Introduction to Adverse Outcome Pathways and the AOP Wiki

Sunday July 20, 2017
10:00 AM - 12:00 PM
Sheraton Seattle, Aspen Room

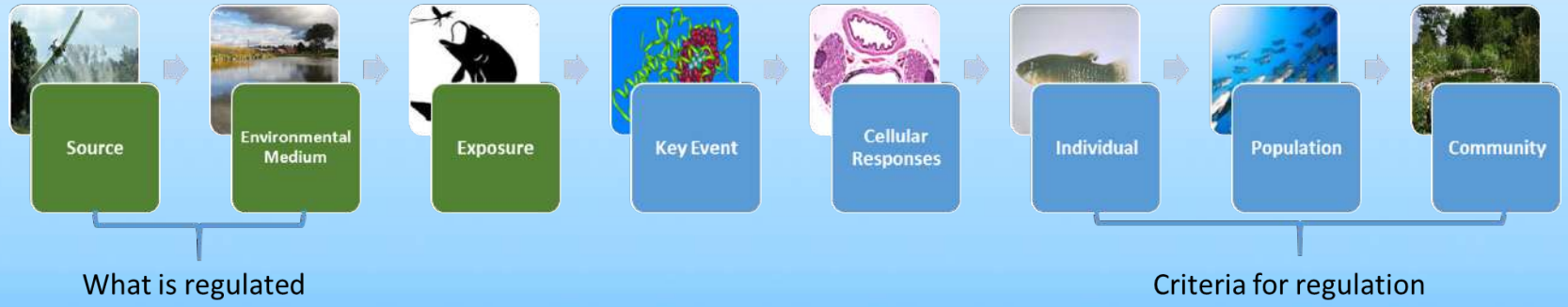
10:00: Introduction to the OECD AOP Programme and Online Training course
Kate Willett, Human Toxicology Project Consortium

10:40: Building AOPs for Neurotoxicity: Perspective from an Academic
Prof. Dr. Ellen Fritsche, IUF – Leibniz Research Institute for Environmental Medicine

11:20: Demonstration and Hands-On Activity with AOP Wiki
Kristie Sullivan, Physicians Committee for Responsibility Medicine

PCRM

HUMAN TOXICOLOGY PROJECT CONSORTIUM



Introduction to the OECD AOP Programme and Online Training course

Catherine Willett, Humane Society of the United States, Humane Society International

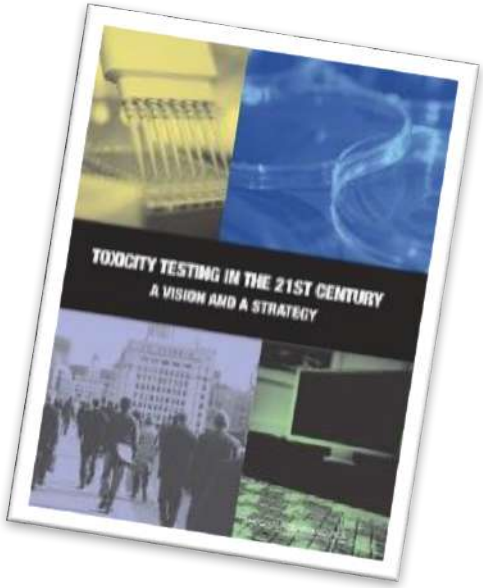
Outline: Adverse Outcome Pathways

- Why
  - Need for faster, predictive approach to toxicology
  - Need for better access/organization of existing and future data
- What
  - Purpose, definition
  - OECD AOP Program
- How
  - AOP Wiki
  - Guidance
  - Evaluation
- When
  - Use in decision making
  - Support of integrated Approaches to Testing and Assessment

Need for faster, predictive toxicology

"Transform toxicity testing from a system based on whole animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cell, cell lines, or cellular components, preferably of human origin."

Including "tests that assess critical mechanistic endpoints involved in the induction of overt toxic effects rather than the effects themselves."

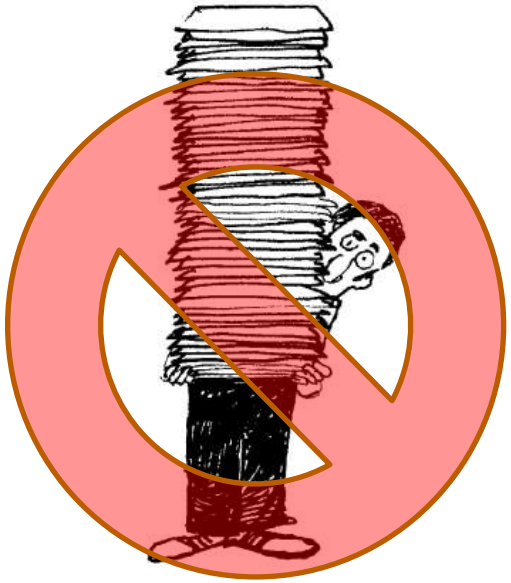


National Academy of Sciences, 2007

Need for better access to and organization of data

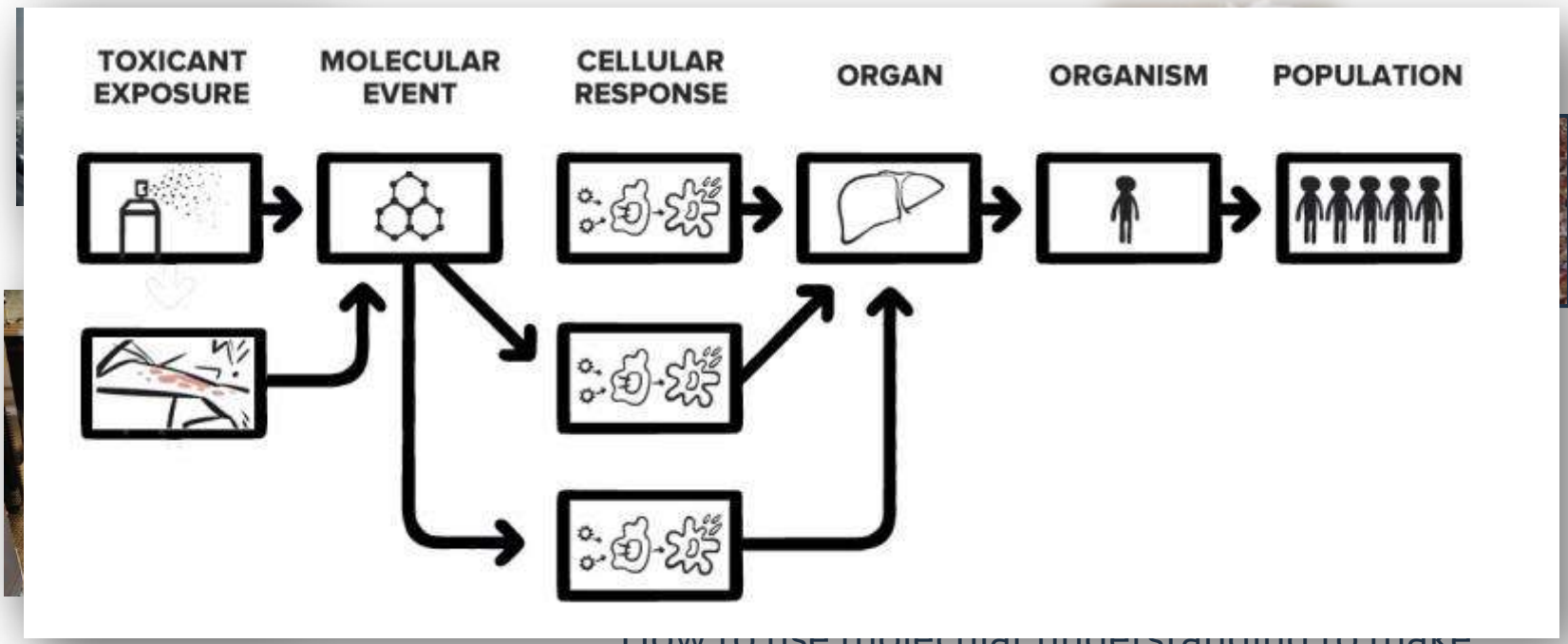
Data in published papers (pdfs), reports, report summaries are not suited to:

- Facilitating collaboration and crowd-sourcing
- Avoiding duplicative effort
- Integration and analysis
- Searching and machine-reading



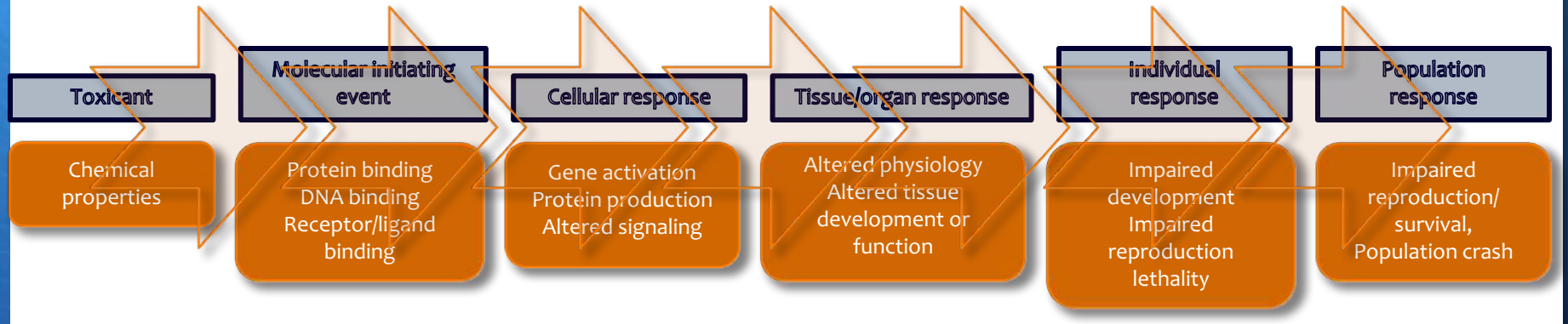
Adapted from D. Villeneuve

Adverse Outcome Pathways: linking molecular initiation to adverse outcomes



How to use molecular understanding to make better decisions about chemical safety

Linking molecular information to adverse outcomes: Adverse Outcome Pathways

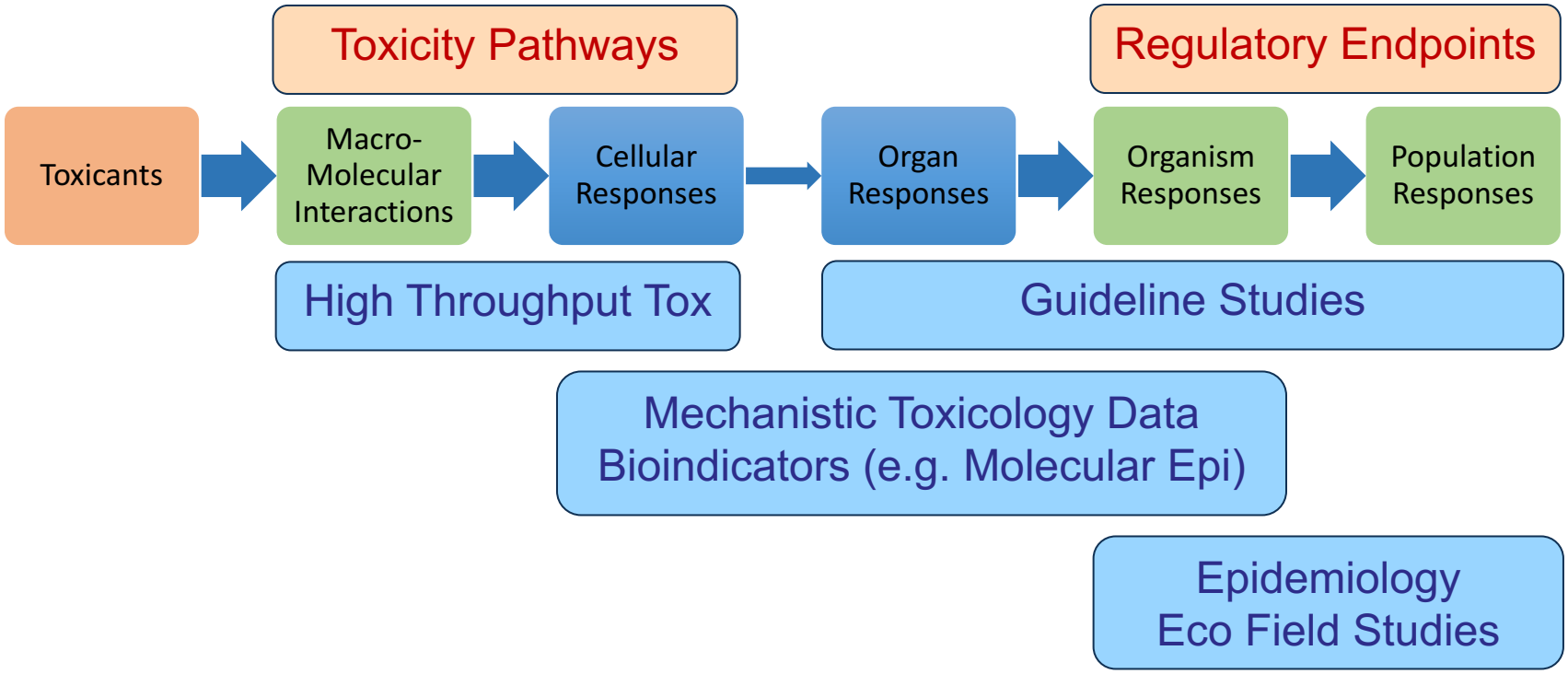


"Conceptually, an AOP can be viewed as a sequence of events commencing with initial interactions of a stressor with a biomolecule in a target cell or tissue (i.e., molecular initiating event), progressing through a dependent series of intermediate events and culminating with an adverse outcome."

"AOPs are typically represented sequentially, moving from one key event to another, as compensatory mechanisms and feedback loops are overcome."

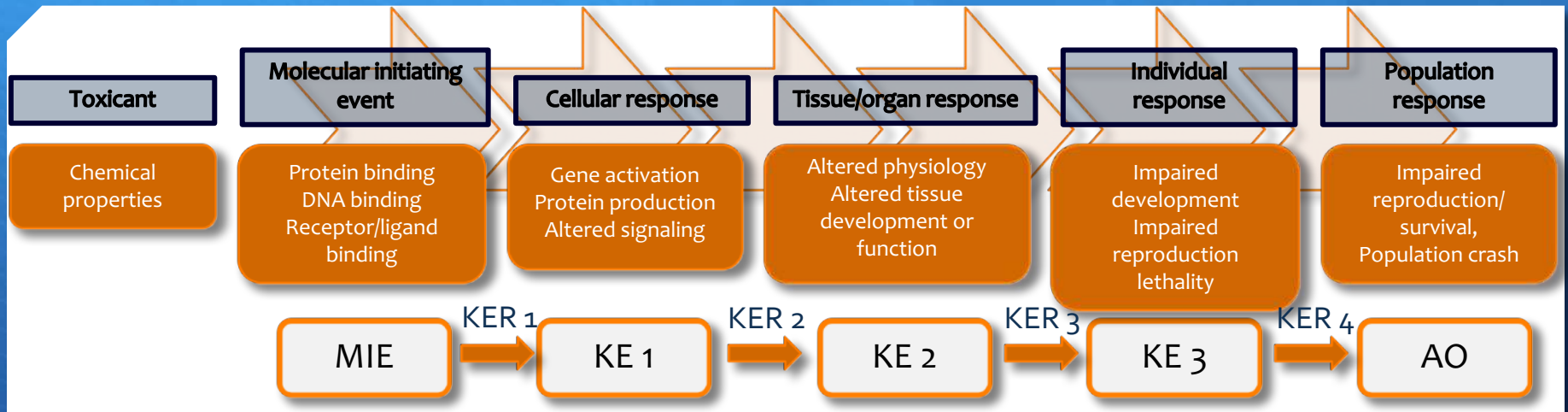
OECD AOP User's Handbook: https://aopkb.org/common/AOP_Handbook.pdf

AOP Provides Understanding & Scaffold for Data



"Borrowed" from Steve Edwards

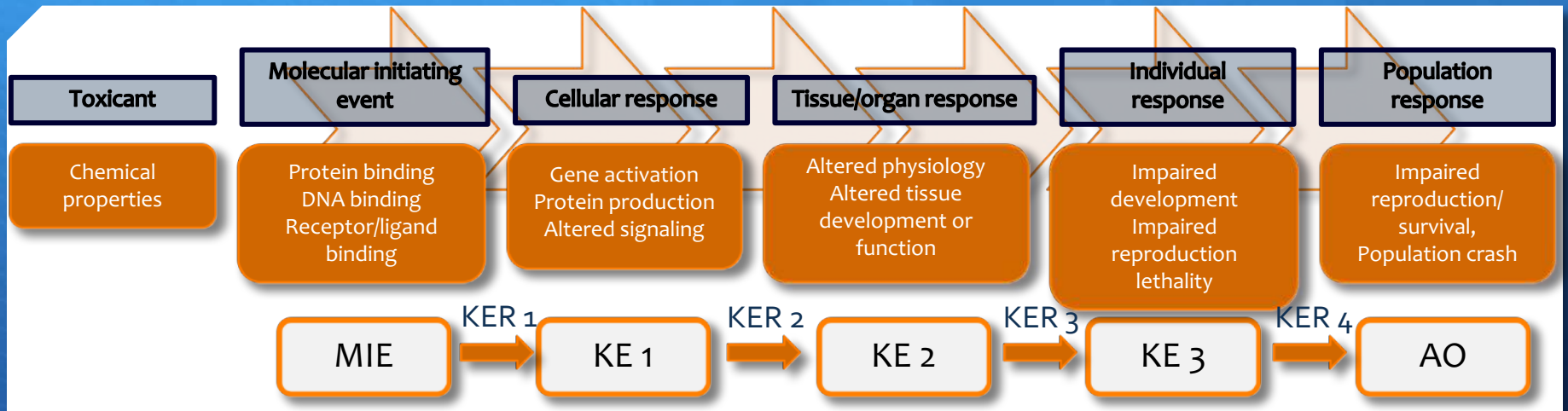
Essential Elements of an AOP



- Molecular Initiating Event (MIE): Initial point of chemical interaction
- Adverse Outcome (AO): Adverse outcome of regulatory significance
- Key Events (KEs) - nodes
  - Change in biological state
  - Measurable and essential for progression
- Key Event Relationships (KERs) - edges
  - Connections between two key events
  - Critical for assembling evidence in support of the AO

Villeneuve, et al. Tox Sci., 2014, 142:312-320

Building an AOP

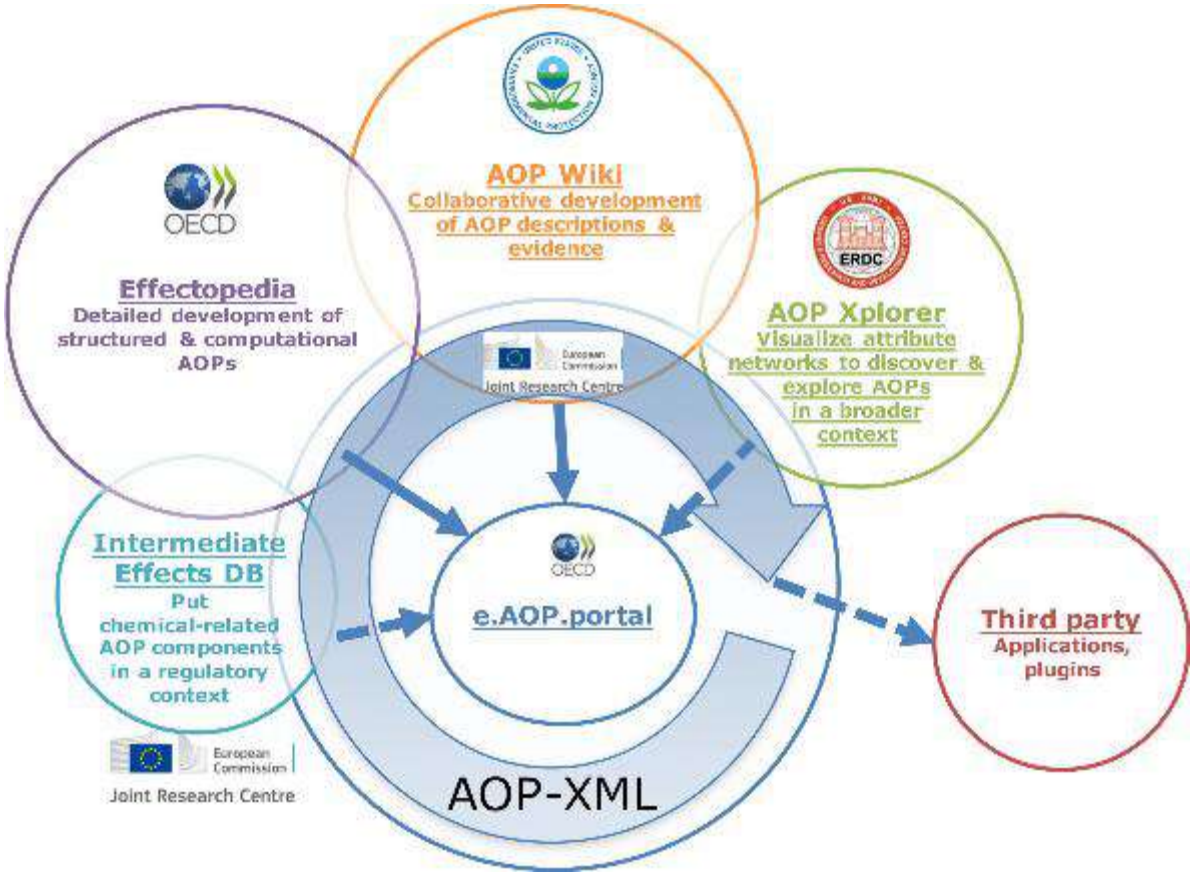


- Start anywhere
- Gather all existing knowledge
- Evaluate and document the information
- Translate and capture information as a pathway

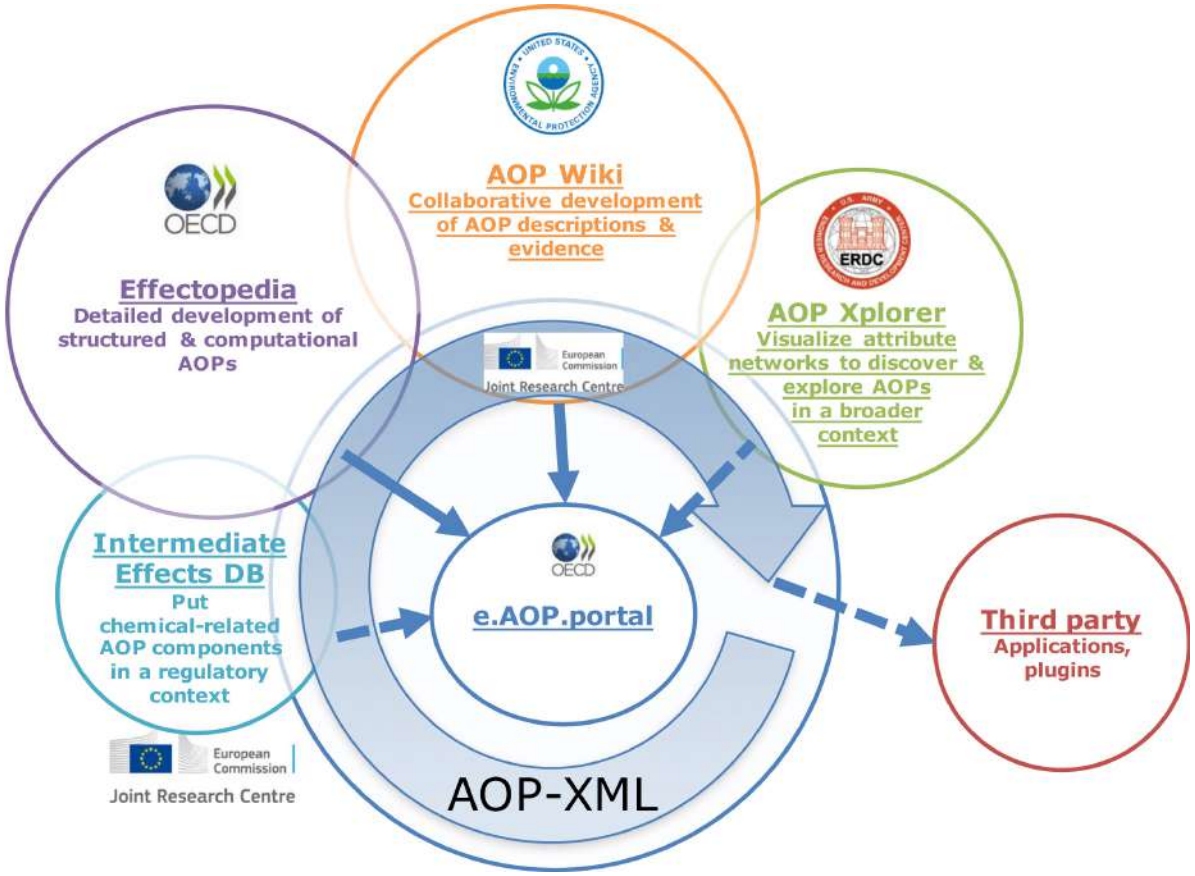
Meek, M. E., Boobis, A., Cote, I. et al. (2014). New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol 34, 1-18. http://dx.doi.org/10.1002/jat.2949

Becker, R.A, Ankely, G. T., Edwards, S.W. et al. (2025) Increasing Scientific Confidence in Adverse Outcome Pathways: Application of Tailored Bradford-Hill Considerations for Evaluating Weight of Evidence. Reg. Toxicol. Pharmacol. In press.

AOP Knowledgebase: information storage, evaluation, and linkage

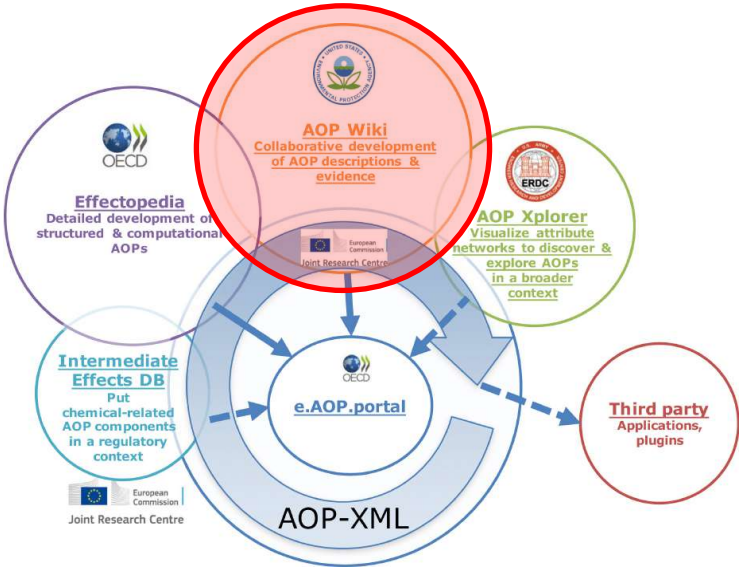


AOP Knowledgebase: information storage, evaluation, linkage, and modeling



AOP Wiki:
information storage, evaluation, and linkage

- Captures and organizes all information and supporting documentation for KEs and KERs
- Supports OECD review and endorsement of formal AOPs
- Quantitative information is written in appropriate sections
- Not computational

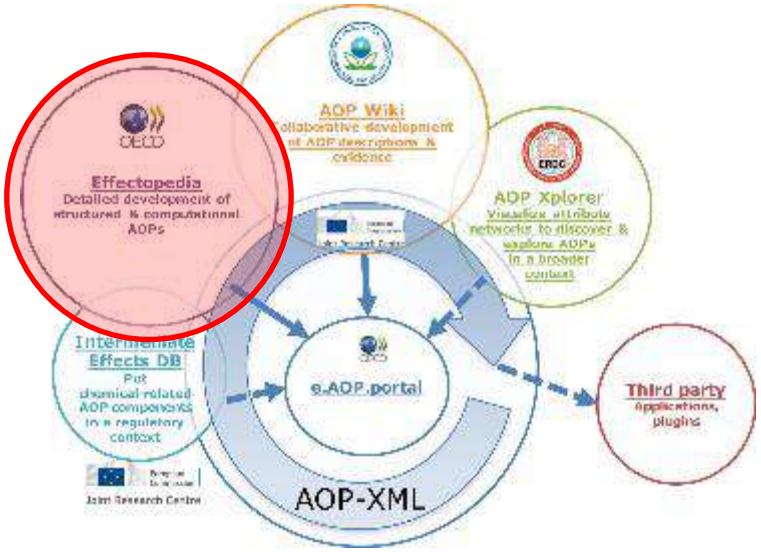


Publically accessible since September 2014

www.aopwiki.org

Effectopedia

- "Explicitly captures quantitative information"
- Supports OECD review & endorsement of quantitative AOPs
- Quantitative information is intrinsic, ultimately also code execution
- 2017



OECD AOP Development Programme

What is an Adverse Outcome Pathway (AOP)

In 2012, the OECD launched a new programme on the development of Adverse Outcome Pathways. An Adverse Outcome Pathway (AOP) is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect (see figure). AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning.

- **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
- **Task force on Hazard Assessment (TFHA)**
- Use of AOPs in regulatory decision making
- Integrated Approaches to Testing and Assessment (IATA)

http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

OECD AOP Development Programme

- **Society for the Advancement of AOPS**
- Not officially part of the OECD programme
- Any person active in developing an AOP in the wiki can join
- Is another way to enter the AOP wiki
- Not necessary to make an official submission to OECD
- Good way to begin preliminary/putative AOPs
- www.saaop.org

OECD AOP Development Programme

AOP Wiki Access: three levels

1. Anyone can access the wiki, search and read entries

2. To leave comments, you will need an account

   Request an account through

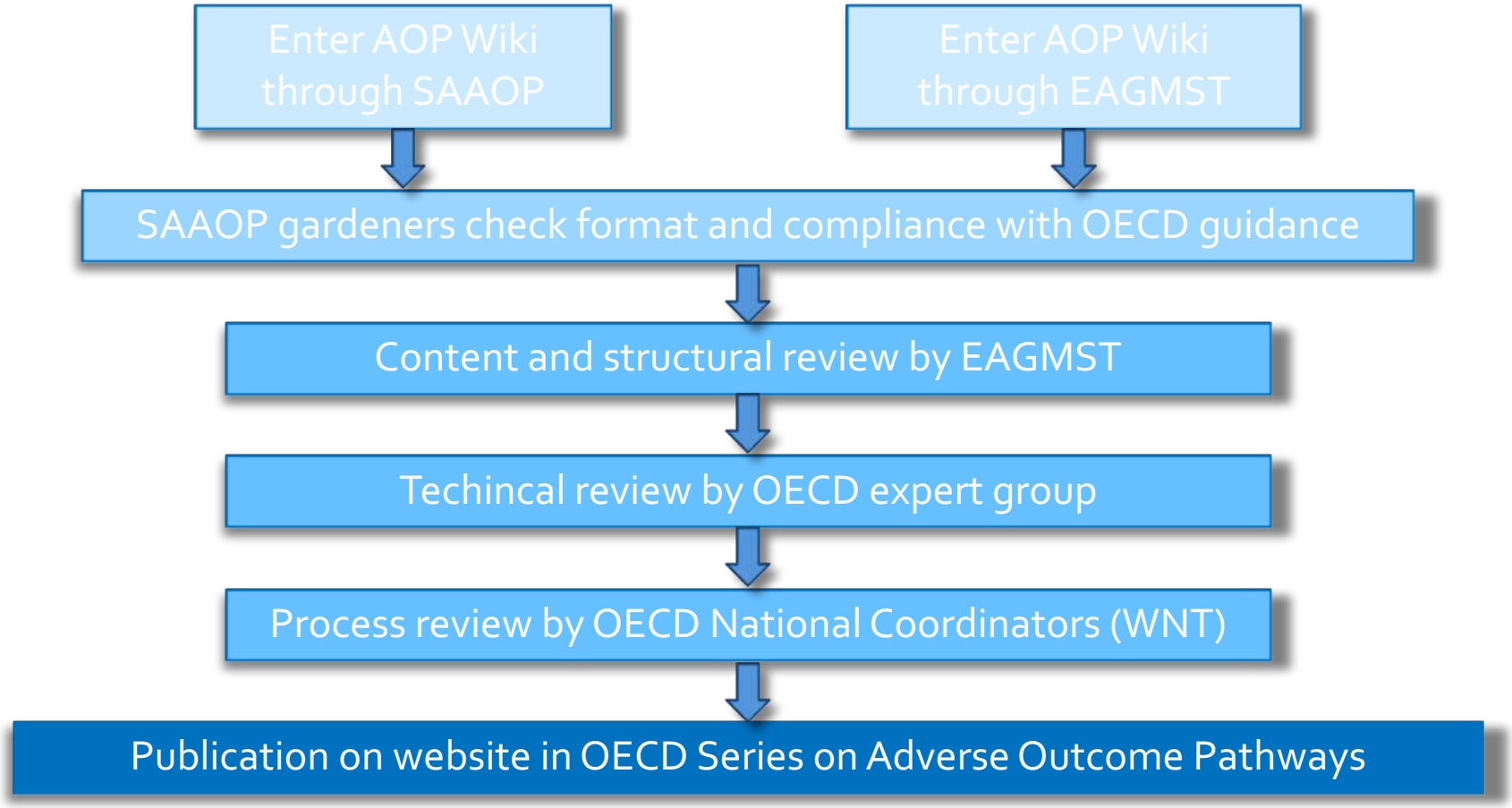
   www.aopwiki.org or www.saaop.org

3. To gain write access

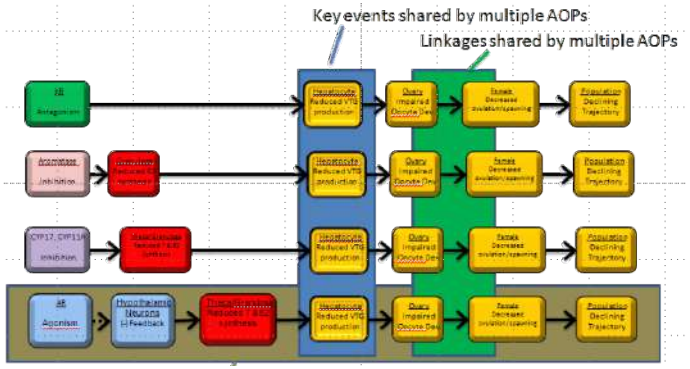
   Request write access the same way

   You should have a familiarity with the wiki and desire to build an AOP

Work Process for Development and Review of AOPs through OECD



AOP-KB supports principles of AOP development



AOPs are modular

- KEs and KERs are shared by multiple AOPs
- No need to re-write the same descriptions over and over
- Reusability (best practices)

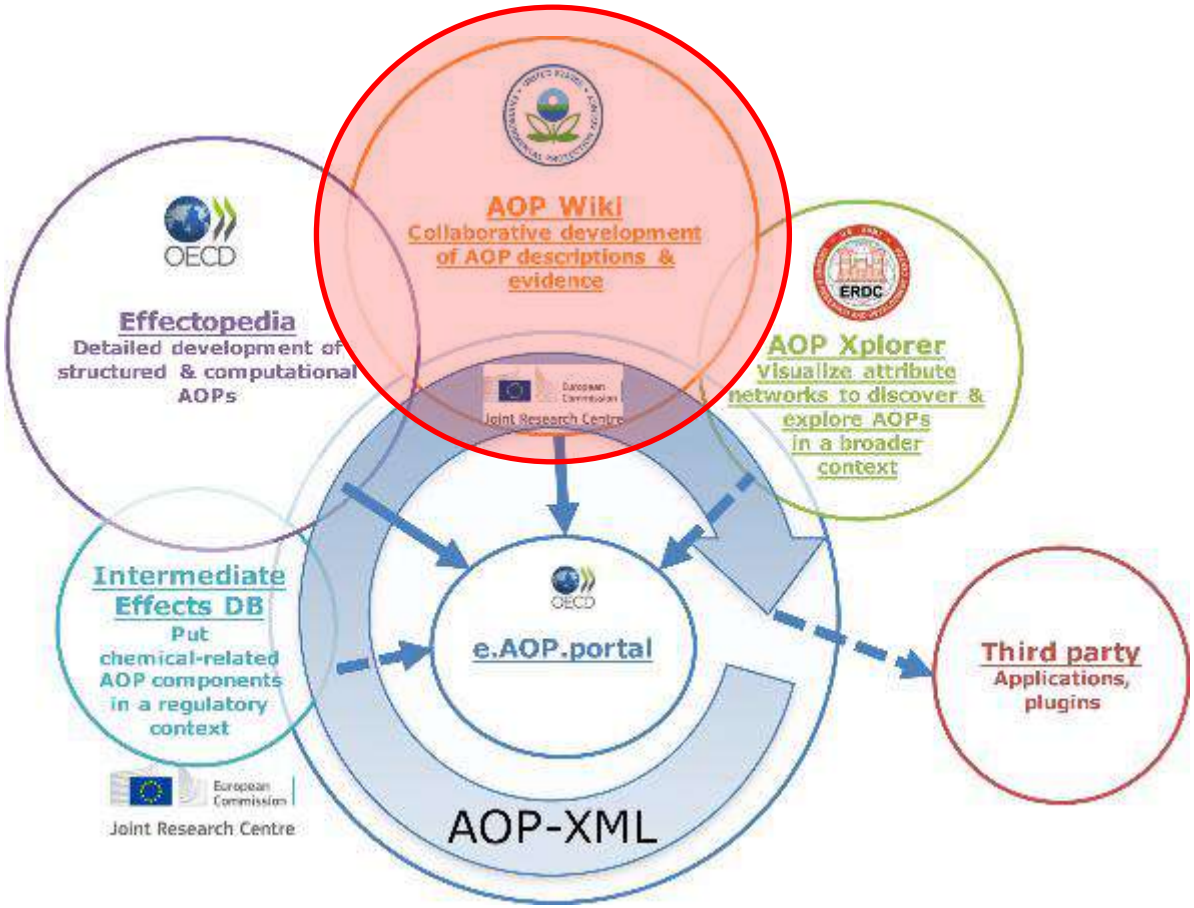
AOPs are living documents

- KE and KER descriptions can be expected to evolve over time
- As descriptions are updated and expanded – all AOP descriptions they link to update automatically

AOP networks for prediction

- Entry of structured information in KB allows for de-facto assembly of AOP networks.

AOP WIKI: information storage and evaluation



AOP WIKI: Home page

AOPWiki AOPs Key Events KE Relationships Stressors sign in sign up

AOP Welcome

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

This wiki represents a joint effort between the European Commision - DG Joint Research Centre (JRC) and U.S Environmental Protection Agency (EPA). This serves as one component of a larger OECD-sponsored AOP Knowledgebase (AOP-KB) 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 Organisation for Economic Co-operation and Development (OECD), the AOP Xplorer, produced by the US Army Corps of Engineers - Engineering Research and Development Center, and the Intermediate Effects DB produced by the JRC. All AOPs from the AOP Knowledgebase are available via the e.AOP.Portal, which is the primary entry point for the AOP-KB.

This wiki is based upon the Chemical Mode of Action wiki developed by the EPA under the auspices of the WHO International Programme on Chemical Safety (IPCS) Mode of Action Steering Group.

Disclaimer

The content of this wiki is the sole responsibility of the individual contributors and does not necessarily represent the views of the authors' organizations nor the organizations responsible for development of the AOP-Wiki or the AOP-KB. Mention of trade names or commercial products does not constitute endorsement by any of these organizations.

Contents

Help About FAQ Metrics

AOP WIKI: search “liver fibrosis”

AOPWiki | AOPs | Key Events | KE Relationships | Stressors | sign in | sign up

API | With OECD status | With SAAOP status | Recent AOPs | liver fibrosis | Search | Find by ID | Find by ID

AOP Title Search Results

Id	Title ▲	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
38	Protein Alkylation leading to Liver Fibrosis	Brigitte Landesmann	Open for citation & comment	Included in OECD Work Plan	Protein alkylation	liver fibrosis	TFHA/WNT Endorsed	1.14

AOP Fulltext Search Results

Id	Title ▲	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
38	Protein Alkylation leading to Liver Fibrosis	Brigitte Landesmann	Open for citation & comment	Included in OECD Work Plan	Protein alkylation	liver fibrosis	TFHA/WNT Endorsed	1.14
34	LXR activation leading to hepatic steatosis	Marina Goumenou	Under development: Not open for comment. Do not cite	Under Development	LXR	liver steatosis		
144	Lysosomal damage leading to liver inflammation	Brigitte Landesmann	Under development: Not open for comment. Do not cite	Included in OECD Work Plan		Liver, Inflammation	Under Development	1.47
131	Aryl hydrocarbon receptor activation leading to uroporphyria	Amani Farhat	Open for comment. Do not cite	Included in OECD Work Plan	AhR	uroporphyria	EAGMST Under Review	1.7

Help | About | FAQ | Metrics

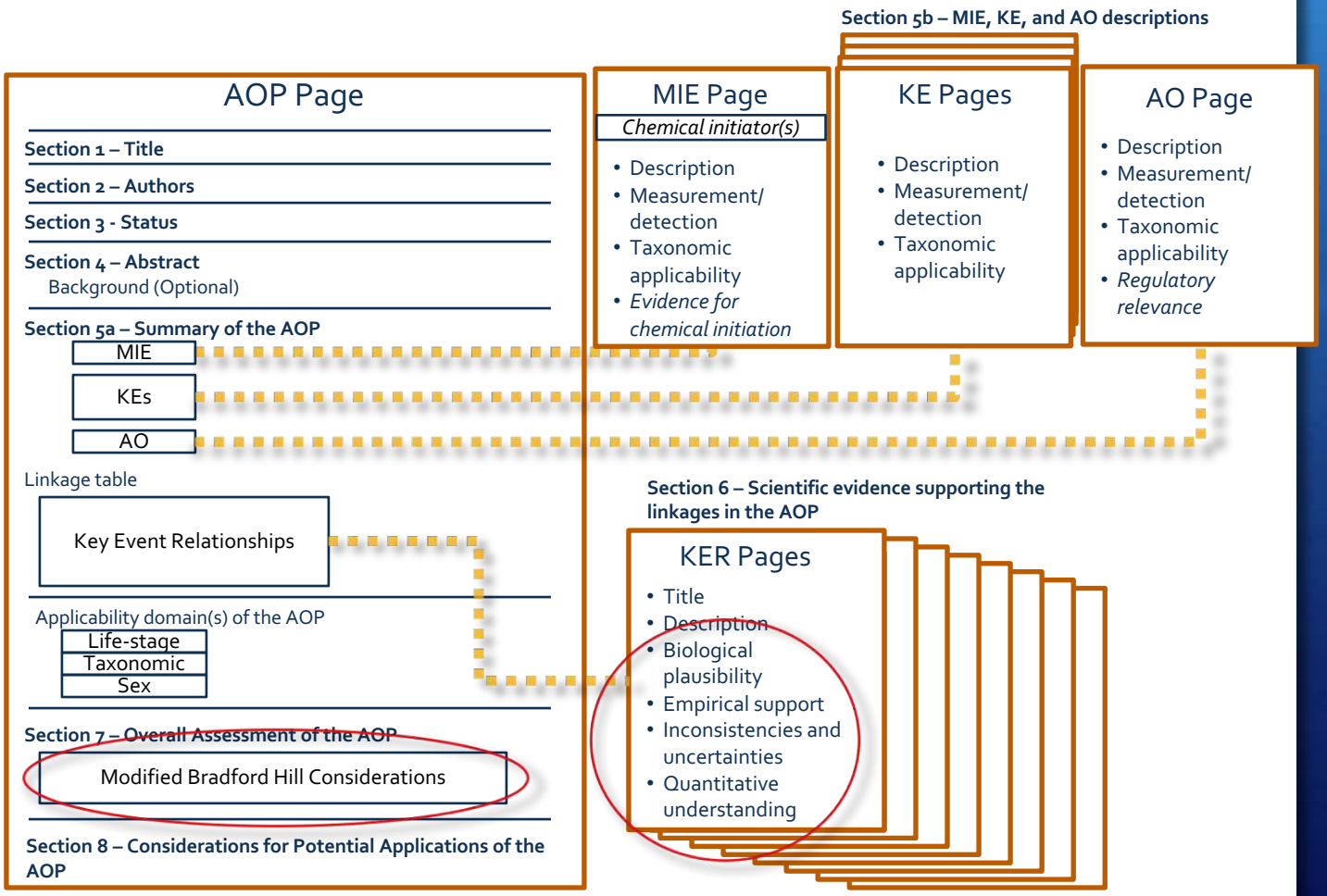
AOP WIKI: information storage and evaluation

OECD Handbook
Step by step guide to AOP development

https://aopkb.org/common/AOP_Handbook.pdf

AOP-Wiki
Provides consistent structure based on the OECD handbook and facilitates collaborative AOP development

http://aopwiki.org/



New version of AOP Wiki available in November, 2016

AOP WIKI: KER and AOP confidence evaluation

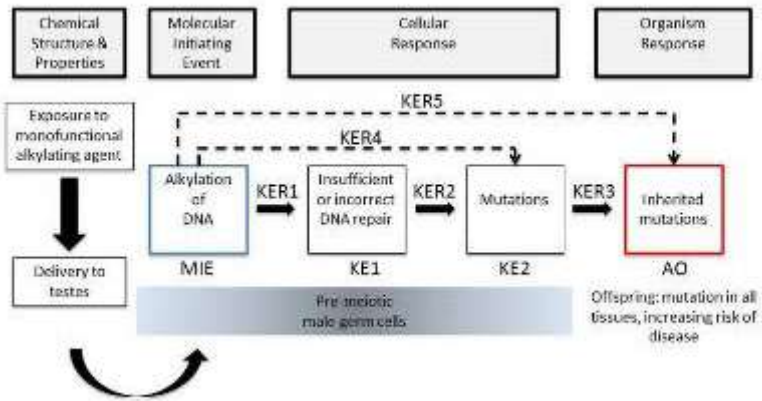
Biological Plausibility: between KE upstream and KE downstream?		
High (strong): Extensive understanding of KER	Moderate: KER is plausible	Low (weak): some empirical support
Essentiality: are downstream KEs prevented if upstream KE's blocked?		
High (strong): direct evidence from experimental studies	Moderate: indirect evidence	Low (weak) No or contradictory evidence
Empirical Evidence: amount, quality, consistent, inconsistent?		
High (strong): extensive evidence for temporal, dose-response	Moderate: multiple reports of consistent evidence, some inconsistent	Low (weak): limited or no studies and/or significant inconsitencies

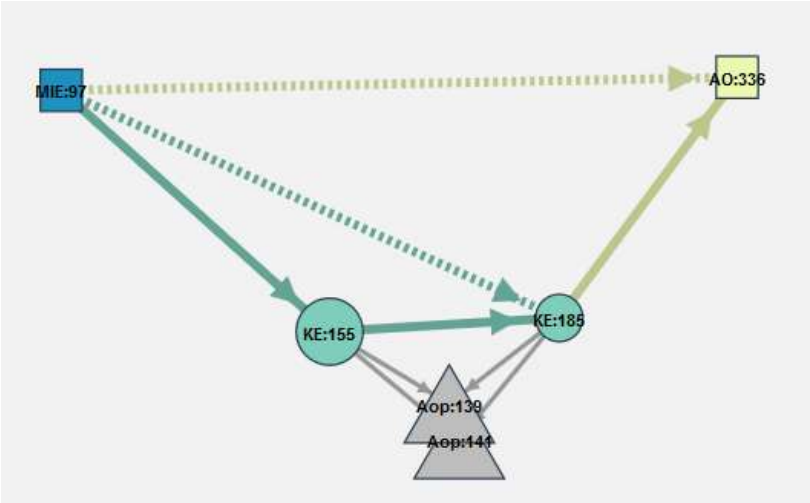
OECD (2014) User's Handbook Supplement to the Guidance Document for Developing and Assessing AOPs. https://aopkb.org/common/AOP_Handbook.pdf.

AOP Title

Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations

Short name: Alkylation of DNA leading to heritable mutations



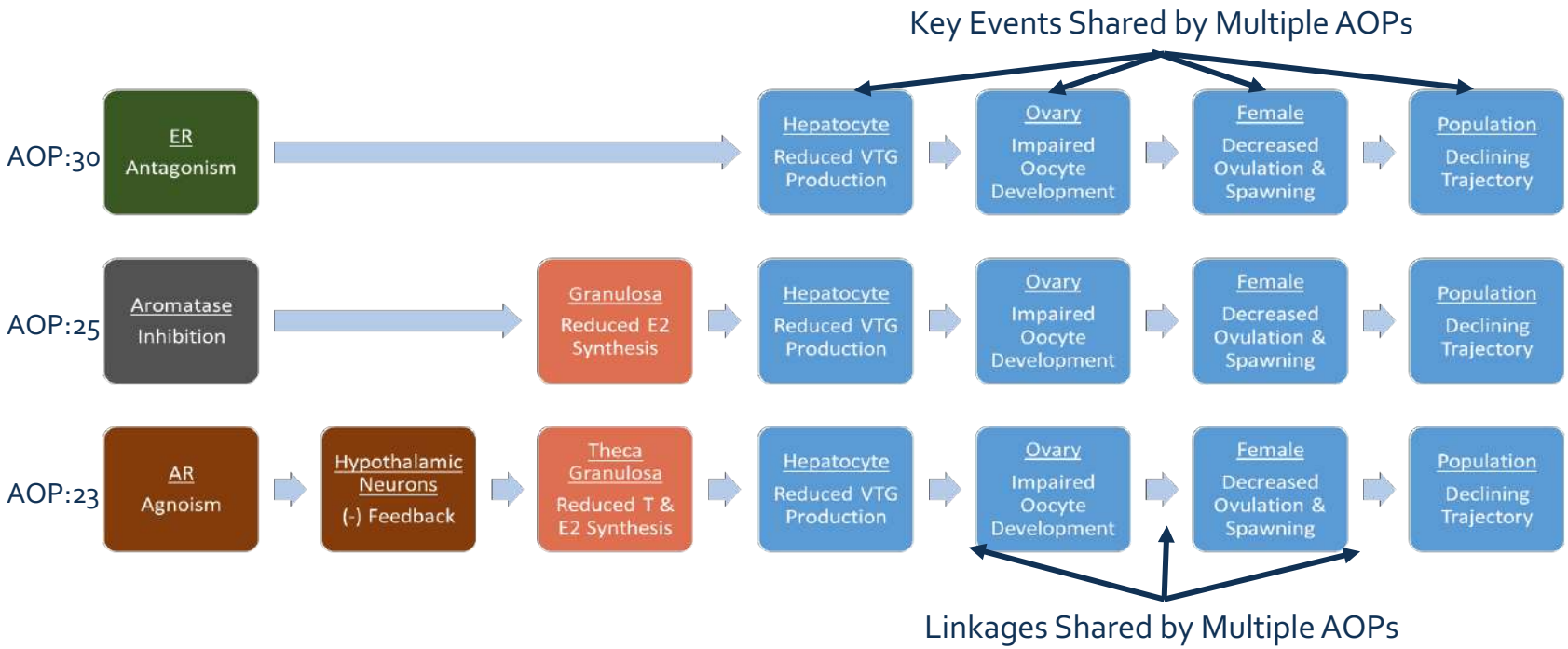


Carole Yauk – https://aopwiki.org/wiki/index.php/Aop:15

Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
DNA, Alkylation	Directly Leads to	Insufficient or incorrect DNA repair, N/A	Strong	Moderate
Insufficient or incorrect DNA repair, N/A	Directly Leads to	Mutations, Increase	Strong	Moderate
DNA, Alkylation	Indirectly Leads to	Mutations, Increase	Strong	Moderate
DNA, Alkylation	Indirectly Leads to	Heritable mutations in offspring, Increase	Strong	Moderate
Mutations, Increase	Directly Leads to	Heritable mutations in offspring, Increase	Strong	Moderate

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

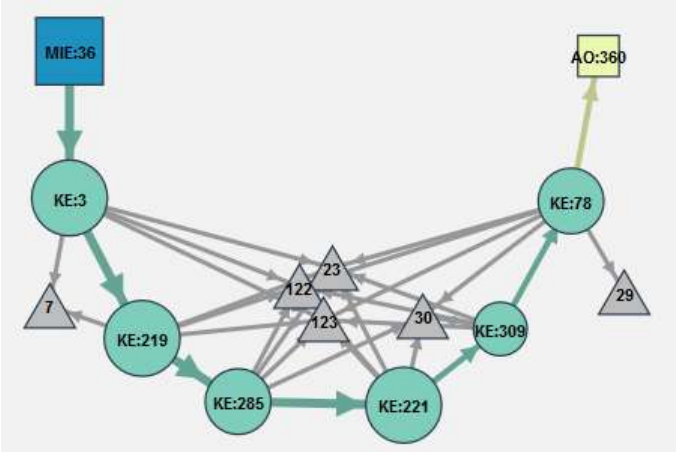


Courtesy of Dan Villeneuve

AOP Title [edit]

Aromatase inhibition leading to reproductive dysfunction (in fish)

Short name: Aromatase inhibition leading to reproductive dysfunction (in fish)



Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
Aromatase, Inhibition	Directly Leads to	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Strong	Moderate
17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Directly Leads to	Plasma 17beta-estradiol concentrations, Reduction	Strong	Moderate
Plasma 17beta-estradiol concentrations, Reduction	Directly Leads to	Transcription and translation of vitellogenin in liver, Reduction	Strong	Moderate
Transcription and translation of vitellogenin in liver, Reduction	Directly Leads to	Plasma vitellogenin concentrations, Reduction	Strong	Moderate
Plasma vitellogenin concentrations, Reduction	Directly Leads to	Vitellogenin accumulation into oocytes and oocyte growth/development, Reduction	Moderate	Weak
Vitellogenin accumulation into oocytes and oocyte growth/development, Reduction	Directly Leads to	Cumulative fecundity and spawning, Reduction	Moderate	Moderate
Cumulative fecundity and spawning, Reduction	Directly Leads to	Population trajectory, Decrease	Moderate	Moderate

AOP Wiki metrics

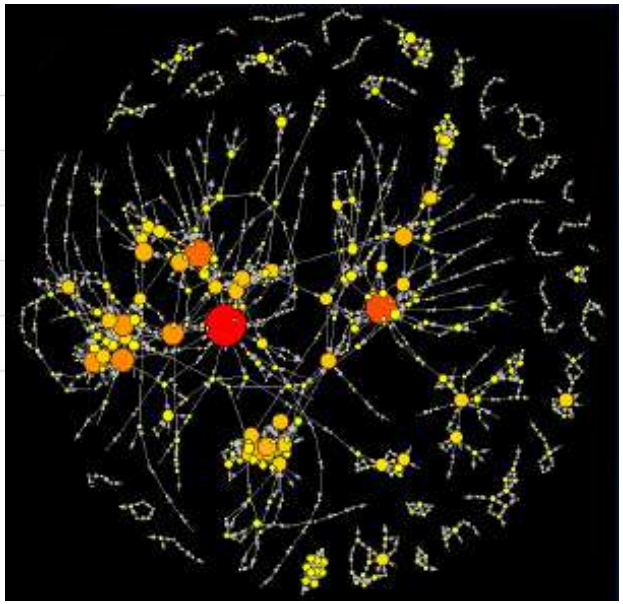
AOPWiki AOPs Key Events KE Relationships Stressors sign in sign up

Available Reports

Summary AOPS Key events KE relationships Stressors

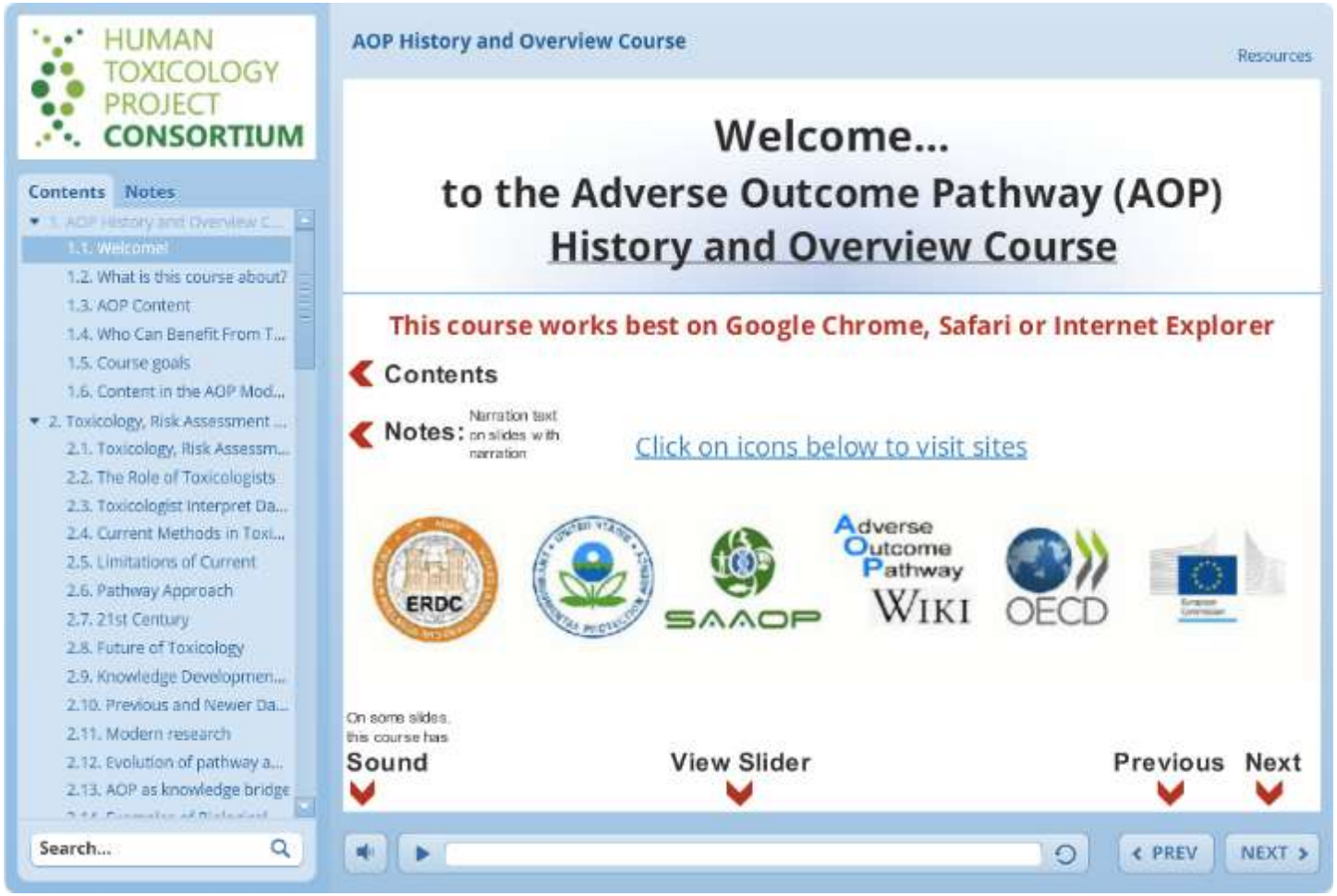
Reports Summary

Report	Count
AOPs	207
Key events	1039
KE relationships	1242
Stressors	302



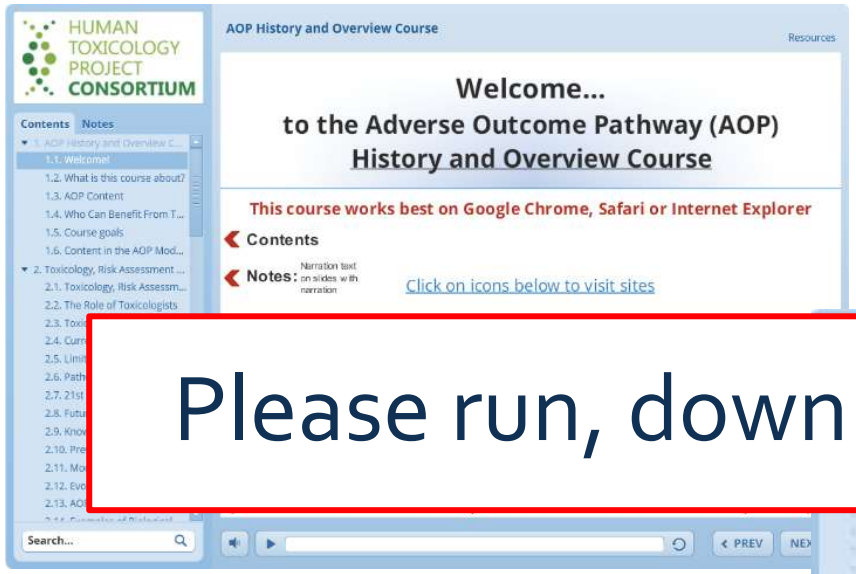
23 June 2017
D. Villeneuve

AOP Online Training Course



AOP Online Training Course

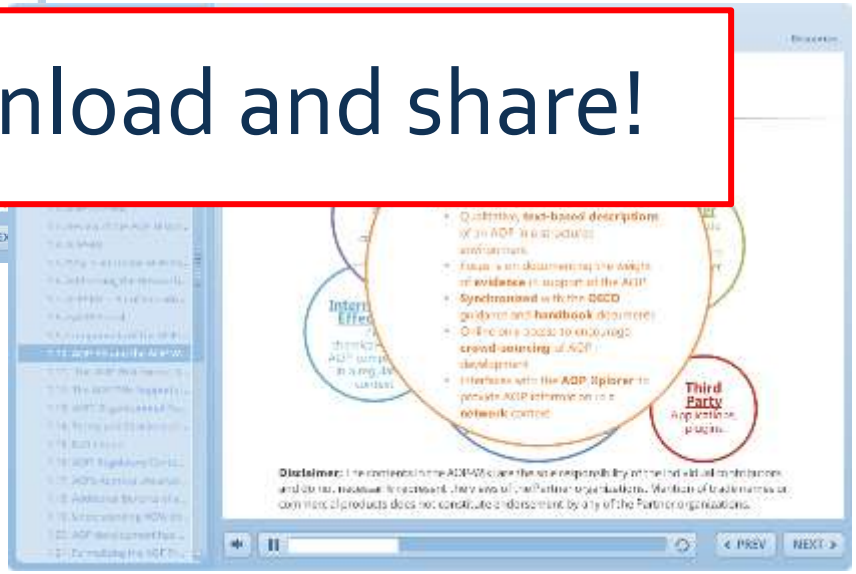
HUMAN TOXICOLOGY PROJECT CONSORTIUM



Two volume course:

1. Introduction and Overview
2. AOP Wiki Training

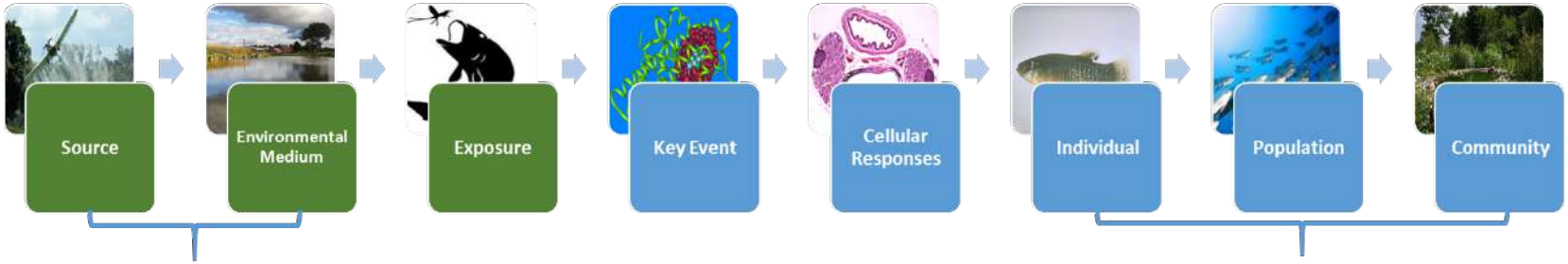
Please run, download and share!



Download:
https://humantoxicologyproject.org/about-pathways-2/aop-online-course/

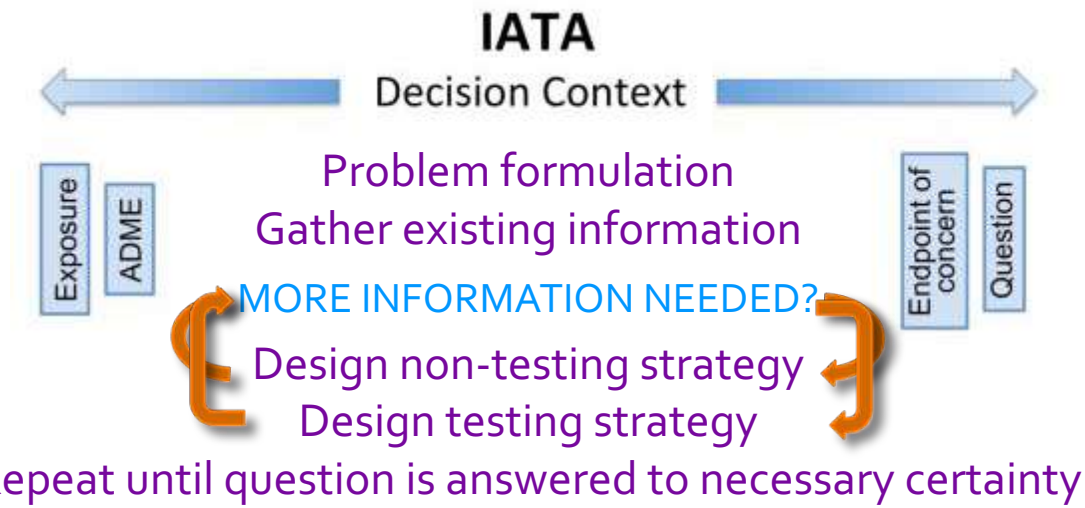
Run:
https://aopwiki.org/

AOP in context of hazard and risk assessment



Adverse Outcome Pathway, Ankley 2010, Villeneuve 2014

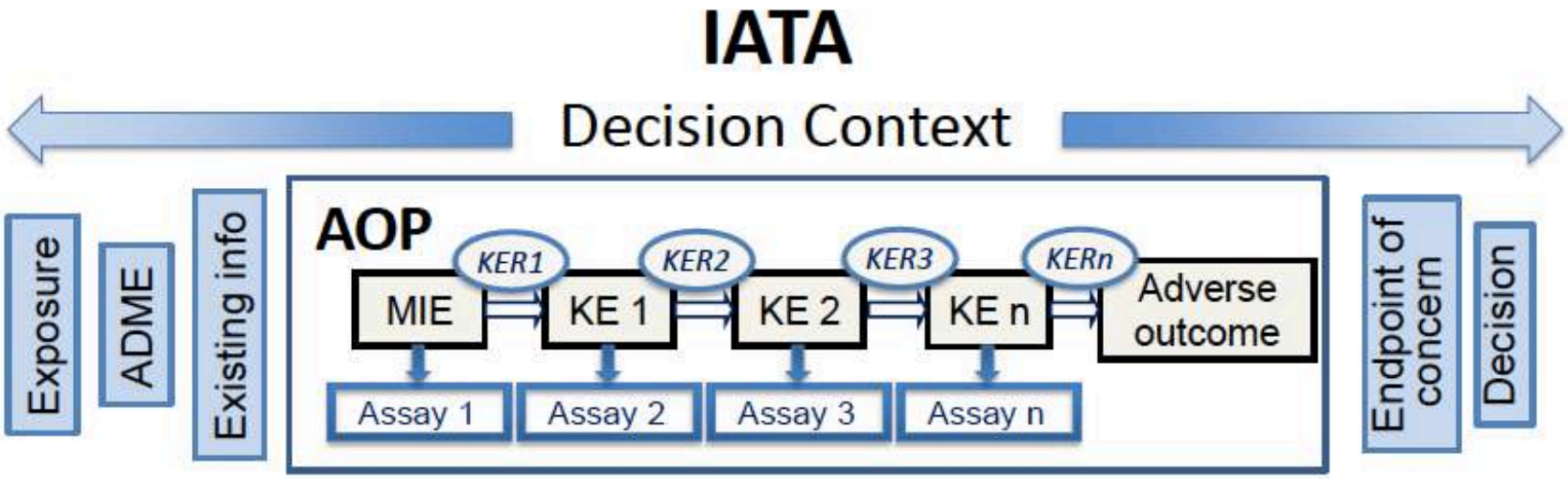
Integrated Approach to Testing and Assessment (IATA): OECD working definition



"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 optimising and potentially reducing the number of tests that need to be conducted."

Report of the Workshop on a Framework for the Development and Use of Integrated Approaches to Testing and Assessment. 2015. OECD Series on Testing and Assessment No. 215

Using an AOP within the context of an IATA



- AOP provides biological rationale
  - For weight-of-evidence interpretation
  - For design of integrated, iterative testing strategy
- Transparent communication of certainty
- Quantitative information allows prediction

Regulatory acceptance of IATA: specific case Defined Approaches (DA)

- Several different possibilities for combining information
- How do regulators deal with different IATA to satisfy same information request?
- Proper guidance is crucial
- DA → possibly covered by MAD?
  - (Mutual Acceptance of Data)

OECD

EURL ECVAM

THE EUROPEAN UNION REFERENCE LABORATORY FOR ALTERNATIVES TO ANIMAL TESTING

(J. Baroso, European Commission. 2014)

Regulatory acceptance of IATA: specific case Defined Approaches

OECD Guidance document 255: Guidance Document on the **Reporting of Defined Approaches to be Used Within Integrated Approaches to Testing and Assessment (2016)**

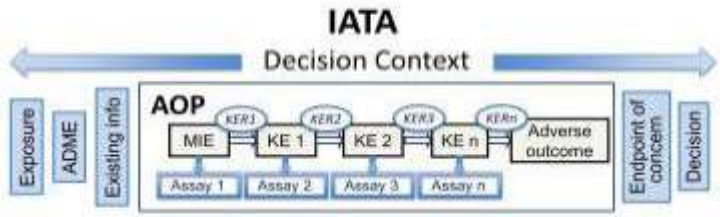
Six Principles: Essential Information for Regulatory Application of an IATA

1. A defined endpoint
2. A defined purpose
3. A description of the rationale underlying the construction of the IATA
4. A description of the individual information sources constituting the IATA
5. A description of how the individual information sources are integrated to derive the final prediction/assessment
6. A description of the known uncertainties associated with the IATA application

+ Guidance on development, evaluation and application of IATA
+ Harmonized template for describing IATA

AOP-supported IATA example: Skin Sensitization

Skin sensitization IATA:



Exposure?

In vitro skin absorption (OECD 428)

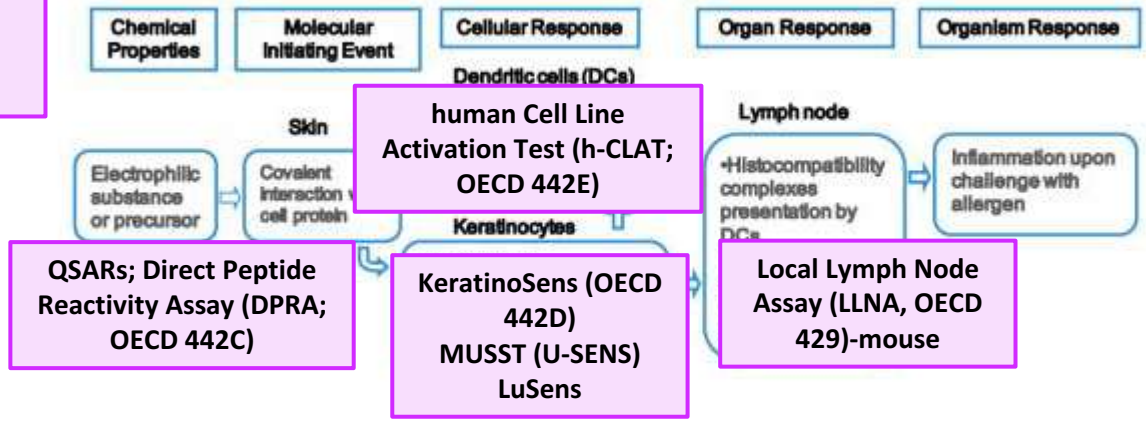
Molecular Initiating

Cellular Effects

Organ Effects

Individual Effects

Question to be answered:
Screening?
Hazard ID?
GHS C&L?
Sub-classification?



Regulatory acceptance of IATA: specific case Defined Approaches

European Commission

OECD Project: Development of a Guidance Document on the Evaluation and Application of IATA for Skin Sensitisation

Unclassified

ENV/JM/MONO(2016)29

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

27-Oct-2016

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

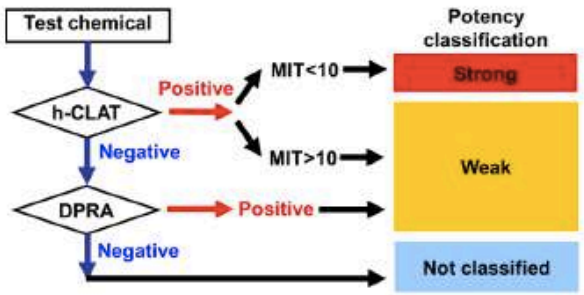
GUIDANCE DOCUMENT ON THE REPORTING OF DEFINED APPROACHES AND INDIVIDUAL INFORMATION SOURCES TO BE USED WITHIN INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA) FOR SKIN SENSITISATION

Series on Testing & Assessment
No. 256

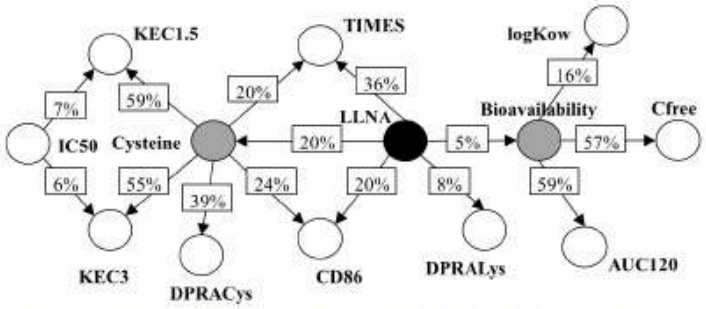
ENV/JM/MONO(2016)29
Unclassified

Regulatory acceptance of IATA: specific case Defined Approaches

Examples of different IATA for skin sensitization:

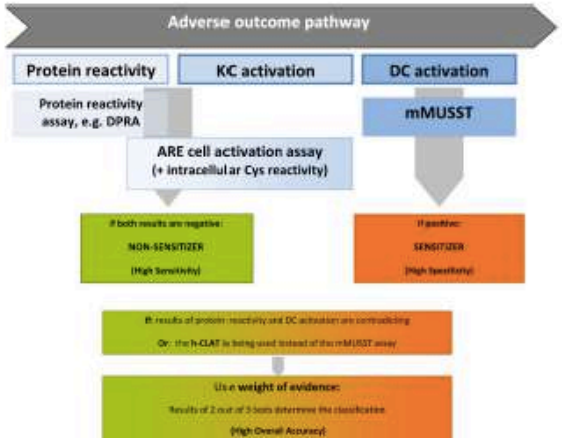


Nukada et al. (2013) Toxicology in Vitro 27, 609-618



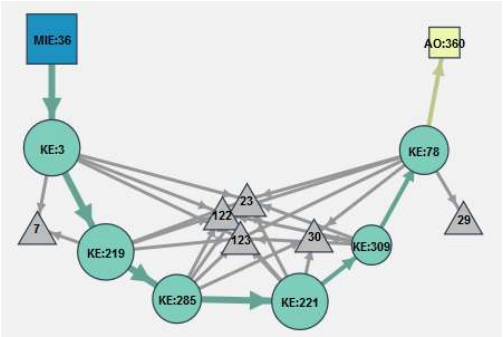
Jaworska et al. (2013) Journal of Applied Toxicology

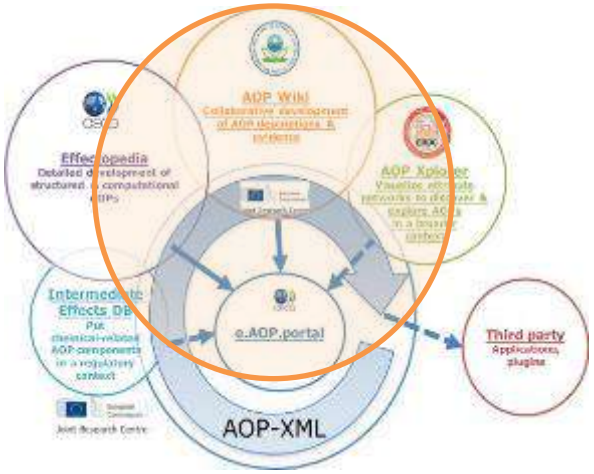
Bauch et al. (2012) Regulatory Toxicology and Pharmacology 63, 489-504



In Summary

- AOPs can support decision making at every level, and in several ways:
  - support WoE arguments
  - support ITS design
  - transparent communication of uncertainty
  - predicting outcome
- AOP Wiki is crowd-sourced, open to everyone
  - *The more participation, the better it will be!*





Thank you!

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HUMANE SOCIETY INTERNATIONAL
国际人道对待动物协会

THE HUMANE SOCIETY OF THE UNITED STATES

HUMAN TOXICOLOGY PROJECT CONSORTIUM

Introduction to Adverse Outcome Pathways and the AOP Wiki

Sunday July 20, 2017
10:00 AM - 12:00 PM
Sheraton Seattle, Aspen Room

10:00: Introduction to the OECD AOP Programme and Online Training course
Kate Willett, Human Toxicology Project Consortium

10:40: Building AOPs for Neurotoxicity: Perspective from an Academic
Prof. Dr. Ellen Fritsche, IUF – Leibniz Research Institute for Environmental Medicine

11:20: Demonstration and Hands-On Activity with AOP Wiki
Kristie Sullivan, Physicians Committee for Responsibility Medicine

PCRM

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