



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

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

NTP Scientific Counselors meeting

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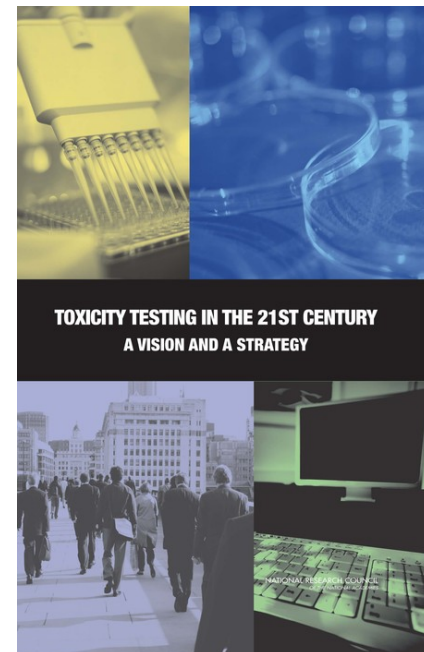
Pioneering Better Science

Global harmonisation is key

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- We live in a global marketplace.
 - Regulations and data requirements can vary by type of substance and geographical region.
 - There can still be variation in practice and interpretation of harmonised guidance.
 - Specific tests may be carried out to meet a few regional requirements.
 - *Business perspective*: companies may take the most risk-averse/extensive approach to ensure regulatory acceptance of safety assessments.

The 3Rs landscape

- The landscape has changed and is still changing.
- Recognition that animals can be poor predictors of humans.
- Large incentives to move away from animal use.
- CROs *in vitro* investment.
- Government pledges to reduce animal use.
- Legislative pressures.





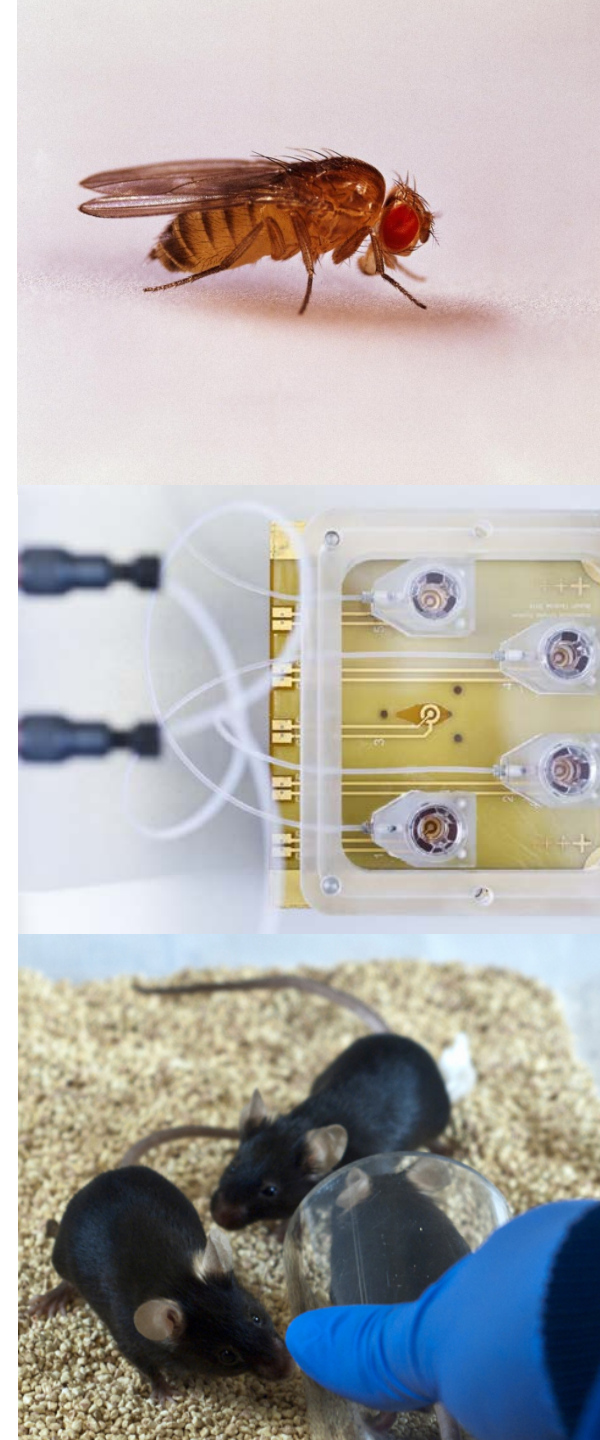
The National Centre for the Replacement, Refinement and Reduction of Animals in Research

- Independent scientific organization.
- Established by Government in 2004 to lead the UK's 3Rs agenda.
- Use the 3Rs as framework to support science, innovation and animal welfare.
- Work across the bioscience sector, with research funders, industry, regulators and academia.
- Budget ~ £10 million per annum.
- 34 staff (25 post-docs).

Our mission

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

- Large programme in toxicology and regulatory sciences.
- 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.

Our approach



Working together to
build an evidence-base
for change

Identify the problem (3Rs need).



Collaborate and form an evidence-base
(share, anonymise and analyse data).



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



Publication of data and results.

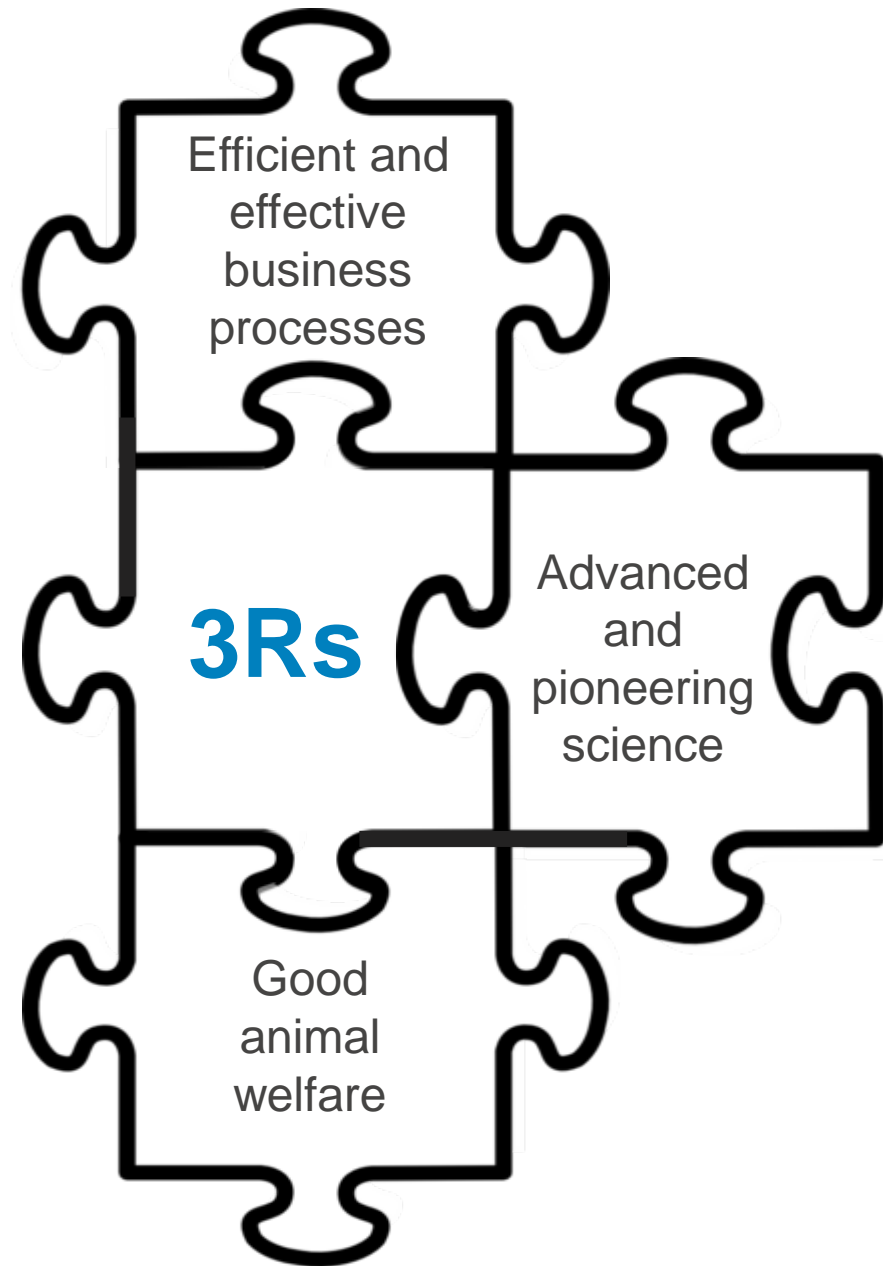


Dissemination and feed into regulatory
guidance/practice where appropriate.

Benefits of cross company collaboration

Sharing experience & challenging current practices in an open environment can lead to:

- Larger evidence-base.
- More relevant study designs.
- Improved scientific confidence and predictivity.
- Shared and reduced risk.
- Improved interaction with regulators.
- Business advantages:
 - Reduced cost \$\$\$\$.
 - Improved efficiency.
 - Streamlined processes.



Evolution *and* revolution

- Short term: identify good practice and take advantage of flexibility within the current requirements to enable immediate change (refinement and reduction).
- Long term: identify opportunities for adoption of new approaches and work towards better harmonisation, and mutual data acceptance across regions.
- Paradigm shift: ultimate aim to work towards implementation of non-animal methods that are *more* predictive than traditional methods and improve safety assessment.

Acute toxicity studies



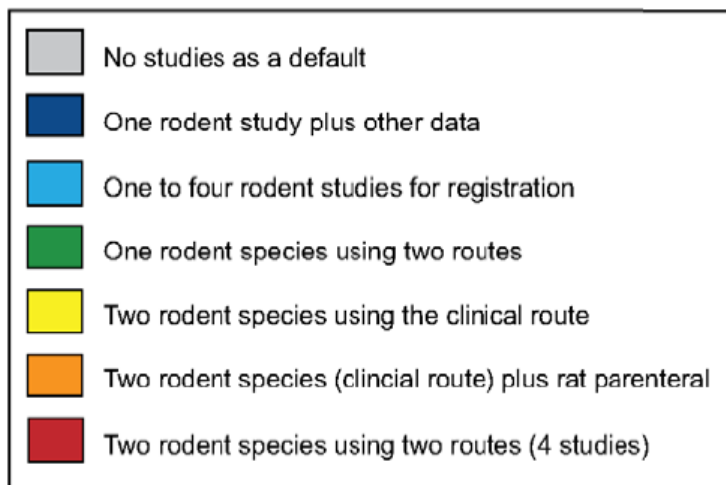
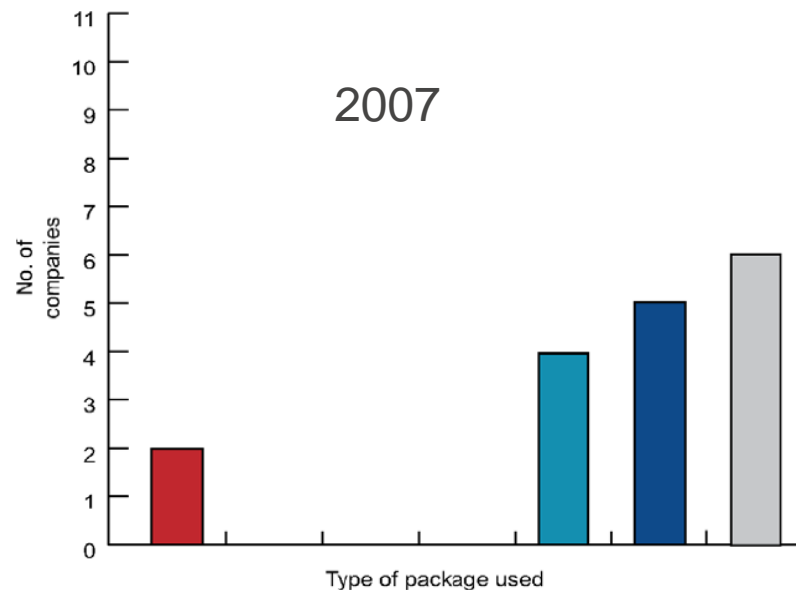
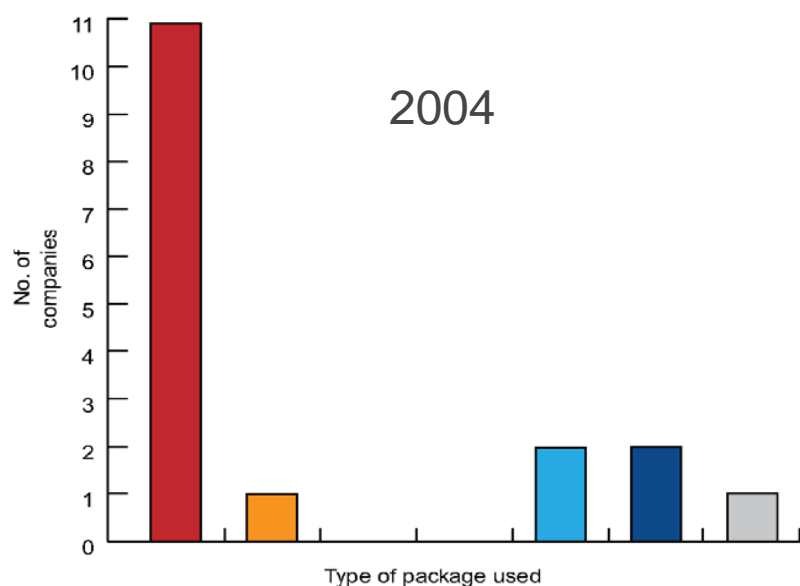
Removal of the requirement for single dose acute toxicity tests in ICH M3

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

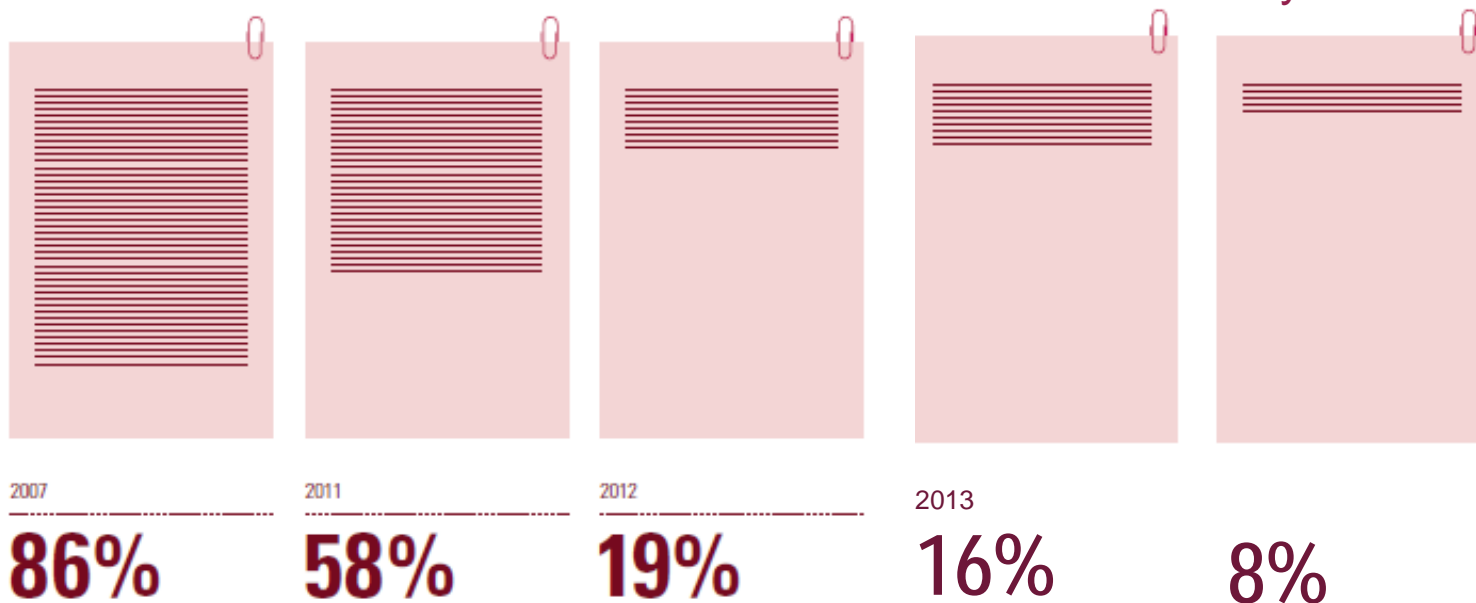


Removal of requirement for acute toxicity studies



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.



Adoption of OECD TG 433



Refining acute inhalation
toxicity studies by
replacing death as an
endpoint

The Fixed Concentration Procedure

- Acute inhalation studies are conducted as part of chemical hazard identification and risk classification.
- FCP uses fewer animals and 'evident toxicity' instead of death as an endpoint – a refinement to existing methods.
- Evident toxicity already an accepted endpoint for acute oral toxicity testing (adopted 2002 – OECD TG 420).
- FCP became an official OECD test guideline in 2017 (OECD TG 433).

Lessons learned



Change at a regulatory level takes time

- The adoption of a new OECD test guideline (or revision to an existing one) can only take place if **ALL OECD member countries agree**.
- Revisions/new test guidelines are approved once a year.
- Not standardised – requirements may differ depending on the experts involved.
- Not always scientifically justified – often political/not evidence-based.
- Even once accepted, not always mutual acceptance of data - choice of TG for the same endpoint, different preferences.
- Not all regions follow OECD test guidelines.

Conclusions

- Aim to move away from reliance on animal toxicity tests towards methods that are **more predictive** of human and environmental outcomes.
- Consensus and *evidence* will increase confidence and drive a reduction in duplicative or unnecessary animal toxicity studies.
- Global harmonisation and collaboration is key.
- We work closely with industry and regulatory bodies to provide an open environment for discussion.
- We act as an honest broker to share data and develop strategies to improve safety assessment using fewer animals.
- Benefits to business (time, cost, resource) and 3Rs.



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Thank you!

For more information

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**Our monthly newsletter provides the latest updates from the NC3Rs,
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