The Global Trend in Ending Animal Testing

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40+ different animal tests entrenched in guidelines & regulations

... and more in development

- Blood/Cardiovascular Toxicity
- Respiratory Toxicity
- Reproductive Toxicity
- Dermal Toxicity
- Epigenetic Alterations/Genetic Toxicity
- Eye Toxicity
- Hepatotoxicity
- Neurotoxicity
- Nephrotoxicity
- Immunotoxicity
- Endocrine disruption
- Nano-toxicology
Complex patchwork of regulations across sectors & countries

**Cosmetics**
Calls for global ban on animal testing & trade

**Chemicals**
New & revised laws impacting ~80K existing + hundreds of new substances each year

**Pesticides & Food**
Extensive pre-market testing required for new active ingredients & formulations

**Pharmaceuticals**
Extensive pre-market testing, including primates & dogs

**Vaccines**
Redundant & sometimes lethal batch-release testing
Numerous ‘1R’ approaches available

» NAMs, IATA, waivers, read-across, \textit{in silico}...

\textbf{Chronic Toxicity in Dogs as a Second Species}

\textbf{OLD TEST}
Both rats and dogs are exposed to a substance daily through their food. After a period of time, the animals are killed and dissected to assess chemical damage to organs and tissues.

\textbf{MODERN APPROACH}
The value of the dog as a second species has been scientifically disproven. This test is no longer required in the USA, Europe, India, Brazil or Canada, and should also be eliminated in Japan and Korea.

\textbf{Skin Allergy}

\textbf{OLD TEST}
Chemicals are applied to the surface of guinea pigs’ skin or to the ears of mice. These skin patches may cause redness, ulcers, scabs, inflammation and itching.

\textbf{MODERN APPROACH}
Tests using human cell samples, chemical reactions, and computer modelling are able to more accurately predict whether a chemical is likely to cause an allergic reaction in humans.

\textbf{Skin Lethal Dose}

\textbf{OLD TEST}
A chemical is applied to the shaved skin of rabbits or rats to calculate the dose that will kill 50 percent. Animals may experience skin ulcers, bleeding, diarrhoea, convulsions, seizures, paralysis and death. No pain relief is provided.

\textbf{MODERN APPROACH}
Data from other required tests can be used to determine if a chemical is toxic. This test is being waived in other countries and could also be waived in India.

\textbf{Testing Each Pesticide Formulation in 6 Animal Tests (“6 Pack”)}

\textbf{OLD TEST}
Each pesticide finished product is normally separately tested separately tested for skin and eye irritation, skin allergy, and oral, skin and inhalation lethal dose tests.

\textbf{MODERN APPROACH}
Calculations using existing toxicity data for individual ingredients eliminates the need for redundant animal testing of each pesticide formulation.

\textbf{Birth Defects in Rats as a Second Species}

\textbf{OLD TEST}
Pregnant female rabbits and rats are force-fed a chemical daily throughout their pregnancy. Mothers are killed the day before they are expected to give birth. Pups are removed and dissected for signs of birth defects.

\textbf{MODERN APPROACH}
The presumed need for separate rat and rabbit tests for birth defects in addition to a rat test for reproductive toxicity is scientifically questionable. European biocides law now examines the second species test requirement on a case-by-case basis.

\textbf{Cancer in Mice as a Second Species}

\textbf{OLD TEST}
Both rats and mice are exposed to a substance daily through their food or water, or via skin or inhalation. After two years, all animals are killed and dissected to assess the presence of cancer.

\textbf{MODERN APPROACH}
The value of the mouse as a second species in cancer testing has been scientifically disproven. This test is being waived in European countries and could also be waived in India.
Achieving replacement in practice

1 test / regulation / country at a time

- All major markets must agree to change
  ➔ even 1 holdout means animal testing will continue
Achieving replacement in practice

» 1 test / regulation / country at a time

Deletion of 1-year dog test

• First scientific redundancy analysis published in late 1990s
• Test requirement deleted in US, India, EU & Canada between 2007-16
• Japan and S Korea took action in 2018
• Brazil is the last major market to move

⇒ Nearly 20 years to delete 1 test !!
Achieving replacement in practice

» encourage major markets to move *en bloc*

**MODERN APPROACH**
Application of “consistency approach”

- Abnormal Toxicity Test & Target Animal Batch Safety Test for Vaccines

- Consensus report & roadmap for implementation (barriers to change & how to overcome)

- European precedent (2019 deletion)

- Multi-national consensus workshop (include developing economies)

- Global agreement & elimination of ATT & TABST requirements

*HUMANE SOCIETY INTERNATIONAL*
**European Union**
- Requirement to use available alternatives established in 1986 Animal Experiments Directive and subsequent regulations

**Brazil**
- 2014 CONCEA Resolution establishes 5-year mandatory phase-out for animal tests with government-recognized replacement

**United States**
- 2016 TSCA Reform Act introduced unprecedented animal protective language in a federal chemical statute

**South Korea**
- 2017 ‘K-REACH’ Reform Bill introduced established first-in-Asia animal protective language in a national chemical law
Legislative reforms

cosmetic animal testing & sales bans

37 national bans already in force
8 state bans in force in Brazil & USA
10+ similar laws in development

- Australia
- Brazil
- Canada
- Chile
- Japan
- Mexico
- South Africa
- Sri Lanka
- United States
- ASEAN region of south-east Asia
Progress in China

» official commitment to AT phase-out

3 NAMs adopted since 2017; more in pipeline

Workgroup on cosmetic alts. research & valid’n established ahead of ChCVAM

Major policy reform expected this year with new cosmetic regul’n
‘Tox21’ paradigm shift

» are we there yet??!
Tox21 paradigm shift

» human biology is complex & non-linear

Tox21 to-do list:

➔ Consolidate global expertise of human patho/physiology in OECD knowledgebase

➔ Identify major modes of action of human toxicity & rate-limiting ‘key events’ and biomarkers

➔ Develop human based micro-physiological (molecular/cell) tests to detect changes in biomarkers

➔ Integrate quantitative outputs from in vitro tests to build complex systems biology models

➔ Define thresholds of adversity

➔ Incorporate exposure (magnitude, duration, time of life, etc.)

“And that’s why we need a computer”
Tox21 paradigm shift

>> animal-free human risk assessment

Adapted from Dr AH Piersma, “Evolution vs Revolution in Innovating Regulatory Toxicity Testing”, 15 June 2018, RIVM
‘Tox21’ paradigm shift
>> bridging the silos

- More multidisciplinary collaboration (clinicians, big data)
- Build models around human patho/physiology (AOPs)
- Describe human physiology in the form of AOPs
- Human micro-physiological systems
- Computational models for prediction
Excelsior!
(ever upward)