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
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 [edit]

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

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
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 17β-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/cleavage</td>
<td></td>
</tr>
<tr>
<td>Cumulative fecundity and spawning, Reduction</td>
<td></td>
</tr>
<tr>
<td>17β-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>
</tr>
</thead>
<tbody>
<tr>
<td>Population trajectory, Decrease</td>
</tr>
</tbody>
</table>
Androgen receptor agonism leading to reproductive dysfunction

**Authors**
Dai, V., Vlahos, L.

**Status**
Alert: The Wifey threat model.
Under development

**Abstract**
This adverse outcome pathway (AOP) involves thyroidal dysfunction of androstenedione aromatization in the liver, leading to increased estrogen production and exposure to thyroidally altered tissues, promoting reproductive dysfunction.

**Summary**

**Molecular in**

**Key Events**
- Key Event: Androgen receptor agonism

**Scientific evidence supporting the linkages in the AOP**

**Overall Assessment of the AOP**

**Weight of Evidence Summary**

<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>1</td>
<td>T-30 estrogen synthesis by ovarian granulosa cells, Reduction</td>
<td>Directly Leads to</td>
<td>T-30 estrogen synthesis by ovarian granulosa cells</td>
<td>Strong</td>
</tr>
<tr>
<td>2</td>
<td>Androgens, circulating concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Androgens, circulating concentrations</td>
<td>Strong</td>
</tr>
<tr>
<td>3</td>
<td>Testosterone synthesis by ovarian theca cells, Reduction</td>
<td>Directly Leads to</td>
<td>Testosterone synthesis by ovarian theca cells</td>
<td>Strong</td>
</tr>
<tr>
<td>4</td>
<td>T-30 estrogen synthesis by ovarian granulosa cells, Reduction</td>
<td>Directly Leads to</td>
<td>T-30 estrogen synthesis by ovarian granulosa cells</td>
<td>Strong</td>
</tr>
<tr>
<td>5</td>
<td>Plasma T-30b estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Plasma T-30b estradiol concentrations</td>
<td>Strong</td>
</tr>
<tr>
<td>6</td>
<td>T-30b estrogen synthesis by ovarian granulosa cells, Reduction</td>
<td>Directly Leads to</td>
<td>T-30b estrogen synthesis by ovarian granulosa cells</td>
<td>Strong</td>
</tr>
<tr>
<td>7</td>
<td>Plasma T-30b estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Plasma T-30b estradiol concentrations</td>
<td>Strong</td>
</tr>
<tr>
<td>8</td>
<td>Testosterone synthesis by ovarian theca cells, Reduction</td>
<td>Directly Leads to</td>
<td>Testosterone synthesis by ovarian theca cells</td>
<td>Strong</td>
</tr>
<tr>
<td>9</td>
<td>Cumulative estrogen exposure, Reduction</td>
<td>Directly Leads to</td>
<td>Cumulative estrogen exposure</td>
<td>Moderate</td>
</tr>
<tr>
<td>10</td>
<td>Androgens, circulating concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Androgens, circulating concentrations</td>
<td>Strong</td>
</tr>
<tr>
<td>11</td>
<td>Plasma T-30b estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Plasma T-30b estradiol concentrations</td>
<td>Strong</td>
</tr>
</tbody>
</table>

**Essentiality of the Key Events**
- Essentiality of the proposed key event is supported by experimental evidence showing the ability of anti-estrogen agents to reduce T or 3-3 production in vivo. In vitro exposure of fetal ovaries to 1,350 T or 1,350 estrogen or androgenic agents does not cause reductions in 3-3T synthesis at concentrations comparable to those that produce significant responses in vivo (i.e., at nontoxic concentrations). Alternatively, androgenic levels may be adequate to induce significant changes in estrogen production, as reported in some rodent studies of androgen treatment in vivo. A decrease in estrogen synthesis is observed in fetal ovaries treated with a combination of anti-estrogen agents and androgens.
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

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Joint Research Centre
United States Environmental Protection Agency

ERDC
AOP Discovery & Development

- Putative AOPs
- Formal AOPs
- Quantitative AOPs

AOP Networks

Using AOPs for Informed Decisions

Properties (QSAR) Disposition (exposure biomarkers)

Toxicity Pathways (HTS assays)

Key Events (bioindicators)

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

Weight of evidence (WoE)

Direct Test Data Exists
Inference Possible
Direct Testing Possible
Research Needed

Key Event
Essentiality

Chemical Information

Taxonomic Applicability

Exposure/ADME
Acknowledgements

- Clemens Wittwehr
- Brigitte Landesmann
- Marina Goumenou
- Sharon Munns
- Maurice Whelan

- Ed Perkins
- Natalia Garcia Reyero
- Tanwir Habib

- Hristo Aladjov
- Joop DeKnecht

- Collaborative Partners
  - OECD External Advisory Group on Molecular Screening & Toxicogenomics
  - IPCS/WHO Mode of Action Steering Committee
Change is Good

Questions?

• 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

**AOP Xplorer**

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

**Effectopedia**

Detailed development of structured & computational AOPs

**Intermediate Effects DB**

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**Third party**

Applications, plugins

**AOP-KB Hub**

Shared chemical, biological and toxicological ontologies
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

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**Intermediate Effects DB**
Put chemical-related AOP components in a regulatory context
- Based on **IUCLID** repository for AOP information
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**Third party Applications, plugins**
**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