21st century risk assessment: perspective of EU Non-Food Scientific Committees

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The current methodology

- *Laboratory animal dependent*. Started in the 1960's. Species selected largely on the basis of convenience and bred for the purpose.
- *Hazard based*. General viability and/or pathological changes the prime endpoints for identification and characterisation of adverse effects.
- *Additional tests* have been added progressively including a few in vitro ones.
- *Arbitrary default factors* used to allow for uncertainty.
- *Insufficient attention to exposure assessment* although it is commonly the weakest part of the RA

Drivers for a major change in current approaches

i) Legislative/public/political. Aversion to the use of animals for testing purposes

ii) Economic. Major resource requirements inhibiting innovation and affecting international competitiveness

iii) Scientific advances. New technical developments and advances in understanding offering potential for more rapid, less costly risk assessment procedures

‘Status quo you know is Latin for ‘the mess we are in’’

Ronald Regan

Long term challenges in risk assessment

- Assessment of life time exposure to all significant stressors at levels that could affect health (exposome)
- Characterisation of accumulated tissue effects arising from this exposure over a lifetime (toxome)

The RA paradigm for the 21st century?

- Exposure led. (low exposure no effect)
- Based on understanding of modes of action (MoA) leading to toxicity. (Assumes that a limited number of initial interactions of a chemical with organism 'receptors' result in toxicity)
- Drawing on research findings in other fields. (medical and biological sciences, ecology)

Scientific advances that enable the new paradigm: hazard

Human and ecological RA (Advantage- better context)

- (Q)SAR and read across

Human RA. (Advantage-high throughput)

- understanding of adverse reaction pathways (AOP, MoA)
- 'Omics' (genomics, proteomics, metabolomics)
- *In vitro* tests for hazard identification and characterisation.

Ecological RA. (Advantage-realistic scenarios)

- Critical factors for ecosystem sustainability
- Developments in field study methodology

Benefits and challenges of ‘new advances’

Benefits.

*High throughput, relatively rapid and low cost. *Enhanced control over experimental conditions

*Potential for examining various factors affecting the impact of chemicals

Challenges.

*Lack of familiarity in application of these techniques for RA purposes (optimising application, interpretation)

*Hazard characterisation to identify in vivo dose response

Use of ‘omics’ for determining adverse outcome pathways

- Already in extensive use in the USA Toxcast programme
- Very large amount of data being generated
- Focussed on initiating events
- Many changes observed with challenges in interpretation eg thresholds.
- Insufficient attention to late changes linked to toxic endpoints

Scientific requirements to optimise progress

- Agreement on 'gold standards' (bench marks) to compare new methods with?
- Accessible, robust data bases to facilitate method design and development.
- Data management systems able to manage high output from new tests
- Internal dose estimation to determine the true dose response relationship.
- Advances in understanding of disease processes utilised for method development and interpretation.

new paradigm: exposure

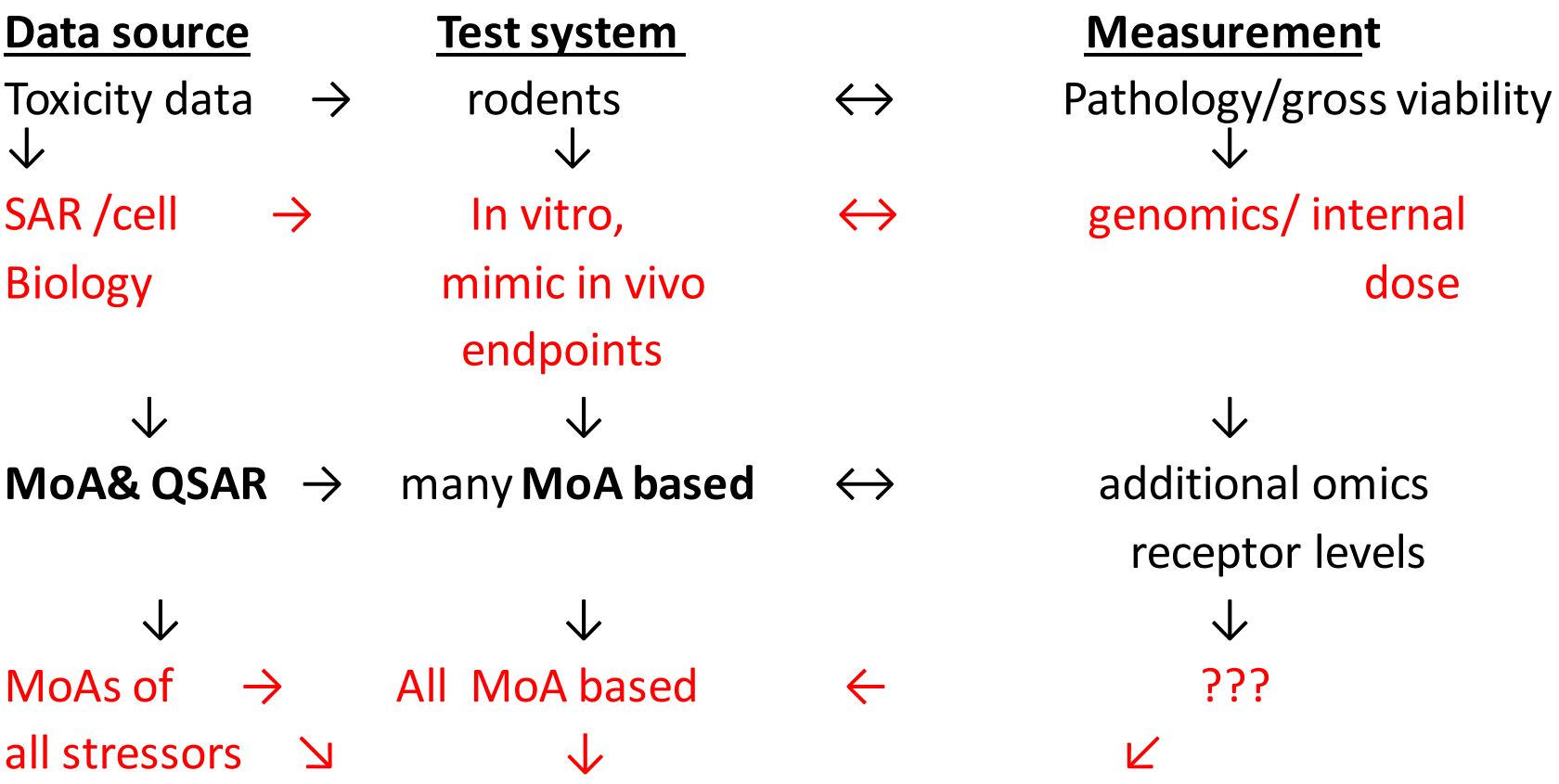
- Developments in modelling verified by ‘real world’ data
- Exposure data base and its use for (Q)SAR purposes
- Remote automated analysers
- Low cost robust personal monitors (air)

(NB: Crucial that exposure science achieves academic recognition?)

What else is needed to establish the new RA paradigm?

- *Greater availability* of the wealth of existing 'confidential data' for the required data bases
- *Wide recognition* of the need for change and the establishment and implementation of an agreed road map
- *Flexible regulatory procedures* for acceptance/ utilisation of suitable tests/studies and withdrawal of outdated methods
- *An international agreed tiered methodology* based on WoE assessments

Road map for future human RA's?



‘We cannot solve our problems with the same thinking we used to create them’

A Einstein