AOP Knowledge Base/ Wiki Tool Set

Stephen W. Edwards
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

Office of Research and Development
Chemical Safety for Sustainability Research Program

Toxicant

Chemical Properties

Macro-Molecular Interactions
  - Receptor/Ligand Interaction
  - DNA Binding
  - Protein Oxidation

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

Properties (QSAR) Disposition (exposure biomarkers)

Toxicity Pathways (HTS assays)

Regulatory Endpoints (adverse outcomes)

Key Events (bioindicators)
Third party Applications, plugins

AOP-KB Hub
Shared chemical, biological and toxicological ontologies

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
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 Eftort by the Extended Advisory Group on Molecular Screening and Toxicogenomics. The other major components of this knowledgebase are Effoctopedia, 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

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
5. AOP
### Adverse Outcome Pathway in Wiki

**Title:** Estrogen receptor agonism leading to reproductive dysfunction

**Authors:**

**Status:**

**Revision:**

#### Key Events

<table>
<thead>
<tr>
<th>Key Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event 1</td>
<td>Event description 1</td>
</tr>
<tr>
<td>Event 2</td>
<td>Event description 2</td>
</tr>
</tbody>
</table>

#### Adverse Outcome

<table>
<thead>
<tr>
<th>Adverse Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome 1</td>
<td>Outcome description 1</td>
</tr>
</tbody>
</table>

#### Relationships Among Key Events and the Adverse Outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event 1</td>
<td>Outcome 1</td>
</tr>
<tr>
<td>Event 2</td>
<td>Outcome 2</td>
</tr>
</tbody>
</table>

#### Graphical Representation

![Graphical representation of the AOP](image)

#### Weight of Evidence Summary

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Summary</th>
<th>Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence Type 1</td>
<td>Summary 1</td>
<td>Table 1</td>
</tr>
<tr>
<td>Evidence Type 2</td>
<td>Summary 2</td>
<td>Table 2</td>
</tr>
</tbody>
</table>

#### References

Widgets Facilitate Data Entry

Summary of the AOP

Molecular Initiating Event

- Add Molecular Initiating Event to Table

<table>
<thead>
<tr>
<th>Molecular Initiating Event</th>
<th>Support for Essentaility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase, inhibition</td>
<td></td>
</tr>
</tbody>
</table>

Key Events

- Add Event to Table

<table>
<thead>
<tr>
<th>Event</th>
<th>Support for Essentaility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma 17beta-estradiol concentrations, Reduction</td>
<td></td>
</tr>
<tr>
<td>Transcription and translation of vitellogenin in liver, Reduction</td>
<td></td>
</tr>
<tr>
<td>Plasma vitellogenin concentrations, Reduction</td>
<td></td>
</tr>
<tr>
<td>Vitellogenin uptake into oocytes and oocyte growth/differentiation</td>
<td></td>
</tr>
<tr>
<td>Cumulative fecundity and spawning, Reduction</td>
<td></td>
</tr>
<tr>
<td>17beta-estradiol synthesis by ovarian granulosa cells, Reduction</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Outcome

- Add Adverse Outcome to Table

<table>
<thead>
<tr>
<th>Adverse Outcome</th>
<th>Support for Essentaility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population trajectory, Decrease</td>
<td></td>
</tr>
</tbody>
</table>

Add a Record

- Action
- Biological Process/Object
- Evidence supporting essentaility

Submit
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
Shared chemical, biological and toxicological ontologies

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

Third party
Applications, plugins
AOP Discovery & Development

- Putative AOPs
- Formal AOPs
- Quantitative AOPs

AOP Networks

[Diagram of AOP Networks]

Adapted from Edwards & Proctor (2003), Tox Sci. 106:212-216
Using AOPs for Informed Decisions

Properties
(QSAR)
Disposition
(exposure biomarkers)

Toxicity Pathways
(HTS assays)

Regulatory Endpoints
(adverse outcomes)

Key Events
(bioindicators)
AOP Confidence + Testing Data -> Regulatory Decision Making

A

Key Event
Essentiality

Chemical
Information

Taxonomic
Applicability

Exposure/
ADME

Weight of evidence (WoE)

Strong
Weak

Direct Test
Data Exists

Inference
Possible

Direct Testing
Possible

Research
Needed

S
W

B

C

Key Event
Essentiality

Chemical
Information

Taxonomic
Applicability

Exposure/
ADME
Acknowledgements

- Clemens Wittwehr
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- Max Felsher
- Harriet Ashcroft
- Kyle Painter
- Dan Villeneuve
- Kevin Crofton
- 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
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

Third party
Applications, plugins
**Effectopedia**
Detailed development of structured & computational AOPs

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

**AOP Wiki**
Collaborative development of AOP descriptions

**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**

**Third party Applications, plugins**

**System Size**
Shared chemical, biological, and toxicological ontologies
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.

### Table

<table>
<thead>
<tr>
<th>Title</th>
<th>Level of Organization</th>
<th>Description</th>
<th>Chemical</th>
<th>Upstream Cause</th>
<th>Downstream Effect</th>
<th>Species</th>
<th>Lifestages</th>
<th>Sex</th>
<th>Evidence Genes</th>
</tr>
</thead>
</table>
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

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