Adverse Outcome Pathway Knowledge Base

Stephen Edwards
US EPA National Health & Environmental Effects Research Laboratory
**Toxicity Pathway:** A cellular response pathway that, when sufficiently perturbed, is expected to result in an adverse health effect.
Application of Research to Levels of Organization Based on Source to Outcome

Mode of Action, IPCS/EPA/ILSI 2001-2008

- Toxicity Pathway, NRC 2007
- Aggregate Exposure Pathway, Teeguarden 2016
- Adverse Outcome Pathway, Ankley 2010, Villeneuve 2014
AOP Components

- **Key Events (KEs) - nodes**
  - Change in biological state
  - Measurable and essential for progression
  - Molecular Initiating Event (MIE): Initial point of chemical interaction
  - Adverse Outcome (AO): Adverse outcome of regulatory significance

- **Key Event Relationships (KERs) - edges**
  - Connections between two key events
  - Critical for assembling evidence in support of the AOP

- **Does not explicitly include chemicals**
OECD AOP Development Programme

- Extended Advisory Group for Molecular Screening & Toxicogenomics (EAGMST)
- Guidance & Training
  - Guidance, User Handbook, many training options
- International Knowledgebase to capture information
  - >100 AOPs at various stages of development

AOP-KB

AOP-XML

e.AOP.portal

Effectopedia
Detailed development of structured & computational AOPs

Intermediate Effects DB
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
Five Principles of AOP Development

1. AOPs are not chemical specific
2. AOPs are modular (consisting of KEs and KERs)
3. An individual AOP is a pragmatic unit of development and evaluation
4. For most real-world applications, AOP networks are the functional unit of prediction
5. AOPs are living documents

Five Principles of AOP Development

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Factors Determining Predictivity of Early Key Events

- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs

Time between exposure and effect increases
Overlapping Phases of AOP Development

Define the AOP
Evaluate the AOP
Quantitatively describe the AOP

- Putative AOPs
- Formal AOPs
- Quantitative AOPs
OECD Handbook
Step by step guide to AOP development

AOP-Wiki
Provides consistent structure based on the OECD handbook and facilitates collaborative AOP development
http://aopwiki.org/
Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations

Short name: Alkylation of DNA leading to heritable mutations

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
<th>Triggers</th>
<th>Weight of Evidence</th>
<th>Quantitative Understanding</th>
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<tr>
<td>DNA, Alkylation</td>
<td>Directly Leads to</td>
<td>Insufficient or incorrect DNA repair, N/A</td>
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<td>Moderate</td>
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<td>Mutations, Increase</td>
<td>Strong</td>
<td>Moderate</td>
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<td>Heritable mutations in offspring, Increase</td>
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</tbody>
</table>

AOP Provides Understanding & Scaffold for Data
AOP Provides Understanding & Scaffold for Data

Toxicants → Toxins

Toxicity Pathways

- Macro-Molecular Interactions
- Cellular Responses
- Organ Responses
- Organism Responses
- Population Responses

High Throughput Tox

Guideline Studies

Mechanistic Toxicology Data
Bioindicators (e.g. Molecular Epi)

Epidemiology
Eco Field Studies
Mixed molecular organelle cellular Level of Biological Organisation

Fadrozole Aromatase Inhibition amphioxus vertebrates

Reduced E2 synthesis amphioxus vertebrates

Sex In-Vitro H295R human cells Fadrozole

In-Vitro Tox21 Aromatase Inhibition Fadrozole

In-Silico Petko Petkov's model Applicability domain Executable source code

Fadrozole f(x)

In-Vivo Fathead minnow Fadrozole Fadrozole

Aromatase Inhibition in primary tissue Fathead minnow Fadrozole

Ex-Vivo Fathead minnow Fadrozole

Effectopedia
Hristo Aladjov

Pathway Elements and quantitative information

In-Vivo Aromatase inhibition in primary tissue Fathead minnow Fadrozole

In-Vitro Tox21 Aromatase Inhibition Fadrozole

In-Silico Model Applicability domain Executable source code

Radio Immuno Assay Fathead minnow Fadrozole

In-Silico Petko Petkov's model Applicability domain Executable source code
In vivo effect, % Bound ERs

In vivo Concentration, [Log M]

Pathway elements – test response mapping

Test response mapping / set of transformation function(s)

Effectopedia Hristo Aladjov
Five Principles of AOP Development

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AOP networks emerge as AOPs are entered into the AOP-Wiki

Key Events Shared by Multiple AOPs

Linkages Shared by Multiple AOPs
AOP Network as Stored in the AOP-Wiki

- Molecular: AR Agonism, Aromatase Inhibition, ER ↓ Signaling
- Cell/Tissue: Granulosa Reduced E2 synthesis, Hepatocyte Reduced VTG expression & production, Oocytes Reduced VTG uptake, impaired development
- Organ: Hypothalamic Neurons (-) Feedback, Circulation Reduced E2 concentrations, Circulation Reduced VTG concentrations
- Individual: Female Decreased spawning and cumulative Fecundity
- Population: Declining trajectory
### Relationships Among Key Events and the Adverse Outcome

<table>
<thead>
<tr>
<th>Event</th>
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<th>Weight of Evidence</th>
<th>Quantitative Understanding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase, inhibition</td>
<td>Directly Leads to</td>
<td>17beta-estradiol synthesis by ovarian granulosa cells, Reduction</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
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<td>Directly Leads to</td>
<td>Plasma 17beta-estradiol concentrations, Reduction</td>
<td>Strong</td>
<td>Moderate</td>
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<tr>
<td>Plasma 17beta-estradiol concentrations, Reduction</td>
<td>Directly Leads to</td>
<td>Transcription and translation of vitellogenin in liver, Reduction</td>
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<td>Moderate</td>
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<td>Directly Leads to</td>
<td>Plasma vitellogenin concentrations, Reduction</td>
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<td>Moderate</td>
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<td>Plasma vitellogenin concentrations, Reduction</td>
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<td>Weak</td>
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<td>Vitellogenin accumulation into oocytes and oocyte growth/development, Reduction</td>
<td>Directly Leads to</td>
<td>Cumulative fecundity and spawning, Reduction</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cumulative fecundity and spawning, Reduction</td>
<td>Directly Leads to</td>
<td>Population trajectory, Decrease</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
AOPs in a Systems Biology Context
Chemical Interactions Emerge from AOP Networks
Modifying Factors Emerge from AOP Networks
Too many AOPs, too little time...
Accelerating AOP Development

Associations derived from public data sources
AOP-KB

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**Third party**
Applications, plugins
Current Status of AOP Development

- >100 putative AOPs in the AOP-Wiki
  (Most not under active development)

- 13 formal AOPs undergoing OECD review
  & 6 endorsed

- Increasing number of quantitative AOPs under development
OECD Endorsed AOPs
Working Group of the National Coordinators for the Test Guidelines (WNT)
Task Force on Hazard Assessment (TFHA)

OECD Endorsed (WNT and TFHA)
Click here for links to the official OECD versions

<table>
<thead>
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</tr>
<tr>
<td>Binding of agonists to ionotropic glutamate receptors in adult brain causes excitotoxicity that mediates neuronal cell death, contributing to learning and memory impairment.</td>
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<tr>
<td>Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities</td>
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<tr>
<td>Covalent Protein binding leading to Skin Sensitisation</td>
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<tr>
<td>Protein Alkylation leading to Liver Fibrosis</td>
</tr>
</tbody>
</table>
OECD AOP-KB Working Group

- Stephen Edwards
- Dan Villeneuve
- Kevin Crofton
- Gary Ankley
- Robert Kavlock
- David Lyons
- Max Felsher
- Rose Combs
- Landon Grindheim
- Cataia Ives
- Brendan Ferrer-Hanberry
- Evgeniia Kazymova

- Clemens Wittwehr
- Brigitte Landesmann
- Ivana Campia
- Sharon Munn
- Ahmed Sayed
- Maurice Whelan
- Hristo Aladjov
- Magda Sachana
- Joop DeKnecht

- Ed Perkins
- Lyle Burgoon
- Natalia Garcia Reyero

- Collaborative Partners
  - OECD External Advisory Group on Molecular Screening & Toxicogenomics
  - IPCS/WHO Mode of Action Steering Committee
AOP-Wiki 2.0 Release – November 2016

• Ability to provide more information through web services
  – Most new web services will come online in 2017
• Will incorporate ontologies to better characterize key events
• Improved snapshots for OECD reviews
• Improved help
• Will include better handling of chemicals
  – Connection with the EPA CompTox Dashboard
    (https://comptox.epa.gov/dashboard)
• Test version available in September
Core AOP Ontology
Describes AOP components only

AOP Ontology Developed & Maintained by Lyle Burgoon:
https://github.com/DataSciBurgoon/aop-ontology
Extending the Core AOP Ontology

- Core AOP Ontology is extended by incorporating existing chemical and biological ontologies
- US ACE – Extending core ontology to illustrate proof of concept for reasoners in risk assessment
- US EPA – Extending core ontology to capture AOP-Wiki information
- EC JRC – Extending core ontology to inform OECD 201 and the Intermediate Effects Database
- OECD Ontology Working Group – Oversees efforts and ensures compatibility with other related ontology efforts
AOP-Wiki Extensions
Initial Focus on Key Events

- Level of Organization:
  - Molecular
  - Cellular
  - Tissue
  - Organ
  - Individual
  - Population

- Context:
  - Cellular (CL)
  - Organ (Uberon)
  - Species (NCBI)

- Event:
  - Title
  - Level of Organization
  - Component(s)
  - Context

- Key Event
- Key Event
- Key Event

- Process
- GO, etc.

- Action
- Increased
- Decreased
- Altered
- Accelerated
- Delayed

Cataia Ives
Context changes across levels of biological organization

Cataia Ives
Using ontology to tag existing wiki entry

https://aopkb.org/aopwiki/index.php/Aop:25
AOP: “Aromatase inhibition leading to reproductive dysfunction (in fish)"
KE: Title “Transcription and Translation of Vitellogenin in Liver, Reduction”

https://aopkb.org/aopwiki/index.php/Aop:25

Cataia Ives
Ontologies that describe key events in existing AOPs

- Stressor
- Level of Organization
  - Molecular
  - Cellular
  - Tissue
  - Organ
  - Individual
  - Population
- Context
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Event Title
- Level of Organ
- Event(s)
- Tissue

Event Component
- Process
- GO, etc.
- Object
- GO, etc.
- Action
- PATO

AOP Components
- AOP
- KER
- (MIE)
- (AO)
OECD AOP Ontology Efforts

- **AOP-KB Ontology Effort**
  - Stephen Edwards
  - Cataia Ives
  - Clemens Wittwehr
  - Ivana Campia
  - Brigitte Landesmann
  - Ahmed Abdelaziz
  - Hristo Aladjov
  - Magda Sachana
  - Lyle Burgoon

- **OECD Ontology WG**
  - Richard Currie (chair)
  - Annamaria Colacci
  - George Fotakis
  - Ignacio Tripodi
  - Nikolai Georgiev Nikolov
  - Nina Jeliazkova
  - Olga Tcheremenskaia
  - AOP-KB Representatives

- **Cataia Ives**
- **Rong-Lin Wang**
- **Lyle Burgoon**
- **Kyle Painter**
Contents

1 Announcements
2 Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)
   2.1 Disclaimer
3 How to add a new AOP
   3.1 Before You Start
   3.2 OECD User Handbook
   3.3 Commenting on AOPs
   3.4 To create a new AOP
   3.5 To edit AOP wiki pages
   3.6 To edit other wiki pages (key events, MIE’s, etc.)

Announcements

There was a minor software upgrade for the AOP-Wiki on 2/13/2016. A list of the bug fixes and new features is available here: Release_Notes#Release_1.5.2831.2F17.2F2016.29. If you notice any problems, please email aopwiki@googlegroups.com and/or report here: Bug Reports.

Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)

If you are interested in contributing AOP-related knowledge to the AOP-KB, please follow the instructions laid out at the OECD Adverse Outcome Pathways, Molecular Screening and Toxicogenomics page. The Guidance on Developing and Assessing AOPs document is the basis for all work related to contributing and sharing AOP-related knowledge. A Users' Handbook Supplement to this Guidance has been written to aid systematic development and transparent assessment of Adverse Outcome Pathways (AOPs). The handbook contains a template to guide AOP description and...
Home

Announcements

OECD User Handbook
Wiki authors please refer to the OECD Users' Handbook when developing your AOP. If you notice any bugs, please report them.

Commenting on AOPs
To avoid spammers, we now require email confirmation before any user is allowed to edit. We apologize for any inconvenience this may cause. Instructions for confirming your email if you already have an account are given here: Confirm Email. If you have any troubles confirming your email, please email us at aopwiki@googlegroups.com. Before commenting on AOPs, please read the AOP Wiki Editing & Comments Policy. Additional guidance for commenting is available here: Commenter Information.

AOP Welcome

Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)
If you are interested in contributing AOP-related knowledge to the AOP-KB, please follow the instructions laid out at the OECD Adverse Outcome Pathways for the Evaluation of Chemicals to Risk Assessment (AOP) wiki - Collaborative Portal. The Guidance Documents and AOPs in AOP-Wiki are a joint effort among member states to create a comprehensive and consistent database of AOPs. This wiki aims to facilitate the exchange of knowledge and expertise among stakeholders, including regulatory agencies, researchers, and industry representatives. By contributing to this wiki, you will be helping to advance the scientific understanding of adverse outcomes and contribute to the development of more effective risk assessment tools.

Help About FAQ Metrics
## AOP Search Results

<table>
<thead>
<tr>
<th>Title</th>
<th>Corresponding Author</th>
<th>Author Status</th>
<th>SAAOP Status</th>
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<th>OECD Status</th>
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<tr>
<td>Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations</td>
<td>Arthur Author</td>
<td>Open for citation &amp; comment</td>
<td>Included in OECD work plan</td>
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<td>DNA alkylation</td>
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Listing of AOPs with OECD status

TFHA/WNT Endorsed

Open for citation & comment

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Listing of AOPs with SAAOP status

Under Development

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User Roles

- **Gardener**
  - Experienced AOP developers to help ensure consistency with published principles and OECD guidelines
- **Author**
  - Can create new AOPs and edit AOP components
- **Authenticated User (self created account)**
  - Can comment on AOPs, KEs, & KERs
- **Anonymous**
  - Read only
<table>
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</tr>
</tbody>
</table>

Edited on AOP page by Authors

Edited on this page by Gardeners

Gardeners only
AOP Authors

• Corresponding author
  – Controls access
  – Point of contact for questions/comments

• Contributors
  – Able to edit the AOP

• Author list
  – Free text field as in current wiki
<table>
<thead>
<tr>
<th>Title</th>
<th>Short name</th>
<th>Authors &amp; Gardeners</th>
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<td>1) Aniline and 2,4-DNT are converted to the reactive hydroxylamino form which oxidizes heme Iron(II) in hemoglobin to Iron(III)</td>
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Editing Aop

Title
Aromatase inhibition leading to reproductive dysfunction (in fist)

Short name
Aromatase inhibition leading to reproductive dysfunction (in fist)

Corresponding author
Undefined

Authors
Dan Villeneuve, US EPA Mid-Continent Ecology Division (villeneuve.dan@epe.gov)

WYSIWYG
Easily create tables and add images

Save changes to all sections with one click

Edit all text sections from a single page
Ontology Tags for Key Events

- Event Components
  - Process
  - Object
  - Action
- Event Context
  - Tied to level of organization
  - Cellular, Organ, Taxonomy
- All terms driven by biological ontologies
Comments

- Modern look & feel
- Allows comments on comments
## Versions of Aop:154

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<th>Aop as of:</th>
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<th>from</th>
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[Compare](#)

## Change log

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Short Name
nothing to show

Authors
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Abstract
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Aop:154 as of June 07, 2016 10:30

nothing to show

nothing to show

Great author

This AOP is concise
Acknowledgements

OECD AOP-KB Working Group

- Stephen Edwards
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- Kevin Crofton
- Gary Ankley
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- Ivana Campia
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Collaborative Partners
- OECD External Advisory Group on Molecular Screening & Toxicogenomics
- IPCS/WHO Mode of Action Steering Committee
- Rose Combs
- Landon Grindheim
- Cataia Ives
- Brendan Ferreri-Hanberry
- Evgeniia Kazymova
Questions?

SYSTEMS TOXICOLOGY