National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

Applying the 3Rs in Toxicology and Regulatory Sciences

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MEB Science Day, 13 February 2020
Jaarbeurs Auditorium, Utrecht

Pioneering Better Science

Today's presentation

- Introduction to the NC3Rs
- NC3Rs toxicology programme and honest-broker role
- Case-studies
  - Acute toxicity studies
  - Reviewing the use of two species
- NC3Rs resources

Focus on better science - The NC3Rs

- Independent, scientific organisation.
- Established by UK Government in 2004.

NC3Rs 15th birthday celebrations, October 2019

Role of the NC3Rs

- Use the 3Rs as a framework to support science, innovation and animal welfare.
- Work across the bioscience sector, with research funders, industry, regulators and academia.
- Budget of ~ €12 million per annum.

EPSRC Pioneering research and skills

wellcome trust

BBSRC bioscience for the future

MRC Medical Research Council

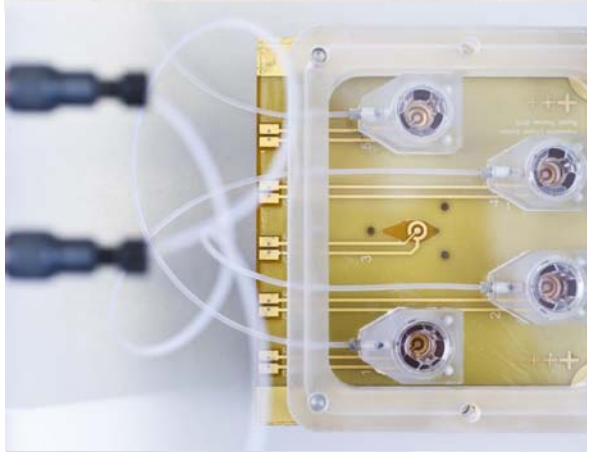
abpi Bringing medicines to life

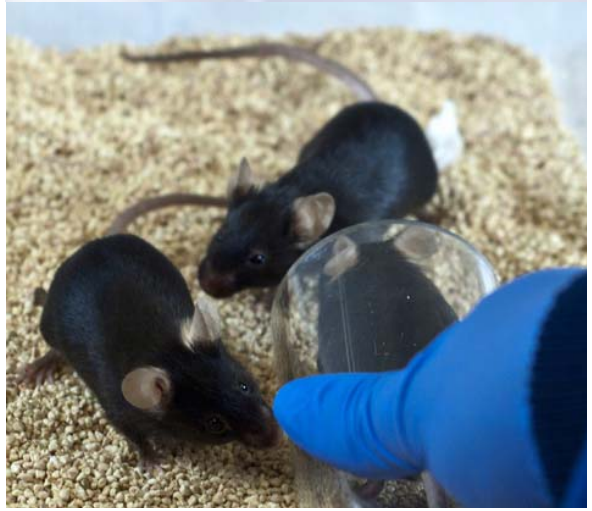
NC 3Rs

Our mission - toxicology

To discover, develop and promote new ways of replacing, reducing and refining the use of animals in research.

To work towards decreased reliance on animal toxicity tests in conjunction with improvements in the science and predictivity of safety assessment.





Our Toxicology Programme

Influencing best practice and regulations globally

NC 3Rs

- Large programme in toxicology and regulatory sciences, covering human and environmental health, across all sectors.
- Emphasis on changing policy, practice and regulations.
- Data sharing and role as honest broker is key to build an evidence-base for change.
- Fostering cross-company and cross-sector collaborations and providing an open forum for discussion.
- Over 50 peer-reviewed publications.
- Events, working groups, workshops and symposia.

OECD

ICH harmonisation for better health

Our approach

Working together to build an evidence-base for change

Identify the problem (3Rs need).

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Convene an expert working group.

NC 3Rs

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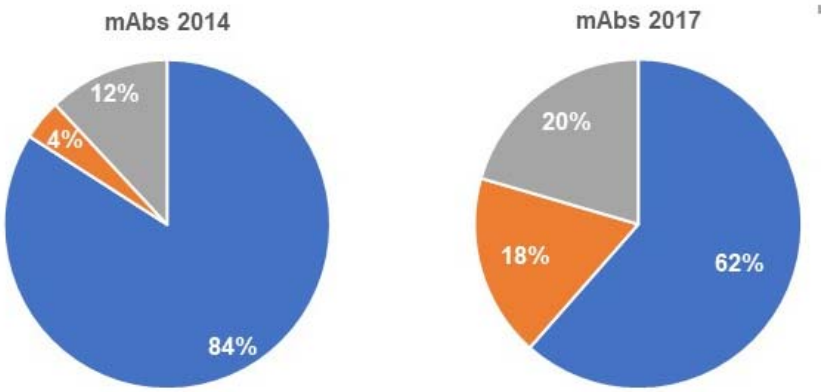
Identify the problem (3Rs need).

Convene an expert working group.

Collaborate and devise questionnaires to collect data and form an evidence-base.
Share, anonymise and analyse data.



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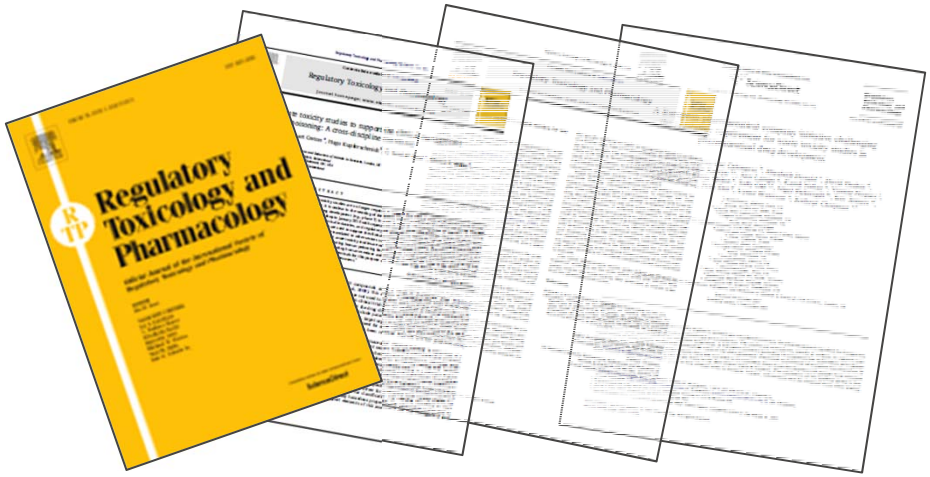
Working together to build an evidence-base for change

Identify the problem (3Rs need).

Convene an expert working group.

Collaborate and devise questionnaires to collect data and form an evidence-base.

Input from scientists, regulators and the NC3Rs to build recommendations.



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⇩

Convene an expert working group.

⇩

Collaborate and devise questionnaires to collect data and form an evidence-base.

⇩

Input from scientists, regulators and the NC3Rs to build recommendations.

⇩

Dissemination and feed into regulatory guidance/practice where appropriate.

NC 3Rs

2019 SOT BALTIMORE

bts THE BRITISH TOXICOLOGY SOCIETY

ICH harmonisation for better health

Acute toxicity studies

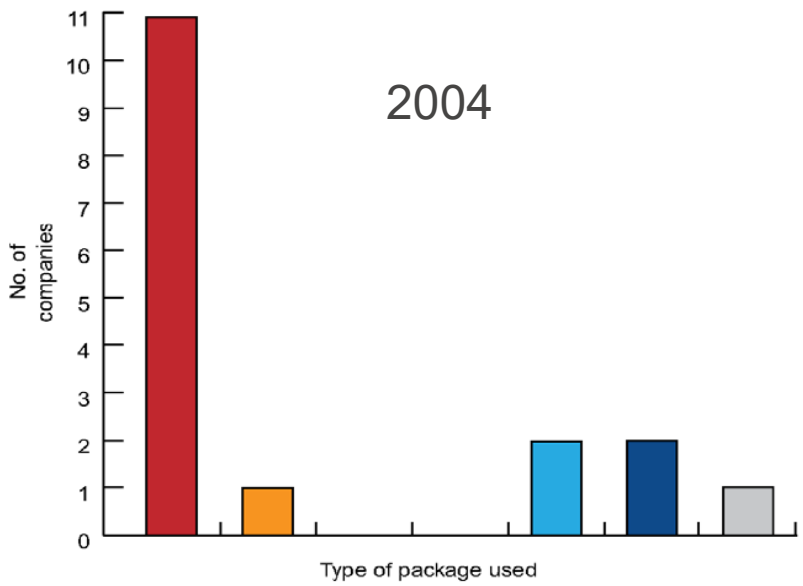
Removal of the requirement for single dose acute toxicity tests in ICH M3

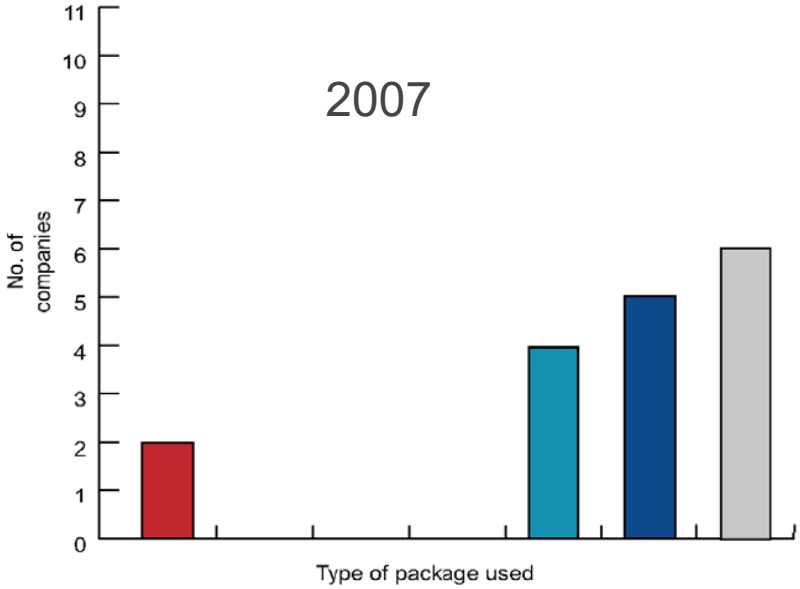
Single dose acute oral toxicity studies for pharmaceuticals

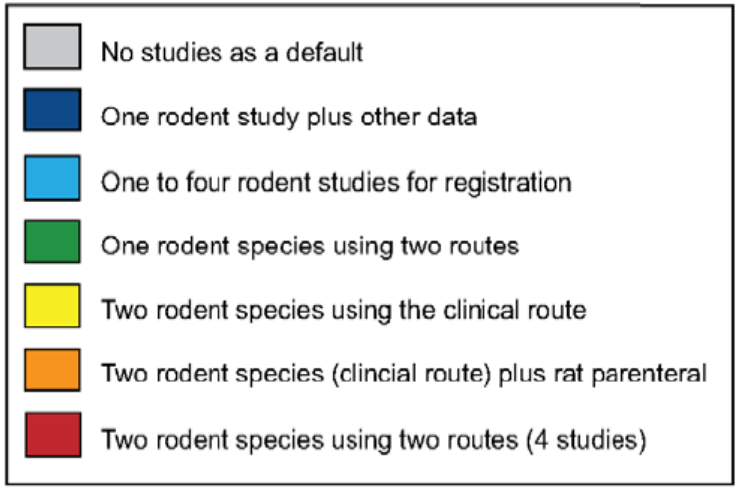
- Used to identify a single acute dose causing lethality or severe toxicity.
- Requirement for two species, two routes.
- Claimed scientific drivers:
  - Identify target organ toxicity.
  - Inform dose setting.
  - Manage effects of overdose.
- But this information was already gained from other studies routinely carried out.

The power of data sharing

Shared data from 17 companies, 70 compounds



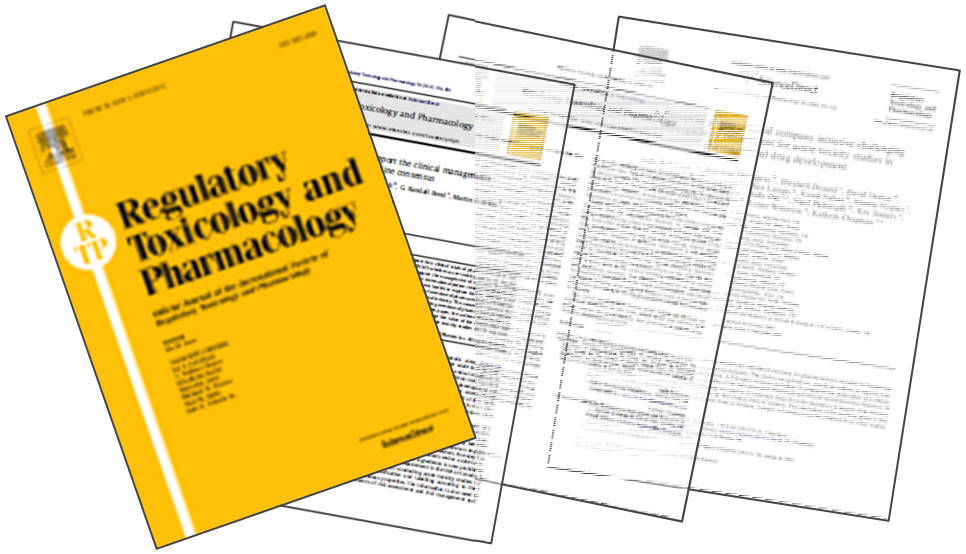




NC 3Rs

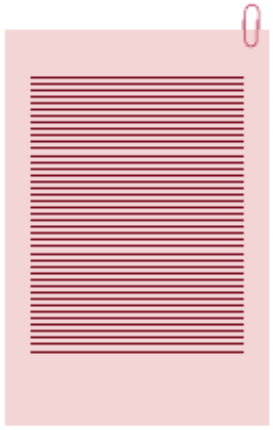
NYCOMED AstraZeneca Boehringer Ingelheim COVANCE SOLUTIONS MADE REAL gsk NOVARTIS Johnson&Johnson charles river BAYER Pfizer Lilly MDS Huntingdon Life Sciences Pharma Services Roche SERVIER aptuit sanofi aventis L'essentiel c'est la santé.

Removal of requirement for acute toxicity studies



Removed from ICH M3 in 2009

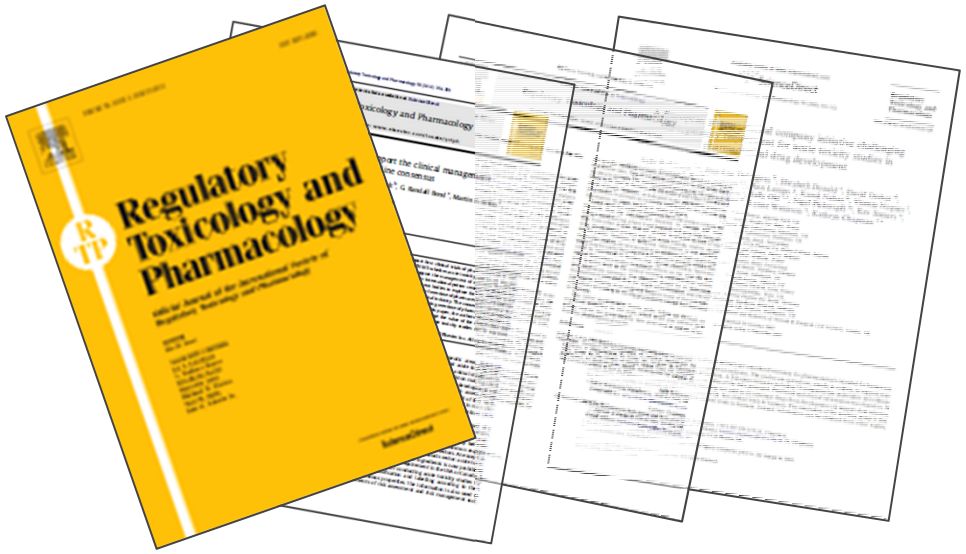
Proportion of clinical trial applications for drugs going into man for the first time in the UK which contain the results from single dose acute toxicity studies.



2007

86%

Removal of requirement for acute toxicity studies



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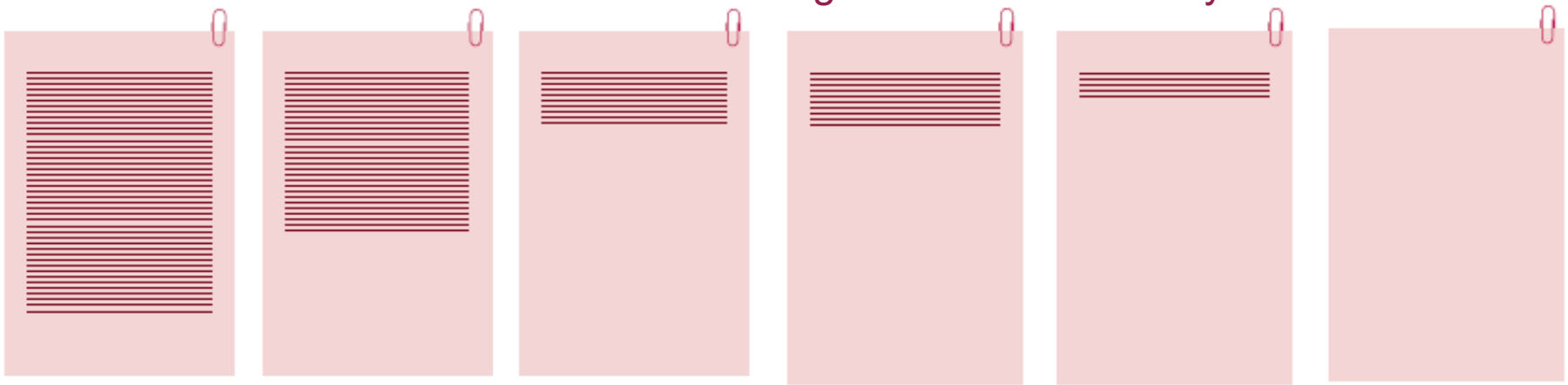


2007	2011	2012	2013	2014	2019 (Aug)
86%	58%	19%	16%	8%	0%

Two species project

Reviewing the use of two species in regulatory toxicology studies

NC 3Rs

Do we still need two species for toxicology studies?

- Often rodent and non-rodent studies conducted at all phases of development.
- Opportunities exist to use a single species in later phases *if toxicities are similar* in short-term studies e.g. biologics ICHS6(R1).
- But are these opportunities being taken? Could this also apply to other modalities?
- When would data from a single species be sufficient for safe progression in humans?
- Addressed by a working group of 42 representatives from 37 organisations.

abpi
Bringing medicines to life

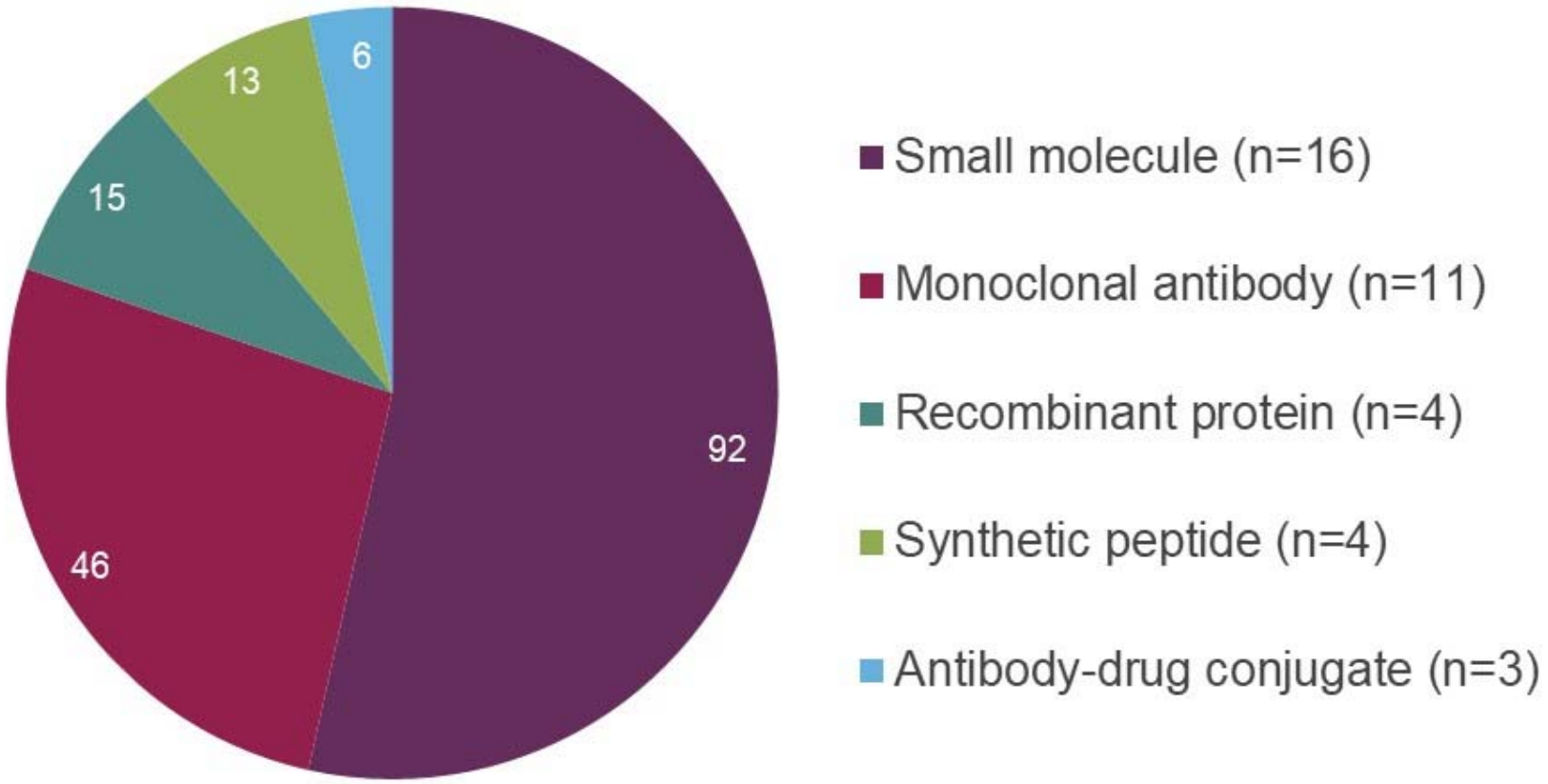
Survey design and data collection

Questions based around species used, studies conducted and impact/value of data for decision making from each species.

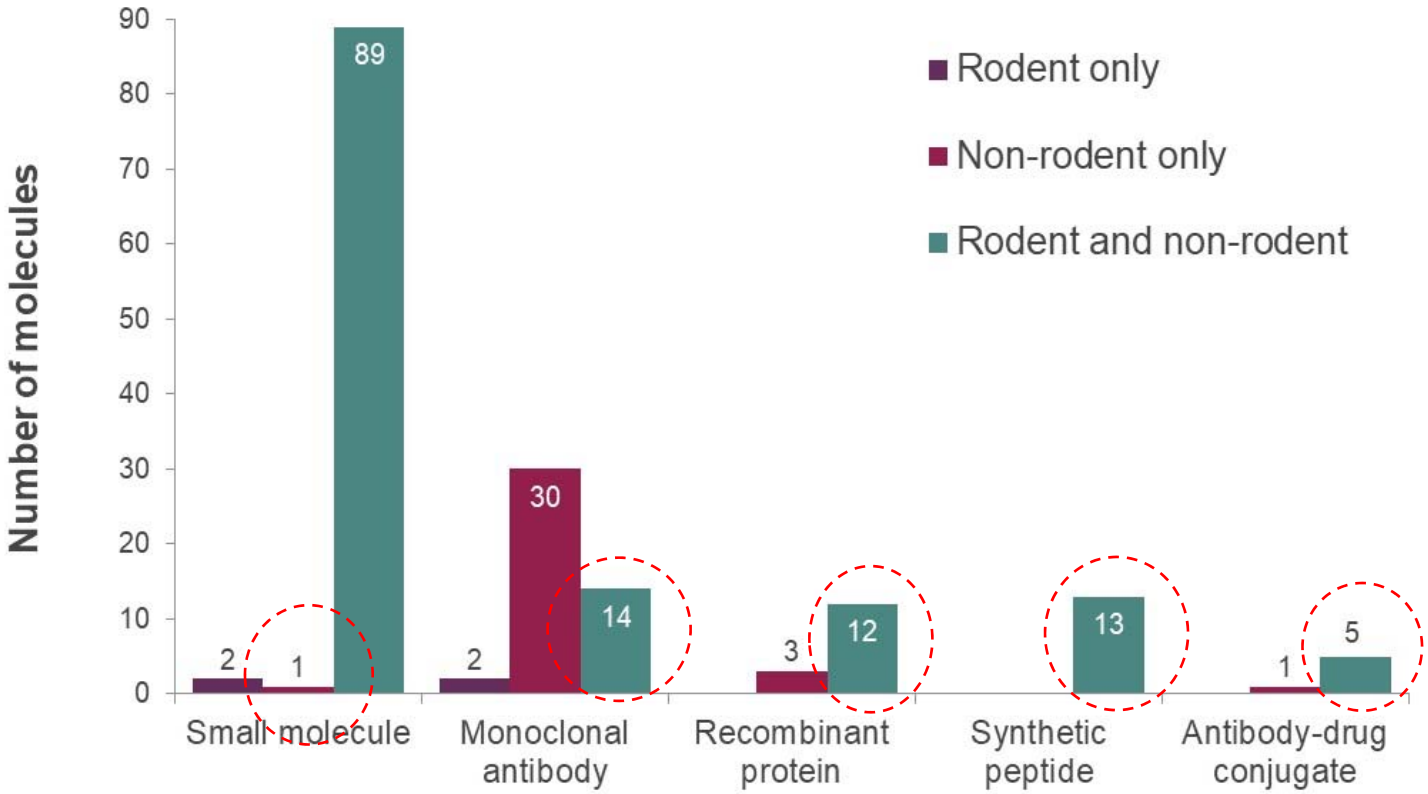
General Information	Species used	Studies conducted
▪ Molecule type ▪ Therapy area ▪ Phase progressed to ▪ Active or stopped ▪ Regulations followed	▪ Rodent and non-rodent species ▪ Justification for species choice	▪ Study type and GLP status ▪ Species ▪ Dose duration and route ▪ Recovery animals ▪ Toxicities identified (target organs affected only) ▪ Impact on molecule progression (internal decision making)
▪ If you used two species, would you have been able to make the same decisions with data from one species only (in hindsight)? ▪ If you used two species, did you reduce to a single species at any point in the package?		

Data collection

- Data for 172 molecules were submitted by 18 companies



Use of one or two species



- Small molecule examples where only one species was used.
- Surprisingly high number of biologics used two species.

Opportunities to reduce to a single species

- Only 8 molecules using two species in pre-FIH or FIH studies reduced to a single species in later studies.

- ICHS6 allows reduction to one species for longer-term studies if toxicities in the two species are *similar* at FIH.

- Dataset had 115 molecules with FIH data for two species. Toxicities reported were compared and categorised as ‘same’, ‘similar’ or ‘different’.

	Toxicities in the two species			
	None	Same	Similar	Different
Small molecule	3	11	10	51
Monoclonal antibody	8	3	-	2
Recombinant protein	1	1	2	7
Synthetic peptide	4	-	1	7
ADC	-	1	-	3

- Opportunity for 45 molecules to reduce to a single species.

Species use in longer-term studies

- Data for both FIH (with two species) *and* post-FIH for 11 molecules - were opportunities to reduce to a single species taken?

Molecule type	Toxicities in the two species at FIH
Monoclonal antibody	None
Monoclonal antibody	None
Monoclonal antibody	None
Monoclonal antibody	Same
Monoclonal antibody	Different
Monoclonal antibody	Different
Recombinant protein	None
Recombinant protein	Different
Synthetic peptide	Similar
Synthetic peptide	Different
Synthetic peptide	Different

- 6 molecules had the same/similar or no toxicities in short-term studies **- only 2 reduced to one species.**

Project Summary

- There are opportunities to reduce to a single species for longer-term toxicity studies, particularly for biologics.
- Potentially opportunities to expand these principles to wider molecule types or therapeutic areas. e.g. small molecules.
- Further data required to determine how and when use of a single species may be sufficient.
- ***Coming soon:*** Main results publication in *Regulatory Toxicology and Pharmacology*.

Commentary

Reviewing the Utility of Two Species in General Toxicology Related to Drug Development

International Journal of Toxicology
2018, Vol. 37(2) 121-124

DOI: 10.1177/1091581818760564
journals.sagepub.com/home/ijt
SAGE

Helen Prior[1], Paul Baldrick[2], Lolke de Haan[2], Noel Downes[2], Keith Jones[2], Elisabeth Mortimer-Cassen[2], and Ian Kimber[3]

Take home messages

Open discussion, data-sharing and *evidence* will increase confidence and drive change.

Global harmonisation and cross-company and cross-sector collaboration are key.

Benefits to science, business and animal welfare.

Keep up to date

Read our e-newsletter Tox News and download our bibliography

Our Toxicology and Regulatory Sciences Resources

Tox News is an e-newsletter which aims to keep the scientific community up to date on news from the NC3Rs Toxicology and Regulatory Science programme. https://nc3rs.org.uk/toxnews

Our bibliography lists and contains links to all publications from the NC3Rs Toxicology and Regulatory Science programme.

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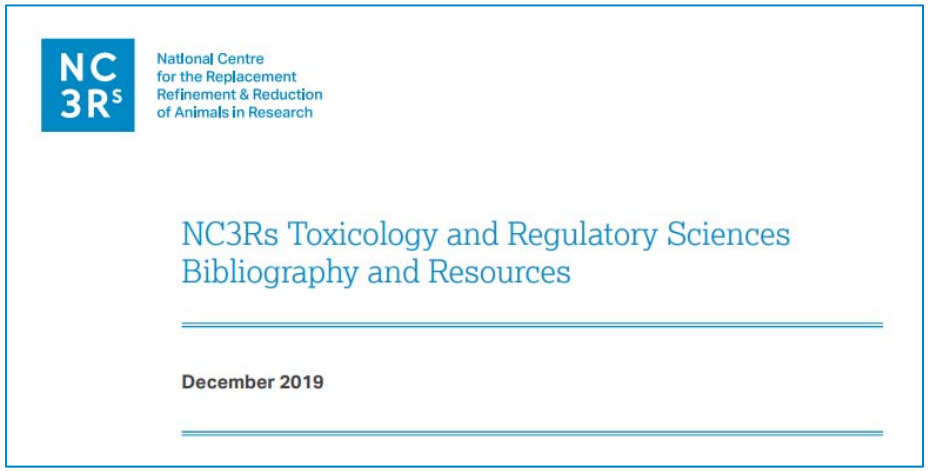

Tech3Rs: a newsletter for animal technicians

Regular features:

- 3Rs papers of interest
- A spotlight feature
- 3Rs Champions
- Pull-out A3 poster
- New 3Rs resources, research and events

- Request hard copies (UK facilities): www.nc3rs.org.uk/tech3rs
- Online copies (can be printed): https://nc3rs.org.uk/tech3rs

Plus NC3Rs general newsletter: www.nc3rs.org.uk/register

International 3Rs prize

To highlight an outstanding and original contribution to scientific and technological advances in the 3Rs.

- For a piece of primary research published in an open access peer-reviewed journal in the last 3 years.
- Prize winner receives a €33k prize grant + €2.3k personal award.

2018 3Rs prize winner: Dr Rickie Patani, UCL Queen Square Institute of Neurology and the Francis Crick Institute

2019 competition

- Open to any international researcher, in academia or industry.
- Paper must be published between 1 September 2016 and 1 September 2019.
- Nominations welcome from anyone familiar with the research paper.
- Applications are assessed by a dedicated Panel. Selection of winners is based on the quality of the published research and its impact on the 3Rs.

Competition deadline - 6 March 2020
(5pm CET)

For more information:

https://www.nc3rs.org.uk/3rsprize

3Rsprize@nc3rs.org.uk

The prize is sponsored by the NC3Rs and GlaxoSmithKline.

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Thank you!

For more information

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