Introduction to the concept of Adverse Outcome Pathways and Integrated Approaches to Testing and Assessment according to the Organization of Economic Cooperation and Development

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Outline

* AOP overview
  o Building
  o Assessing confidence
* OECD AOP programme
  o Template, guidance, knowledgebase
  o AOP wiki
* Using AOPs to support decision making
* Integrated Approach to Testing and Assessment
  o Regulatory use
  o Evaluating confidence/appropriateness
* Summary
AOPs delineate the documented, plausible, and testable processes by which a chemical induces molecular perturbations (Molecular Initiating Events) and the associated biological responses (Key Events) that describe how the molecular perturbations cause effects (Adverse Outcomes) at the subcellular, cellular, tissue, organ, whole animal, and population levels of observation.

Building an AOP

- Start anywhere
- Gather all existing knowledge
- Evaluate and document the information
- Translate and capture information as a pathway
Assessing Confidence in an AOP

1. the quality, nature (e.g. qualitative or quantitative) and amount of supporting information used to inform various elements of the pathway (e.g. KEs and KERs)

2. the availability, quality and appropriateness of assays and prediction models used to query the pathway and predict the AO.
OECD template and guidance address development:

* Allows substantiation of all supporting information (data summary, references)
* Guidance for evaluating the WoE of the information supporting each element → low, medium or high confidence
* Guidance for evaluating the WoE for the AOP overall
Guidance for creating, documenting, implementing AOPs in the AOP Wiki

* **Template** format for project proposals
* **Guidance document on developing and assessing AOP** (2013), No. 184 Series Testing and Assessment
* **User handbook** updated guidance including assessing the confidence of the AOP and its elements (https://aopkb.org)
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

Description “borrowed” from Steve Edwards
# Assessing Confidence in AOP Elements

**Biological Plausibility:** Is there a mechanistic relationship between the KE\textsubscript{upstream} and the KE\textsubscript{downstream} consistent with established biological knowledge?\textsuperscript{1}

<table>
<thead>
<tr>
<th>High (Strong) Confidence: Extensive understanding of the KER</th>
<th>Moderate Confidence: The KER is plausible</th>
<th>Low (Weak) Confidence: Some empirical support</th>
</tr>
</thead>
</table>

**Essentiality:** Are downstream Key Events and/or the Adverse Outcome prevented if an upstream Key Event is blocked?

<table>
<thead>
<tr>
<th>High (Strong) Confidence: Direct evidence from experimental studies</th>
<th>Moderate Confidence: Indirect evidence</th>
<th>Low (Weak) Confidence: No or contradictory evidence</th>
</tr>
</thead>
</table>

**Empirical Evidence:** consistent, inconsistent?

<table>
<thead>
<tr>
<th>High (Strong) Confidence: Extensive evidence for temporal, dose-response</th>
<th>Moderate Confidence: multiple reports of consistent evidence, with</th>
<th>Low (Weak) Confidence: Limited or no studies and/or significant</th>
</tr>
</thead>
</table>


Using AOPs: confidence is related to potential use

The extent to which an AOP can be relied upon to inform decisions is related to the amount of supporting information and the confidence in the AOP.
Using an AOP in decision making

- Support WoE evaluations of existing information
- Identify missing information (necessary for decision)
- Form the basis of prediction models
- Design integrated testing strategy (ITS) to provide additional information
- Identify assays for ITS
“a structured approach that strategically integrates and weights all relevant data to inform regulatory decisions regarding potential hazard and/or risk and/or the need for further targeted testing and therefore optimizing and potentially reducing the number of tests that need to be conducted.”

Use of an IATA for Regulatory Decisions

IATA
Decision Context

AOP

- Start with problem formulation (decision context)
- Identify information needs
- Incorporate integrated, iterative testing strategy
- AOP provides biological rationale

OECD IATA workshop, Nov 2014
Use of IATA in Regulatory Decisions

**IATA**

**Decision Context**

- **AOP**
  - **KER1**
  - **KER2**
  - **KER3**
  - **KERn**

- **Adverse outcome**
  - **Assay 1**
  - **Assay 2**
  - **Assay 3**
  - **Assay n**

- **KE 1**
- **KE 2**
- **KE n**

**Exposure**

**ADME**

**Existing info**

**Endpoint of concern**

**Decision**

Could IATA function to harmonize use of non-standard information/approaches/assays?

How to evaluate applicability/ confidence in IATA?
Assessing assays and IATA for regulatory use

* Step 1: Assessing the assays
  o Used in the context of an integrated strategy → do not predict the AO on their own
  o How to assess performance?
  o Use a subset of ECVAM validation principles, QSAR assessment principles and concepts from performance-based test guidelines

Assessing the assays

* **ECVAM validation modules**
  - Test definition
  - Reproducibility
  - Transferability
  - Inter-lab reproducibility
  - Predictive capacity
  - Applicability domain
  - Performance standards

* **QSAR validation principles**
  - Defined endpoint
  - Unambiguous algorithm
  - Defined domain of applicability
  - Goodness–of-fit, robustness, predictivity
  - Mechanistic interpretation

* **Performance Standards**
  - OECD/ICCVAM
  - essential test method components
  - a minimum list of reference chemicals
  - comparable levels of accuracy and reliability
Assessing the assays

* Basic elements
  o **Test definition**: essential components, defined endpoint
  o **Reproducibility**: intra-lab (inter-lab optional)
  o Defined list of **reference chemicals**
  o **Accuracy** of prediction of (mechanistic) endpoint
    • *Relative to other assays, known reference chemicals*
  o **Sensitivity/specificity**
    • *Relative to known reference compounds/assays*
  o **Transparent Interpretation/Prediction models**
    • Limitations
  o Defined applicability domain

See Patlewicz et al. 2015. Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory use. Regul. Toxicol. Pharm. 71:463-477.
Regulatory acceptance: evaluating the IATA

IATA

Decision Context

AOP

- MIE
  - KE 1
    - KE 2
      - KE n
        - Adverse outcome

Assay 1
Assay 2
Assay 3
Assay n

Exposure
ADME
Existing info

Endpoint of concern
Regulatory question

* Step two: assess the reliability of the IATA over-all
  - A similar set of criteria could be used to assess the IATA overall, taking
In summary

Summary

* AOPs (the AOP wiki, and related databases) allow maximal use of experimental information from a wide variety of sources
  * Transparent evaluation of confidence
  * Relational framework of information based on biological understanding
  * Provide support for WoE, instruct ITS design

* IATA provide a flexible framework for answering questions
  * Include ITS informed by AOPs

* IATA could be evaluated for regulatory use
  * Using subsets of established validation criteria, WoE
  * Use of IATA could facilitate regulatory application of non-standard information sources
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