AOP Knowledge Base/
Wiki Tool Set

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Adverse Outcome Pathways: From Research to Regulation

This talk does not necessarily reflect the views of the Environmental Protection Agency.
Outline

• Why an AOP Knowledgebase?

• Components of the AOP Knowledgebase

• AOP-Wiki

• What’s next?
AOP Timeline

- 2010 AOP development
  - relatively poorly defined *ad hoc* process
- 2012 Launch of OECD AOP Development Programme
- 2013 OECD Guidance on Developing and Assessing AOPs
  - [http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282013%296&doclanguage=en](http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282013%296&doclanguage=en)
- 2014
  - AOP Workshops
    - Part of National Society meetings: SOT, SETAC, EMGS
    - *Advancing AOPs for Integrated Toxicology and Regulatory Applications* (Somma Lombardo, Italy)
    - *Adverse Outcome Pathways: From Research to Regulation* (Bethesda, MD)
  - Development of an OECD User Handbook as a supplement to the 2013 guidance
AOP-KB History

- Effectopedia (International QSAR Foundation)
  - Developed since 2006, alpha releases since 2010
- Chem MOA Wiki (WHO/IPCS) -> AOP Wiki
  - EPA – Fall 2012
- AOP-KB for OECD AOP Programme
  - Joint proposals EPA, JRC, & USACE – March 2013
  - Initial Wiki beta release – July 2013
  - Formal inclusion of OECD (Effectopedia) – Dec. 2013
  - Most recent Wiki release – June 2014
AOP Key Concepts

- Organize existing knowledge
- Systematic evaluation of evidence
- Avoid duplication of the same key event
- Always expand description to include new science
- Provide a framework for utilizing 21st century toxicity testing
AOP as a Knowledge Bridge

Chemical Properties

- Receptor/Ligand Interaction
- DNA Binding
- Protein Oxidation

Macro-Molecular Interactions

Cellular Responses

- Gene activation
- Protein production
- Altered signaling

Organ Responses

- Altered physiology
- Disrupted homeostasis
- Altered tissue development/function

Organism Responses

- Lethality
- Impaired Development
- Impaired Reproduction

Population Responses

- Structure
- Recruitment
- Extinction

Toxicant Cellular Responses Organism Responses Population Responses

Properties (QSAR) Disposition (exposure biomarkers) Toxicity Pathways (HTS assays) Key Events (bioindicators) Regulatory Endpoints (adverse outcomes)
AOP-KB
Shared chemical, biological and toxicological ontologies

**Effectopedia**
Detailed development of structured & computational AOPs

**Intermediate Effects**
Put chemical-related AOP components in a regulatory context

**AOP Xplorer**
Visualize attribute networks to discover & explore AOPs in a broader context

**AOP Wiki**
Collaborative development of AOP descriptions & evidence

**Third party Applications, plugins**
Welcome to the Collaborative Adverse Outcome Pathway KnowledgeBase (AOP-KB) Wiki

This wiki represents a joint effort between the European Commission – DG Joint Research Centre and U.S. Environmental Protection Agency. This serves as one component of a larger OECD-sponsored AOP Knowledgebase effort and represents the central repository for all AOPs developed as part of the OECD AOP Development Effort by the Extended Advisory Group on Molecular Screening and Toxicogenomics. The other major components of this knowledgebase are Effectopedia, produced by the International QSAR Foundation, and the AOP Network tool, produced by the US Army Corps of Engineers - Engineering Research and Development Center.

This wiki is based upon the Chemical Mode of Action wiki developed by the US EPA under the auspices of the WHO International Programme on Chemical Safety (IPCS) Mode of Action Steering Group.
Structuring and Storing AOP Information

1. Chemical
2. Molecular Initiating Event (MIE)
3. Key event \( i \)
4. Key event \( i+1 \)
5. Adverse Outcome

**AOP Components are mapped to specific entities in the KB**

1. Chemical initiator
2. Key event (including MIE; node)
3. KE Relationship (linkage; edge)
4. Adverse Outcome
AOP Page in Wiki

Structured Content

Free Text

Structured Content

Free Text
Widgets Facilitate Data Entry

Summary of the AOP

**Molecular Initiating Event**
- Aromatase, Inhibition

**Key Events**
- Plasma 17β-estradiol concentrations, Reduction
- Transcription and translation of vitellogenin in liver, Reduction
- Plasma vitellogenin concentrations, Reduction
- Vitellogenin uptake into oocytes and oocyte growth/differentiation, Reduction
- Cumulative fecundity and spawning, Reduction
- 17β-estradiol synthesis by ovarian granulosa cells, Reduction

**Adverse Outcome**
- Population trajectory, Decrease

List of Key Events, including the MIE and AO
AOP Page

Section 1 – Title
Section 2 – Authors
Section 3 - Status
Background (Optional)

Section 4 – Abstract

Section 5a – Summary of the AOP
- MIE
- KEs
- AO

Key Event Relationships

Applicability domain(s) of the AOP
- Life-stage
- Taxonomic
- Sex

Section 6 – Scientific evidence supporting the linkages in the AOP

Linkage table

Section 7 – Overall Assessment of the AOP
Modified Bradford Hill Considerations

Section 8 – Considerations for Potential Applications of the AOP

Wiki Matches OECD Guidance & Handbook

MIE Page
- Chemical initiator(s)
- Description
- Measurement/detection
- Taxonomic applicability
- Evidence for chemical initiation

KE Pages
- Description
- Measurement/detection
- Taxonomic applicability

AO Page
- Description
- Measurement/detection
- Taxonomic applicability
- Regulatory relevance

KER Pages
- Title
- Description
- Biological plausibility
- Empirical support
- Inconsistencies and uncertainties
- Quantitative understanding
**AOP Snapshot from the AOP-Wiki**

**Androgen receptor agonism leading to reproductive dysfunction**

**Authors:**
- Daan Vliegenthart, L. Rice, B. Miller

**AOP Title:**
- Chemical Safety for Sustainability Research Program

**Key Events**
- Testosterone synthesis by ovarian theca cells, Reduction
- Androgen receptor agonism

**Overall Assessment of the AOP**

<table>
<thead>
<tr>
<th>Step</th>
<th>Event</th>
<th>Description</th>
<th>Triggers</th>
<th>Weight of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Testosterone synthesis by ovarian theca cells, Reduction</td>
<td>Directly Leads to</td>
<td>17Beta-estradiol synthesis by ovarian granulosa cells, Reduction</td>
<td>Strong</td>
</tr>
<tr>
<td>3</td>
<td>Androgen receptor, circulating concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Testosterone synthesis by ovarian theca cells, Reduction</td>
<td>Strong</td>
</tr>
<tr>
<td>4</td>
<td>Androgen receptor, circulating concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Testosterone synthesis by ovarian granulosa cells, Reduction</td>
<td>Strong</td>
</tr>
<tr>
<td>5</td>
<td>Plasma 17Beta-estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Plasma 17Beta-estradiol concentrations, Reduction</td>
<td>Strong</td>
</tr>
<tr>
<td>6</td>
<td>Plasma 17Beta-estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Plasma 17Beta-estradiol concentrations, Reduction</td>
<td>Strong</td>
</tr>
<tr>
<td>7</td>
<td>Plasma 17Beta-estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Plasma 17Beta-estradiol concentrations, Reduction</td>
<td>Strong</td>
</tr>
<tr>
<td>8</td>
<td>Testosterone uptake into oocytes and oocyte growth, Reduction</td>
<td>Transitively Leads to</td>
<td>Testosterone uptake into oocytes and oocyte growth, Reduction</td>
<td>Moderate</td>
</tr>
<tr>
<td>9</td>
<td>Testosterone uptake into oocytes and oocyte growth, Reduction</td>
<td>Transitively Leads to</td>
<td>Testosterone uptake into oocytes and oocyte growth, Reduction</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Essentiality of the Key Events**

- Testosterone synthesis by ovarian theca cells, Reduction
- Plasma 17Beta-estradiol concentrations, Reduction
- Plasma 17Beta-estradiol concentrations, Reduction

**References**
AOP-Wiki Status

- 41 AOPs as of September 1, 2014
  - 8* with documented evaluation of evidence
  - 4 with descriptions of all/most components
  - 22* with components defined
  - 8 stubs

- New code & template release September 2014
  - Will be consistent with updated AOP Handbook

- Public access starting September 25, 2014
Third party Applications, plugins

AOP-KB Hub

AOP Wiki
Collaborative development of AOP descriptions & evidence

AOP Xplorer
Visualize attribute networks to discover & explore AOPs in a broader context

Effectopedia
Detailed development of structured & computational AOPs

Intermediate Effects DB
Put chemical-related AOP components in a regulatory context

AOP-KB
Shared chemical, biological and toxicological ontologies
AOP Discovery & Development

- Putative AOPs
- Formal AOPs
- Quantitative AOPs

AOP Networks

- Adapted from Edwards & Hutzler (2018), Tox Sci. 106(2):223-241
Using AOPs for Informed Decisions

Toxicant

Chemical Properties
- Receptor/Ligand Interaction
- DNA Binding
- Protein Oxidation

Macro-Molecular Interactions

Cellular Responses
- Gene activation
- Protein production
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Organism Responses
- Altered physiology
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Organ Responses
- Lethality
- Impaired Development
- Impaired Reproduction

Population Responses
- Structure Recruitment
- Extinction

Properties (QSAR) Disposition (exposure biomarkers)

Toxicity Pathways (HTS assays)

Key Events (bioindicators)

Regulatory Endpoints (adverse outcomes)
AOP Confidence + Testing Data -> Regulatory Decision Making

A

Key Event
Essentiality
Chemical
Information
Taxonomic
Applicability
Exposure/
ADME

Chemical Class
Molecular Initiating Event
Cellular Response
Organ Response
Organism Response
Population Response

Weight of evidence (WoE)
- Strong (S)
- Weak (W)

Direct Test Data Exists
Inference Possible
Direct Testing Possible
Research Needed

B

Key Event
Essentiality
Chemical
Information
Taxonomic
Applicability
Exposure/
ADME

C

Key Event
Essentiality
Chemical
Information
Taxonomic
Applicability
Exposure/
ADME

- Chemical Class
- Molecular Initiating Event
- Cellular Response
- Organ Response
- Organism Response
- Population Response

- Strong (S)
- Weak (W)

- Direct Test Data Exists
- Inference Possible
- Direct Testing Possible
- Research Needed
Acknowledgements

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•Dan Villeneuve
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•Gary Ankley
•Lyle Burgoon
•Robert Kavlock

• Collaborative Partners
  – OECD External Advisory Group on Molecular Screening & Toxicogenomics
  – IPCS/WHO Mode of Action Steering Committee
• Any interest in hiring a very talented scientist currently completing postdoctoral work in my group, please contact
  – Shannon Bell, Bell.Shannon@epa.gov

• Anyone interested in a postdoctoral position in my group, please contact me (Edwards.Stephen@epa.gov) or see the following ad
  – Google search: orise epa aop stephen edwards

Research Opportunity Description

Bioinformatics Approaches to Grouping Chemicals Using High-Throughput Screening Data
Research Participation Program
Office of Research and Development
National Health and Environmental Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC
EPA-ORD/NHEERL-ISTD-2014-01
AOP Wiki

Collaborative development of AOP descriptions & evidence

- Qualitative, **text-based descriptions** of an AOP in a structured environment
- Focus is on documenting the weight of **evidence** in support of the AOP
- **Synchronized** with the OECD guidance and handbook documents
- Online only access to encourage **crowd-sourcing** of AOP development
- Interfaces with the **AOP Xplorer** to provide AOP information in a **network** context
Effectopedia
Detailed development of structured & computational AOPs

- Visual interface for design and collaborative editing of AOP and chemical case studies
- AOP structure guidance is embedded in the system
- Ability to store and process quantitative information, including formal description of test methods, algorithms and models along with their applicability domains and verification methods
- Provides offline editing capabilities and robust capabilities for managing data access
- Embeds the concept of AOP networks directly in the system
- Provides capabilities for sharing, discussing, and reviewing AOPs
**Intermediate Effects DB**

Put chemical-related AOP components in a regulatory context

- **IUCLID** repository for AOP information
- Based on **OECD Harmonized Templates** (OHTs)
- Will profit from new OHT for "Intermediate Effects"
- Manages observations and conclusions concerning the nature and extent to which a **chemical** triggers an Intermediate Effect
- Links chemical information to AOPs
- Rich source of **quantitative data** for Effectopedia
AOP Xplorer
Visualize attribute networks to discover & explore AOPs in a broader context

- Allows user to **explore AOPs** in a **network context** based on shared key events
- Provides additional **bioinformatics analysis tools** for annotating key events and traversing the network
- Incorporates **putative AOP** information and facilitates **AOP discovery**
AOP Xplorer

- Explore AOPs in a network context based on the shared key events.
- Search for shared key events between AOPs or chemicals.
- Nodes and edges are clickable, that displays their attributes on the same page.
- Export AOP network into feature rich visualization and analysis tools such as Cytoscape.
AOP-KB Hub

- Central hub for all **shared information** among the AOP-KB components
- Operates via web services for maximum **flexibility** in implementation of the other modules and to provide access for third party tools
- Based on **established** chemical, biological and toxicological **ontologies** unified by a specifically-designed AOP ontology