJ, Clutton RE, Lilley E, Hansen KEA & Brattelid T. PREPARE:Guidelines for Planning Animal Research and Testing. *Laboratory Animals*, 2017, DOI: 10.1177/0023677217724823.
2. Kilkenny C, Browne WJ, Cuthill IC *et al.* Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research. *PloS Biology*, 2010; DOI: 10.1371/journal.pbio.1000412.

Further information
https://norecopa.no/PREPARE / *post@norecopa.no* / @norecopa

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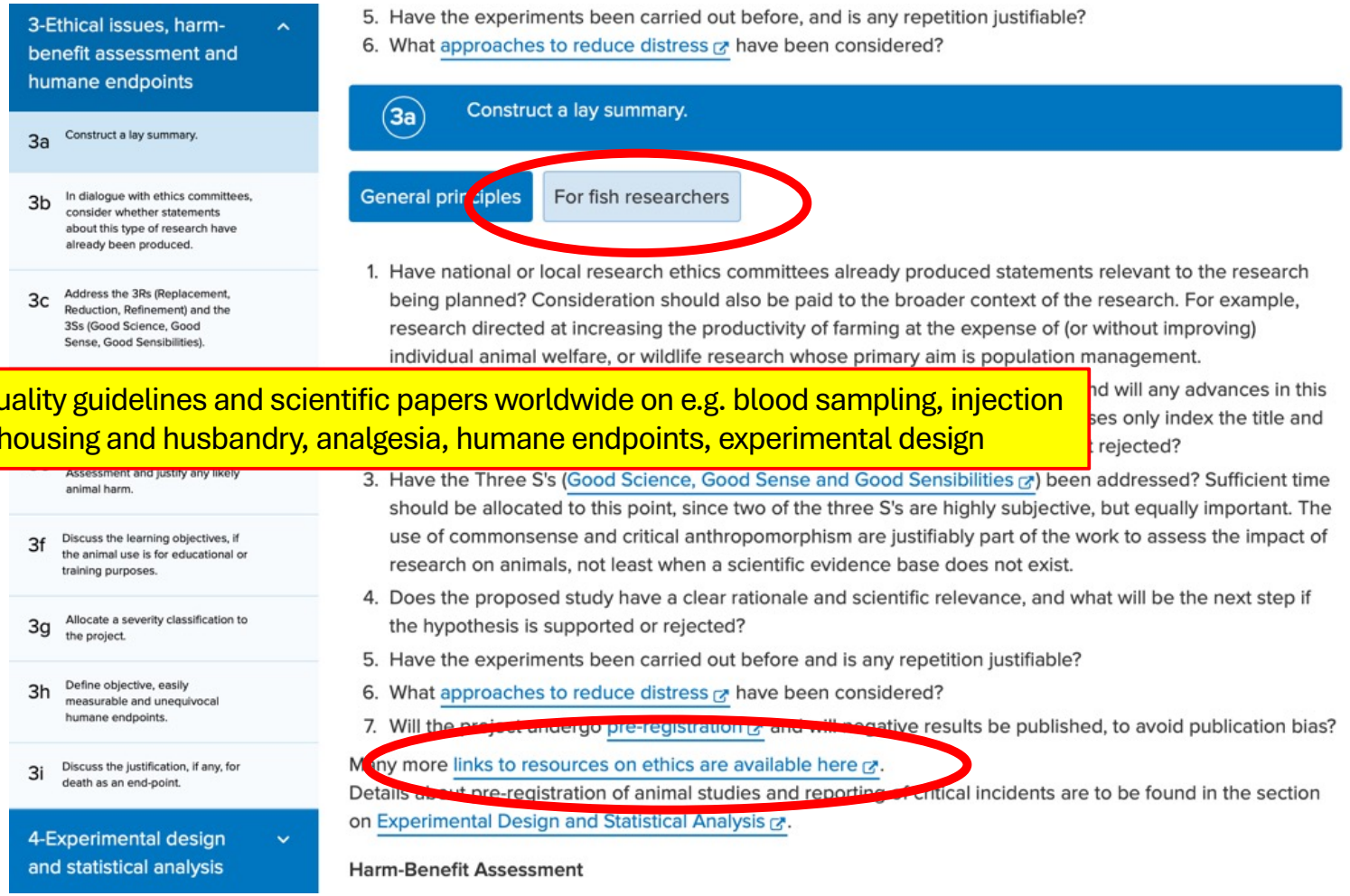
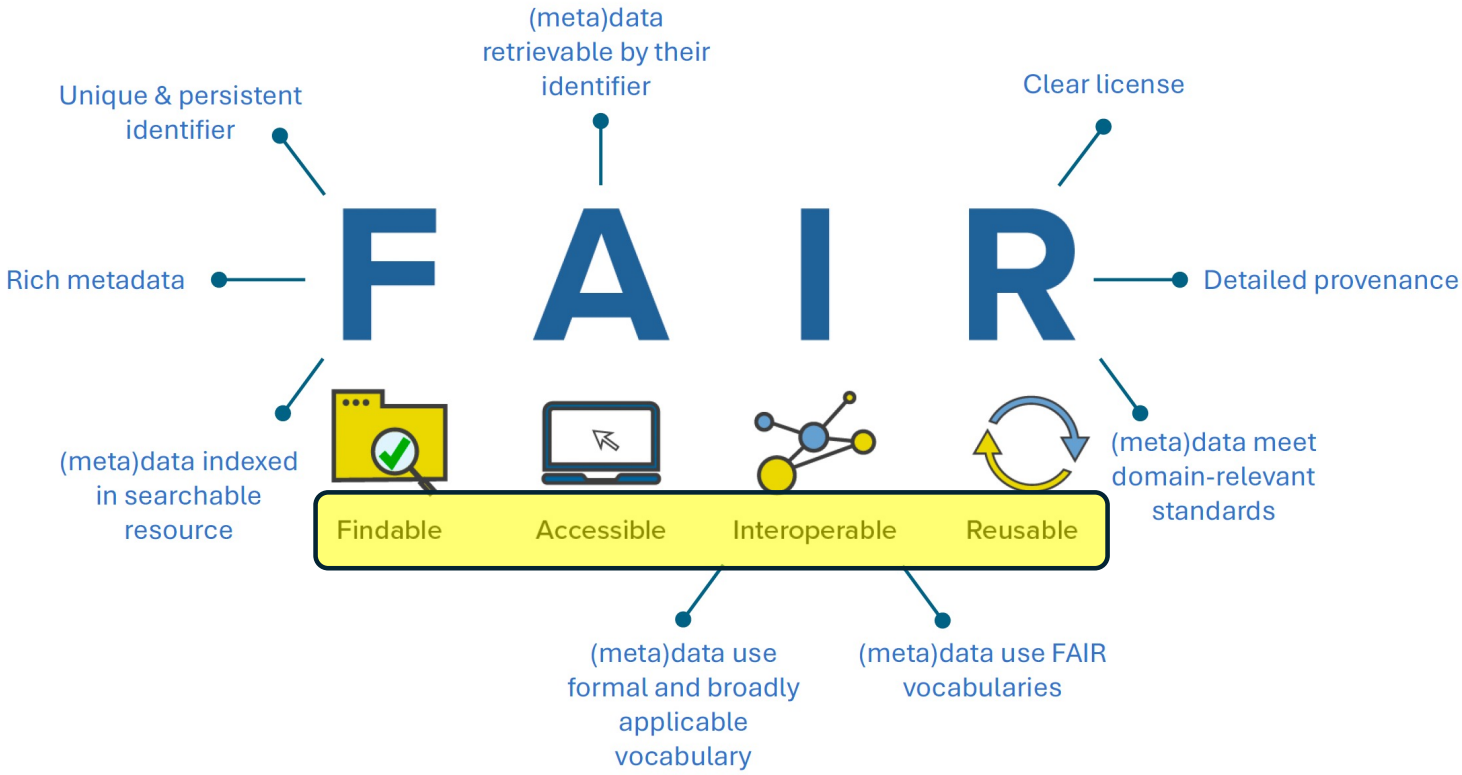


Links to quality guidelines and scientific papers worldwide on e.g. blood sampling, injection volumes, housing and husbandry, analgesia, humane endpoints, experimental design

FAIR—Findable, Accessible, Interoperable, Reusable.

https://www.nature.com/articles/sdata201618

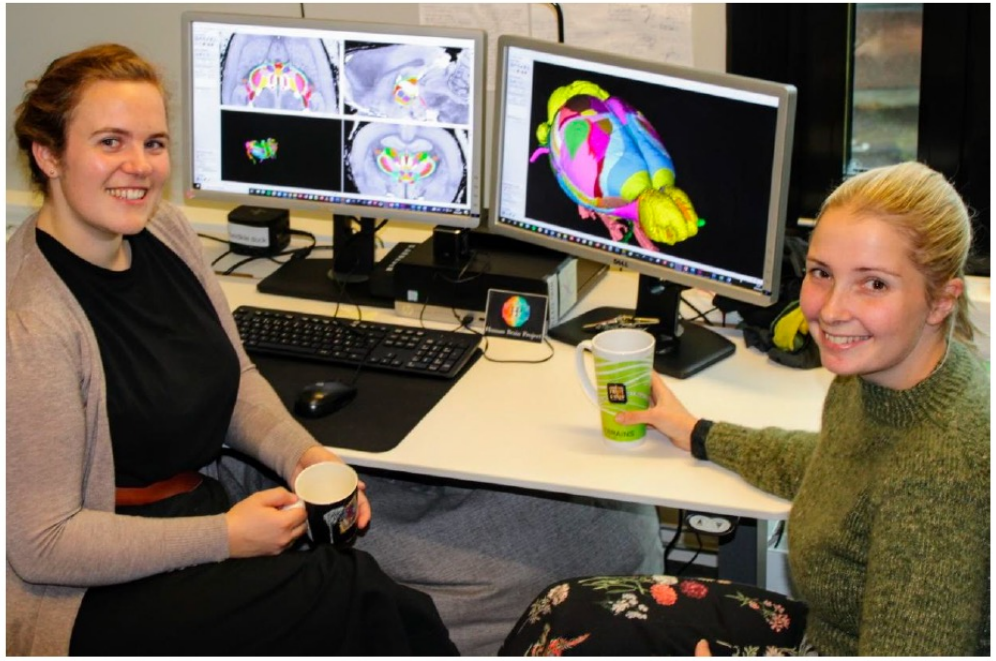


https://norecopa.no/media/mj4jt0m0/bjerke-200525.pdf

https://www.nature.com/articles/sdata201618

https://www.nlm.nih.gov/oet/ed/cde/tutorial/02-200.html

A critical window for becoming FAIR



- Teach young researchers to:
  - Plan for data sharing
  - Collect metadata systematically
  - Use public data
  - Share their research through repositories

Norecopa: PREPARE for better Science https://norecopa.no/media/mj4jt0m0/bjerke-200525.pdf

Better reporting of 3R advances

foto: NMBU

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

We need more species- and situation-specific guidelines!!

Aaberge I.S. *et al.*, Infection & Immunity, 1992, 60 (10): 4146-4153
https://journals.asm.org/doi/10.1128/iai.60.10.4146-4153.1992

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"We ARRIVED, because we were PREPARED"

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- ✓ *Improved animal welfare*
- ✓ *Advancement of the 3Rs*
- ✓ *Safer working environment*

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