Presentation Outline

• OECD AOP Development Programme
  – Background
  – OECD work on predictive toxicology
  – Main milestones
  – IT tools
Background
Use of animals for human and ecological risk assessments

- Skin sensitization
- Dermal toxicity
- Acute toxicity
- Chronic toxicity
- Genotoxicity
- Carcinogenicity
- Reproduction toxicity
- Neurotoxicity
- Eye irritation / corrosion
- Skin irritation / corrosion
- Development toxicity
Data quality ensured by

OECD Test Guidelines

OECD Principles of Good Laboratory Practise and Compliance Monitoring Procedures

Mutual Acceptance of Data
Growing concern over lack of toxicological data

Chemicals on the market

Only 10 - 20% has been fully assessed
Countries are improving their legislation to assess more chemicals in a shorter time frame.
Standard toxicity testing is costly, time consuming and requires many animals.

- 5000 animals / chemical
- Test duration: 30 – 720 days
- Costs: €2,000 - €2,000,000
Promoting the use of non-animal methods

- OECD Test Guidelines based on non-animal methods (skin and eye corrosion/irritation, phototoxicity, skin absorption and sensitisation, genotoxicity)

- Development of models to predict the toxicity of chemicals (grouping of chemicals and read across)

- Computational methods
Need for mechanistic understanding

Test Chemical

Developmental & Reproductive toxicity
Identifying the mechanism(s)

Adverse Outcome Pathway

Molecular Initiating Event → ... → Adverse Outcome

Level of Biological Organisation

Molecular | Organelle | Cellular | Tissue | Organ | Organism | Population

Pathogenesis/Time

= Key Event
= Key Event Relationship
OECD work on Predictive Toxicology
AOP’s central role in OECD work on predictive toxicology

OECD Test Guidelines Programme

Identification of new in vitro test methods that are candidates to become OECD Test Guidelines

OECD QSAR Project

Identification of new methods/profiling for grouping chemicals

AOPs

Development of IATA for defined hazard endpoints

OECD Hazard Assessment activities
Key events can be measured with non-animal tests, which can be used to predict the adverse outcome.
Selection of methods for Test Guideline development/refinement
Development of (Q)SARs
General workflow in IATA

Problem formulation

Gather existing information

Weight of Evidence Assessment: Adequate information for decision-making?

YES

NO

Generate additional information

Weight of Evidence assessment: Adequate information for decision-making?

YES

NO

YES

Regulatory conclusion

Multiple strategies e.g. in house data, mining of relevant databases, literature search
Framework for how an AOP can be applied to inform and structure IATA

**Problem formulation**
- regulatory need, endpoint, constraints, acceptable uncertainty

**Gather existing information**
- organise and structure information using an AOP as a frame

**Weight of Evidence Assessment: Adequate information for decision-making?**

**Generate additional information**
- use an AOP to help identify and/or develop targeted testing, testing strategy or assay development and apply

**Weight of Evidence assessment: Adequate information for decision-making?**

**Regulatory conclusion**
Milestones achieved
Main milestones achieved since the launch of the OECD AOP Development Programme

2012
OECD AOP Development Programme

2013
Guidance document on developing and assessing AOPs

2014
AOP-KB and Users’ Handbook supplement to the guidance document for AOPs

2015
External review of AOPs and training material for AOP development

2016
5 AOPs were published in the new OECD Series on AOPs

Future: Increase the AOP-KB content and facilitate the use of AOPs in a regulatory context
OECD Series on Adverse Outcome Pathways

An Adverse Outcome Pathway (AOP) describes a logical sequence of causally linked events at different levels of biological organisation, which follows exposure to a chemical and leads to an adverse health effect in humans or wildlife. AOPs are the central element of a toxicological knowledge framework, promoted by member countries through OECD, built to support chemical risk assessment based on mechanistic reasoning. These AOPs are available in the AOP Wiki, an interactive and virtual encyclopedia for AOP development. Following their development and review, the endorsed AOPs are published the OECD Series on Adverse Outcome Pathways. As scientific knowledge progresses, the publication of an AOP in this series does not preclude the regular update or new contributions to a given AOP in the AOP Wiki. While the AOP Wiki is a dynamic tool, only impactful changes to the AOP will be reflected in subsequent updates of the published AOP. The number 1 in the OECD Series on Adverse Outcome Pathways is the Users’ Handbook, which is a supplement to the Guidance Document for developing and assessing AOPs. This handbook contains an updated template for AOP development and provides focused and practical instructions for both AOP developers and reviewers. For more information, please visit the OECD website on AOPs.
Skin sensitisation AOP and alternative method toolbox

- Chemical Structure/Properties
- MIE
- Cellular Level
- Tissue Level
- Organ Level

- Electrophilic Chemicals
- Covalent Protein Binding to Skin Proteins
- Keratinocyte Activation
- Dendritic Cell Activation
- T-cell Activation and Proliferation
- Skin Sensitisation

- In vitro skin absorption (TG 428)
- QSARs
- In silico toxicokinetic models

- TG 442C (DPRA)
- TG 442D (ARE-Nrf2 Luciferase test method, KeratinoSens™) LuSens
- h-CLAT (TG 442E) U-SENS™
- Sens-is
- IL-8 Luc assay RhE IL-18

- In vitro T cell priming/proliferation
- Guinea Pig Maximisation Test
- Buehler Test
- Local Lymph Node Assay

AOP from ENV/JM/MONO(2012)10/PART1

https://aopwiki.org/wiki/index.php/Aop:40
Skin sensitisation: many possibilities of combining information

Test chemical

- h-CLAT
  - Positive: MIT<10 → Strong
  - Negative: MIT>10 → Weak

- DPRA
  - Positive: Not classified

Potency classification

- Strong: 7
- Weak: 2-6
- Not classified: 0-1


<table>
<thead>
<tr>
<th>Score</th>
<th>h-CLAT MIT</th>
<th>DPRA depletion</th>
<th>DEREK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>≤10 µg/mL</td>
<td>≥42.47%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>&gt;10, ≤150 µg/mL</td>
<td>≥22.62, &lt;42.47%</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>&gt;150, ≤5000 µg/mL</td>
<td>≥6.376, &lt;22.62%</td>
<td>Alert</td>
</tr>
<tr>
<td>0</td>
<td>not calculated</td>
<td>&lt;6.376%</td>
<td>No alert</td>
</tr>
</tbody>
</table>

Hirota et al. (2015) J. Appl. Toxicol.: Artificial Neural Network

Jaworska et al. (2015) Arch. Toxicol.: Bayesian Network

Natsch et al. (2015) Toxicological Science: Global/domain-based assessment
Registrants to use alternative test methods for skin sensitisation

ECHA/NI/16/32

The REACH requirements for skin sensitisation are changing, making non-animal testing the default requirement. Registrants are encouraged to consider their testing strategies now for the 2018 registration deadline.

Helsinki, 5 July 2016 - The amended REACH annexes concerning skin sensitisation are expected to enter into force in autumn 2016. The information needed for the classification or risk assessment of a substance will then be obtained through non-animal methods as a first step. In vivo methods can only be used if the in chemico or in vitro test methods are not adequate for the substance or cannot be used for classification and risk assessment.

With the amended requirements, if a substance is predicted to be a skin sensitisier based on the available data, skin sensitisation potency should also be assessed. There is currently no standardised way to assess potency with the in vitro methods and therefore the in vivo test may still be necessary.

However, estimating potency is not necessary if an existing in vivo study does not allow potency estimation and the study has been performed according to internationally-adopted test methods and good laboratory practice.
AOP-KB
AOP-KB modules

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

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

**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

**Third party**
Applications, plugins

**e.AOP.portal**

**AOP-XML**
Main Page

Contents [hide]

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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_281.2F17.2F2016.29. 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
Effectopedia is an open-knowledge aggregation and collaboration tool designed to facilitate the interdisciplinary efforts for delineating adverse outcome pathways (AOPs) in an encyclopedic manner with greater predictive power. As a response to the growing awareness that a paradigm shift in chemical risk assessment is needed, Effectopedia provides a capability to move beyond the last half-century's phenomenological approach with animal testing to a more mechanistic and hypothesis-driven approach. The 21st-Century shift to more prospective hypothesis generation requires more strategic use of systems biology, QSAR and archived toxicological information in the form of AOPs. Effectopedia is designed as a new technology both to reduce multidisciplinary barriers in the development of AOPs and to integrate AOPs with historical case studies.
## Retrieve all Adverse Outcome Pathways

Enter query to retrieve matching AOP titles, or leave blank to display all AOPs

*Example: Androgen*

![START QUERY »](image-url)

### Results

<table>
<thead>
<tr>
<th>AOP Title</th>
<th>View in native app</th>
<th>AOP Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-hydroxytryptamine transporter (5-HTT) inhibition leading to population increase</td>
<td>AOP195</td>
<td><a href="https://aopwiki.org/">https://aopwiki.org/</a></td>
</tr>
<tr>
<td>5-hydroxytryptamine transporter (5-HTT; SERT) inhibition leading to decreased shelter seeking and increased predation</td>
<td>AOP98</td>
<td><a href="https://aopwiki.org/">https://aopwiki.org/</a></td>
</tr>
</tbody>
</table>
As in the current e.AOP Portal show a paginated list of AOPs sorted in alphabetic order of the titles form all available data sources (AOP-Wiki and Effectopedia). Allow user to choose different sorting criteria arrange with combo box or list of options: (which can allow users to choose between ascending or descending order)

Sort by: status, title, creation date, last modification date

**Aromatase inhibition leading to reproductive dysfunction (in fish)**
https://aopkb.org/aopwiki/index.php/Aop:25
Aromatase, Inhibition; 17beta-estradiol synthesis by ovarian granulosa cells, Reduction; Cumulative fecundity and spawning, Reduction; Plasma 17beta-estradiol concentrations, Reduction; Plasma vitellogenin concentrations, Reduction; Transcription and translation of vitellogenin in liver, Reduction; Vitellogenin uptake into oocytes and oocyte growth/development, Reduction; Population trajectory, Decrease …

Created on 01.01.2014, Last updated 14.01.2016, Status: EAGMST Approved, Project number, Review Report, i-Library
Source AOP-Wiki
Interlinkages between systems - data exchange
Websites for further information


• e.AOP.Portal:
  – Test platform http://aopkb-pp.oecd.org/
  – Production platform http://aopkb.oecd.org/ when the domain name will be transferred

• Wiki platform: https://aopkb.org/aopwiki
• Effectopedia: http://www.effectopedia.org/
THANK YOU
Types of IATA

Flexible
Judgement-based

Prescriptive
Rule-based

Non-formalised approaches
e.g. grouping and read-across

"Structured approaches"
e.g. Integrated Testing Strategy (ITS)

OECD IATA Case Studies Project

OECD Project on defined approaches
Defined approaches

• A defined approach to testing and assessment consists of a fixed data interpretation procedure (DIP) (e.g. sequential testing strategies, regression models, 2 out of 3 WoE, scoring systems, machine learning approaches, Bayesian networks, etc...) applied to data generated with a defined set of information sources (formalised decision-making approach)

• The result can either be used on its own, or together with other information sources within an IATA