Alternative approaches: drivers and visions

the National 3R Centre perspective

norecopa.no/EPAA

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"The opinions expressed here are my own and not necessarily those of Norecopa"

Norecopa

Norway's National Consensus Platform for the

Three Rs: Replacement, Reduction and Refinement

and a source of global 3R resources

https://norecopa.no

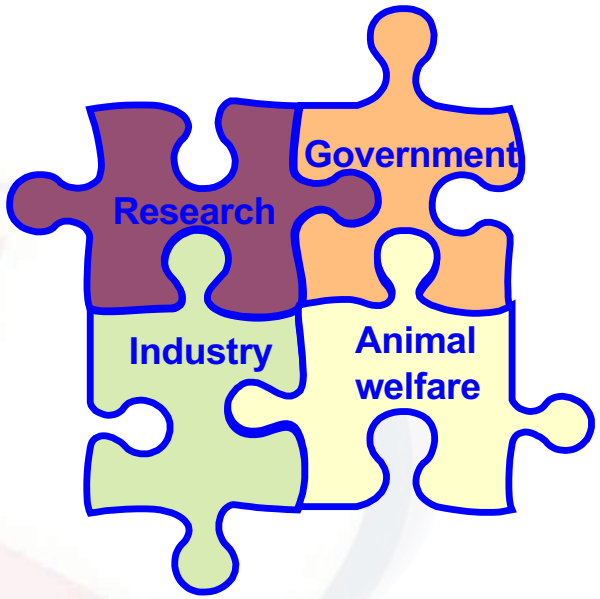
Norecopa: PREPARE for better Science

European Consensus-Platform for Alternatives

ecopa.eu

ecopa supports the establishment of National Consensus Platforms (NCPs) where all 4 stakeholders are equally represented in the governing body:

Founding Members:
Denmark
Finland
France
Germany
Italy
Norway
Spain
Sweden



Members of ecopa today

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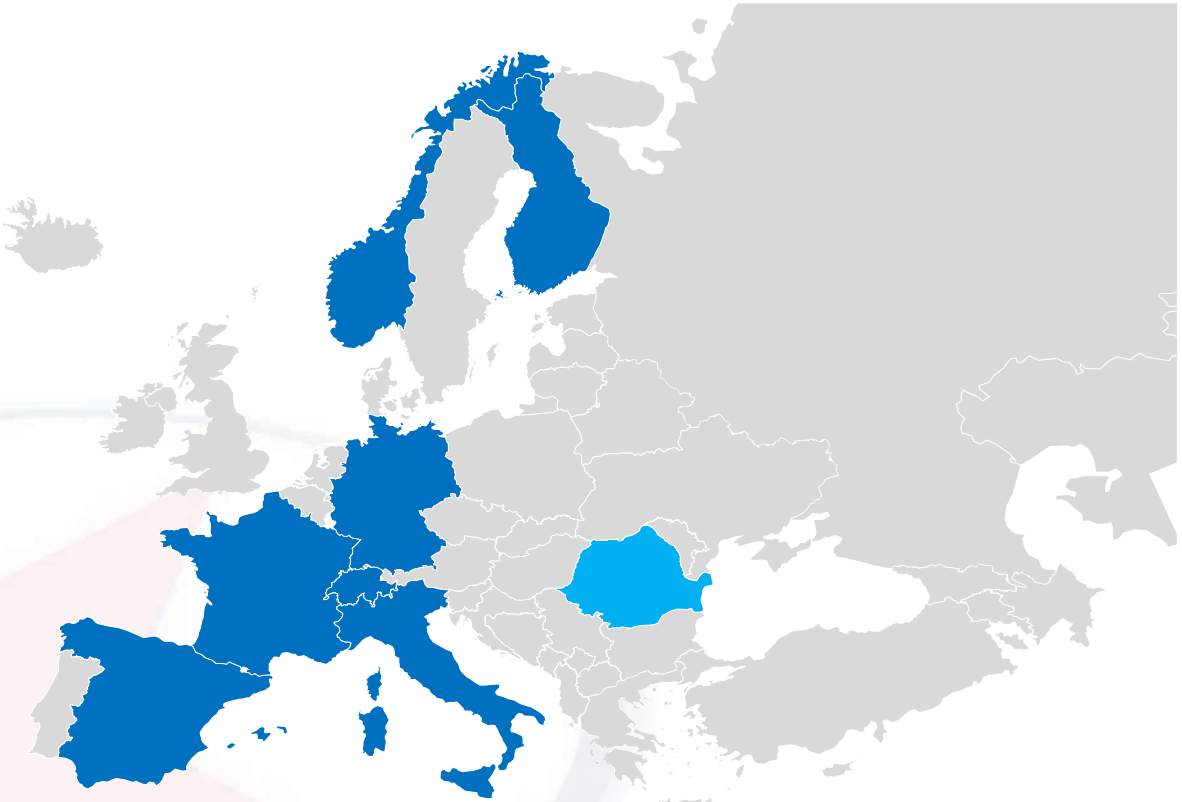
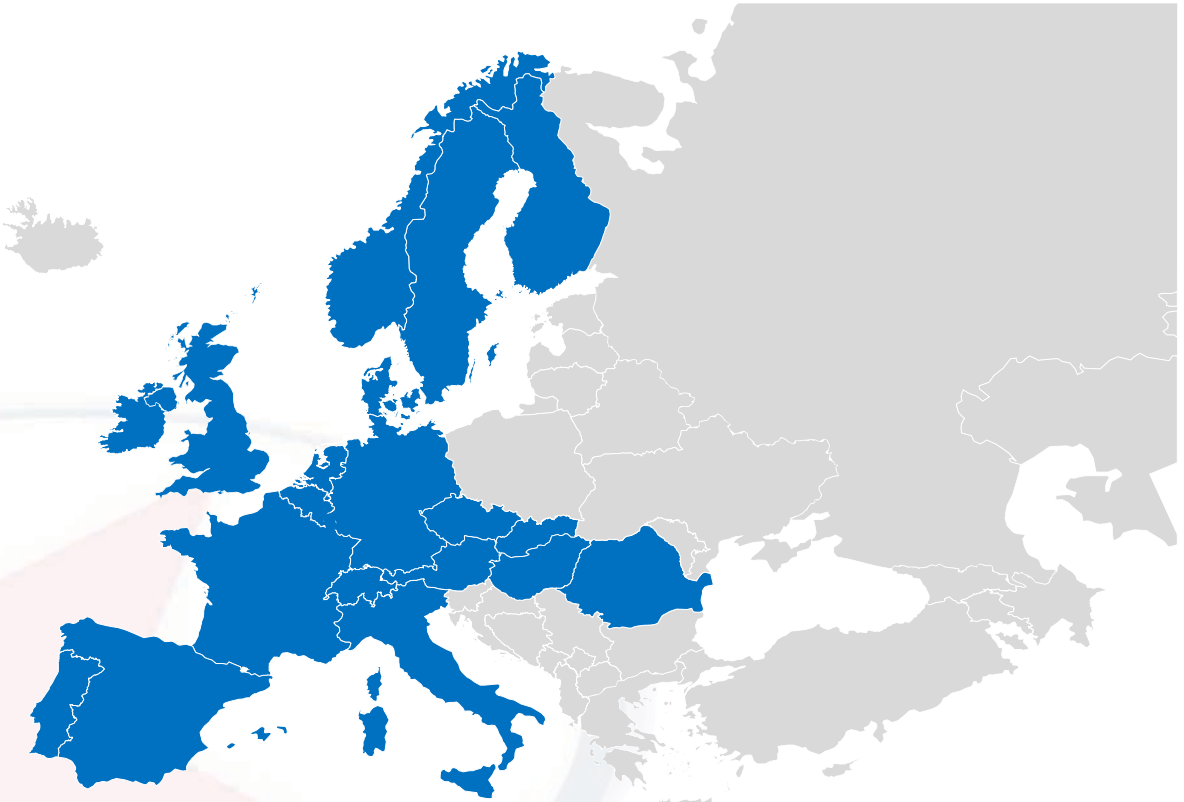
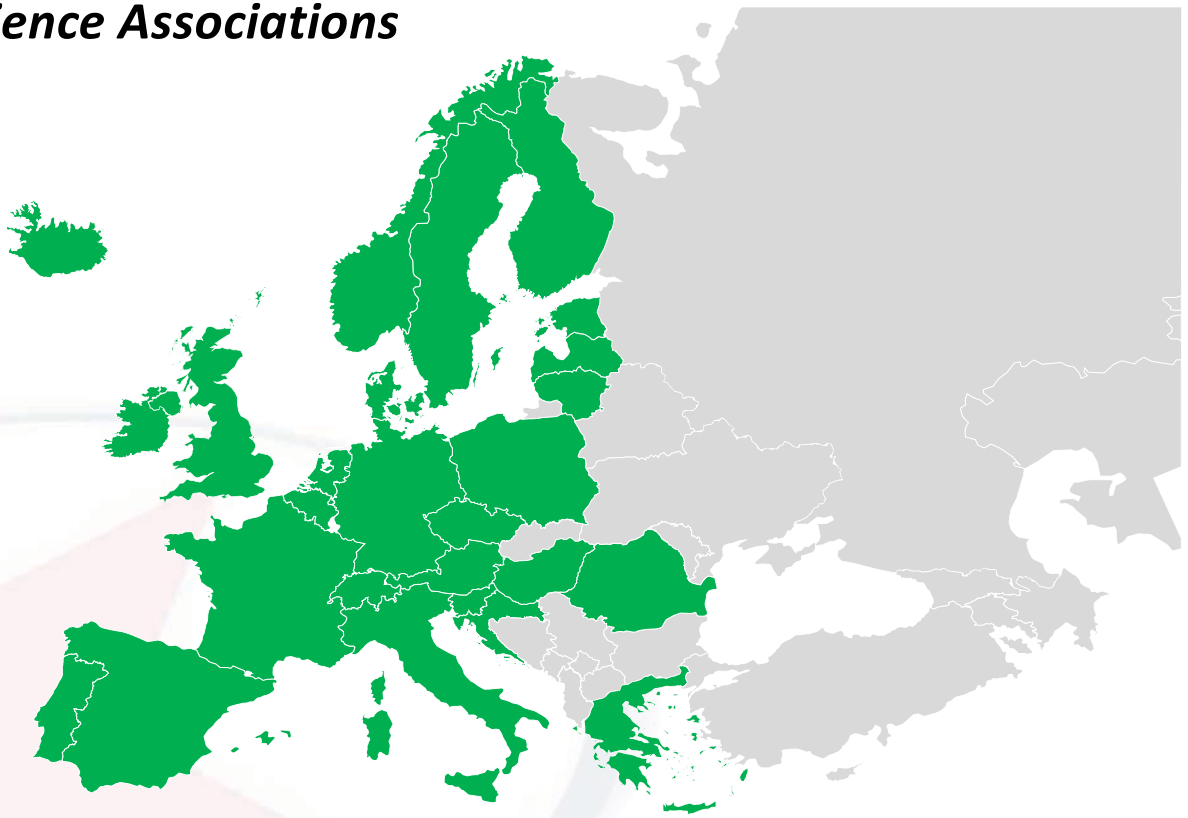


Countries with 3R Centres

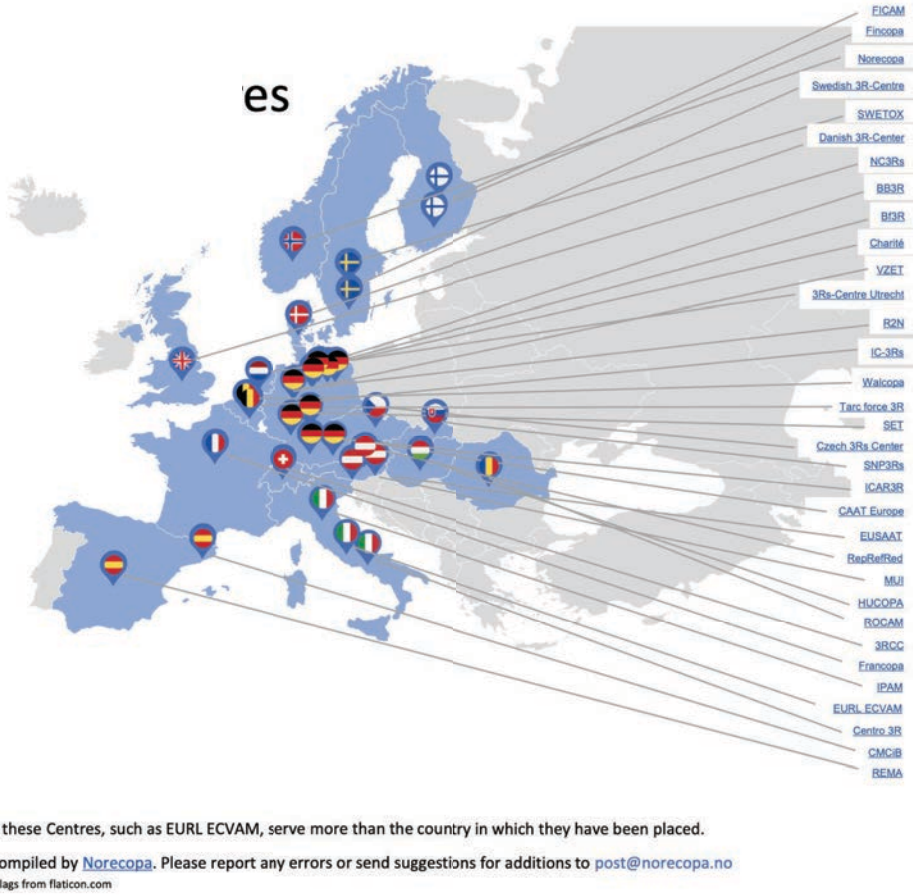


Countries with/affiliated to Laboratory Animal Science Associations



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

Interactive map:
norecopa.no/3REuropeOverview

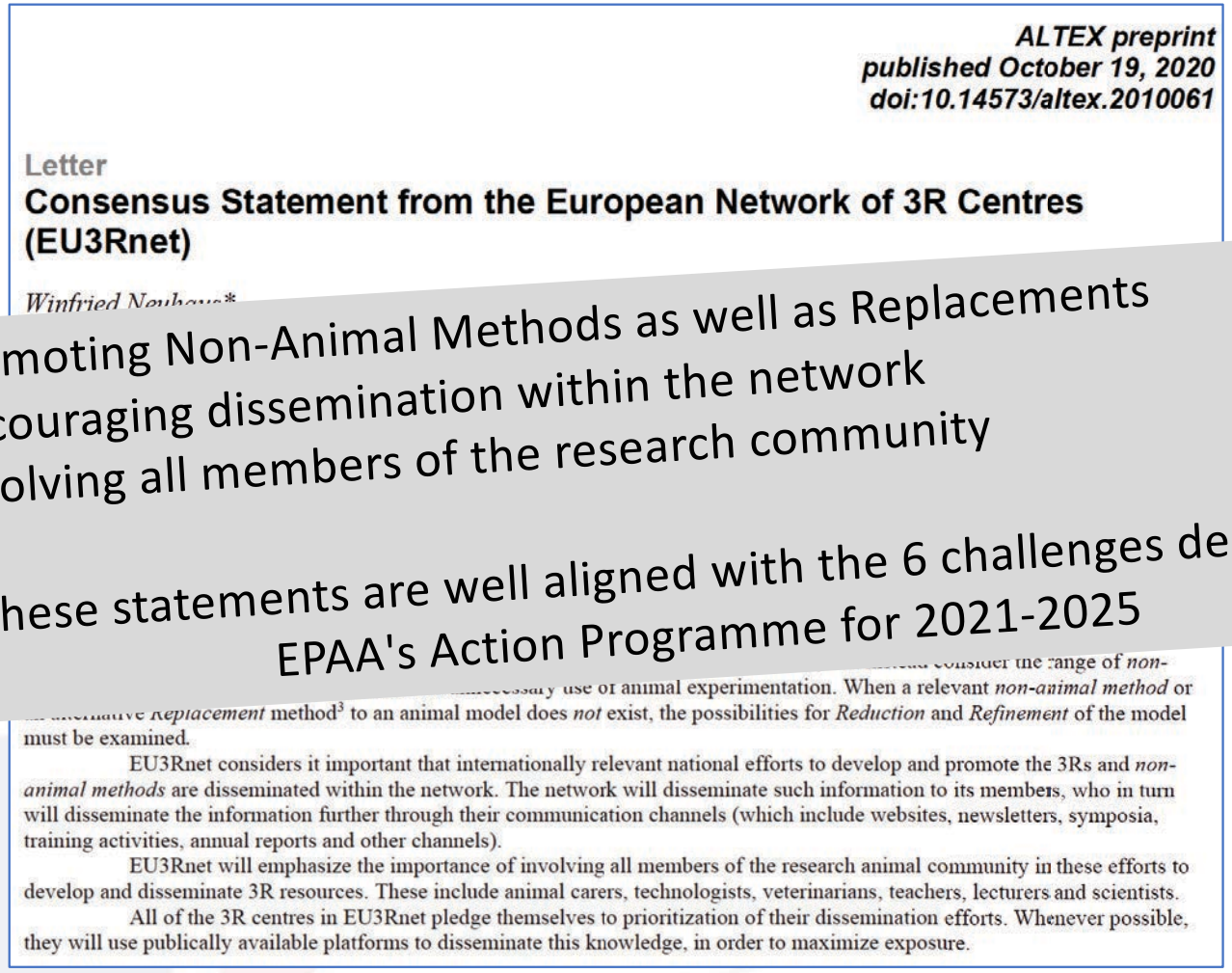


Winfried Neuhaus

Horst Spielmann & Monica Schäfer-Korting

3R Centre meeting in March 2019

Norecopa: PREPARE for better Science



ALTEX preprint
published October 19, 2020
doi:10.14573/altex.2010061

Letter

Consensus Statement from the European Network of 3R Centres (EU3Rnet)

*Winfried Neuhaus**

- Promoting Non-Animal Methods as well as Replacements
- Encouraging dissemination within the network
- Involving all members of the research community

These statements are well aligned with the 6 challenges described in EPAA's Action Programme for 2021-2025

...consider the range of *non-*
...unnecessary use of animal experimentation. When a relevant *non-animal method* or
...alternative *Replacement* method[3] to an animal model does *not* exist, the possibilities for *Reduction* and *Refinement* of the model must be examined.

EU3Rnet considers it important that internationally relevant national efforts to develop and promote the 3Rs and *non-animal methods* are disseminated within the network. The network will disseminate such information to its members, who in turn will disseminate the information further through their communication channels (which include websites, newsletters, symposia, training activities, annual reports and other channels).

EU3Rnet will emphasize the importance of involving all members of the research animal community in these efforts to develop and disseminate 3R resources. These include animal carers, technologists, veterinarians, teachers, lecturers and scientists.

All of the 3R centres in EU3Rnet pledge themselves to prioritization of their dissemination efforts. Whenever possible, they will use publically available platforms to disseminate this knowledge, in order to maximize exposure.

Preparing an application for a COST Action

Working title: *3Rs for better Science*

A contribution towards the efforts to meet the reproducibility crisis,
by applying methods developed within the 3Rs field

Working groups focusing on

- Dissemination
- Quality and translatability of science
- Implementation and Education

with ethics integrated into each of these areas

- Closing the gaps between current EU projects
- Ensuring that basic research is also covered, i.e. not just a focus on testing

ECVAM meeting in 1999:
Belgium, Germany and the Netherlands

World Congresses on Alternatives and Animal Use in the Life Sciences

2021

Maastricht

3R Centre meetings arranged by ECVAM in 2015 og 2016

10th World Congress
August 20-24, 2017
Seattle, Washington, USA

9th World Congress
August 24-28, 2014
Prague, Czech Republic

8th World Congress
August 21-25, 2011
Montreal, Canada

7th World Congress
August 30 – September 3, 2009
Rome, Italy

6th World Congress
August 21-25, 2007
Tokyo, Japan

5th World Congress
August 21-25, 2005
Berlin, Germany

4th World Congress
August 11-15, 2002
New Orleans, Louisiana, USA

3rd World Congress
August 29 – September 2, 1999
Bologna, Italy

workshop about national platforms

2nd World Congress
October 20-24, 1996
Utrecht, Holland

1st World Congress
November 14-19, 1993
Baltimore, Maryland, USA

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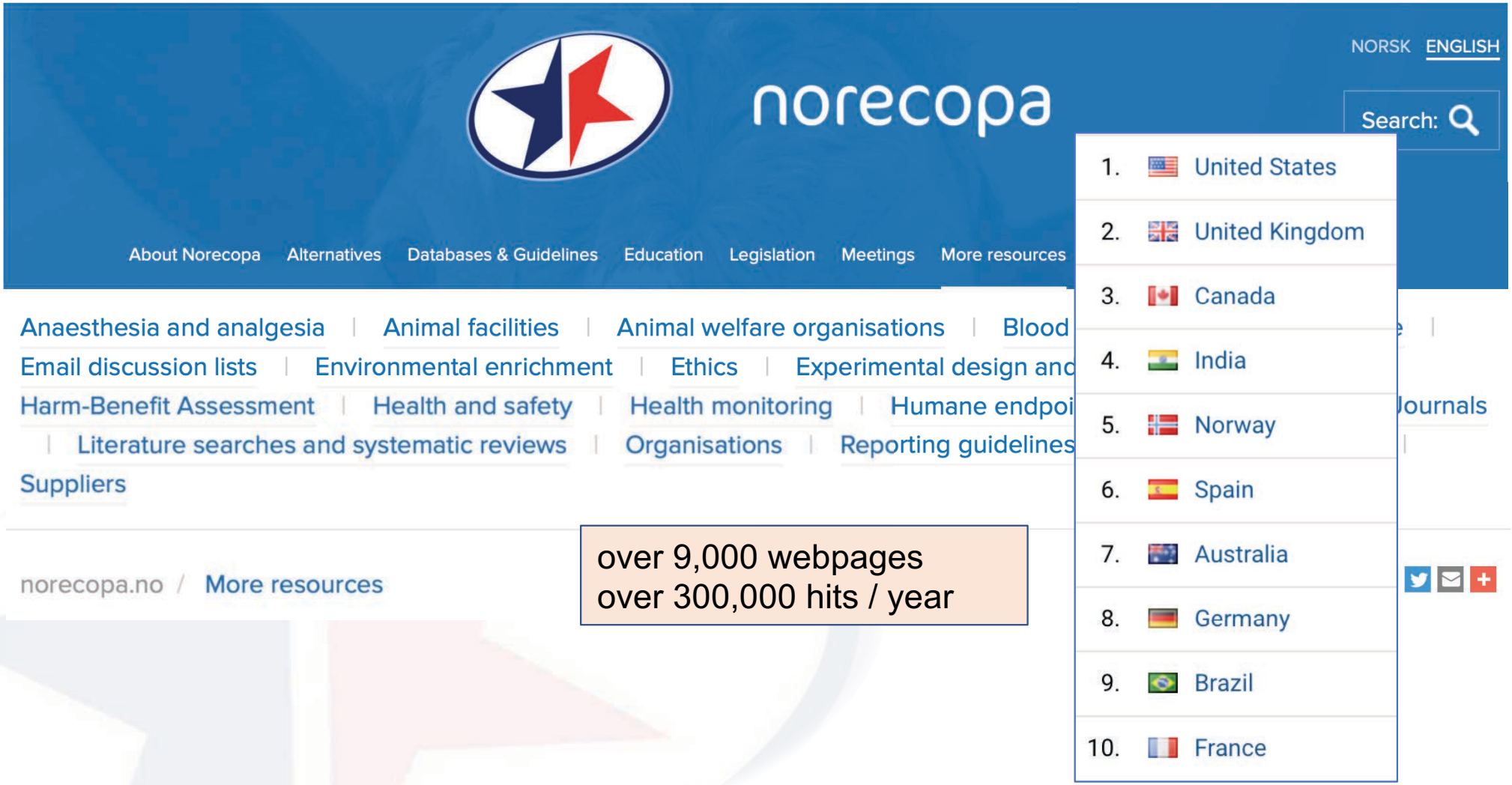

over 9,000 webpages
over 300,000 hits / year

"The Reproducibility Crisis"

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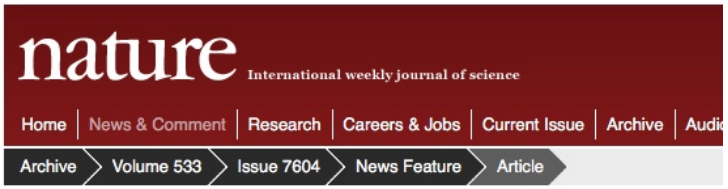

NATURE | NEWS FEATURE

1,500 scientists lift the lid on reproducibility

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.

Why Most Published Research Findings Are False

John P. A. Ioannidis

Published: August 30, 2005 • https://doi.org/10.1371/journal.pmed.0020124

Avoidable waste in the production and reporting of research evidence

Iain Chalmers, DSc • Prof Paul Glasziou, RACGP

Published: June 15, 2009 • DOI: https://doi.org/10.1016/S0140-6736(09)60329-9

Norecopa: PREPARE for better Science

norecopa.no/PREPARE/prepare-checklist

PREPARE

The PREPARE Guidelines Checklist

Planning Research and Experimental Procedures on Animals: Recommendations for Excellence

Adrian J. Smith[a], R. Eddie Clutton[b], Elliot Lilley[c], Kristine E. Aa. Hansen[a] & Trond Bratteli[d]

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PREPARE[1] consists of planning guidelines which are complementary to reporting guidelines such as ARRIVE[2].
PREPARE covers the three broad areas which determine the quality of the preparation for animal st

1. **Formulation of the study**
2. **Dialogue between scientists and the animal facility**
3. **Quality control of the components in the study**

The topics will not always be addressed in the order in which they are presented here, and some topi
checklist can be adapted to meet special needs, such as field studies. PREPARE includes guidance on
facilities, since in-house experiments are dependent upon their quality. The full version of the guidelin
website, with links to global resources, at **https://norecopa.no/PREPARE**.
The PREPARE guidelines are a dynamic set which will evolve as more species- and situation-specific guidelines are produced, and as best practice within Laboratory Animal Science progresses.

Topic	Recommendation
(A) Formulation of the study	
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.

Three Rs!

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 [illegible]tion	☐ Conduct a physical inspection of the facilities, to evaluate building and equipment standards and needs. ☐ Discuss staffing levels at times of extra risk.
[illegible]ation and	☐ Assess the current competence of staff members and the need for further education or training prior to the study.
[illegible] risks, waste disposal and decontamination	☐ Perform a risk assessment, in collaboration with the animal facility, for all persons and animals affected directly or indirectly by the study. ☐ Assess, and if necessary produce, specific guidance for all stages of the project. ☐ Discuss means for containment, decontamination, and disposal of all items in the study.
(C) Quality control of the components in the study	
9. Test substances and procedures	☐ Provide as much information as possible about test substances. ☐ Consider the feasibility and validity of test procedures and the skills needed to perform them.
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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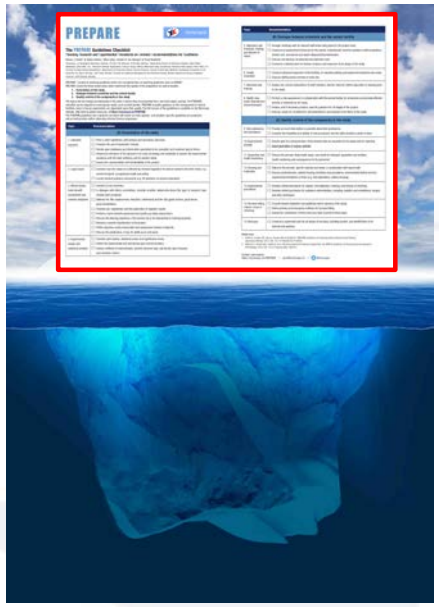
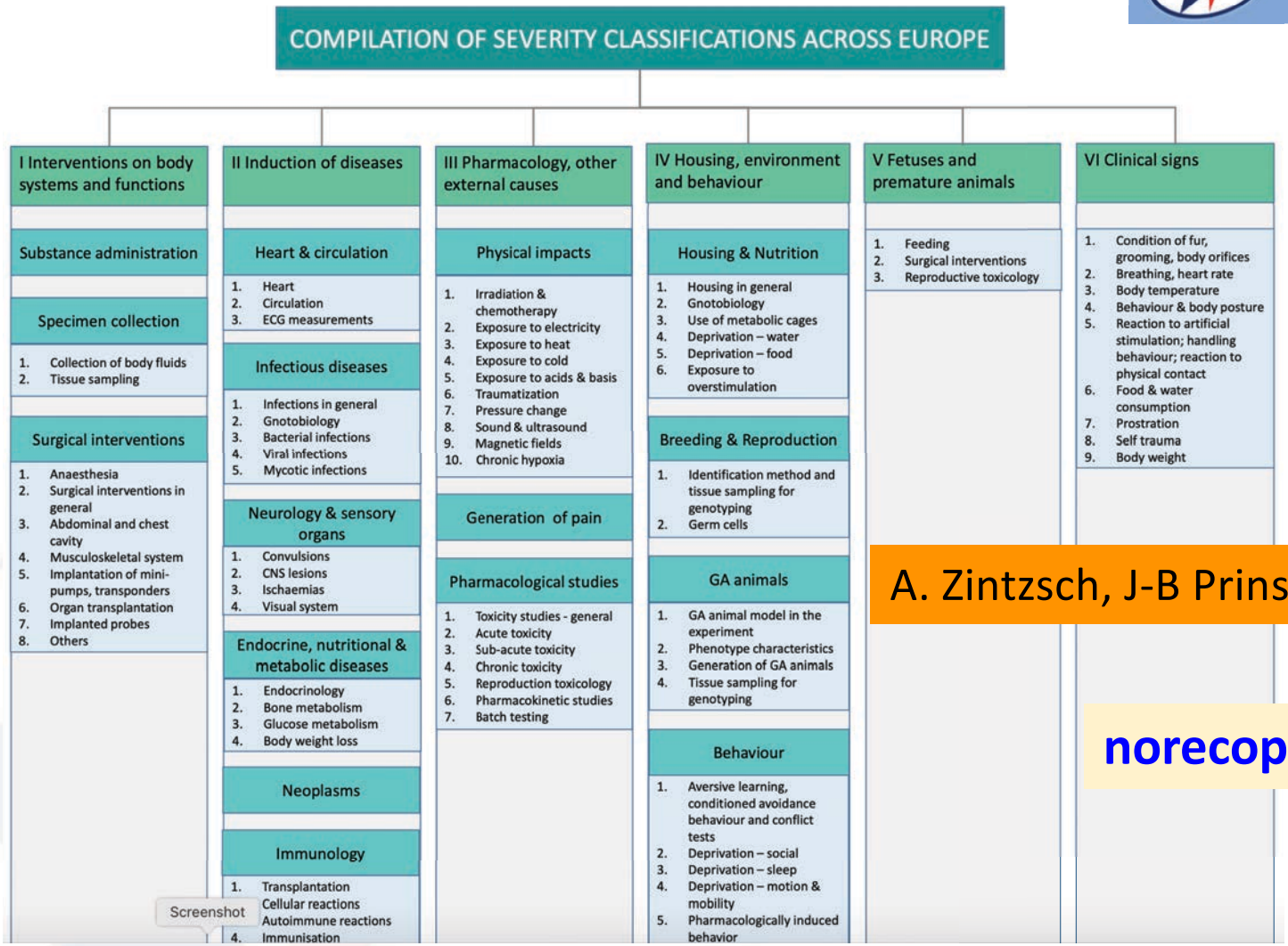
In addition to the checklist, much more information is available on:

norecopa.no/PREPARE

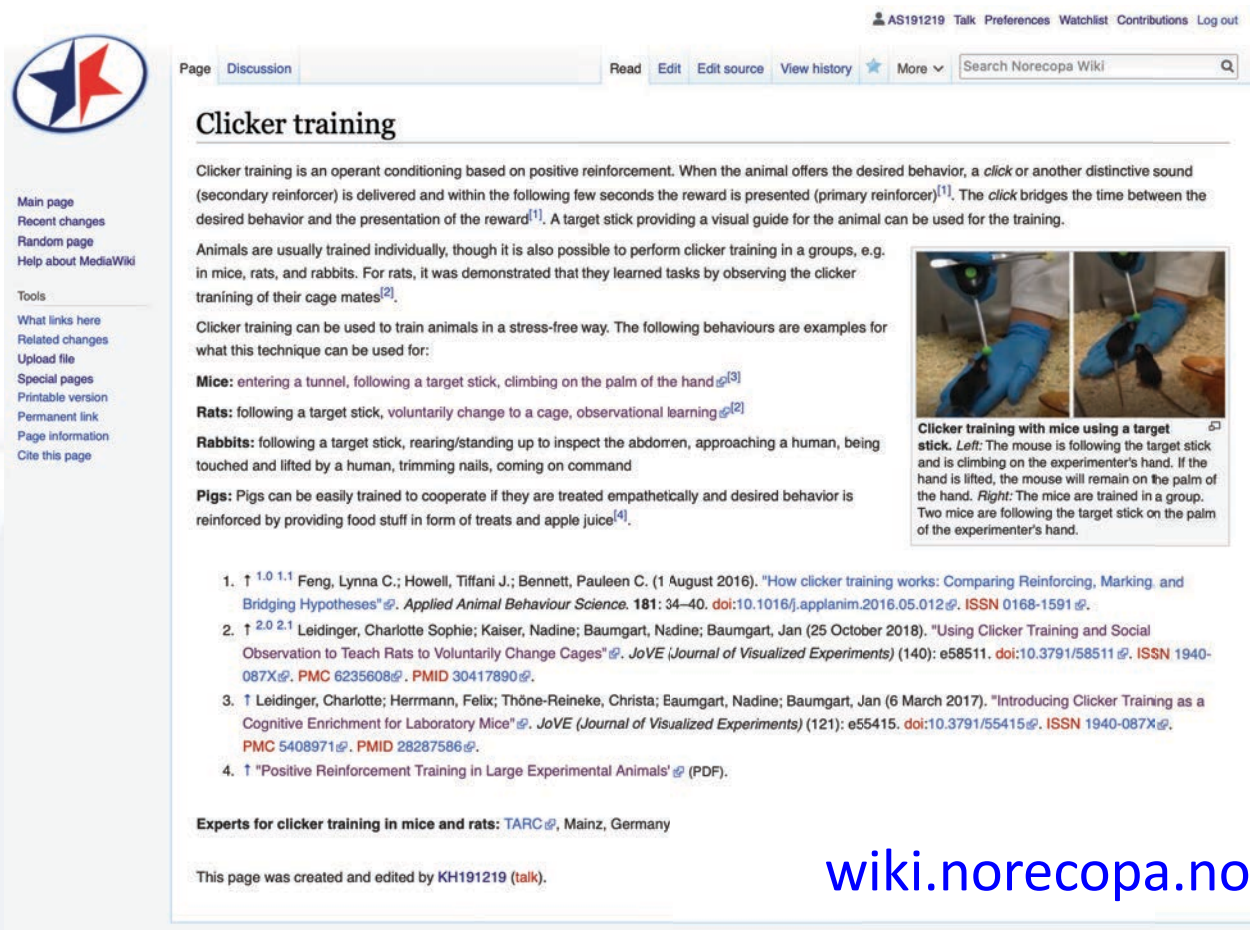




A. Zintzsch, J-B Prins & N Kostomitsopolous

norecopa.no/severity

A Refinement Wiki



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Clicker training

Clicker training is an operant conditioning based on positive reinforcement. When the animal offers the desired behavior, a *click* or another distinctive sound (secondary reinforcer) is delivered and within the following few seconds the reward is presented (primary reinforcer)[1]. The *click* bridges the time between the desired behavior and the presentation of the reward[1]. A target stick providing a visual guide for the animal can be used for the training.

Animals are usually trained individually, though it is also possible to perform clicker training in a groups, e.g. in mice, rats, and rabbits. For rats, it was demonstrated that they learned tasks by observing the clicker tranining of their cage mates[2].

Clicker training can be used to train animals in a stress-free way. The following behaviours are examples for what this technique can be used for:

Mice: entering a tunnel, following a target stick, climbing on the palm of the hand[3]

Rats: following a target stick, voluntarily change to a cage, observational learning[2]

Rabbits: following a target stick, rearing/standing up to inspect the abdomen, approaching a human, being touched and lifted by a human, trimming nails, coming on command

Pigs: Pigs can be easily trained to cooperate if they are treated empathetically and desired behavior is reinforced by providing food stuff in form of treats and apple juice[4].

Clicker training with mice using a target stick. *Left:* The mouse is following the target stick and is climbing on the experimenter's hand. If the hand is lifted, the mouse will remain on the palm of the hand. *Right:* The mice are trained in a group. Two mice are following the target stick on the palm of the experimenter's hand.

1. ↑ [1.0] [1.1] Feng, Lynna C.; Howell, Tiffani J.; Bennett, Pauleen C. (1 August 2016). "How clicker training works: Comparing Reinforcing, Marking and Bridging Hypotheses". *Applied Animal Behaviour Science*. **181**: 34–40. doi:10.1016/j.applanim.2016.05.012. ISSN 0168-1591.
2. ↑ [2.0] [2.1] Leidinger, Charlotte Sophie; Kaiser, Nadine; Baumgart, Nadine; Baumgart, Jan (25 October 2018). "Using Clicker Training and Social Observation to Teach Rats to Voluntarily Change Cages". *JoVE (Journal of Visualized Experiments)* (140): e58511. doi:10.3791/58511. ISSN 1940-087X. PMC 6235608. PMID 30417890.
3. ↑ Leidinger, Charlotte; Herrmann, Felix; Thöne-Reineke, Christa; Baumgart, Nadine; Baumgart, Jan (6 March 2017). "Introducing Clicker Training as a Cognitive Enrichment for Laboratory Mice". *JoVE (Journal of Visualized Experiments)* (121): e55415. doi:10.3791/55415. ISSN 1940-087X. PMC 5408971. PMID 28287586.
4. ↑ "Positive Reinforcement Training in Large Experimental Animals' (PDF).

Experts for clicker training in mice and rats: TARC, Mainz, Germany

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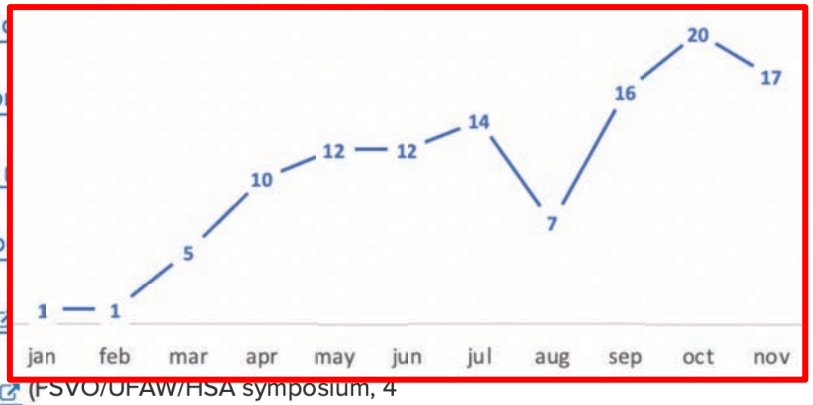
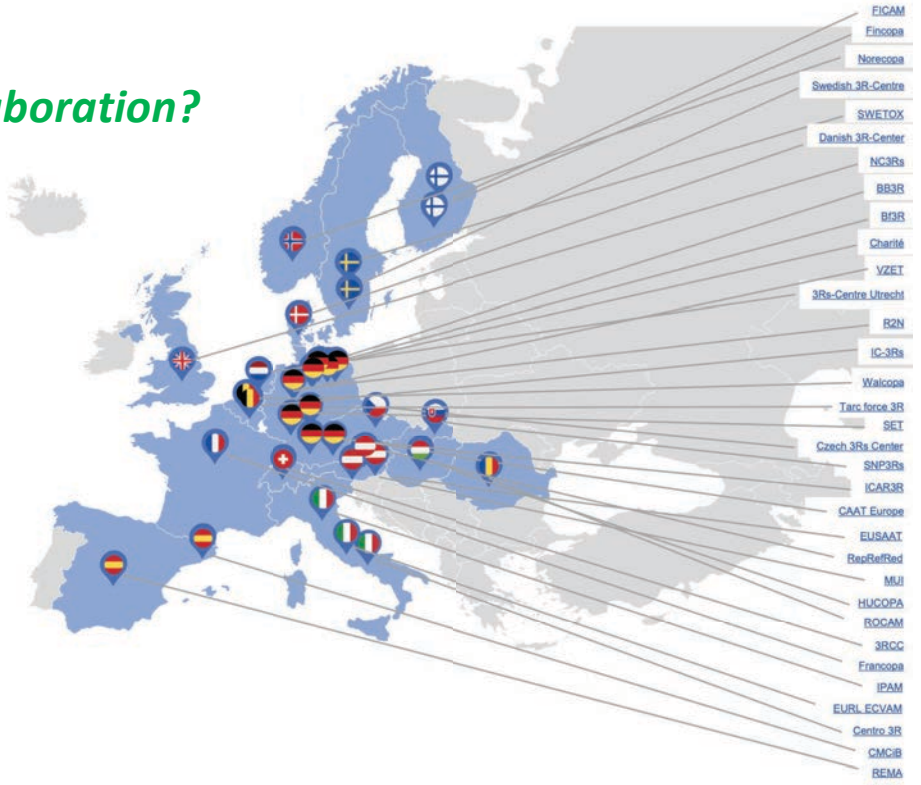
Over 100 webinars within Lab Animal Science & Welfare in 2020



European network of 3R Centres:

Quo vadis?
Networking, competition or active collaboration?

Society is unity in diversity
George Herbert Mead



Interactive map:
norecopa.no/3REuropeOverview

Please note that some of these Centres, such as EURL ECVAM, serve more than the country in which they have been placed.

This overview has been compiled by Norecopa. Please report any errors or send suggestions for additions to post@norecopa.no

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