The Role of Adverse Outcome Pathways in Streamlining Hazard and Risk Assessment

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Outline

- The need for a new approach to toxicology
- The Adverse Outcome Pathway concept
- Examples in progress
- Strategies for the future
The argument for a new approach

• **Pharmaceuticals:**
  - 92% of drug candidates fail in clinical studies
  - Need to assess novel chemistries (i.e. nanomaterials)

• **Industrial chemicals:**
  - Growing concern over lack of data for possibly tens of thousands of chemicals on the market and in the environment world-wide
  - REACH (EU, China, S.Korea)

• **Pesticides:**
  - Registration requires the use of approximately 10,000 animals, millions of USD, and many years (decades)
  - Need to identify “greener” chemistries

• **Cosmetics**
  - European Cosmetics Directives ban on animal testing
  - Consumer concern over safety and animal testing worldwide
The argument for a new approach

- Capitalize on advances in chemistry, biology, and engineering
- Fully utilize all existing knowledge
- Increase relevance to humans
- Increase assessment capacity (through-put)
- Increase efficiency (benefit/cost)
- Better predictivity

The Adverse Outcome Pathway Concept

- A chemical and biological description of what occurs when a substance interacts with a living organism and results in an adverse reaction.
- A biological map from the molecular initiating event through the resulting adverse outcome that describes both mechanism and mode of action.

The Adverse Outcome Pathway Concept

Human Relevance Frameworks*
- Characterize MoA of each class of carcinogens
- Determine which rodent MoA is possible relevant to humans
- Built using case studies

DNA reactive vs non-DNA reactive (epigenetic)
- Genotox battery
- Cell transformation assays

Case examples of AOPs

- OECD skin sensitisation project
- Estrogen receptor-mediated effects
- Thyroid hormone pathway
OECD sensitization project

OECD 2012. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins.

OECD, OECD 2012. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins.
OECD sensitization project

Chemical Properties
- Electrophilic substance or precursor

Molecular Initiating Event
- Covalent interaction with cell protein

Cellular Response
- Dendritic cells
  - Induction of inflammatory cytokines and surface molecules
  - Mobilization of DCs
- Keratinocyte
  - Activation of inflammatory cytokines
  - Induction cyto-protective gene pathways

Organ Response
- Lymph node
  - Histocompatibility complexes presentation by DCs
  - Activation of T cells
  - Expansion of activated T-cells

Organism Response
- Skin (epidermis)
  - Inflammation upon challenge with allergen

Aeby et al. (2010). *Toxicol In Vitro* 24, 1465 – 1473
Bauch et al. (2011). *Toxicol In Vitro* 25, 1162–1168
McKim et al. *Cutan Ocul Toxicol* Apr 12. [Epub ahead of print]
ER-mediated reproductive impairment

- Molecular initiating event: ER Binding
- Cellular response: Altered Gene/Protein Expression
- Tissue/organ response: Altered Proteins Ova/testis
- Individual response: Sex Reversal, Altered Behavior, Reproduction
- Population response: Skewed Sex Ratios, Reproduction

ER-mediated reproductive impairment

In vivo

In vitro

QSAR

Toxicity Pathway

Adverse Outcome Pathway


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Thyroid hormone pathway(s)

Crofton, K. US EPA. Presented at DC area SOT, May 2012.
Thyroid hormone pathway

Crofton, K. US EPA. Presented at DC area SOT, May 2012.
The Adverse Outcome Pathway Concept

Near-term use:
- Inform chemical categories and structure activity relationships
- Increase certainty of interpretation of both existing and new information
- Develop integrated testing strategies that maximize useful information gained from minimal testing

Longer-term use:
- Identify key events for which non-animal tests can be developed, thereby facilitating mechanism-based, non-animal chemical assessment
- Create predictive toxicological assessments with low uncertainty and high human relevance
- Eventually without the use of animals
Strategy for the future

• Build Biological and adverse-outcome “pathways”
  • OECD integration of AOPs into the Test Guidelines program
  • Guidance

• Improve predictive tools
  • NIH National Center for Advancing Translational Sciences
  • EPA’s Computational Toxicology Research
  • OECD QSAR tool box
  • Hamner Institute

• Develop assessment systems for complex endpoints
  • Reconstructed tissues and organ systems
    • Human skin, eye, lung
    • Liver-on-a-chip
    • Stem-cell derived
  • Integrate absorption, metabolism and distribution information
    • QSAR
    • Liver cells, tissues, extracts, reconstructed tissues

• Integrated databases and “knowledge bases”
  • **ACToR and MetaPath**: EPA – all available chemical toxicity data on over 500,000 environmental chemicals searchable by chemical name and structure
  • **Kegg pathway database**: collection of manually drawn pathway maps representing current knowledge on the molecular interaction and reaction networks
  • **Effectopedia**: open knowledge aggregation and collaboration tool that provides a means of describing adverse outcome pathways in an encyclopedic manner.

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Strategy for the future

Effectopedia

- an open source knowledge aggregation and collaboration tool that provides a means of describing adverse outcome pathways in an encyclopedic manner

- creates a common organizational space that
  - (1) helps experts identify exactly where more detailed knowledge is needed in order to extend the causal linkages of biological responses and
  - (2) creates a web-based conference room for dialogue and synthesis by experts with interest in a specific AOPs.

This kind of common, encyclopedic resource is necessary for forming the framework to establish the **quantitative** linkages required for true use of AOPs in risk assessment.

www.effectopedia.org
Articulating the Vision:
Communicating the purpose and goals of TT21C

Implementation:
facilitating scientific and technical approaches to accomplishing the vision globally

Lobbying/Funding:
in the US and internationally
Thank You

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