ADVERSE OUTCOME PATHWAYS: WHERE DO YOU START?

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THE AIM OF MY PRESENTATION is to discuss how one gets started in developing an adverse outcome pathway (AOP).
A framework comprised of the events at the different levels of biological organization and other key dimensions (e.g., gender, life stage etc.) and their causal relationships. A means of providing the mechanistic basis for justifying the use of alternative approaches.

living workflow.
Aspects & Features of an AOP
Stages of an AOP
The Role of OECD
Tools for Informing & Documenting AOPs
WORKFLOW FOR AN AOP

Molecular initiating event (MIE)

Intermediate events or predictive relationships spanning levels of biological organization

Adverse outcome relevant to the assessment

Anchor 1

Evidence from the literature or targeted testing

Anchor 2
Identification of the mechanism/reaction of the chemical-biological interaction - anchor 1.

Understanding of the final outcome elicited by the MIE - anchor 2.

Often not enough information to accept a prediction, especially for no effect.
Single Molecular Initiating Event (MIE)- One interaction of the chemical of interest with a biological molecule.

Single Final Outcome- One regulatory adverse effect of interest.

Key Events- Testable intermediate events which are mechanistically linked to the MIE and the final outcome.
KEY EVENTS ARE seminal intermediate events that are toxicologically relevant to the final outcome. The basis for hypothesis development and testing. Thus, must be experimentally quantifiable.

Typically quantified with rapid screening methods including protocols which assess *in chemico* and *in vitro* biomarkers and signatures (i.e., surrogates for *in vivo* outcome).
DEVELOPMENT OF AN AOP

Molecular initiating event (MIE)  

Intermediate events or predictive relationships spanning levels of biological organization

Evidence from the literature or targeted testing

Adverse outcome relevant to the assessment

Anchor 1  

Anchor 2
Documentation - Experimental evidence in the literature required to support all noted events.

Plausible Cause and Effects - Believable and likely relationships which follow mechanistic understanding.

Testable - Able to formulate hypotheses and test them.
Separating mechanisms from symptoms.

Separating events that control potency from events that confirm the AOP is being followed.

Getting agreement on key events.

Getting agreement on the methods for assessing a key event.
Maturity of an AOP

grows with better understanding of intermediate events and the ability to identify key events.

grows with increased characterization of the AOP.

How well are the initiating and other key events causally linked to the outcome?

What are the limitations in the evidence in support of the AOP?
STAGES OF AN AOP

Incomplete AOP
Qualitative AOP
Semi-Quantitative AOP
Quantitative AOP
INCOMPLETE AOP

Has only qualitative or limited quantitative understanding of one or two cause and effect linkages between key events; often based on a few compounds tested in two assays.

Not all key events have been identified.

Not able to assess the Weight-of-Evidence supporting the AOP by applying Bradford Hill criteria.

Not able to assess the reliability and robustness of the AOP.

Not able to determine the response-to-response relationships required to scale in vitro effect to in vivo outcome.
QUALITATIVE AOP

Has qualitative understanding of the AOP - assessment of the experimental evidence and empirical data across the key events; often based on one or a few well-studied compounds.

All key events have been identified.

Able to assess the Weight-of-Evidence supporting the AOP by applying many of the Bradford Hill criteria.

Weak assessment of the reliability and robustness of the AOP; able to evaluate the experimental support of one or two of the key events.

Not able to determining the response-to-response relationships required to scale in vitro effect to in vivo outcome.
Has semi-quantitative understanding of the AOP - assessment of the experimental evidence and empirical data across the key events; based on multiple compounds studied at the key events.

All key events have been identified.

Able to assess the Weight-of-Evidence supporting the AOP by applying most of the Bradford Hill criteria.

Moderate assessment of the reliability and robustness of the AOP; able to evaluate the experimental support of most of the key events.

Not able to determining the response-to-response relationships required to scale *in vitro* effect to *in vivo* outcome.
Has quantitative understanding of the AOP - assessment of the experimental evidence and empirical data across the key events; based on many compounds studied at the key events.

All key events have been identified.

Able to assess the Weight-of-Evidence supporting the AOP by applying all of the Bradford Hill criteria.

Strong assessment of the reliability and robustness of the AOP; able to evaluate the experimental support of all the key events.

Able to determining the response-to-response relationships required to scale in vitro effect to in vivo outcome.
The AOP programme is coordinated by the Molecular Screening and Toxicogenomics Programme in conjunction with the QSAR Toolbox Project.

http://www.oecd.org/env/ehs/testing/molecularscreeningandtoxicogenomics.htm

http://www.oecd.org/env/ehs/testing/listsofprojectsontheaopdevelopmentprogrammeworkplan.htm
OECD AOP PROJECTS

1. Formal AOPs
2. Case Studies (preliminary AOPs)
3. Guidance Documents
4. Knowledge Management Tools
5. Others
Currently undergoing revision and further development

Scheduled for release in Q3 2014
OECD AOP DEVELOPMENT PROCESS

1. Proposal by a stakeholder to develop an AOP.
2. Development of an AOP on the AOP-KB.
4. Approval by sub-bodies of the Joint Meeting of OECD, and declassification and publication of the AOP by OECD.

http://www.oecd.org/chemicalsafety/testing/toxicogenomics.htm#Introduction
“AOP-KB Wiki” is a joint sponsored project:

It is a Wiki-base tool that provides a verbal description of an AOP following the OECD guideline and using the OECD template.

http://aopwiki.org

AOP-KB WIKI DEVELOPMENT TIMELINE

Currently – Beta version available for OECD AOP development teams (Must submit a proposal to the OECD Secretariat).

Q4 2014 – Production release with broader access (To be determined by OECD External Advisory Group in November)

Integration with other AOP-KB components

Effectopedia
(Developed by the International QSAR Foundation)

AOP Network Tool
(Developed by the US Army Corps of Engineers – Engineering Research and Development Center)
Thank You....

If time permits, I will be happy to answer any questions.