Adverse Outcome Pathways (AOP)

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This presentation reflects the views of the author. It has not been reviewed or approved by, and may not necessarily reflect the views, of the U.S. Consumer Product Safety Commission.
AOP Brief Overview

- Conceptual construct outlining the sequence of events from exposure through the adverse effect
- Mechanistic understanding of a chemical’s effect at the molecular and cellular level
Molecular Initiating Event (chemical-biological interaction)

Biologic Inputs

Exposure

Tissue Dose

Biologic Interaction

Perturbation

Early Cellular Changes

Adaptive Stress Responses

Normal Biologic Function

Cell Injury

Morbidity and Mortality

Adverse Outcome

NAS Report: Toxicity Testing in the 21st Century: A Vision and A Strategy; Pat Schneider EPA
General AOP Framework

Chemical Structure
- Parent Chemical (Metabolites/Speciation)

Molecular Interactions
- Receptor/ligand interaction, DNA binding, Protein Oxidation

Cellular Response
- Gene activation, Protein production, Altered signaling

Tissue/Organ
- Altered Tissue Structure (pathology), Function

Individual/Population
- Altered Function, Behavior; Pathology

Toxicity Pathway

Adverse Outcome Pathway
AOP Applications: Chemical Extrapolation

Test Multiple Chemicals to Extrapolate within Agency inventories (QSAR; Categories; Analogues)

Chemical Structure

- Parent Chemical (Metabolites/Speciation)

Molecular Targets

- Receptors, Enzymes, Ion channels, Membrane proteins, etc

Cellular Response

- Altered Cell Structure, Cell Function

Tissue/Organ

- Altered Tissue Structure (pathology), Function

Individual/Population

- Altered Function, Behavior; Pathology

Toxicity Pathway

Adverse Outcome Pathway
AOP Applications

• To develop chemical categories
  – Derive SARs, further develop QSAR toolbox
  – Prioritize chemicals for further assessment

• Inform data gaps for development of *in vitro, in silico*, et. al., assays

• To develop integrated approaches to testing and assessment; tiered testing approach

• Increase confidence in chemical hazard and risk assessments
Projects in the OECD AOP development program work plan

- 1.1 – Skin sensitization initiated by covalent binding to proteins (Secretariat)
- 1.2 – Nonpolar narcosis (US)
- 1.3 – Acetylcholinesterase inhibition (US)
- 1.4 – Cell signaling pathways (5) associated with cell proliferation and differentiation conserved across species (Secretariat)
- 1.5 – Mitochondrial toxicity (2) (Secretariat)
- 1.6 – Embryonic vascular disruption & developmental defects (US)
- 1.7 – Sustained activation of the avian aryl hydrocarbon receptor (Canada, BIAC)
- 1.8 – Mutagenic MOA for cancer (US)
- 1.9 – Upregulation of thyroid hormone catabolism via activation of hepatic nuclear receptors, and subsequent adverse neurodevelopmental outcomes in mammals (US)
Projects in the OECD AOP development program work plan (cont.)

- 1.10 – Xenobiotic induced inhibition of thyroperoxidase and decreased TH synthesis and subsequent adverse neurodevelopmental outcomes in mammals (US)
- 1.11 – Heritable germ-cell derived disease (3) (Canada)
- 1.12 – AOPs linking aromatase inhibition, androgen receptor agonism, estrogen receptor antagonism, or steroidogenesis inhibition, to impaired reproduction in small repeat-spawning fish species (US)
- 1.13 – Neurotoxicant-induced neuroinflammation: a converging key event (Switzerland)
- 1.14 – Protein alkylation to liver fibrosis (European Commission)
- 1.15 – Neurotoxicity induced by GABAA receptor inhibition (US)
- 1.16 – Hematotoxicity due to nitroaromatics and n-hydroxyl anilines (US)
- 1.17 – CAR and PPARα-mediated pathways to non-genotoxic rodent liver cancer (US)
- 1.18 – CAR and PXR-mediated pathways to rodent liver hyperplasia (US)
AOP references

- http://aopwiki.org/
  - The AOP Wiki represents one component of a larger effort to build a comprehensive AOP knowledgebase (AOP KB). Other components include an AOP Network tool, being developed by the US Army Corps of Engineers - Engineering Research and Development Center, and Effectopedia, being developed by the International QSAR Foundation. Following completion, an integrated AOP KB will be formed with a focus on formalizing AOP information to facilitate computational modeling.
- http://www.epa.gov/nheerl/articles/2011/Chemical_Safety_Assessments.html
**Skin Sensitization Pathway**

**INDUCTION**

1. Skin Penetration, Electrophilic, Low MW

2. Migration to Local Lymph Node
   - IL-1β, IL-6, IL-12, IL-18

3. Langerhans Cell (LC)

4. Migration to Local Lymph Node
   - IL-1β, TNF-α, GM-CSF

5. T-cell Lymphocyte Proliferation

**ELICITATION**

- EDEMA AND ERYTHEMA
- Cellular influx
- Cytokines, costimulatory, adhesion molecules increase
- Specific inflammatory response
- “Primed” lymphocytes

*Illustration by D. Sailstad*
Key Events in the Skin Sensitization AOP

**INDUCTION**
- Skin penetration, Electrophilic, Low mw

**EVENTS AND ASSAYS**
- *In silico* toxicokinetic model, QSARs, permeability methods

1. Haptenation: attachment of allergen to skin protein (DPRA, PPRA, EASA)
2. Epidermal inflammation: release of pro-inflammatory signals by epidermal keratinocytes (KeratinoSensSM, AREc32, LuSens, SENS-IS, NCTC, SenCeeTox, NCTC)
3. Dendritic cell (DC) activation and maturation (h-CLAT, MUSST, PBMDC, VITOSens, GARD, Sensi-Derm)
4. DC migration: movement of DC bearing hapten-protein complex from skin to draining local lymph node
5. T-cell proliferation: clonal expansion of hapten-peptide specific T-cells (local lymph node assay [LLNA], hTCPA)

*Illustration by D. Sailstad*
ICCVAM Activities

• Electrophilic Allergen Screening Assay (EASA), nominated by NIOSH; AOP Key event 1

• NICEATM collaboration to develop and evaluate chemical structure-activity relationship (SAR) models to predict skin sensitization

• NICEATM collaboration with industry scientists to develop an open-source Bayesian network as an operational framework for an ITS

• NICEATM evaluation of various high-throughput screening assays in coordination with NIEHS Tox21 activities
Thank you!