Utrecht University

Veterinary Medicine

Thoughts on a future without laboratory animals

Danish 3R center

9 November 2022

Merel Ritskes-Hoitinga
Prof in Evidence-Based Transition to Animal-Free Innovations
Institute for Risk Assessment Sciences (IRAS) TOX

https://www.uu.nl/en/news/merel-ritskes-hoitinga-new-professor-of-evidence-based-transition-to-animal-free-innovations

Overview

- The circle of my life: how did I get here?
- Where is the evidence? History of legal requirements for animal studies and alternatives
  - waiting for crises before taking legislative action?
  - what is the scientific evidence behind legislation?
  - COVID-19 pandemic crisis - case study Comirnaty – change is possible?
- Can we use scientific evidence better? History and impact of preclinical systematic reviews
- Can we act more upon scientific evidence?
- Accelerating the transition to animal-free innovations

tpi.

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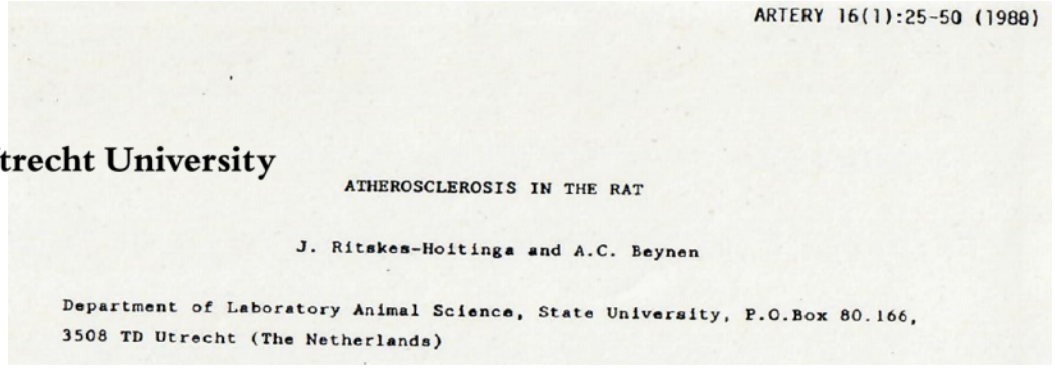

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J. Ritskes-Hoitinga and A.C. Beynen

Department of Laboratory Animal Science, State University, P.O.Box 80.166, 3508 TD Utrecht (The Netherlands)

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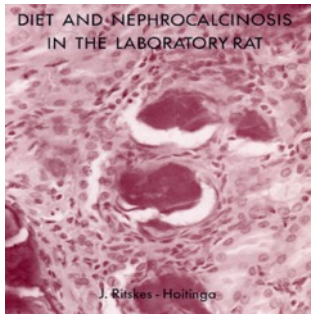

3R Research Centre
Refine Reduce Replace

www.ritskes-hoitinga.eu

The story of my life:
from Refinement to Replacement

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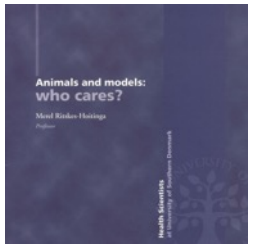

Honorary SKOU professorship at AU
AUGUST Aarhus University http://august.au.dk/about-august/

AARHUS UNIVERSITY

Activities on preclinical systematic reviews:

Birgitte Kousholt
Gregers Wegeners

2015 symposium and workshop

2017 symposium and workshop

2017 ScandLAS session

2019 NorDoc PhD summit

Oct 2019 inauguration Aarhus University

Fall 2021-Spring 2022 Online seminar series

A history of regulatory animal testing: What can we learn?

Public health disasters force acute decisive regulatory action:

•***Sulfanilamide elixer*** disaster led to finally passing the Food, Drugs and Cosmetics Act in US in 1938

– this act had been under discussion since the beginning of the 1900s

•***Thalidomide*** disaster led to new animal testing demands for drugs for market authorisation in the 1960s

Where is the evidence behind all of this?!

Vanda court case against the FDA: regulations are in place that do not contribute to the safety of a drug

Swaters D, van Veen A, van Meurs W, Turner JE, Ritskes-Hoitinga M. A History of Regulatory Animal Testing: What Can We Learn? Altern Lab Anim. 2022 Aug 19:2611929221118001. doi: 10.1177/02611929221118001.

Do we wait to act until there is a crisis

instead of using good scientific evidence to act upon?

What about the COVID-19 pandemic crisis actions?

Vaccines approved in one year instead of ten?

Conclusions COVID-19 case study

EMA shortened its approval timeline by reducing the nr of animal studies and promoting alternative methods for COVID vaccine Comirnaty: conditional marketing approval after one year!

mRNA so well characterised that no animal tests needed for batch releases

Pharma showed clear readiness to contribute to these changes actively, also expressing the wish to continue on this road

EMA more careful towards future developments, still heavily relying on animal studies because of risk aversion (even though animal studies also incorporate risks)

Further cooperation between pharma and regulators provides promise for future fast and effective developments of new vaccines, with fewer animal studies and more use of alternatives

Continue research on this road, as COVID-19 has shown such huge potential

Ritskes-Hoitinga M, Barella Y, Kleinhout-Vliek T. The Promises of Speeding Up: Changes in Requirements for Animal Studies and Alternatives during COVID-19 Vaccine Approval-A Case Study. Animals (Basel). 2022 Jul 5;12(13):1735.

animals

MDPI

Communication

The Promises of Speeding Up: Changes in Requirements for Animal Studies and Alternatives during COVID-19 Vaccine Approval–A Case Study

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Let’s use scientific evidence more please?

Systematic reviews (SR) bring us the most

objective and complete scientific evidence,

but strangely enough are not yet mainstream preclinically,

in contrast to the clinic / evidence-based medicine.

History of preclinical systematic reviews in the UK and the Netherlands from 2000-2022 – Invitation by Sir Iain Chalmers, one of the founders of the Cochrane

skes-Hoitinga - Microsoft PowerPoint

Hulpmiddelen voor tekenen

The role of systematic reviews in

/doi/10.1177/01410768221093551

Journal of the Royal Society of Medicine

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The role of systematic reviews in identifying the limitations of preclinical animal research, 2000–2022: part 1

Merel Ritskes-Hoitinga, Pandora Pound

First Published May 3, 2022 | Other | Check for updates

https://doi.org/10.1177/01410768221093551

Article information

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Journal of the Royal Society of Medicine; 2022, Vol. 115(5) 186–192

DOI: 10.1177/01410768221093551

The role of systematic reviews in identifying the limitations of preclinical animal research, 2000–2022: part 1

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Introduction

A thousand years ago, the Persian physician Ibn Sina issued a strong warning about the pitfalls of using animals to develop medicines for humans:

> Experiments should be carried out on the human body. If the experiment is carried out on the bodies of [other animals] it is possible that it might fail for two reasons: the medicine might be hot compared to the human body and be cold compared to the lion's

conducted in the field of animal research and clearly demonstrated the value of synthesising studies which, if considered individually, might be misleading. Ibn Sina had warned about the problems of extrapolating findings from one species to another, but systematic reviews pointing to further problems – limitations in the way research was being conducted and interpreted.

Two decades earlier, in what has been described as a rallying call for evidence synthesis,[6,7] the Scottish

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Merel Ritskes-Hoitinga, Pandora Pound

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The role of systematic reviews in identifying the limitations of preclinical animal research, 2000–2022: part 2

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In Part 1 of this publication we provided a partial history of preclinical systematic reviews in both the UK and the Netherlands during the years 2000–2022.[1] Here in Part 2, we conclude by considering some of the evidence generated by these reviews, and its implications for preclinical research and for medicine.

Evidence from systematic reviews

of CAMARADES, showed in her 2014 overview.[10] In short, systematic reviews provided overwhelming evidence that animal studies suffer from poor experimental design and a lack of scientific rigour, raising doubts about the robustness of their findings and consequently, their clinical relevance.

Selective analysis and biased outcome reporting – the practice of reporting only the most positive outcomes and analyses from among the many performed and studied – was also revealed to be a problem in animal research.[8] Again, this leads to an overestimate

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Merel Ritskes-Hoitinga[1,2] and Wynand Alkema[3,4]

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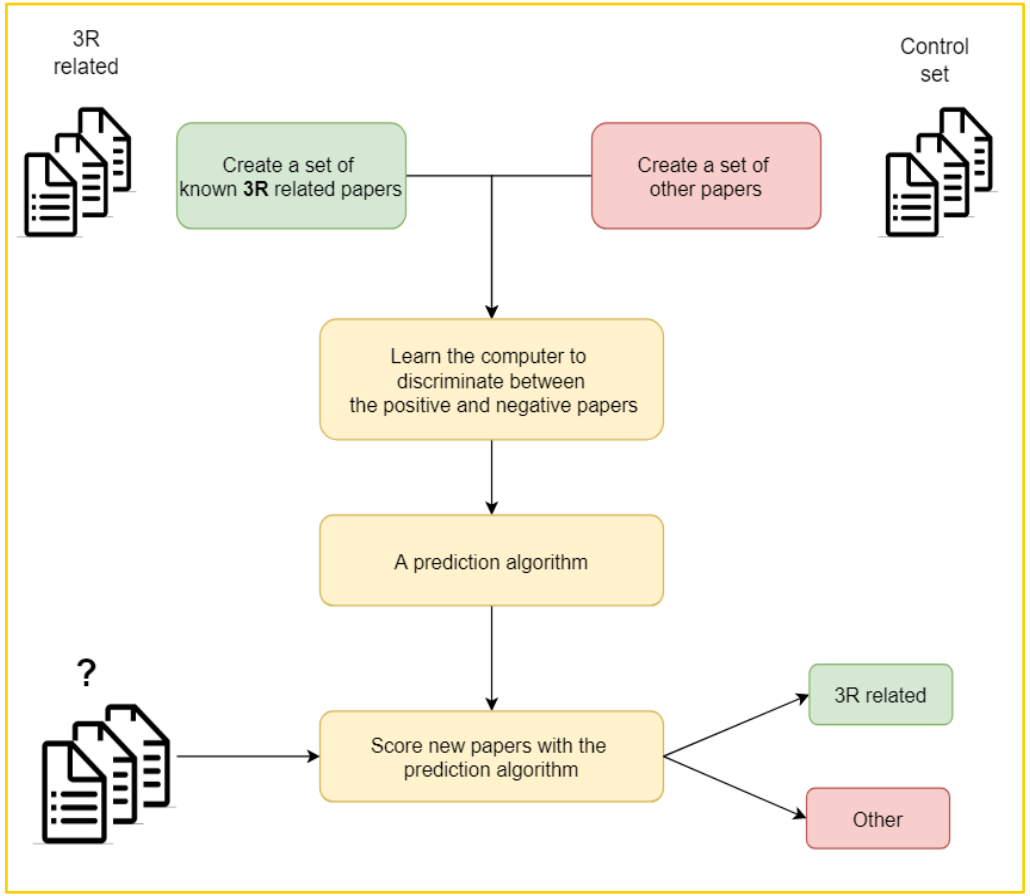


https://www.open3r.org/

What is the impact of performing preclinical systematic reviews (SR)?

Program 2012-2020 in NL

Utrecht University

Veterinary Medicine

ZonMw

SYRCLE

ZonMW MKMD grant scheme

Identify potential impact

1

Funding + Workshop

- Funding *(enablement)*
- Workshops *(education + training)*

2

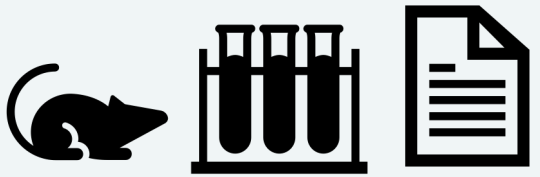
Coaching

- Coaching *(training + enablement)*

- Inventory
- Questionnaires
- Interviews

-Participants receive grant
-Participants follow the workshops

Participants perform Preclinical SRs



Impact on **research** ?

Impact on **researchers** ?

SR results: low publication quality

and low translation of animal studies to

humans is made transparant.

Need for change.

Changes coincide with resistance.

It needs perseverance and

managing transitions:

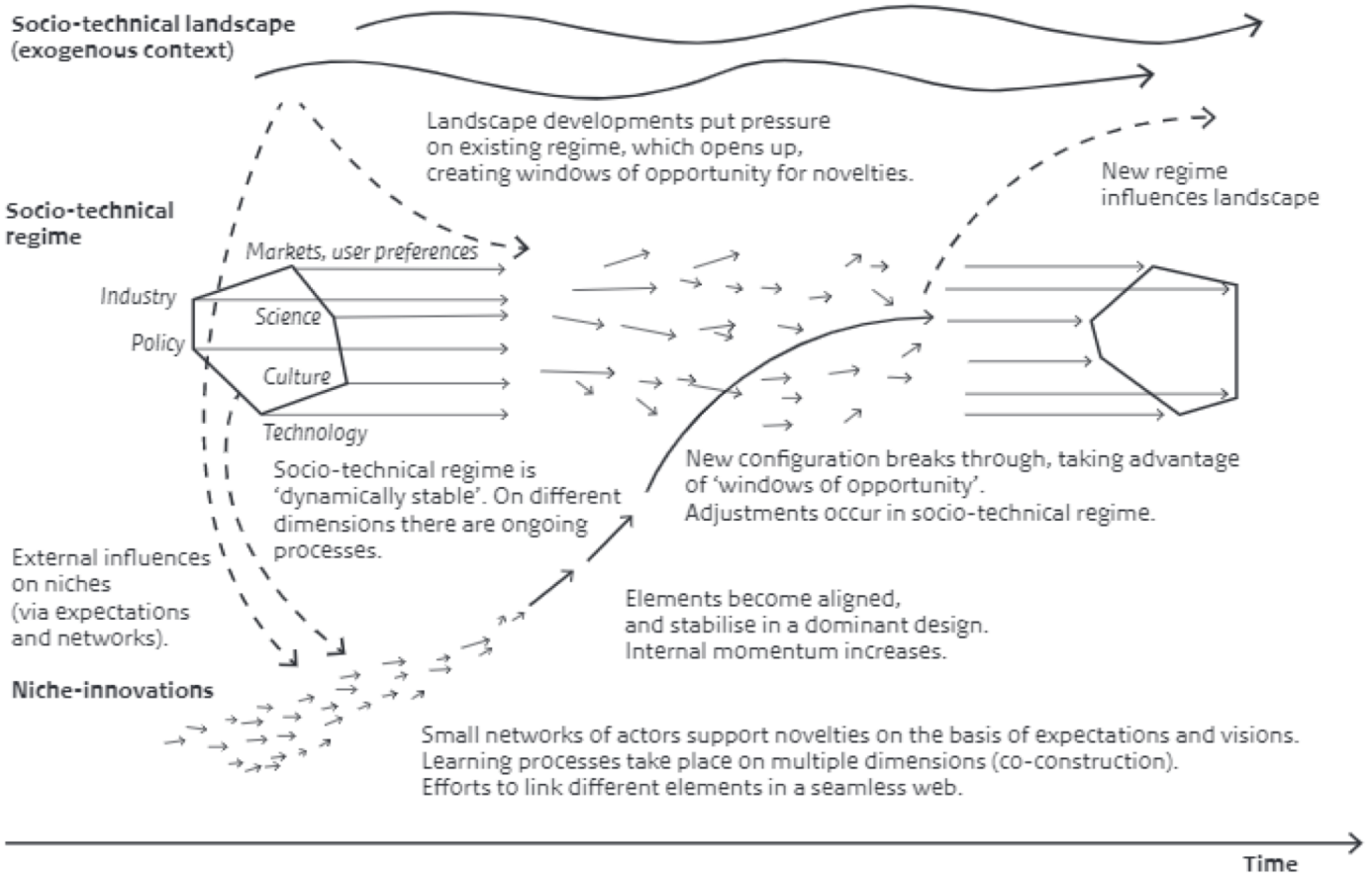
Transition science

Multi-level perspective transition analysis

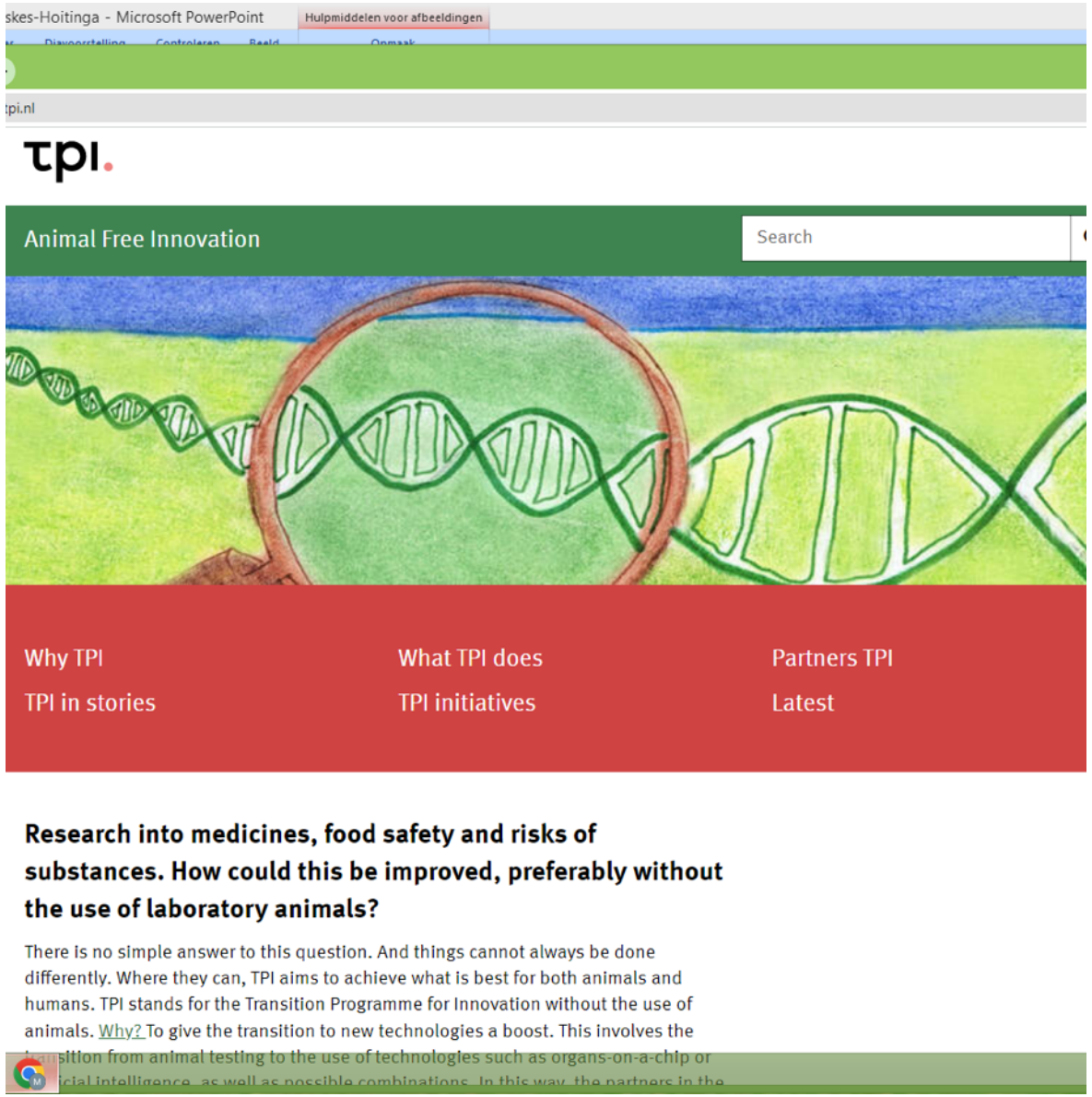
Identify:
Barriers, leverages and opportunities

Niche: Alternative system
Regime: Dominant system
Landscape: Societal trends

Goal:
Identify opportunities to accelerate the transition



Geels, F. W. (2011). The multi-level perspective on sustainability transitions: Responses to seven criticisms. Environmental innovation and societal transitions, 1(1), 24-40.



Transition science urgently needed

TPI Netherlands, Utrecht

https://www.animalfreeinnovationtpi.nl/

https://www.uu.nl/en/research/life-sciences/communities/tpi-utrecht

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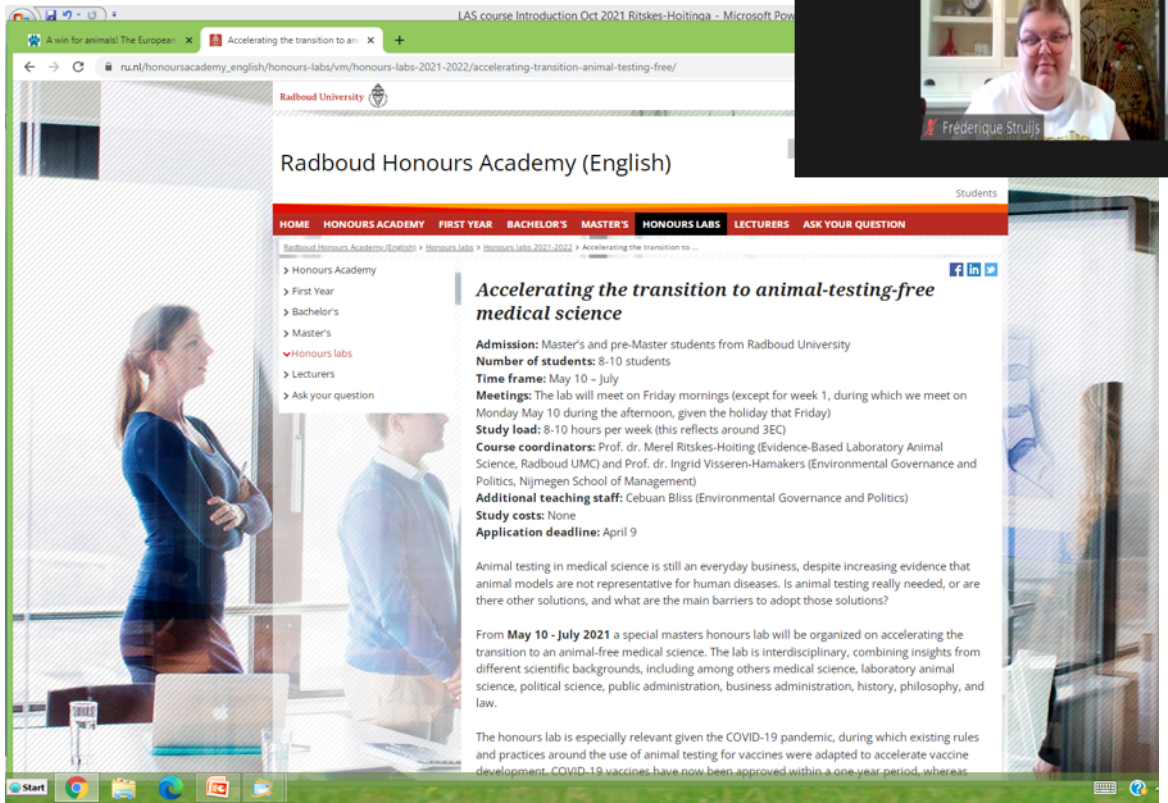
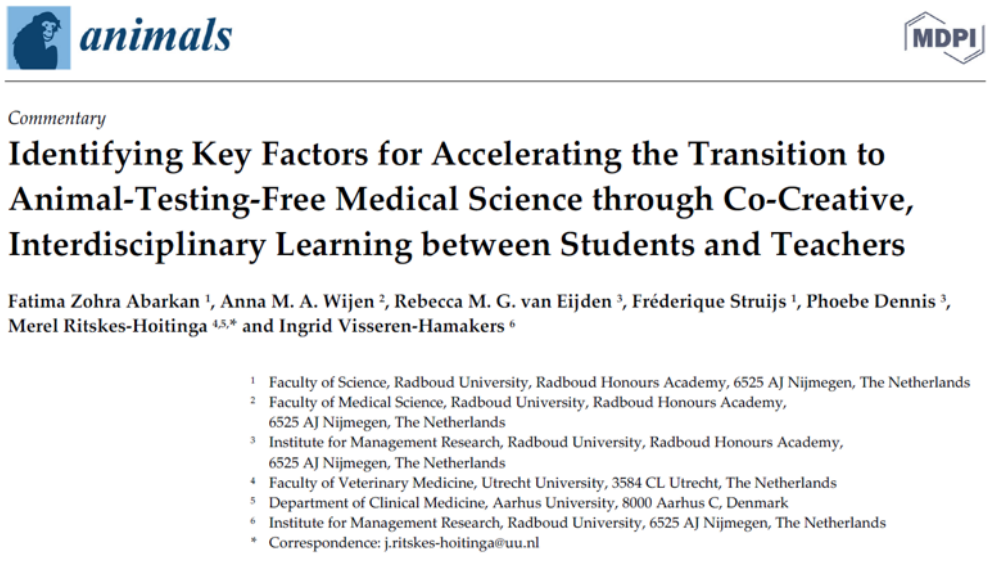
Multi-level perspective transition analysis





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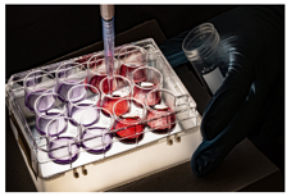
News › Three consortia awarded funding for acceptance and implementation of animal-free models in safety assessment

Three consortia awarded funding for acceptance and implementation of animal-free models in safety assessment

25 August 2022



Within the Dutch Research Agenda (NWA) 'Non-animal models: acceptance and implementation', three consortia will research on the acceptance and implementation of existing animal-free models. A total of about € 2.9mln has been awarded for this research. This programme is a collaboration between the Dutch Ministries of Infrastructure and Water Management (I&W), Public Health, Welfare and Sport (VWS), Economic Affairs and Climate (EZK), Agriculture, Nature and Food Quality (LNV), Defense (Def), ZonMw and NWO.

This programme focuses on the acceptance and implementation of existing animal-free models in the safety assessment of substances for humans with associated legislation and regulations. People are exposed to numerous chemical substances on a daily basis, such as those found in medicines and

Characteristics

Research programme
Animal-free assessment models: acceptance and implementation

Themes
Knowledge Utilisation
Health
Open Science
Key Technologies
Safety
Food

Type
Awards

Dossiers Podcasts Press and Media

25 August 2022

Funding for implementation and acceptance of animal test free research

Juliëtte Legler (Professor of Toxicology) and her team have received a NWO grant of approximately €1 million for the project "Animal testing for endocrine disruption - from science to regulatory acceptance". She is working with experts from the Faculty of Veterinary Medicine, Geosciences, REBO and the RIVM, as well as various stakeholders from industry, regulation and NGOs.

Endocrine disrupting chemicals (EDCs) are harmful to humans and animals. The European Commission has created legislation for the identification of EDCs, but

VHP4SAFETY
virtual human platform for safety assessment

Ingrid Visseren-Hamakers of Radboud University.

The funding is part of the programme 'Non-animal models: acceptance and implementation' of the Dutch Research Agenda (NWA). In total, three research consortia will receive this subsidy. The projects focus on the underlying causes of societal barriers, the acceptance of existing animal-free models by end-users and regulators, and the values of stakeholders and institutions on data from animal-free models. A budget of €955,000 has been set aside for each project.

Accelerating the transition to animal-free NGRA: A transformative governance approach

This research project was developed by Ingrid Visseren-Hamakers, Professor of Environmental Governance and Politics at Radboud University and Merel Ritskes-Hoitinga, Professor of Evidence-based transition to animal-free innovations at Utrecht University. It analyzes how the acceleration of the transition to animal-free safety assessment can be governed. The project focuses on Next Generation Risk Assessment (NGRA), and analyzes the transitions to animal-free safety assessment for chemicals and pharmaceuticals in the EU, the Netherlands, and the USA. The transdisciplinary consortium will experiment with transformative governance approaches through action research.

Consortium: Radboud University, Utrecht University, TNO, TenWise, Johns Hopkins University, The Good Lobby, Prof. dr. Howard White (consultant), Unilever, Eurogroup for Animals and PETA UK.

More information about the NWA programme and the other two programmes via: https://www.nwo.nl/en/news/three-consortia-awarded-funding-acceptance-and-implementation-animal-free-models-safety-assessment

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We need mixed methods research and flexible approaches: combining quantitative and qualitative research

We need inter- and transdisciplinary research

Providing scientific evidence is clearly not sufficient to make real changes

What about the COVID-19 crisis?

A personal take on science and society

World view

By Merel Ritskes-Hoitinga

Medical regulators: look beyond animal tests

Flexible approaches used to accelerate COVID-19 vaccines deserve wider uptake.

Scientists

Protection Agency are collaborating to test 40 chemicals using this next-generation risk-assessment approach, which should provide insight for regulatory policy.

Many current safety-testing requirements came about

27 April 2022 Nature World View
https://www.nature.com/articles/d41586-022-01110-6

History lessons

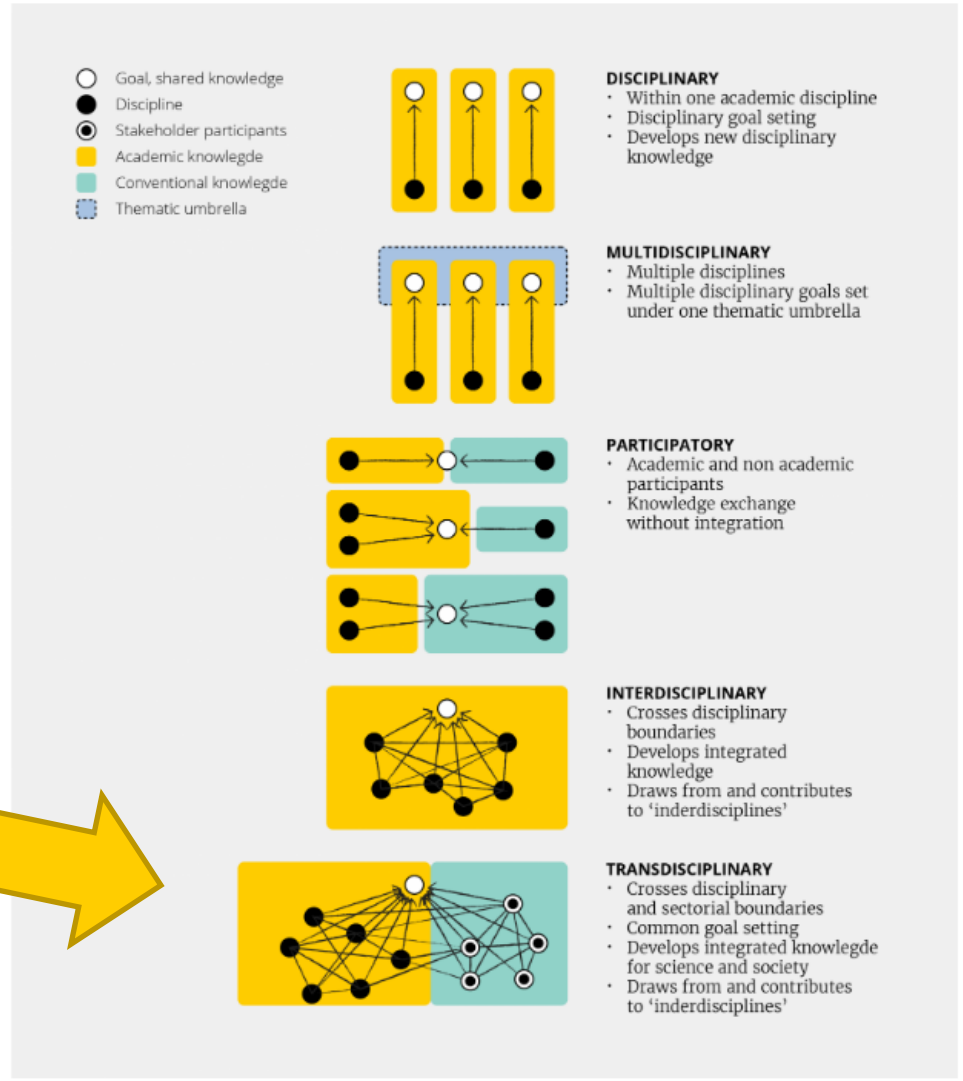
"Regulations should be critically examined and altered where necessary, so that they are no longer a barrier in the transition towards animal-free testing and more human relevant science."

ATLA. September 2022, Swaters D et al.

‘The mission of pathways to sustainability is to create a vibrant community fostering new research collaborations to explore pathways to sustainability, guided by the principle that ***scientific rigor meets societal relevance’***

disciplinary-field-guide/get-started/what-is-transdisciplinary-research

but goes beyond that to generate ‘socially-robust knowledge’ (Nowotny et al. 2003). This double accountability makes transdisciplinary research both exciting and challenging!



Schematic representation of transdisciplinary research. Adapted from Morton et al. (2015), originally from Tress et al. (2005).

Promising recent developments –

transition *is* happening

Goal Sanofi-Aventis: global commitment to 50% reduction in animal use 2020-2030

First clinical trial approved by FDA without asking for new animal tests and based on NAMs (existing drug for a new goal - repurposing)

Article Peta-OECD-JRC-EPA etc on building scientific confidence in NAMs – van der Zalm A et al. Archives Toxicology 2022

Citizen's intitiative and European Parliament asking for a roadmap

EU Parliament debate

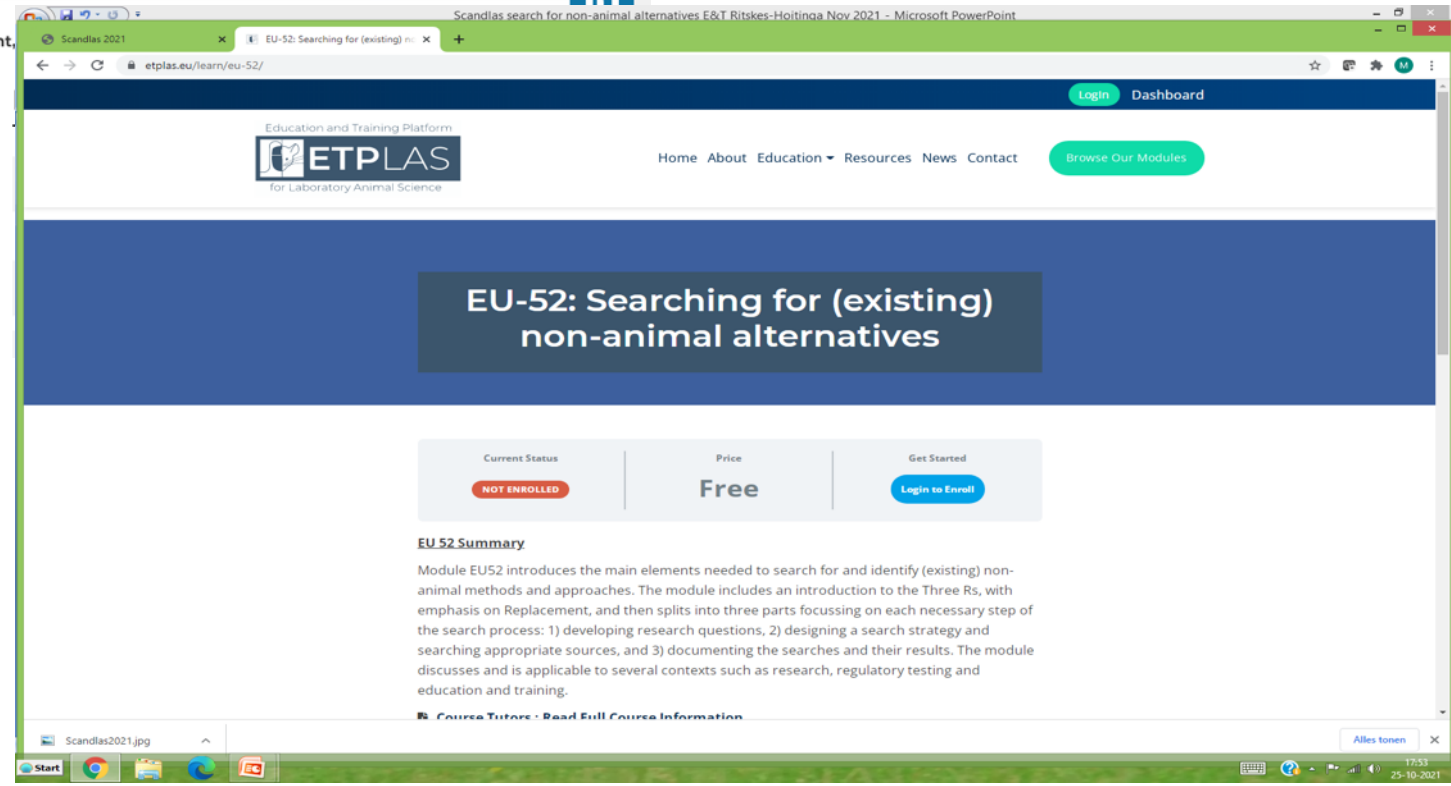
https://etplas.eu/learn/eu-52
https://etplas.eu/learn/eu-60

Home > News > **The Revision of EU Chemicals Legislation as a step towards human-relevant,**

24 OCT 2022

Experts on New (non-animal) approach methodologies (NAMs) informed the Intergroup on Animal Welfare that it is high time we moved away from using animals in laboratory testing.

Chaired by MEP Tilly Metz (the Greens/EFA, LU), the Intergroup heard from a variety of speakers, bringing innovative solutions for alternatives to animal testing. Elisabeth Berggren from the European Commission's Joint Research Centre provided a vision for what"Chemicals 2.0" could look like; with the proposal of a pragmatic, long term and robust chemical safety strategy, by categorising and testing substancesaccording to concern, with a "phase-out" period, to immediately reduce and ultimately replace animal testing, while maintaining full protection for human health and the environment.



https://www.animalwelfareintergroup.eu/news/revision-eu-chemicals-legislation-step-towards-human-relevant-new-approach-methods

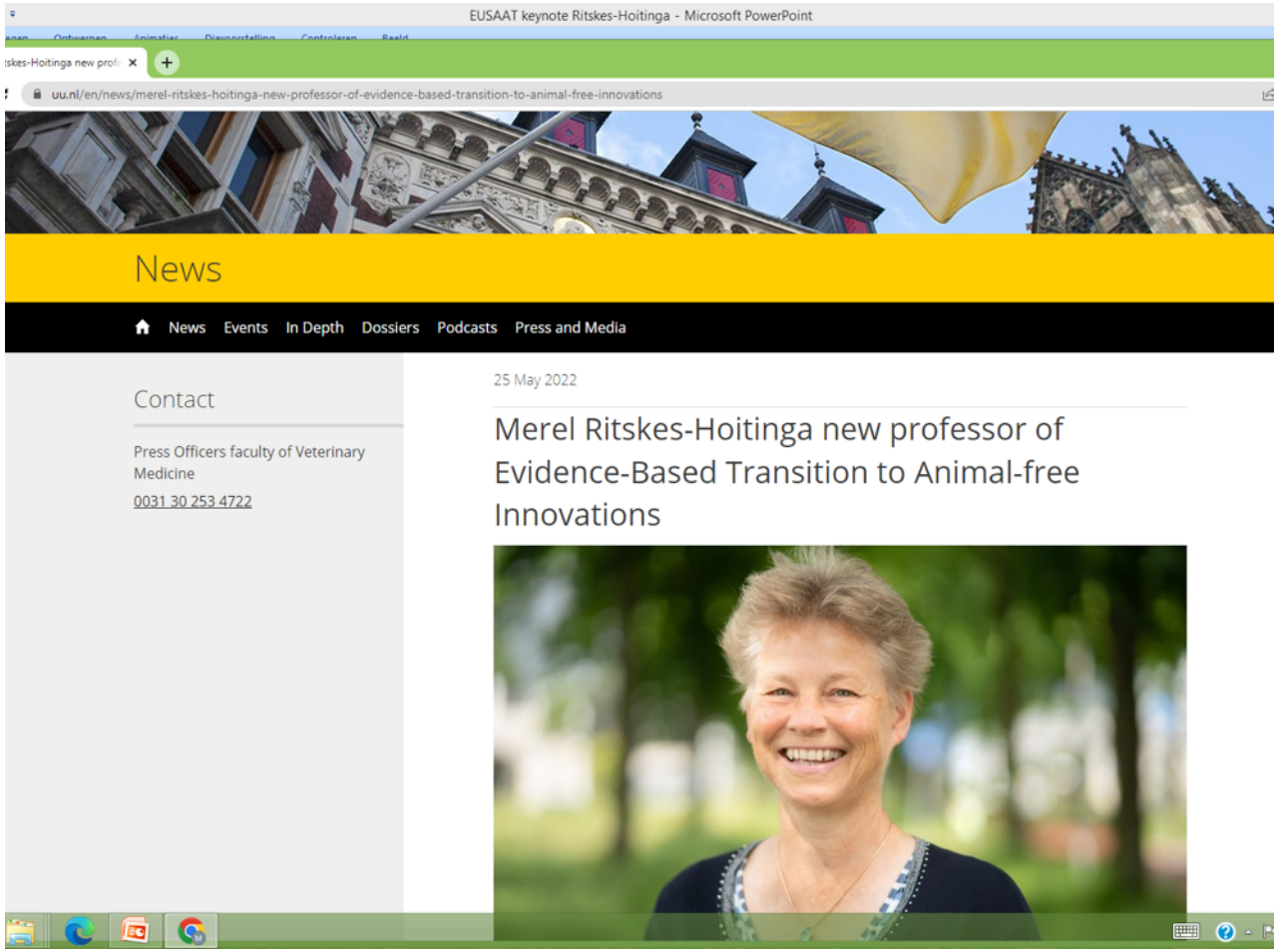
Let's make it happen!
Phase out animal studies and embrace alternatives asap for the benefit of animals and humans. The science and technology *are* here!

New (academic) pathways:

Evidence-based decision making

Transdisciplinary research and education – connect stakeholders

Multilevel perspectives, transition science and transformational governance



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