POTENTIAL ROLES OF OMICS DATA IN THE USE OF ADVERSE OUTCOME PATHWAYS FOR ENVIRONMENTAL RISK ASSESSMENT

Geoff Hodges, Thomas H. Hutchinson, Emma Butler, Markus Hecker, Knut Erik Tollefsen, Natalia Garcia-Reyero, Peter Kille, Dorthe Becker, Erica Brockmeier, Kevin Chipman, John Colbourne, Tim Collette, Andrew Cossins, Mark Cronin, Peter Graystock, Steve Gutsell, Dries Knapen, Ioanna Katsiadaki, Ange Lange, Stuart Marshall, Stewart Owen, Edward J Perkins, Stewart Plaistow, Anthony Schroeder, Daisy Taylor, Mark Viant, Gerald Ankley and Francesco Falciani
The science that underpins the safety assessment of chemicals is currently undergoing a paradigm shift.

Catalysed by:
- the growth of systems biology,
- the need to assess large numbers of chemicals with finite scientific resources
- need for a reduced reliance on *in vivo* studies (notably vertebrates) in chemical safety assessment.
China: new and evolving risk assessment (RA) framework.
USA: shift towards increasing use of mechanistic information in support of RA
Europe: calling for more ecological realism to support risk-based decision making
OECD: new Task Force developing Adverse Outcome-Pathway (AOP) framework
PRINCIPLES OF ENVIRONMENTAL RISK ASSESSMENT

PEC

Predicted Environmental Concentration

V

PNEC

Predicted No Effect Concentration

Exposure

Hazard
PRINCIPLES OF ENVIRONMENTAL RISK ASSESSMENT

PEC \( \vee \) PNEC

is safety margin acceptable (PEC<PNEC)?

Refine PEC and/or PNEC or risk manage

yes → stop

no → Refine PEC and/or PNEC or risk manage
PNEC: DATA UNCERTAINTIES

- Intra- and inter-laboratory variation
- Intra- and inter-species variations (species relevance/ extrapolation)
- Individual to population extrapolation
- Short-term to long-term toxicity extrapolation
- Laboratory data to field extrapolation (mixture effects)
PNEC: DATA UNCERTAINTIES

QSARs & Read-across

Acute ecotoxicity (L/EC\textsubscript{50})

- 48hrs
- 96hr
- 72hr

Chronic ecotoxicity (NOEC)

- 60d
- 21d
- 72hr

Mesocosms (artificial ecosystems)

AF=1000

AF=1-5

- Intra- and inter-laboratory variation
- Intra- and inter-species variations (species relevance/extrapolation)
- Individual to population extrapolation
- Short-term to long-term toxicity extrapolation
- Laboratory data to field extrapolation (mixture effects)
SOME ERA CHALLENGES

• Increased robustness of read-across of chemicals and extrapolation approaches across species/taxa through greater mechanistic understanding of toxicity pathways

• The ability to better link understanding of individual (or sub-individual) effects to population level effects relevant to risk assessment.

• Need to increase confidence in RA by increasing mechanistic understanding to justify or reduce the use of AFs.
The adverse outcome pathway (AOP) which is part of the Source to Outcome (S2OP) framework, provides a conceptual basis through which linkages between Key Events can be explicitly assessed across biological levels of organization.
CHALLENGES WITH AOP/ S2OP

Limited AOPs with causal links between KEs
There is a need to better link molecular responses to phenotypic endpoints.
Limited AOPs for population relevant chronic endpoints.
WORKSHOP OF SEPTEMBER 18TH
UNIVERSITY OF LIVERPOOL

R&D - SEAC
OBJECTIVE OF WORKSHOP

To discuss and define the role of ‘omics’ techniques as part of the AOP framework to support environmental risk assessment of chemicals.

A specific focus on:

1. The role of omics in understanding species sensitivity differences.
2. The role of data-driven computational learning in extrapolating from molecular events to population relevant endpoints.
AOPS IN PREDICTING SPECIES SENSITIVITY

• Current approaches to species extrapolation rely on the assumption that effects in a lab model species can be applied to native species of concern (use of AF)

• Great uncertainty due to large diversity of species.

• Fundamental biological functions (e.g. reproduction, metabolism etc.) are more likely to be conserved across larger ranges of species

• Increasing evidence of interspecies differences in sensitivity arising (in part) from differences in molecular targets.
AOPS IN PREDICTING SPECIES SENSITIVITY

- Scale of molecular targets + the chance of inter-species differences = need for multiple approaches for predicting species sensitivity differences.

- Tiered approach using omics + well developed AOPs.

- Species similarity maps to identify ‘forecaster’ species

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Consult AOP to identify applicability of biological target to taxonomic group

- YES
  - OMICs based characterization of molecular target (seqAPASS, de novo transcriptomics, etc.)
  - Validation of predictive relationships/ forecaster species
    - Computational Models
- NO
  - Chemical group unlikely to be relevant to taxonomic group
    - MIE/KE modelling
    - In vitro verification
    - In vivo validation

Test for biological context: target identification and characterisation

ADME (TK/TD)
EXTRAPOLATING FROM MOLECULAR EVENTS TO POPULATION RELEVANT ENDPOINTS

Can predictions of individual (population relevant) effects be made from ‘omics data?

• Significant challenge for the AOP framework to enable links between key genes, proteins and metabolites and phenotypic responses relevant to understanding population effects.
A CHANGE IS NEEDED

A dramatic shift in our investigative approach is required to introduce greater fundamental, mechanistic understanding to the current risk assessment approach.

Without this we will be unable to generate sufficient relevant data to:

• derive genuine species-species extrapolation and chemical read-across.
• Make ecologically (population) relevant predictions
CHALLENGES FOR ERA

1. **Big Science**: Utilising the large scale ongoing ‘omics efforts to identify conserved biological pathways

2. **Coordinated research**: A need for coordinated research programs to simultaneously evaluate omics data (transcriptomics, proteomics & metabolomics) in conjunction with intermediate key events and adverse outcomes.

3. **Reliable Species sensitivity extrapolation**: A need for a combined approach of omics alongside well developed AOPs to facilitate the development of predictive models for reliable species-sensitivity extrapolations.
4. **Conservation of targets**: A need for understanding the conservation of protein classes targeted by chemicals between species to provide a rational basis for developing AOPs applicable to multiple species.

5. **Mode of Action (MoA) and chemical grouping**: Need to provide mechanistic evidence to support chemical grouping.

6. **Population**: Case studies are needed to critically evaluate the evidence for predicting population impacts from using molecular events (multistep approach).
7. **Tiered Testing Strategies**: The AOP framework can play a powerful role in tiered testing strategies by providing scientific directions and guide selections of species, endpoints, life stages, and indexing to standardized tests.
SUMMARY

1. Use AOPs as a platform for identifying key processes driving species sensitivity

2. Tiered strategy proposed to understand species sensitivity

3. Development of AOPs needed (particularly in microbial, plant and invertebrate species)

4. Development of ‘omics tools to:
   » Generate/interrogate sequence data to establish species similarities and
   » Identify unknown targets (secondary toxicity)

5. Extrapolating from molecular events to population relevant endpoints = significant challenge (multistep)
THANKS TO:

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