Directive 2010/63/EU

Progress, challenges and future directions

Copenhagen, Denmark
5-6 November 2018

Susanna Louhimies
DG Environment, European Commission

Progress, challenges and future directions

- *Review of the Directive*
- *State of play with the Three Rs*
- *Current and upcoming activities*
- *Conclusions*

Review of Directive

Article 58

"The Commission shall review this Directive ***by 10 November 2017,*** *taking into account advancements in the development of alternative methods not entailing the use of animals, in particular of non-human primates, and shall propose any amendments, where appropriate"*

- ***The progress towards Directive aims***
- ***The continued relevance of the Directive***

Timing of the Review

- *Last transposition in 2015*
- *EC conformity checks on-going*
- *Housing and care standards from 2017*
- *EU Implementation report (2019)*
- *First EU statistics (2019)*

➢ *MS, users and stakeholders will have had **limited experience** of the Directive*

Review Report

1. Harmonisation and level playing field

2. Animal welfare and uptake of the Three Rs

- **AW and application of *existing* alternatives**
- **Development and validation of *new* alternatives**

3. Transparency

Overall conclusions

- *Timing of the review premature*
- *Regulatory framework considered appropriate*
- *No significant gaps – remains fit for purpose*
- *Impact largely determined by*
  - **Previous national legislation**
  - **Progress in implementation**

Article 58 Directive Review

COM(2017) 631 final…

*"Areas identified by stakeholders as **needing further attention** and progress include the **efficiency and consistency of project evaluation and authorisation processes** as well as access to, and **quality** and **transparency** of **information** on the use of animals."*

Results - 1. Harmonisation

Positive:

- *Some progress especially in harmonisation of welfare standards*

Requiring further work:

- *Uniform understanding of terms and concepts*
- *Varied views and practices of PE/PA processes: need to improve efficiency and consistency*
- *Role of National Committee in consistency*
- *Obstacles remain for staff to move within EU*

Uniform understanding

- *"Procedure"*
- *"Project"*
- *"Multiple generic project"*
- *"Simplified procedure"*

➢ ***More experience & working together!***

Efficiency and consistency

- ***Complementary*** *elements safeguarding* ***animal welfare*** *and* ***good science***
- *Directive* ***requires no duplication*** *of processes*
- *Need to*
  - **use efficiently as designed**
  - **incorporate common sense**
  - **communicate**

Efficiency and consistency

- *Foundation, conditions*
- *Internal support*
- *Internal safety net*
- *Internal control*
- *External control*

If all parts function as designed, ***no need for duplication***

Free resources to ***focus on essential***

Results - 2. Animal Welfare and the 3Rs

Positive:

- *Raised animal welfare standards*
- *Animal Welfare Bodies already delivering*
- *Increased focus on Three Rs owing to PE and AWB*
- *Promotion of culture of care*
- *Recognition of the link between animal welfare and good science*

Requiring further work:

- *Consistency in project evaluation*
- *Access to and full application of the Three Rs*

Achieving an effective AWB

Obstacles may include

- *Insufficient resources*
- *Insufficient expertise*
- *Insufficient management support*
  - *Failing to take advice/enforce advice*
  - *Empowerment*
- ***Access to and awareness of Three Rs resources** and search tools*

Achieving an effective NC

Many still under development; obstacles may include

- *Composition, competencies and **expertise** in NCs*
- *Structures and working practices*
- *Engagement with AWB (how, what issues, when)*
- *Insufficient resources*
- ***Access to and awareness of Three Rs resources** and search tools*

Results – 3. Transparency

- *Timing of the review premature*

Positive:

- *Increase in transparency commented by user community and MSs – however, criticised by Animal Welfare NGOs*

Requiring further work:

- ***Access** to and **quality** of information on the use of animals*

Alignment of reporting

(43) COM, MSs and stakeholders should explore possibilities of **a central repository** of (or provide **easy, searchable access** to) all non-technical project summaries at EU level taking into account the legal requirements and linguistic limitations

EUROPEAN
COMMISSION

Brussels, 31.5.2018
COM(2018) 381 final

2018/0205 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on the alignment of reporting obligations in the field of environment policy and thereby amending Directives 86/278/EEC, 2002/49/EC, 2004/35/EC, 2007/2/EC, 2009/147/EC and 2010/63/EU, Regulations (EC) No 166/2006 and (EU) No 995/2010, and Council Regulations (EC) No 338/97 and (EC) No 2173/2005

Alignment of reporting

Issues with publication of NTS:

- *Varying*
  - **speed,**
  - **access and**
  - **search possibilities**
- *1/3 of NTS **not** updated with the results of Retrospective Assessment*
- *Administrative burden (collection/publication)*

Non-technical project summaries

Value already demonstrated if

- timely,
- accurate
- accessible and
- searchable

PLOS BIOLOGY

META-RESEARCH ARTICLE

Rethinking 3R strategies: Digging deeper into *AnimalTestInfo* promotes transparency in in vivo biomedical research

Bettina Bert[1], Antje Dörendahl[1], Nora Leich[1], Julia Vietze[1], Matthias Steinfath[1], Justyna Chmielewska[1], Andreas Hensel[1], Barbara Grune[1], Gilbert Schönfelder[1,2]*

1 German Federal Institute for Risk Assessment (BfR), German Centre for the Protection of Laboratory Animals (Bf3R), Berlin, Germany, **2** Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Institute of Clinical Pharmacology and Toxicology, Berlin, Germany

* Gilbert.Schoenfelder@bfr.bund.de

Check for updates

OPEN ACCESS

Citation: Bert B, Dörendahl A, Leich N, Vietze J, Steinfath M, Chmielewska J, et al. (2017) Rethinking 3R strategies: Digging deeper into *AnimalTestInfo* promotes transparency in in vivo biomedical research. PLoS Biol 15(12): e2003217. https://doi.org/10.1371/journal.pbio.2003217

Academic Editor: Malcolm Macleod, University of Edinburgh, United Kingdom of Great Britain and Northern Ireland

Received: June 7, 2017

Accepted: November 7, 2017

Published: December 14, 2017

Data Availability Statement: Relevant data are within the paper and its Supporting Information files. MS Excel-Files for allocation of ICD-10 codes

Abstract

In the European Union (EU), animal welfare is seen as a matter of great importance. However, with respect to animal experimentation, European citizens feel quite uninformed. The European Directive 2010/63/EU for the protection of laboratory animals aims for greater transparency and requires that a comprehensible, nontechnical summary (NTS) of each authorised research project involving animals is published by the respective Member State. However, the NTSs remain sleeping beauties if their contents are not easily and systematically accessible. The German web-based NTS database *AnimalTestInfo* is a unique channel for scientists to communicate their work, and provides the opportunity for large-scale analyses of planned animal studies to inform researchers and the public. For an in-depth meta-analysis, we classified the duly completed NTSs submitted to *AnimalTestInfo* in 2014 and 2015 according to the International Classification of Diseases and Related Health Problems (ICD) system. Indexing the NTSs with ICD codes provided a fine-grained overview of the prospective uses of experimental animals. Using this approach, transparency, especially for highly controversial animal research involving, for example, nonhuman primates, is fostered, as it enables pinpointing the envisaged beneficiary down to the level of the addressed disease. Moreover, research areas with many planned projects involving animals can be specified in detail. The development of 3R (replacement, reduction, and refinement) measures in these research areas may be most efficient, as a large number of experimental animals would benefit from it. Indexing NTSs with ICD codes can support governments and funding agencies in advancing target-oriented funding of 3R research. Data drawn from NTSs can provide a basis for the development, validation, and implementation of directed 3R strategies as well as guidance for rethinking the role of animal research models.

Alignment of reporting

Proposal addresses three elements on this Directive:

- Replaces 3-yearly **statistical** reports by **annual release of data** with **summary analysis**
- **Central EU database** for the publication of **non-technical project summaries**
- Replaces 5-yearly **implementation reports** by **summary analysis** and **access to MS reports**

Alignment of reporting

- *Centralise information storage for both NTS and results of Retrospective Assessments improving*
  - **availability and access (one-stop shop)**
  - **usefulness (search facility)**
  - **timeliness and relevance of information**
- *Considerable potential to improve uptake of the Three Rs in line with Directive objectives*

Directive Review: Staff Working Document

- *Detailed information of the reviewed areas*
- *An opportunity to bring real benefits to both animals and science:*
  - ***45 recommendations to move forward!***

Review Report COM/2017/0631 final:
http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1510219889073&uri=COM:2017:631:FIN

Staff Working Document SWD(2017) 353 final/2:
http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=SWD:2017:353:REV1&from=EN

Progress, challenges and future directions

- *Review of the Directive*
- *State of play with the Three Rs*
- *Current and upcoming activities*
- *Conclusions*

Three Rs in the Directive

- *Full **Replacement** is the ultimate goal*
- *Progress only by exhausting **all opportunities** to **Replace**, **Reduce** and **Refine***

➢ *Three Rs is **a legal obligation** in **all interaction** with animals, also when **not** in a project*

Applying the Three Rs

- *Project application by the user*
- *Project evaluation by the competent authority*

Survey on NTS

- *Survey on randomly selected 600 NTS from Germany (300) and UK (300) from 2013 and 2014 by Taylor, Rego and Weber*
  - **EU template**
  - **Objective review of adverse effects**
  - **Subjective review of potential benefits and the application of the Three Rs**

https://www.altex.org/index.php/altex/article/view/90/831

NTS survey: Replacement

These studies require the use of living animals due to the complexity of the cellular and tissue responses

We have to use animals in order to be able to study behaviour and cannot use humans because appropriate drugs and other relevant procedures are either not available or are ethically unacceptable. We shall use rodents, mainly mice, because such tasks are easy to implement and because the general details of brain structure and function are already well understood and are sufficiently similar to humans to allow extrapolation.

NTS survey: Replacement

Unfortunately, the extreme complexity and sophistication of the immune system cannot be featured by using in vitro system and the use of whole organism is required to generate and study the very many components (both cells and molecules) of the immune system and their role in the regulation of the immunity. In our laboratory, we are currently using human specimen (biopsies) from the local hospital to establish in vitro organ culture using human biopsies. However, the intrinsic ***difficulties in maintaining the intestinal tissue viable in culture for long time prevent us for using this approach*** *for a variety of experiments. Also, in vitro systems are being exploited. We are thus well set to seek all possible types of replacement for animal research.*

We are already studying HSP27-blockers in Primary Cell Culture (PCC). PCC is a technique which grows cancer cells directly from a human tumour; it better reflects the diversity of cancer cells within a tumour than cell lines. This should reliably predict the magnitude of the effect of HSP27-blockers in solid tumours. However ***no laboratory models are able to reproduce or predict the interaction between cancer cells and WBCs seen in real tumours****. It is therefore vital for us to use an animal model to establish the effects of HSP27-blockers on both chemotherapy response and the tumour-associated WBCs.*

Epilepsy models in vitro e.g. Brain slice cultures are already used extensively in our group and allow a significant reduction of the number of animals. Nevertheless, these are in vitro models for the inspection of epileptogenesis, as ***in slice cultures only part of the neural network is obtained****, and* ***the culture time is max. three weeks****.* ***To understand the epileptic development in humans, the disease must be replicated in living mice in vivo.***

NTS survey: Refinement

*Sheep are the only suitable species for such studies since they are the only species of seasonal mammal with a sequenced genome. The husbandry conditions at the **facility** where the animals are maintained are **outstanding**, and the **staff highly experienced**, thus **allowing us to minimise harm** to the animals during periods of housing in artificial photoperiods.*

*The mice are placed in a **specially protected environment** to reduce the risk of infection. The animals are **kept in stable groups** and **fed with nesting material**. The **trial model has been tested** and the veterinary **surgeons have experience with the system**, minimizing the duration of the procedure.*

*The **implantation of a catheter** in rats makes it possible to remove blood from the animals without repeatedly puncturing the veins of the animal. We also use **painkillers for venous catheterization** after surgery. Furthermore, the health of the animals is monitored daily. The total withdrawal rate of blood **will not exceed 10%** of the total blood volume within 24h, so that no impairments of the normal physiology of the animal are to be expected.*

Project evaluation

- *The aims and objectives of the project*
- ***Application of the Three Rs***
- *Severity classification of procedures*
- ***Harm-benefit analysis** of the project*
- *Determine the need for a retrospective assessment*

Efficiency and consistency
Project Evaluation

Justification for the animal models?

How were alternatives searched?

Experimental design? Reducing bias?

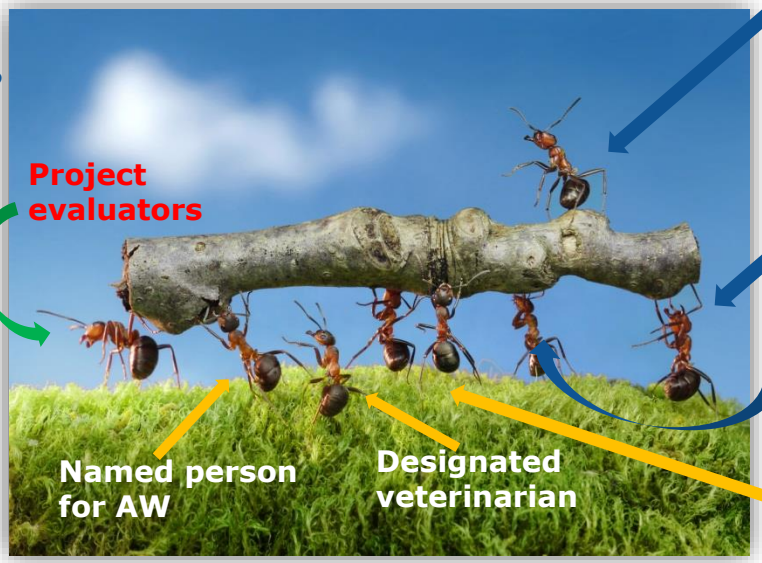
Origin of animals & training?

Refinement during procedures?

Use of humane end-points, observational strategy?

Access to study data?

Dissemination of results?



Named person responsible for establishment compliance

Named person responsible for project compliance

Named person responsible for staff competence

Competent staff

- ✓ Pain relief, anaesthesia
- ✓ Animal welfare and care respect legal requirements
- ✓ Competent staff, properly educated and trained
- ✓ Compliant housing, appropriate to the species

Applying the Three Rs

- ✓ *Three Rs considered during planning and project evaluation*
- ✓ *Project authorisation*
- ➢ ***During the project?***
- ➢ *After the project?*

Three Rs in the Directive

- *Full **Replacement** is the ultimate goal*
- *Progress only by exhausting **all opportunities** to **Replace**, **Reduce** and **Refine***

➢ *Three Rs is **a legal obligation** in **all interaction** with animals, also **during the lifetime** of the project*

Legal responsibility

- *Project **authorisation holder** in Article 40(2)(b)*
- *Person **responsible for the compliance** in an **establishment** in Article 20(2)*
- *AWB required to keep the staff informed on **technical and scientific developments** in the application of **the Three Rs***

➢ ***Better models, improved predictivity, better science!***

"Three Rs not applicable in our work"

"We have been in business for 24 years and always complied"

"We already work to the highest standards"

"We have already Replaced, Reduced and Refined"

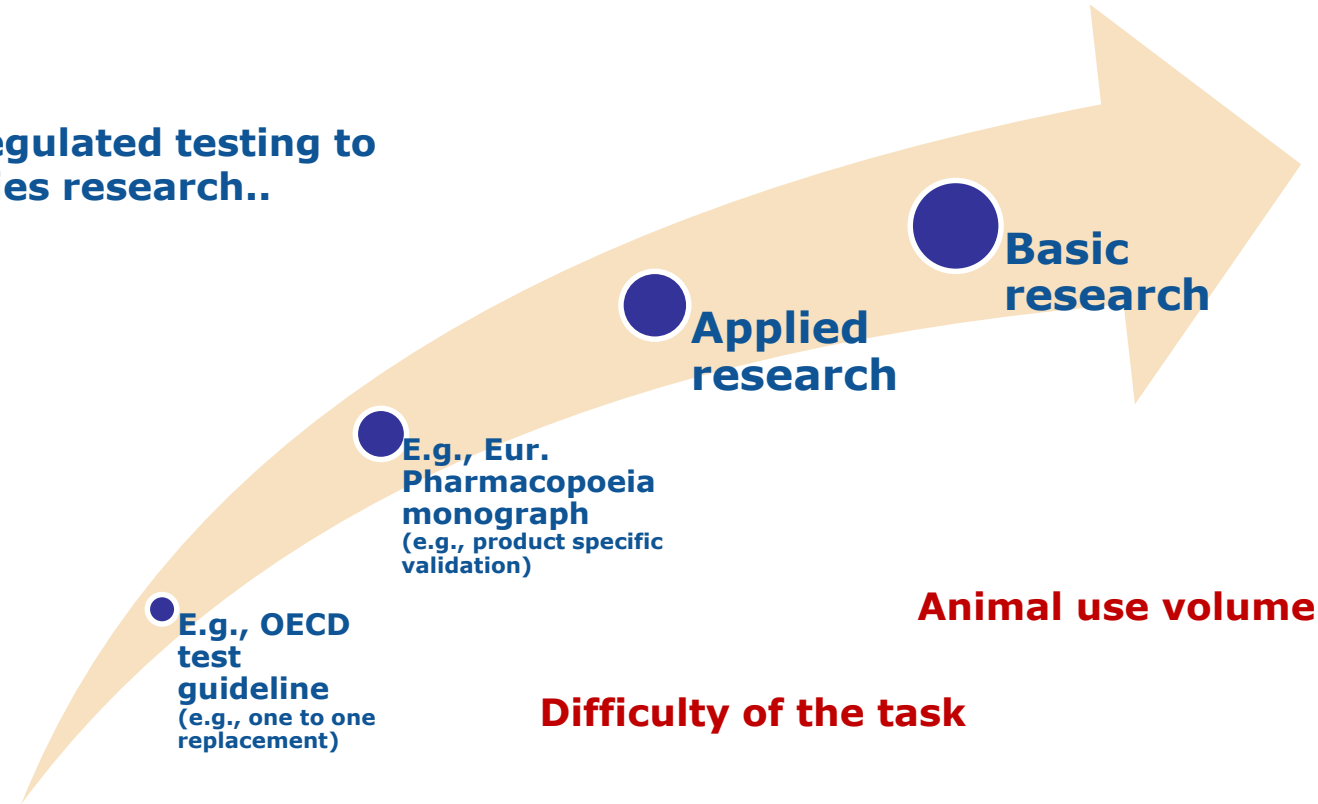
Finding the Three Rs

- *Scientists*
- *Animal technicians and care takers*
- *Competent authorities*
- *Inspectors*

➢ *All need Three Rs information – from where and how?*

Finding the Three Rs

From regulated testing to blue skies research..



Project authorisation

- *Up till **5 year-authorisation***
- *Possibly under **multiple generic projects***
- *Regulatory use:*
  - **often for multiple tests for multiple endpoints to satisfy regulatory data requirements**
  - **enforcement by different authorities (e.g., chemicals, pharma, food safety)**

Finding the Three Rs

- *E&T including lifelong learning (CPD)*
- *Support functions within establishments:*
  - *Designated Veterinarian*
  - *Named persons for animal welfare and information*
  - *Animal Welfare Bodies*
- *Support function at national level*
  - *National Committee / 3Rs centres*
- *Stakeholder organisations*

Finding the Three Rs

- *EU agencies such as ECHA, EMA, EFSA etc.*
- *Sectoral national authorities*
- *Industry associations, expert associations*
- *Other initiatives, platforms, events e.g., EPAA, EUROTox*
- *Specialised journals, scientific events*
- *Scientific communities*

10 November 2016
EMA/CHMP/CVMP/JEG-3Rs/742
Committee for Medicinal Produ

Reflection paper
regulatory testin
human use and
3R
Dra

21 April 2016
EMA/CHMP/CVMP/JEG
Committee for Medicin

Reflection paper pro
regulatory testing re
products and opport
Draft

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
Limulus polyphemus or *Tachypleus tridentatus)*		administration.	Amoebocyte Lysate obtained from blood cells (amoebocytes) of horseshoe crabs (*Limulus polyphemus*, *Tachypleus tridentatus*). As	
Abnormal Toxi Test (ATT) (Mi				
Physiological distribution (Usually rats o mice)				

Reflection paper o
opportunities for i
EMA/CHMP/CVMP/

Topic	Regulatory provision	Animal testing requirements	Implemented 3R opportunities	Newly identified opportunities for 3R implementation
	veterinary drugs in human food: general approach to testing (EMEA/CVMP/VICH/486/02-Rev.2)			
Neurotoxicity	Annex V of Regulation 2377/90 Volume 8 of The rules governing medicinal products in the EU VICH Topic GL33 on studies to evaluate the safety of residues of veterinary drugs in human food: general approach to testing (EMEA/CVMP/VICH/486/02-Rev.2)	Required for certain groups of substances known to be associated with neurotoxicity as well as for other substances which have shown relevant toxicological effects in other toxicity tests. Possible tests to consider include a neurotoxicity test in rodents (OECD test guideline 424), developmental neurotoxicity testing (usually in rats) (OECD test guideline 426), delayed neurotoxicity of organophosphorus substances following acute exposure in hens (OECD test guideline 418) or repeated exposure (OECD test guideline 419).	Not routinely required.	Acceptance of the extended one generation reproductive toxicity test would allow integration of developmental neurotoxicity testing, where appropriate, into reproductive toxicity testing.
Testing for effect on the human intestinal flora	Annex V of Regulation 2377/90 Volume 8 of The rules governing medicinal products in the EU VICH Topic GL36(R) on studies to	The VICH guideline recommends possible in vitro and in vivo approaches.	Only required for compounds with antibacterial properties. In vitro approaches are already identified in the guideline.	In vitro approaches are already identified in the guideline.

European Commission

RIVM 3R's Quarterly informs you on news and developments of 3R methods and innovations for risk assessment of chemical substances and food, and for safety and efficacy assessment of medicines.

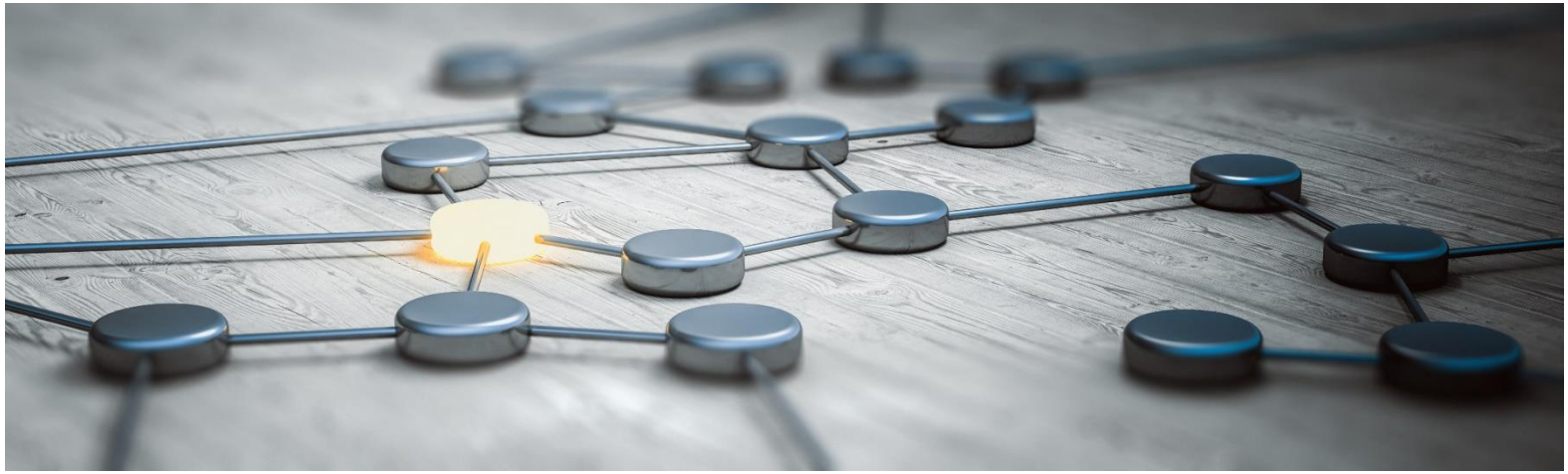
https://www.rivm.nl/en/Topics/R/Replacement_reduction_refinement_of_animal_use/Replacement_reduction_refinement_of_animal_use_webpage

Three Rs Centres

- *Increasing number of centres*
- *Remits and tasks vary covering, inter alia,*
  - Co-ordination, communication
  - Education
  - Funding
  - Active development of Three Rs tools
- *Resources vary significantly*

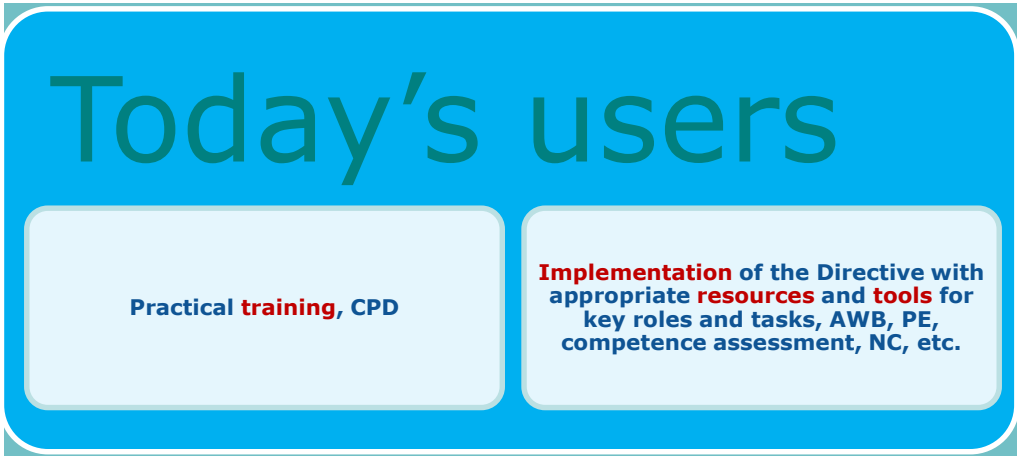
Strategic specialisation

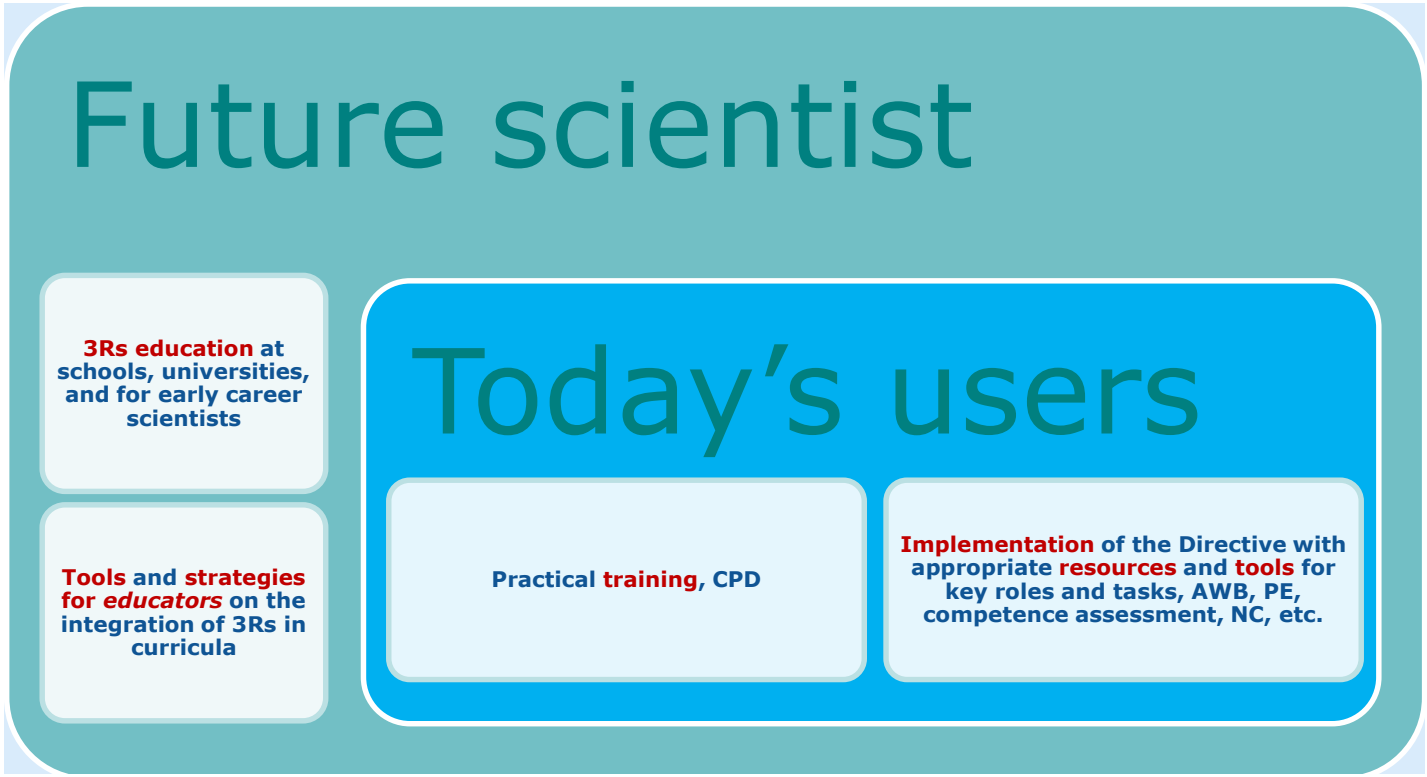
- Multiply resources
- Clear focus with efficient use of limited resources
- Consistency of advice
- Significantly wider outreach



Progress, challenges and future directions

- *Review of the Directive*
- *State of play with the Three Rs*
- *Current and upcoming activities*
- *Conclusions*


Today's users
Practical training, CPD
Implementation of the Directive with appropriate resources and tools for key roles and tasks, AWB, PE, competence assessment, NC, etc.


Future scientist
3Rs education at schools, universities, and for early career scientists
Tools and strategies for educators on the integration of 3Rs in curricula
Today's users
Practical training, CPD
Implementation of the Directive with appropriate resources and tools for key roles and tasks, AWB, PE, competence assessment, NC, etc.

Support networks and tools

- **3Rs information sources**, networks, dissemination platforms
- Central platform for LAS E&T **ETPLAS**
- **Multi-disciplinary approach** to cross-fertilise research tools
- **R&D** on modern non-animal research tools
- **Regulatory application**, incl. validation and acceptance
- Tools for **measuring progress**

Future scientist

- **3Rs education** at schools, universities, and for early career scientists
- **Tools** and **strategies for educators** on the integration of 3Rs in curricula

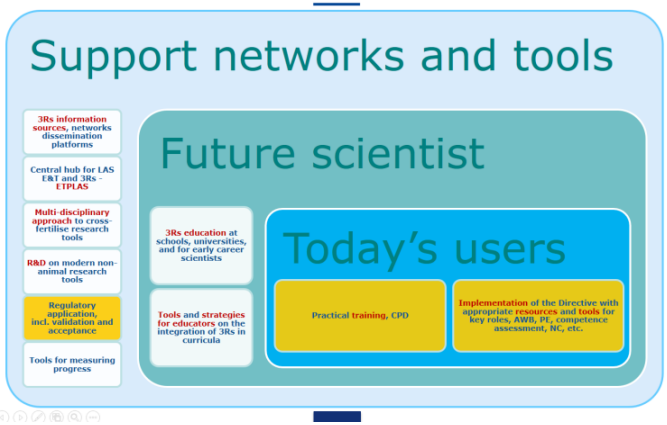
Today's users

- Practical **training**, CPD
- **Implementation** of the Directive with appropriate **resources** and **tools** for key roles and tasks, AWB, PE, competence assessment, NC, etc.

1M EP Pilot on alternatives

- *Development of **open access, eLearning training modules***
- *Facilitate the process of mutual recognition of, and access to quality education and training through the Education and Training Platform for Laboratory Animal Science, **ETPLAS***
- *Create practical **teaching resources** on the Three Rs as a follow-up to JRC Report 'Accelerating progress in the Replacement, Reduction and Refinement of animal testing through better knowledge sharing'.*

EP Pilot on alternatives

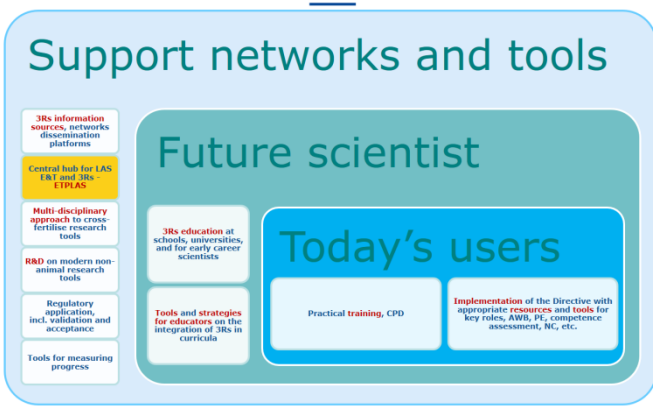


1. *Development of open access, interactive training modules*

   - Call 1: **"Searching for non-animal alternatives**" and "**Developing alternatives for regulatory application**" in close collaboration with EURL ECVAM - *focus on non-animal alternatives*

   - Call 2: on the implementation of the Directive including on "**Severity Assessment Framework**", "**Project evaluation**" and "**Design of procedures and projects**" - *focus on all Three Rs and the implementation of the Dir*

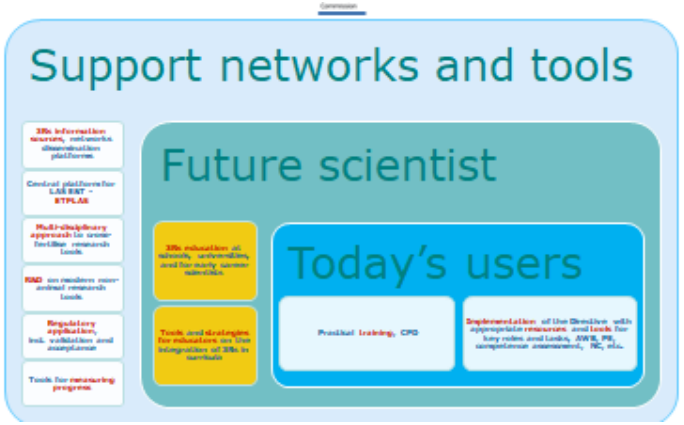
EP Pilot on alternatives



2. Support ETPLAS to promote consistency and harmonisation in approach to LAS E&T

- **Assessment of Learning Outcomes**
- **Competence Assessment**
- **Further development of central database learning resources**
- **Quality assurance**

EP Pilot – EURL ECVAM



3. Support the development of Three Rs E&T strategy with guidance and practical training resources

- *Development of Three Rs guidance for **education decision makers***
- *Practical teaching resources tailor-made to support learning for **high school**, **university** and **early-career scientists***

Support networks and tools

- 3Rs information sources, networks dissemination platforms
- Central platform for LAS E&T - ETPLAS
- Multi-disciplinary approach to cross-fertilise research tools
- R&D on modern non-animal research tools
- Regulatory application, incl. validation and acceptance
- Tools for measuring progress

Future scientist

- 3Rs education at schools, universities, and for early career scientists
- Tools and strategies for educators on the integration of 3Rs in curricula

Today's users

- Practical training, CPD
- Implementation of the Directive with appropriate resources and tools for key roles and tasks, AWB, PE, competence assessment, NC, etc.

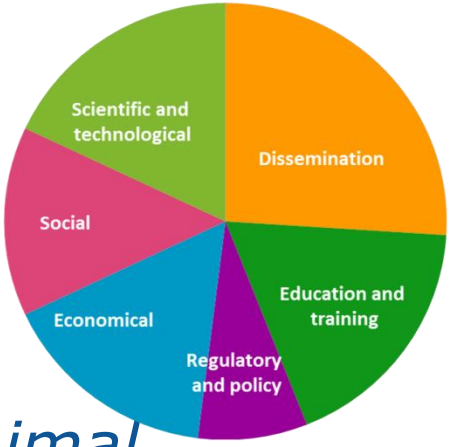
Review of Three Rs E&T resources

- *Overview of existing E&T opportunities worldwide in the area of Three Rs*
- *Review combining targeted search and survey (June- July 2018)*

➢ *Snapshot view as inventory tool to help identify opportunities for targeted initiatives in 3Rs E&T*

- *On-going study until end 2018 (EURL ECVAM)*

Feasibility study on Three Rs indicators



Measuring *and* ***monitoring*** *the level of* ***development*** *and* ***uptake*** *of non-animal methods in all areas of animal use*

- *Highlight trends*
- *Drive new opportunities for research and future funding*
- *Inform and support policies*

- *On-going study until end 2018 (EURL ECVAM)*

Review of Non-animal methods in Biomedical Research

On-going study till mid 2019

Neurodegenerative diseases

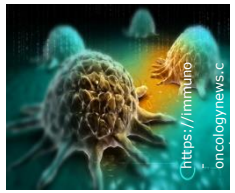
Respiratory tract diseases

Breast cancer

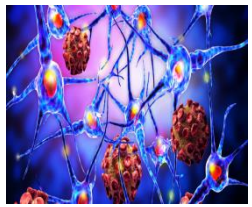
Immunogenicity testing for advanced therapy medicinal products

Cardiovascular diseases

Five new areas: just launched



Immune Oncology Models



Autoimmune diseases

EURL ECVAM

BridgE Across Methods in bioSciences (BEAMS)

EURL ECVAM initiative to support greater connectivity between biosciences

- *Emerging of new technologies, methods and techniques with high levels of specialisation and expertise*
- *Demand for greater knowledge sharing, co-operation and interdisciplinary*

Workshop in June 2018 with representatives of key organisations in biosciencies

EU Report on the Implementation of the Dir

- *MS reports on implementation due 10 Nov 2018*
  - **Annex I to Commission Implementing Decision 2012/707/EU**
- *EU implementation report due by* ***10 Nov 2019***

Statistical report on the use of animals in EU

- *Statistical data requirements in*

  Annex II to Commission Implementing Decision 2012/707/EU

- *Annual publication by Member States since 2015*
- *First EU report due by **10 Nov 2019***

Conclusions

- *Call for all stakeholders to take up Directive Review recommendations*
- *Several on-going and new initiatives at EU level with specific focus on E&T and non-animal alternatives in biomedical research*
- *EU Implementation and statistical reports both due next year*

Conclusions

The Three Rs !

Thank you for your attention!

More information at:

http://ec.europa.eu/animals-in-science