Barriers to and opportunities for the increased use of NAMs in the regulation of agrochemicals and biocides

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REGULATIONS

Agrochemicals – Retained Reg 1107/2009 (as it applies in GB)

Biocides – Retained Reg 528/2012 (as it applies in GB)

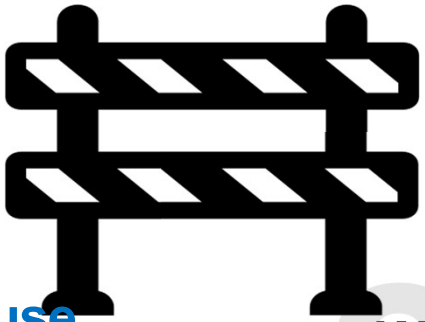
However, Art 62 of both Regs:

"Testing in vertebrates only where no other methods are available (P) or as last resort (B)"

Tox data requirements – include animal tests for RDT, C, R, neurotox

Data appropriate for hazard classification under retained CLP (as it applies in GB) and RA. Hazard classification determines exclusion criteria but also needs addressing for HCL or MCL (in GB)

Therefore,… what are the barriers?



1 What is preventing the use of NAMs for complex endpoints in the regulation of agrochemicals and biocides?

2 What are the obstacles and hurdles?

Barrier 1 – the LAW

Barriers

- **PPPR/BPR** – In vitro tests already implemented for skin and eye irritation, skin sens, genotox, endocrine activity **BUT** no suitable in vitro alternatives for complex endpoints;
- **CLP** – Complex endpoints – criteria based on apical toxicity effects, not on in vitro bioactivity responses;
- **CLP** - Criteria can be changed but validated in vitro methods required and analysis to show similar sensitivity and specificity of in vivo tests

Solutions

- Change the law, but only when the science can support the change
- Longer-term objective

Barrier 2 – Validated test methods

Barriers

- Regulatory tests – validated OECD TG
- Ensure robustness, standardisation, harmonisation and mutual acceptance of data
- Not standard tests – usually mechanistic only

Solutions

- Accelerate validation process of alternatives or create a new system of standards at OECD level otherwise decades for full validation of so many NAMs
- Short- and medium-term objective

Barrier 3 – Science & Technology limits

HSE

Barriers

- S&T for complex Tox endpoints has not progressed sufficiently
- Eg: Organs-on-the chip – how many do we need to cover toxicological space?
- In vitro bioactivity assays and omics – how molecular changes correlate and predict apical endpoints? What do they mean in relation to human pathologies? How many to cover tox space? Hugely conservative? Is it sustainable?

Solutions

- Invest further in these areas of research
- Short- and medium-term objective

However,……..opportunities?

1 What can be done now?

2 What are the most promising NAMs that can be used for regulatory purposes in the short-term?

Opportunity 1

- Structural and mechanistic read-across
- Agumented by omics technology
- More robust, more viable
- Widening application to many more chemicals
- Suitable for hazard classification and RA

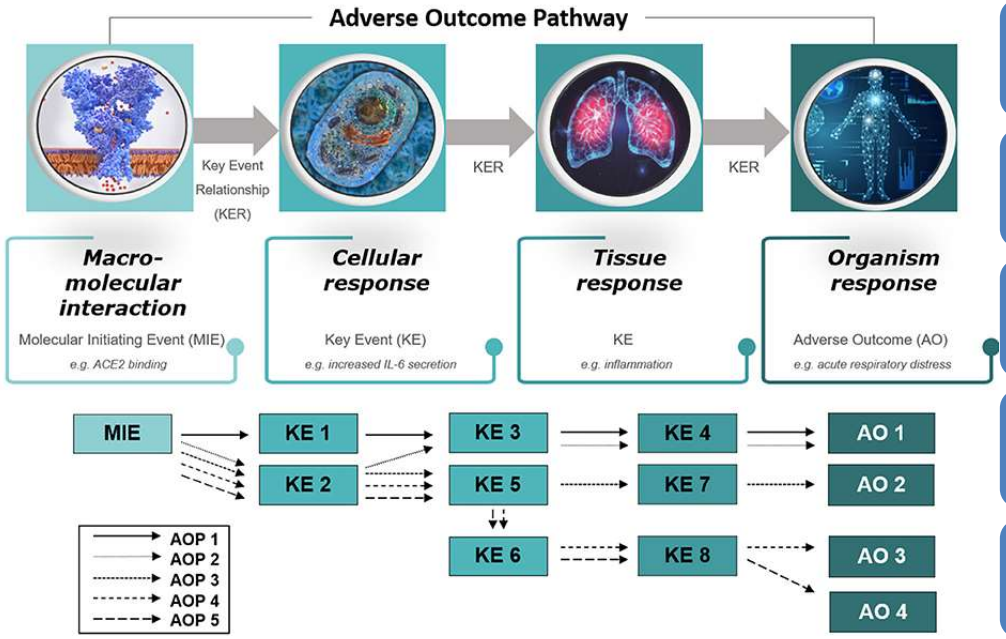
Opportunity 2

QSAR

- Increase the chemical space by incorporating mountains of “private” data
- More robust, more reliable
- Needs collaboration among companies and QSAR developers
- Suitable for hazard classification and RA

Opportunity 3

AOPs



- Increasing mechanistic understanding of path from exposure to adverse effect (via omics, bioinformatics, etc)
- Molecular – Cellular – Organ – System -Individual
- Develop AOPs for many more adverse effects
- Then test in vitro up to organ level to identify KEs at the lower biological organization level
- Infer from these KEs associated upstream adverse effect
- Suitable for hazard classification and RA (via IVIVE)

Opportunity 4

Integration of different NAMs in WoE approach (IATA)

- Combine QSAR, read-across, AOPs + existing info/knowledge to develop IATAs
- No single NAM alone sufficient to investigate complex Tox endpoints
- More robust, more reliable
- Less uncertainty and less conservatism
- Suitable for hazard classification and RA

Opportunity 5

Exposure-based waiving and testing

- If exposure negligible, no need for hazard testing
- If exposure low/limited, only targeted testing or conservative in silico predictions or bioactivity tests in a first-tier
- Suitable for RA and limited hazard classification

Long-term Vision

Batteries of in-vitro tests for complex endpoints

- No single in vitro test can cover in vivo complex endpoint
- Develop batteries investigating different events and targets
- Example: DNT IVB
- Use initially for prioritization until standardisation
- If negative, no animal test; if positive, proceed in vivo

Thank you for listening