NC3Rs Workshop
Application of non-animal approaches for decision-making in chemical safety assessment

Using non-animal data for hazard or risk assessment – can we have our cake and eat it?

London, 10-11 December 2018

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Risk has two components
Differentiation between hazard and risk is crucial

Hazard: x Exposure = Risk

Hazard:
Intrinsic property of a chemical which describes the potential to cause harm

Exposure:
The amount of a substance a person is confronted with.
The rate of absorption distinguishes external from internal exposure.
OECD Test Guidelines using *in vitro* techniques are available for

- skin/eye corrosion and irritation
- skin sensitisation
- skin absorption
- genotoxicity
- endocrine disruption.
A paradigm shift (NRC, 2007)

- **Where we are:**
  - Complex array of studies
  - Evaluate observable outcomes in whole animals
  - Time-consuming and resource-intensive

- **Where we need to be:**
  - Broad coverage of chemicals, chemical mixtures, outcomes, and life stages
  - Reduce the cost and time of testing
  - Use fewer animals
  - Robust scientific basis for assessing health effects
Integrated Approaches to Testing and Assessment (IATA)

- Pragmatic, science-based approaches for chemical hazard or risk characterization that rely on an integrated analysis of existing information in a weight of evidence assessment coupled with the generation of new information using testing strategies.

- Range of IATA
  - Flexible, non-formalized, judgment-based approaches (e.g. grouping, read-across)
  - Structured, prescriptive, rule based approaches [e.g. Integrated Testing Strategy (ITS)]

- Integrating results from one or many methodological approaches or omic methodologies

- An IATA should be mechanistically informed

Activation of a toxicity pathway (NRC, 2007)

- Exposure
- Tissue Dose
- Biologic Interaction
- Perturbation

Biologic Inputs

Normal Biologic Function

Early Cellular Changes

Adaptive Stress Responses

Cell Injury

Morbidity and Mortality

Activation of a toxicity pathway (NRC, 2007)
A hypothesized mode of action is considered to comprise a set of critical key events from administration of the substance to a final specific toxic outcome.

Mode of action is to be distinguished from mechanism of toxicity, which is a detailed knowledge of the molecular interactions leading to the toxic effect.

The mechanism of toxicity is fully elucidated for only a few chemicals… but many more chemicals have a reasonably well understood MOA, in that the key events are known, measurable, necessary, and consistent.

Mode of Action or Adverse Outcome Pathway?

Mode of Action

- ‘The terms mode of action and adverse outcome pathway should be interchangeable, representing essentially the subdivision of the pathway between exposure and effect in either individuals or populations into a series of hypothesized key events at different levels of biological organization.’

- ‘It should be noted, though, that the term mode of action, per se, does not imply adversity of outcome.’

**Mode of Action or Adverse Outcome Pathway?**

**Adverse Outcome Pathway**
- Chemical agnostic
- Endpoint is adversity

**Mode of Action**
- Chemical specific
- Endpoint is a measurable effect which may or may not be adverse
Why use AOPs?

- How do we identify chemicals that may cause adverse effects before we see impacts on human health or wildlife populations?
- We need to understand
  - HOW chemicals cause adverse outcomes and
  - Biological activities that lead to/are associated with progression toward those AOs
- Creates opportunities to use new types of data for hazard identification and/or risk-based decision-making

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**Table:**

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Macro-Molecular Interactions</th>
<th>Cellular Responses</th>
<th>Organ Responses</th>
<th>Organism Responses</th>
<th>Population Responses</th>
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<tbody>
<tr>
<td>Chemical Properties</td>
<td>Receptor/Ligand Interaction</td>
<td>Gene activation</td>
<td>Altered physiology</td>
<td>Lethality</td>
<td>Structure</td>
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<td>DNA Binding</td>
<td>Protein Oxidation</td>
<td>Protein production</td>
<td>Disrupted homeostasis</td>
<td>Impaired Development</td>
<td>Extinction</td>
</tr>
<tr>
<td>Protein Oxidation</td>
<td></td>
<td>Altered signaling</td>
<td>Altered tissue development/function</td>
<td>Impaired Reproduction</td>
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</tbody>
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OECD, 2013
Data integration in an AOP context

Framework for AOP application to IATA

Problem formulation
- regulatory need, endpoint, constraints, acceptable uncertainty

Gather existing information
- organise and structure information using an AOP as a frame

Weight of Evidence Assessment: Adequate information for decision-making?

Generate additional information
- use an AOP to help identify and/or develop targeted testing, testing strategy or assay development

Weight of Evidence assessment: Adequate information for decision-making?

Regulatory conclusion

Linking exposure and adverse outcome

Justin G. Teeguarden; Yu-Mei Tan; Stephen W. Edwards; et al.  
DOI: 10.1021/acs.est.5b05311  
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In Vitro – In Vivo Extrapolation (IVIVE)

- **Utilisation of in vitro experimental data to predict phenomena in vivo**
  - Biokinetics
    - Fate of chemicals in the body (ADME)
    - Physiologically-based kinetic (PBK) modelling
  - Biodynamics
    - Effect of chemicals/metabolites at biological target *in vivo*
    - Assay design/selection important; perturbation as adverse/therapeutic/adaptive effect; reversible/ irreversible …

Adapted from:
Barbara Wetmore
IVIVE Webinar, Oct 7, 2015
From Tox21 to risk assessment

Chemical Research in Toxicology

Estimating Toxicity-Related Biological Pathway Altering Doses for High-Throughput Chemical Risk Assessment

Richard S. Judson,∗† Robert J. Kavlock,† R. Woodrow Setzer,† Elaine A. Cohen Hubal,† Matthew T. Martin,† Thomas B. Knudsen,† Keith A. Houck,† Russell S. Thomas,‡ Barbara A. Wetmore,‡ and David J. Dix†

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High throughput chemical risk assessment

Flowchart outlining the incorporation of human dosimetry into high-throughput in vitro toxicity testing.

Comparison of human oral equivalent doses (OEDs) and exposure predictions for 163 ToxCast Phase II chemicals

Barbara A. Wetmore et al.: Incorporating High-Throughput Exposure Predictions With Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing
Distribution of AER values for 163 ToxCast Phase II chemicals

Data-driven 21st century risk assessment framework

Key Points

- Non-animal testing methods are presently used in regulatory toxicology primarily in hazard assessment.
- The use of such methods for risk assessment requires:
  - An integrated approach (IATA) to data generation and analysis using quantitative understanding of key events leading to adverse outcomes.
  - An understanding of the relationship of predicted in vivo effects (PD/TD) to real-life human exposures (PK/TK).
• Development of causal computable biological network models that link the system’s interaction of a toxicant with the organ-level responses.

• As more mechanistic knowledge derived from quantitative measurements accumulates, dynamic models linking the exposure with the organ-level responses can be developed.

• Ultimately, the link between the exposure and the population outcome can be represented by mathematical models that enable the simulation of population-level effects of an exposure.