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AOPs Knowledge Base
Processes, Organization, Evaluation

Presented by Ludek Blaha, MU

… using and acknowledging materials from many others:

Dan Villeneuve – US EPA

Markus Hecker – University of Saskatchewan, Canada

Mirjam Luijten – RIVM, Netherlands

and many other AOP-developers and trainers

15th RECETOX Summer School
3rd HMB4EU Training School
Brno 18th June 2019, MU-RECETOX, Brno, Czech Republic

HBM4EU
science and policy
for a healthy future

- Testing of chemicals
- Assessment of chemicals
- Risk management of chemicals
- Chemical accident prevention, preparedness and response
- Pollutant release and transfer register
- Safety of manufactured nanomaterials
- Agricultural pesticides and biocides
- Biosafety - BioTrack

Adverse Outcome Pathways, Molecular Screening and Toxicogenomics

The OECD Environmental, Health and Safety (EHS) Programme has been helping member countries to make better use of increased knowledge of how chemicals induce adverse effects in humans and wildlife, through the so-called Adverse Outcome Pathways.

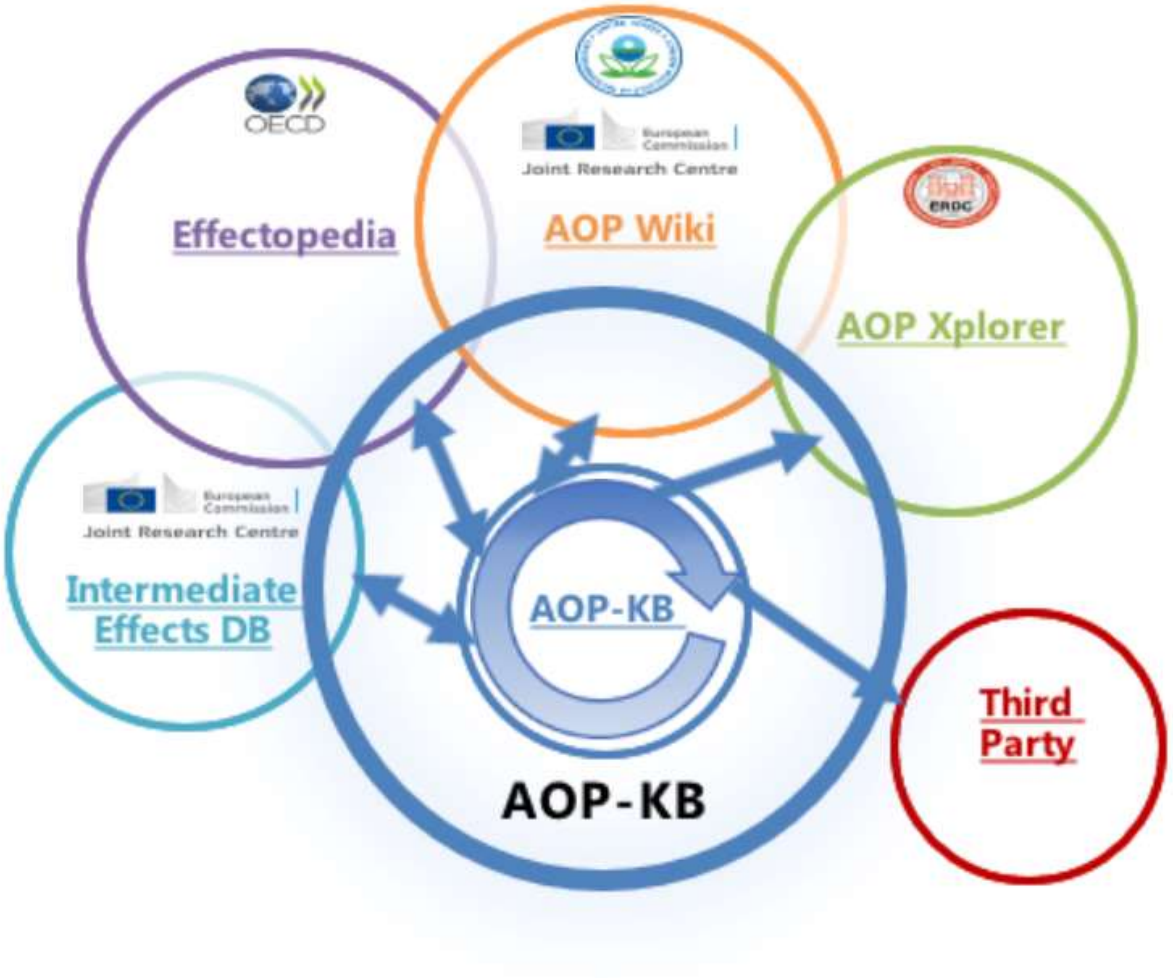
What's new

OECD releases three publications on Adverse Outcome Pathways (AOPs)

- Adverse Outcome Pathway on Inhibition of the mitochondrial complex I of nigro-striatal neurons leading to parkinsonian motor deficits, Anna Bal-Price, et al. | 12 October 2018
- Adverse Outcome Pathway on chronic binding of antagonist to N-methyl-D-aspartate receptors during brain development leading to neurodegeneration with impairment in learning and memory in aging, Florianne Tschudi-Monnet and Rex FitzGerald | 12 October 2018
- Adverse Outcome Pathway on Androgen receptor agonism leading to reproductive dysfunction (in repeat-spawning fish), Dan Villeneuve | 12 October 2018

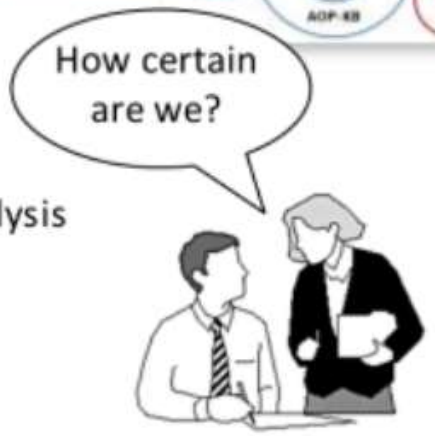
All publications in the Series on Adverse Outcome Pathways can be found here.

AOP-KB


OECD
Effectopedia
Joint Research Centre
AOP Wiki
ERDC
AOP Xplorer
Joint Research Centre
Intermediate Effects DB
AOP-KB
AOP-KB
Third Party

Why is an Online AOP-KB Needed?

Complex Biology

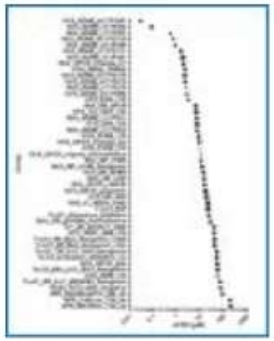


Uncertainty Analysis

How best to implement the OECD Guidance on Developing and Assessing AOPs?

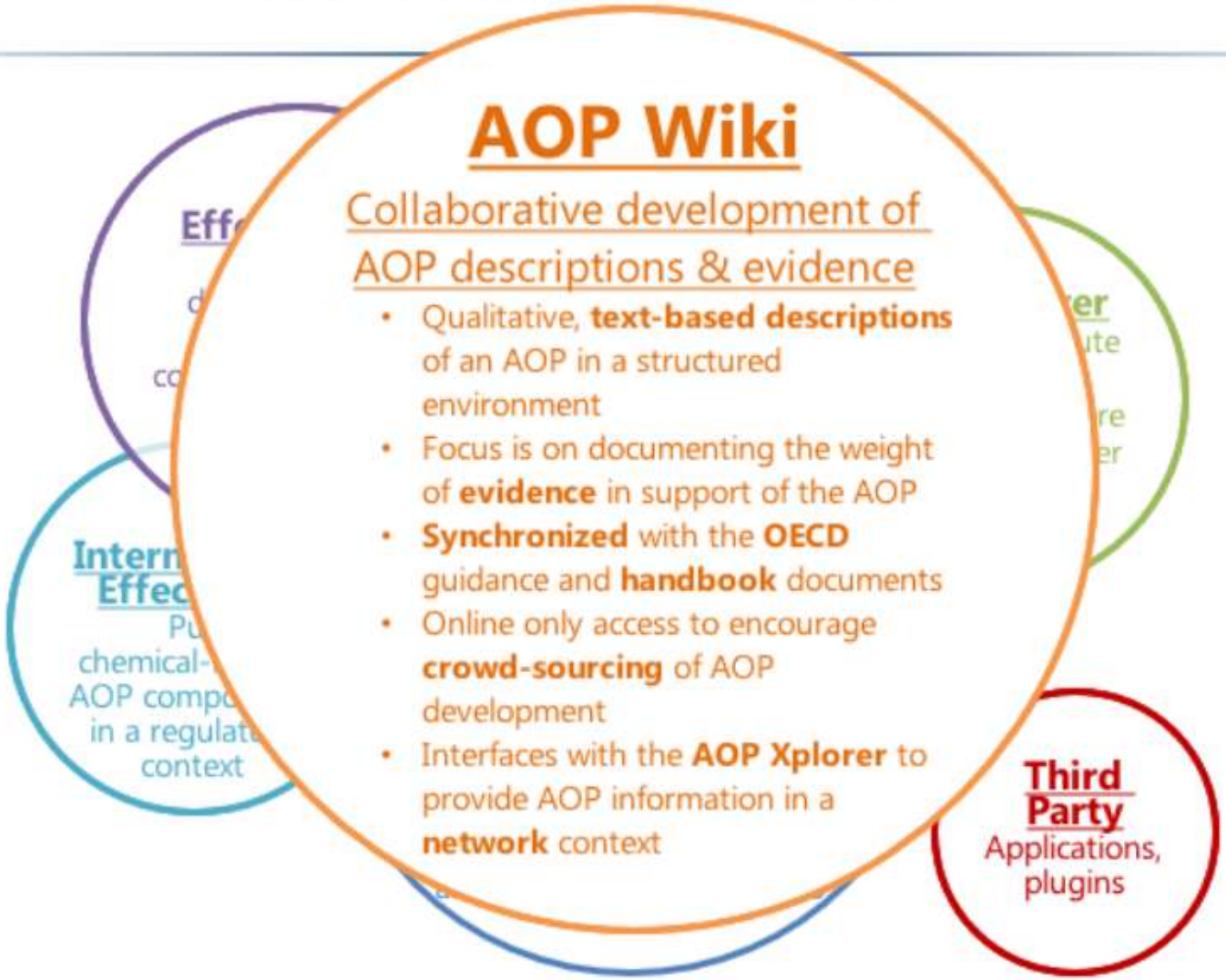
Documents are not ideal for developing and updating AOPs.

How best to incorporate new data types into AOPs?



Pathway-based bioactivity profile → Potential/ probable AO

AOP-KB and the AOP-Wiki



AOP Concept in Ecotoxicology

1992 — **SETAC Pellston workshop on biomarkers – identified need for linkages across levels of organization to support use of biomarkers in ERA.**

Mid 90s — Schmieder, Bradbury, Veith, others in ecotox community – concept to support application of QSARs and biomarkers in ERA.

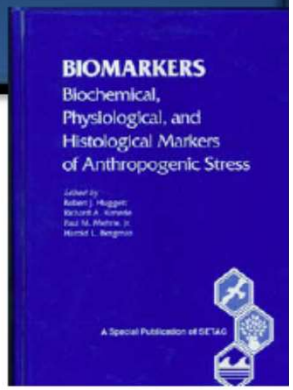
2004 — **Bradbury et al. (ES&T Dec. 1, 2004) – publication of the concept as a means to support greater use of in silico and in vitro approaches in risk assessment – termed "Toxicity Pathway"**

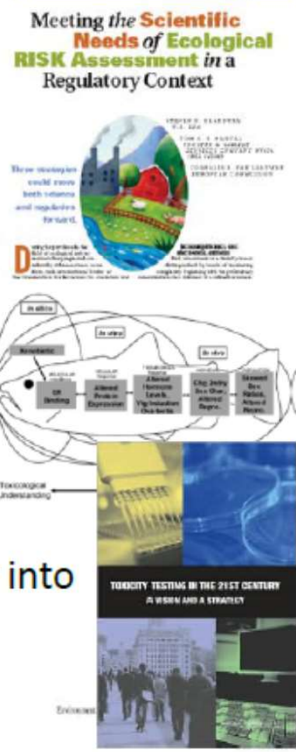
2004 — **Schmieder et al. (ES&T 38:6333-6342) – published a "toxicity pathway" linking ER binding to potential population-level consequences.**

2007 — **NRC report on Toxicity Testing in the 21st Century – advocated paradigm similar to Bradbury et al – defined "toxicity pathway" as "*cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects*"**

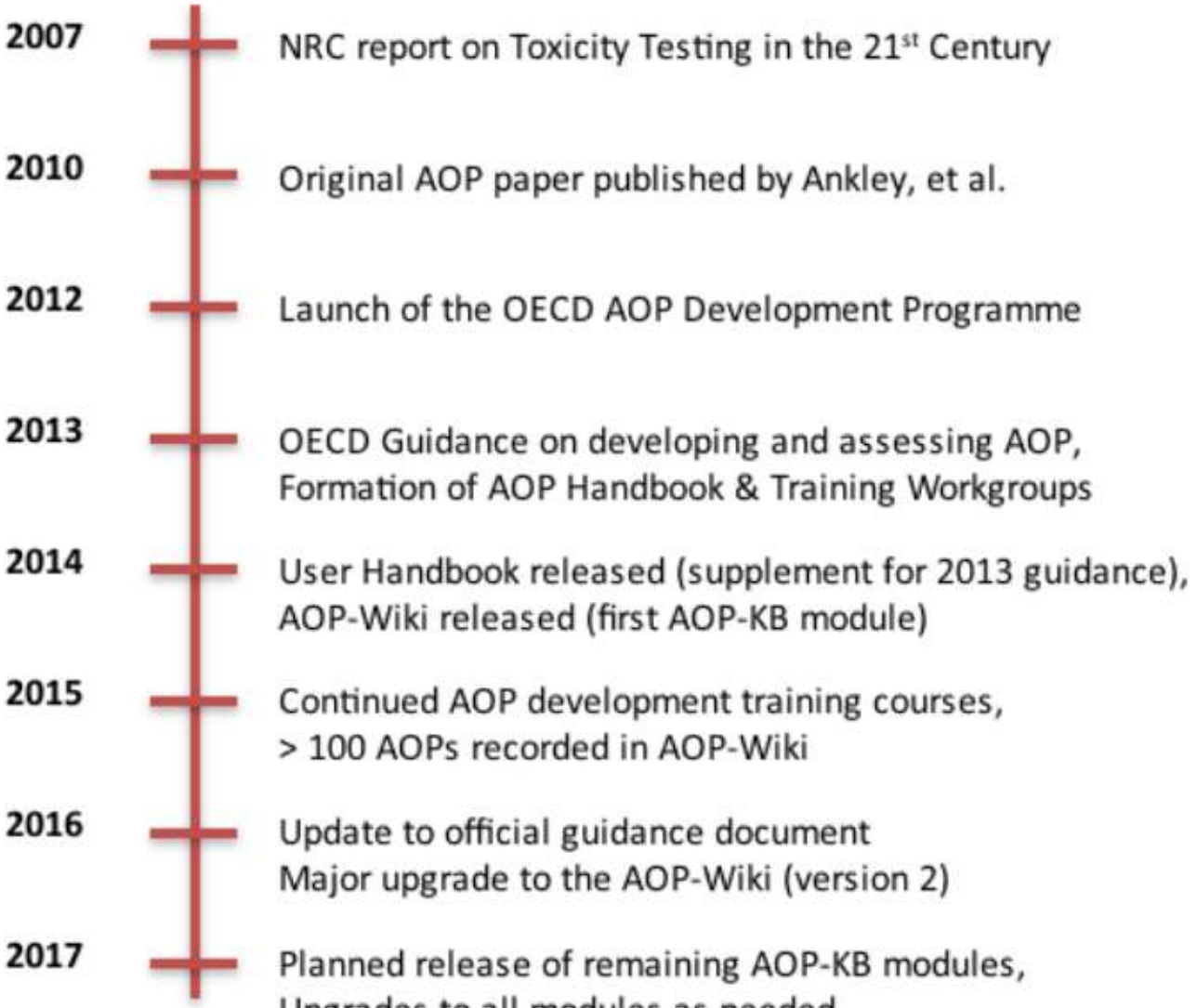
2009, 2010 — Use of AOP term at McKim conferences – introduction of AOP terminology into OECD QSAR tool-box discussions

2010 — **MED working group published definition of "Adverse Outcome Pathways", describe application in Ecotox and Ecological Risk Assessment. ET&C 2010.**



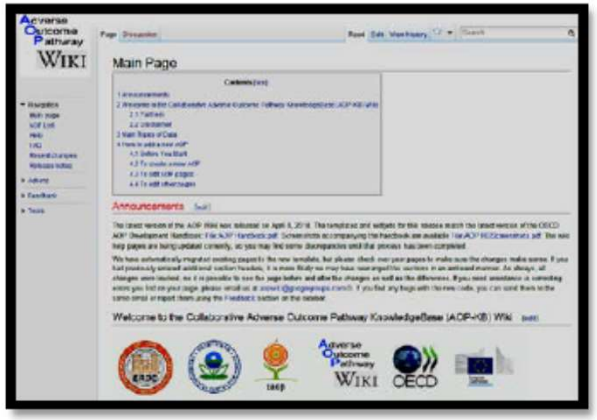


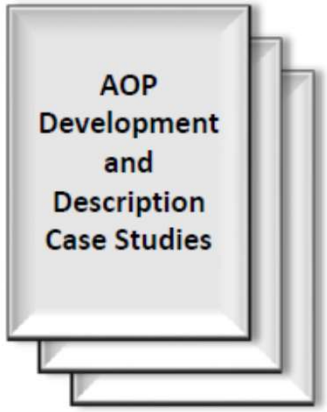
Evolution of the OECD AOP-KB Development Programme



Current State of the AOP Framework

- 2012 launch of OECD AOP development programme
- 2013 OECD Guidance on Developing and Assessing AOPs
  - Conventions and terminology
  - Information content of an AOP description
  - Weight of evidence evaluation
  - Introduce standardization and rigor to AOP development





Users' handbook supplement to OECD guidance document for developing and assessing AOPs.

- March 2014 – *Advancing AOPs for Integrated Toxicology and Regulatory Applications Workshop*

OECD AOP Development and Review Process

The AOP Development Programme at OECD

The AOP Development Programme is overseen by the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST). EAGMST members are nominated by their National Coordinators.

- The EAGMST is a large group of experts from various areas of toxicology, and are designated by governmental or non- governmental affiliations (academia, agencies, industry, animal welfare groups, scientific societies, etc.)
- EAGMST members play an active role in the development of AOPs, as well as in the internal review and approval process.
- The EAGMST meets once a year before summer and holds a teleconference, usually in December to keep pace with new developments.

> Biodiversity, water and natural resource management
> Chemical safety and biosafety
> Testing of chemicals
> Assessment of chemicals
> Risk management of chemicals
> Chemical accident prevention, preparedness and response
> Pollutant release and transfer register
> Safety of manufactured nanomaterials
> Agricultural pesticides and biocides
> Biosafety - BioTrack

National co-ordinators of the Test Guidelines programme

The development of Test Guidelines (TGs) is overseen by the Working Group of National Co-ordinators of the TGs programme (WNT) who takes decisions on TGs (approve and update of TGs) and decide on project proposals to include in the work plan. The WNT meets annually, usually in April. National co-ordinators represent regulatory authorities in OECD Member countries and countries adhering to MAD; and nominates experts and scientists from research and regulatory areas to work together on developing tools and guidance. In addition, expertise and input is gathered from the Business and Industry Advisory Committee (BIAC), Environmental non-governmental organisations , and the International Council on Animal Protection (ICAPO). Broad participation in work on TGs development helps to ensure sound science and international regulatory acceptance of test methods.

CONTACT YOUR NATIONAL CO-ORDINATOR TO LEARN MORE ABOUT THE TEST GUIDELINES ACTIVITIES IN YOUR COUNTRY

- Argentina
- Australia
- Austria
- Belgium
- Brazil
- Canada
- Czech Republic
- Denmark
- Estonia
- European Commission
- Finland
- France
- Germany
- Greece
- Hungary
- India
- Ireland
- Israel
- Italy
- Japan
- Korea
- Luxembourg
- Malaysia
- The Netherlands
- New Zealand
- Norway
- Poland
- Portugal
- Singapore
- Slovak Republic
- Slovenia
- South Africa
- Spain
- Sweden
- Switzerland
- Thailand
- Turkey
- United Kingdom
- United States

Who's who?

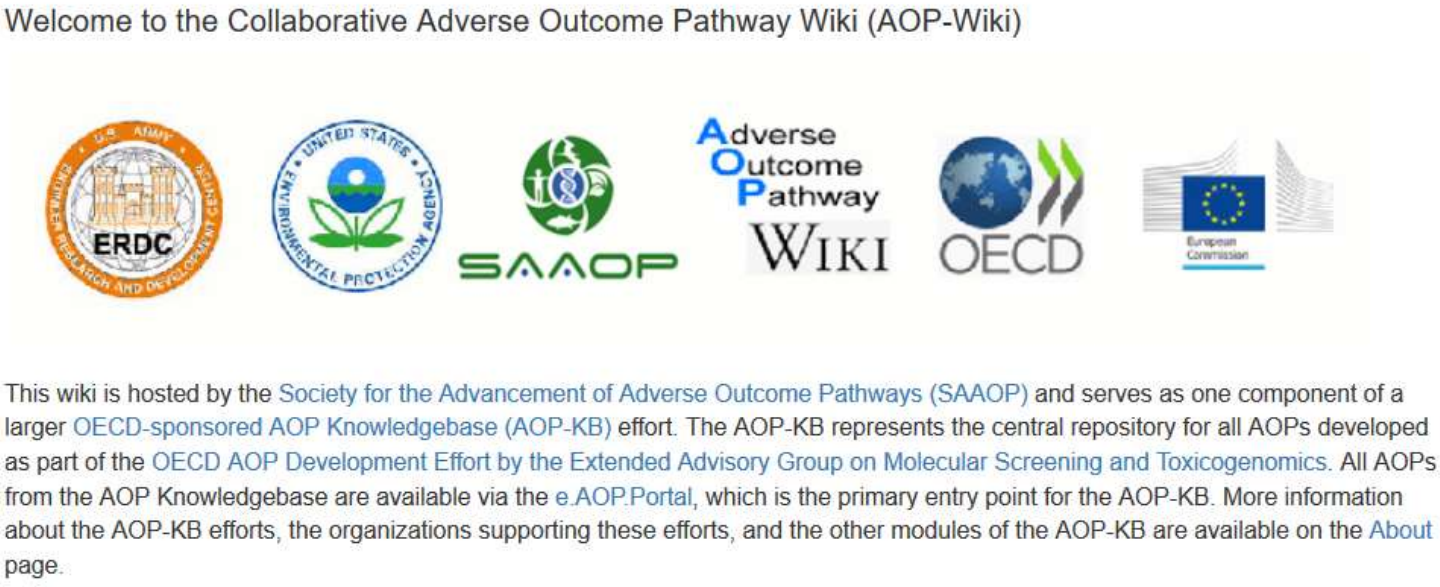
OECD committees involved:

- EAGMST: Extended Advisory Group on Molecular Screening & Toxicogenomics
- WPHA: Working Party on Hazard Assessment
- WNT: Working Group of National Coordinators Test Guidelines

Programme JRC: Joint Research Centre

U.S. EPA: U.S. Environmental Protection Agency

SAAOP: Society for the Advancement of AOPs



Submitting an AOP Project Proposal to OECD

Submitting a project proposal: Project proposals for developing an AOP can be sent at any time of the year to the OECD Secretariat (env.tgcontact@oecd.org) who then makes them available to the EAGMST for their review.

Who can submit a proposal: Project proposals to develop new AOPs can be made by members of the EAGMST or government representatives, academic experts, industry experts, non-governmental organisations, scientific societies, etc.). The National Coordinators of the Test Guidelines Programme are available for queries, and should be informed about proposals submitted.

Proposal Review: Twice a year, project proposals are reviewed, and if justified and in line with the objectives of the Programme, included in the work plan. The AOP Development Programme maintains a rolling work plan, updated twice a year with new project proposals and new information on existing projects.

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2 Abstract
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3 Summary of the AOP
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    2 Molecular Initiating Event
    3 Key Events
    4 Adverse Outcome
    5 Relationships Between Two Key Events
    6 Network View
    7 Life Stage Applicability
    8 Taxonomic Applicability
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4 Graphical Representation
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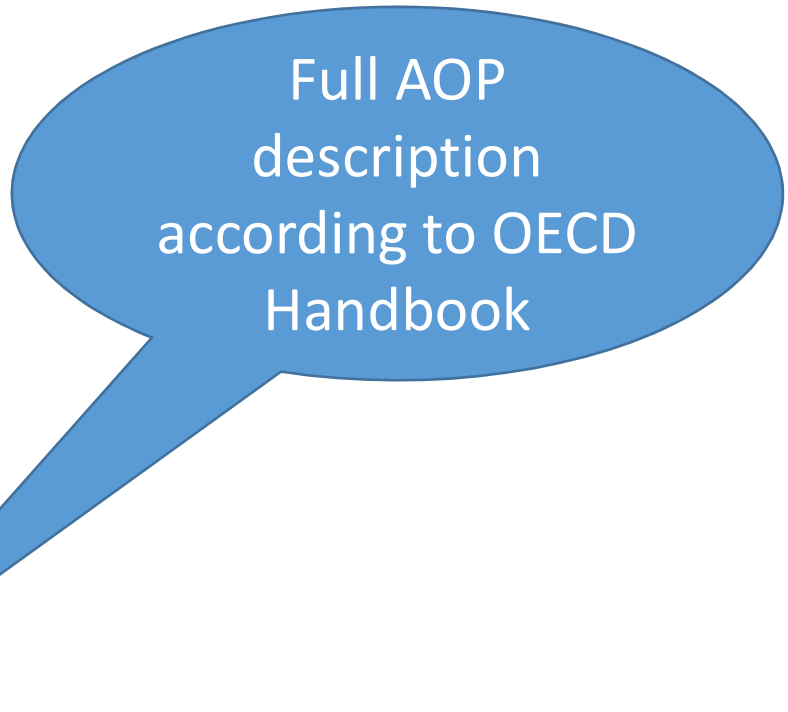
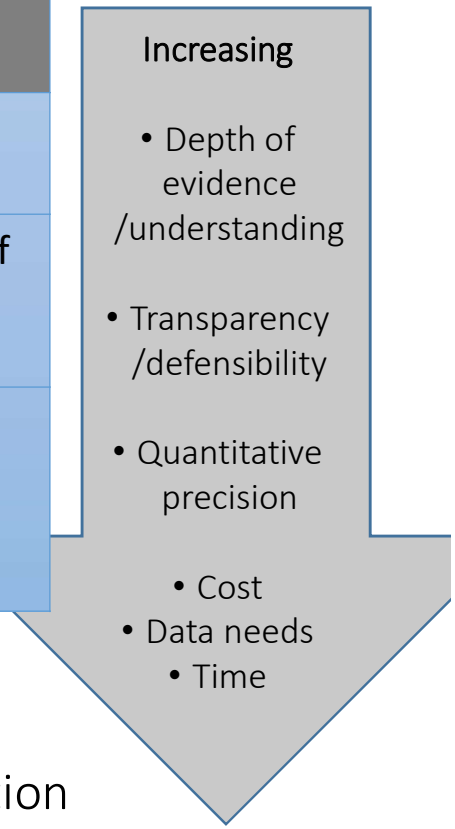


Principles of AOP Development

5. AOPs are living documents

Operationally-defined “stages” of AOP development

Stages of AOP Development	Characteristics
Putative AOPs:	Hypothesized set of KEs and KERs primarily supported by biological plausibility and/or statistical inference
Formal AOPs:	Include assembly and evaluation of the supporting weight of evidence – developed in AOP knowledgebase in accordance with internationally-harmonized OECD guidance
Quantitative AOPs:	Supported by quantitative relationships and/or computational models that allow quantitative translation of key event measurements into predicted probability or severity of adverse outcome



- All stages have potential utility
- Level of development desired/required depends on the application

AOP Development and Review Process

Read access

- Open to anyone, no account needed.
- Access to endorsed AOPs on the OECD site or the e.AOP.portal for all AOPs.

Commenting access

Create a user account on the AOP-Wiki site, no approval needed.

Development & write access

Anyone can start building an AOP in the Wiki after first sending a request for write privileges to the Society for the Advancement of AOPs (SAAOP). *(http://www.saaop.org/)*

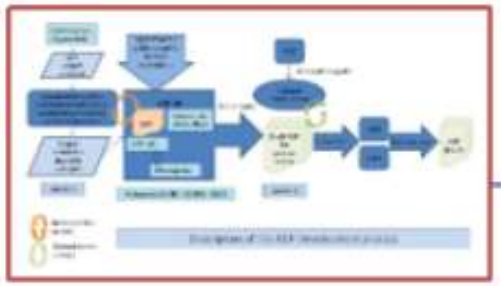
Review & endorsement by OECD

- If official recognition/review/regulatory application is sought, the AOP development project must be submitted to the OECD AOP development plan; the EAGMST then accepts (or refuses) the proposal. The proposal submission form is on the OECD site.
- An AOP considered mature enough by the authors is submitted to the internal OECD review, which is conducted by EAGMST members. The EAGMST either asks for further development or declares the AOP fit for external review, which is performed by external experts in the specific field and by regulators.
- The final step is the endorsement by the OECD Working Groups/Task Forces, Working Group of the National Coordinators of the Test Guidelines Programme (WNT) and Task Force on Hazard Assessment (TFHA), and publication in the Series on Adverse Outcome Pathways on the OECD website.

Click to see

OECD Site

Proposal Submission Form



The OECD Review Process for Submitted AOPs

The AOP Review Process is Split into Two Phases:

1) Internal Review - conducted within the EAGMST, by EAGMST members. The main objective of the internal review is to check compliance of the AOP structure and content with the User's Handbook and guidance principles.

2) External Review - conducted by experts who have scientific expertise in the hazard area/endpoint covered by the AOP, and who are not involved in the development of the specific AOP. The objective of the external review is to assess the scientific/technical content of the AOP.

Annual cycle for AOP reviews:

- Internal reviews generally take place between February and April;
- External reviews generally organised between September and December.

Publication: The OECD Series on AOPs

ISSN: 2415-170X (online)
DOI: 10.1787/2415170X

If the AOP passes the OECD review process, it can subsequently be "endorsed" by the Working of the National Coordinators of the Test Guidelines Programme (WNT) and by the Task Force on Hazard Assessment (TFHA). The AOP is then published in the OECD Series on AOPs.

Note: The publication in the OECD Series does not preclude publication (by the authors) of the AOP in the scientific literature, nor does it preclude any updating of the AOP in the AOP Wiki based on new scientific knowledge. Only "impactful" changes to the AOP will be reflected in subsequent updates of the AOP published in this series.

Evaluating AOPs weighing the evidence (WoE)

What is WoE?

- Involves an evaluation of the relative values/weights of the scientific evidence

- Applies expert judgment to the available scientific information

Why Woe?

BETTER POLICIES FOR BETTER LIVES

Helpful in coordinating between research/regulatory purposes:

- Identifies critical and recurring data gaps relevant to regulatory application
- Facilitates communication for purpose specific applications

Criteria to assess the WoE supporting AOPs

BETTER POLICIES FOR BETTER LIVES

- Draws on experience in mode of action (MOA) analysis for regulatory application
  - Modified for AOPs (non-chemical specific biological pathways)

- Based on modified Bradford Hill (B/H) considerations
  - Initially introduced to assess causality of associations observed in epidemiological studies in humans
  - later adapted to impacts on wildlife ("eco-epidemiology")

Evaluating AOPs Using Modified Bradford Hill Criteria

Sir Austin Bradford Hill (1897–1991)

Original 1965 Criteria
Strength - Strength of the association between suspected cause and observation.
Consistency - Repeatability of an association by different persons, in different places, circumstances and times.
Specificity - The association is limited to a specific population and to particular sites and types of disease.
Temporality - The exposure occurs before the effect.
Biological gradient - Risk of disease increases with increasing exposure.
Plausibility - Biological knowledge supports suspected causation.
Coherence - The association agrees with the generally known facts of the history and biology of the disease.
Experiment - Experimental evidence alters frequency of associated events.

Evaluating AOPs Using Modified Bradford Hill Criteria

Sir Austin Bradford Hill (1897–1991)

Original 1965 Criteria	Modified Criteria for MOA Evaluations
Strength - Strength of the association between suspected cause and observation.	**Strength** - N/A. Not considered as applicable to MOA data as specificity and consistency.
Consistency - Repeatability of an association by different persons, in different places, circumstances and times.	**Consistency** - Is the pattern of effects across species/strains/organs/test systems what would be expected?
Specificity - The association is limited to a specific population and to particular sites and types of disease.	**Essentiality of key events** - Is the sequence of events reversible if dosing is stopped or a key event prevented?
Temporality - The exposure occurs before the effect.	**Temporal concordance** - Are the key events observed in hypothesized order?
Biological gradient - Risk of disease increases with increasing exposure.	**Dose–response concordance** - Are the key events observed at doses below or similar to those associated with the end (adverse) effect?
Plausibility - Biological knowledge supports suspected causation.	**Biological plausibility** - How well established is the MOA in the biological database; does the proposed MOA conflict with biological knowledge?
Coherence - The association agrees with the generally known facts of the history and biology of the disease.	**Coherence** - N/A. Not considered as applicable to MOA data as consistency and plausibility.
Experiment - Experimental evidence alters frequency of associated events.	**Experiment** - N/A Not considered applicable to MOA data.

Principles of AOP Development

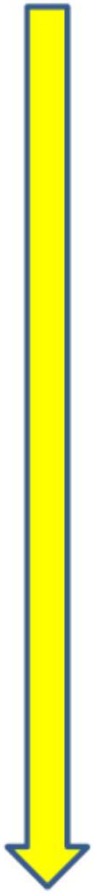
Modified BH Considerations	Conclusions
Biological Plausibility	KER is consistent with current biological understanding – plausible.
Essentiality of Key events	Effects are reversible if the stressor is removed (e.g., Villeneuve et al. 2009; EHP 117: 624-631)
Concordance of Empirical Observations	**Dose response** – The key events observed at doses below or similar to those associated with the apical effect? **Temporality** – The key events are observed in hypothesized order? **Incidence** – The frequency of occurrence of the apical effect less than that for the key events?
Consistency	Same pattern of effects has been observed in several test species (e.g., fathead minnow, zebrafish, medaka)
Analogy	Similar pattern of effects observed for three well known aromatase inhibitors (FAD, LET, PRO)

Adapted from Meek et al. 2014, J. Appl. Toxicol.

Focus/Consistent Terminology

- Biological Plausibility – ***KERs***
  - Biology of the pathway
- Essentiality – ***KEs within AOP***
  - Necessity of Key Events
  - Experimental support from specialized studies to block or modify key events, stop/recovery studies
- Empirical Support – ***KERs***
  - Quantitative Associations among Key Events tested through application of stressors

More important



Less important

Biological Plausibility of Each of the KERs

Defining Question: **Is there a mechanistic (i.e., structural or functional) relationship between KE_{up} and KE_{down} consistent with established biological knowledge?**

Degrees of Confidence and Examples:

Strong: well understood pathway based on extensive previous documentation, established mechanistic basis and broad acceptance

- e.g., direct interaction with DNA, leading to mutation and tumours

Moderate: plausible but scientific understanding incomplete

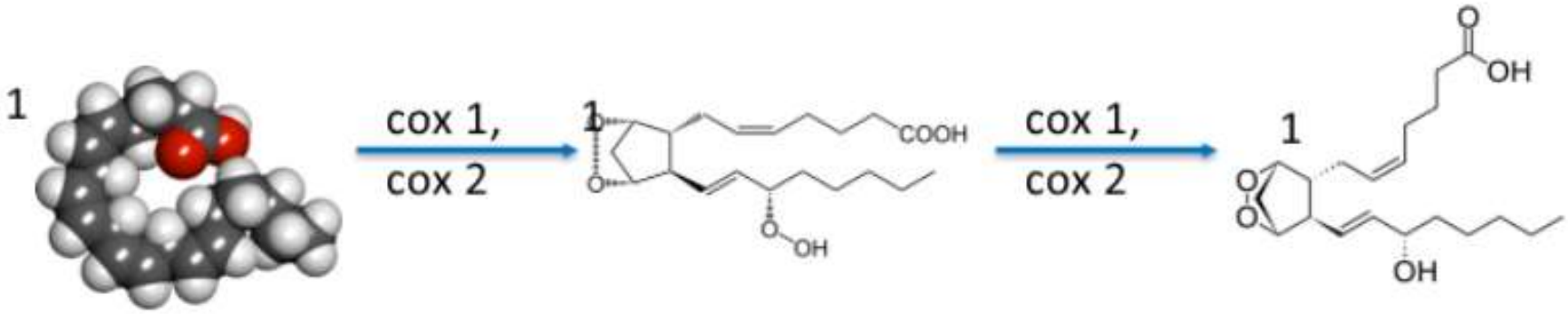
Weak: previously undocumented pathway; structural or functional relationship between KEs not understood (largely empirical observation)

Example: Enzyme catalyzes a reaction

Arachidonic acid

PGG_2

PGH_2

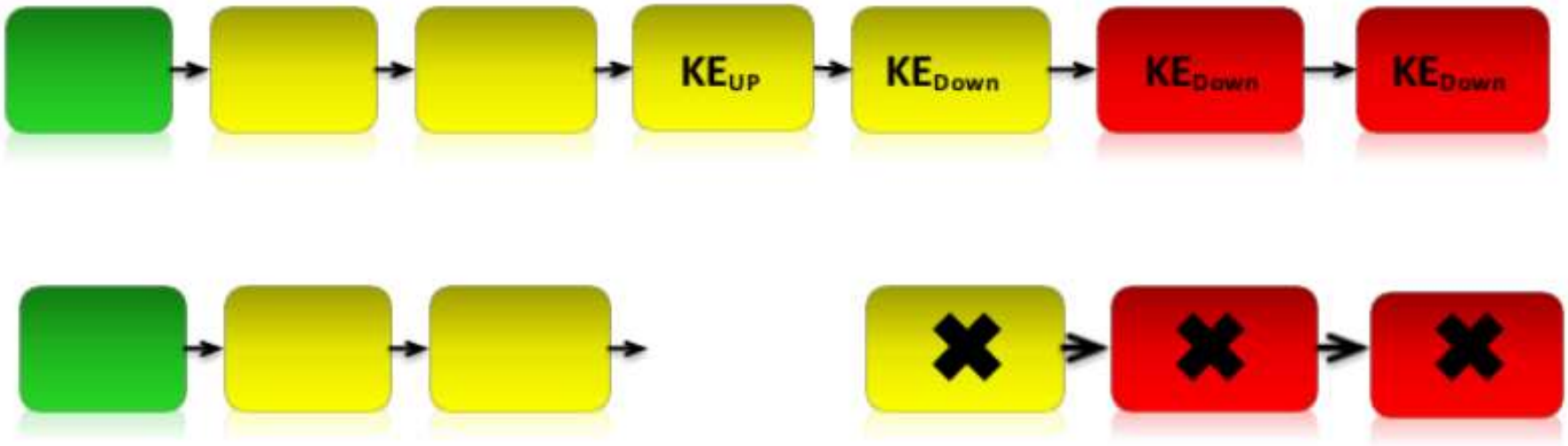


"Normal" biology: we know, the cox enzyme catalyzes conversion of arachidonic acid to prostaglandins.

Inference re: perturbed biology: It is plausible that if you inhibit the cox enzyme, you will reduce conversion of arachidonic acid to prostaglandins.

Essentiality of Key Events in the AOP

If we block/prevent/counter-act a KE, does that prevent all downstream KEs in that pathway?



In this example, YES…

Caveat: Downstream events can still be activated if there is an alternate path resulting from an intersection with another AOP in an AOP network that leads to the same downstream events.

Essentiality – KEs within the AOP

Defining Question:

Are downstream KEs and/or the AO prevented if an upstream event is blocked?

- KEs are **necessary** elements of an AOP

Degrees of Confidence and Examples:

Strong: direct evidence from specifically designed experimental studies illustrating essentiality for at least one of the important key events
(e.g., AO prevented in test system that has been genetically modified to disable or remove an upstream KE demonstrating that the downstream events subsequently does not occur)

Moderate: indirect evidence that experimentally induced change in a modulating factor that affects the activity of an upstream key event, subsequently lessens or greatens the effects on the downstream key event
(e.g., a modulating factor increases the proliferative response in a KE_{up} leading to an increase in tumour formation in a KE_{down} or AO)

Weak: no or contradictory experimental evidence of the essentiality of any of the KEs
(e.g., AO is not prevented in test systems where the key event has been removed)

Concordance - Empirical Support for Each of the KERs

Defining Question:

Is the pattern of dose-response, temporal and incidence concordance for the KERs as expected and supportive of the AOP

Degrees of Confidence:

Strong: dependent change in both key events following exposure to a wide range of specific stressors with no or few data gaps or conflicting data.

Moderate: data with smaller number of stressors; some explainable inconsistencies

Weak: limited or no relevant studies; unexplainable inconsistencies

Example: Concordance for Incidence, Timing, and Dose-Response for KEs

Dose – Response and Temporality

Temporal

Dose (mg/kg bw/day)	*Key event 1*	*Key event 2*	*Key event 3*
0.2 (2 ppm)	+ 4 weeks	+ 52 weeks	
1 (10 ppm)	++ 4 weeks	++ 52 weeks	+ 107 weeks
4 (40 ppm)	+++ 4 weeks	+++ 13 weeks	++ 52 weeks

Dose-Response

+ = severity

Extent of Quantitative Understanding	Characteristics
High	• Change in KE_{down} can be precisely predicted based on a relevant measure of KE_{up} • Uncertainty can be estimated • Modulating factors are accounted for • Generalizable – applicability domain
Moderate	• Change in KE_{down} can be precisely predicted based on a relevant measure of KE_{up}. • Less certainty in other elements
Weak	• Only a qualitative or semi-quantitative prediction of the change in KE_{down} can be determined from a measure of $Ke_{up;}$ • Modulating factors not accounted for • Narrow applicability domain

Summary

- Biological Plausibility:
  - How well do we ***understand the structural/functional relationships*** of the pathway?
  - Do we know enough to be able to ***"predict"*** what happens if we ***disturb*** the pathway (experimentally)

- Empirical Support:
  - The ***nature of the expected quantitative impact*** on downstream KEs if we "disturb" earlier KERs
  - Tested by considering dose-response relationships for stressors which impact the pathway

Overall Assessment of the AOP

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Full AOP description according to OECD Handbook

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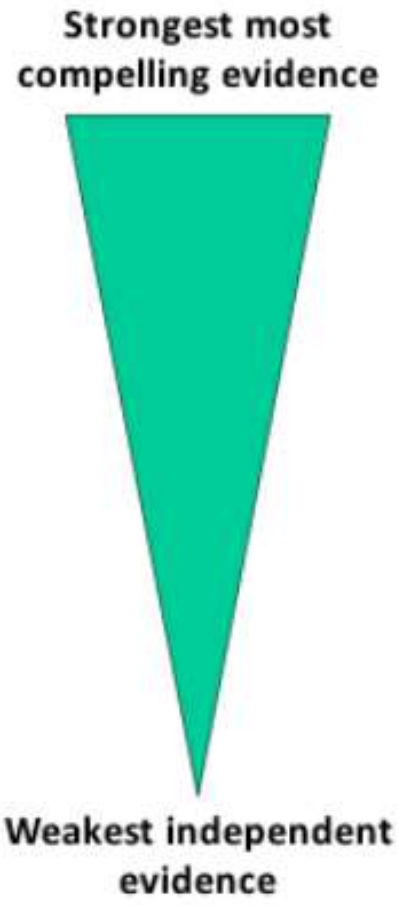
  4 Quantitative Considerations

AOP Evaluation



1. **Plausibility** – Most important supporting evidence
2. **Essentiality** – KE event sequence
3. **Empirical support** (including quantitative understanding)
   - Dose-response concordance
   - Temporal concordance
   - Incidence concordance

QUANTITATIVE AOPs

What can we learn about qAOPs

… for now and within HBM4EU

science and policy
for a healthy future

„Quantitative adverse outcome pathway“[Title/Abstract] on Pubmed – 6 hits

Building and Applying Quantitative Adverse Outcome Pathway Models for Chemical Hazard and Risk Assessment.
Perkins EJ, Ashauer R, Burgoon L, Conolly R, Landesmann B, Mackay C, Murphy CA, Pollesch N, Wheeler JR, Zupanic A, Scholz S.
Environ Toxicol Chem. 2019 May 25. doi: 10.1002/etc.4505. [Epub ahead of print] Review.

A Cross-species Quantitative Adverse Outcome Pathway for Activation of the Aryl Hydrocarbon Receptor Leading to Early Life Stage Mortality in Birds and Fishes.
Doering JA, Wiseman S, Giesy JP, Hecker M.
Environ Sci Technol. 2018 Jul 3;52(13):7524-7533. doi: 10.1021/acs.est.8b01438. Epub 2018 Jun 19.

Neurodevelopment and Thyroid Hormone Synthesis Inhibition in the Rat: Quantitative Understanding Within the Adverse Outcome Pathway Framework.
Hassan I, El-Masri H, Kosian PA, Ford J, Degitz SJ, Gilbert ME.
Toxicol Sci. 2017 Nov 1;160(1):57-73. doi: 10.1093/toxsci/kfx163.

Quantitative Adverse Outcome Pathways and Their Application to Predictive Toxicology.
Conolly RB, Ankley GT, Cheng W, Mayo ML, Miller DH, Perkins EJ, Villeneuve DL, Watanabe KH.
Environ Sci Technol. 2017 Apr 18;51(8):4661-4672. doi: 10.1021/acs.est.6b06230. Epub 2017 Apr 7.

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BMC
Systems Biology

RESEARCH ARTICLE Open Access

A computational model of the hypothalamic - pituitary - gonadal axis in female fathead minnows (*Pimephales promelas*) exposed to 17α-ethynylestradiol and 17β-trenbolone

Zhenhong Li[1], Kevin J Kroll[2], Kathleen M Jensen[3], Daniel L Villeneuve[3], Gerald T Ankley[3], Jayne V Brian[4], María S Sepúlveda[5], Edward F Orlando[6], James M Lazorchak[7], Mitchell Kostich[7], Brandon Armstrong[8], Nancy D Denslow[2] and Karen H Watanabe[1*]

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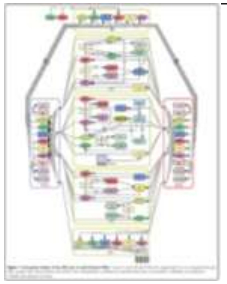
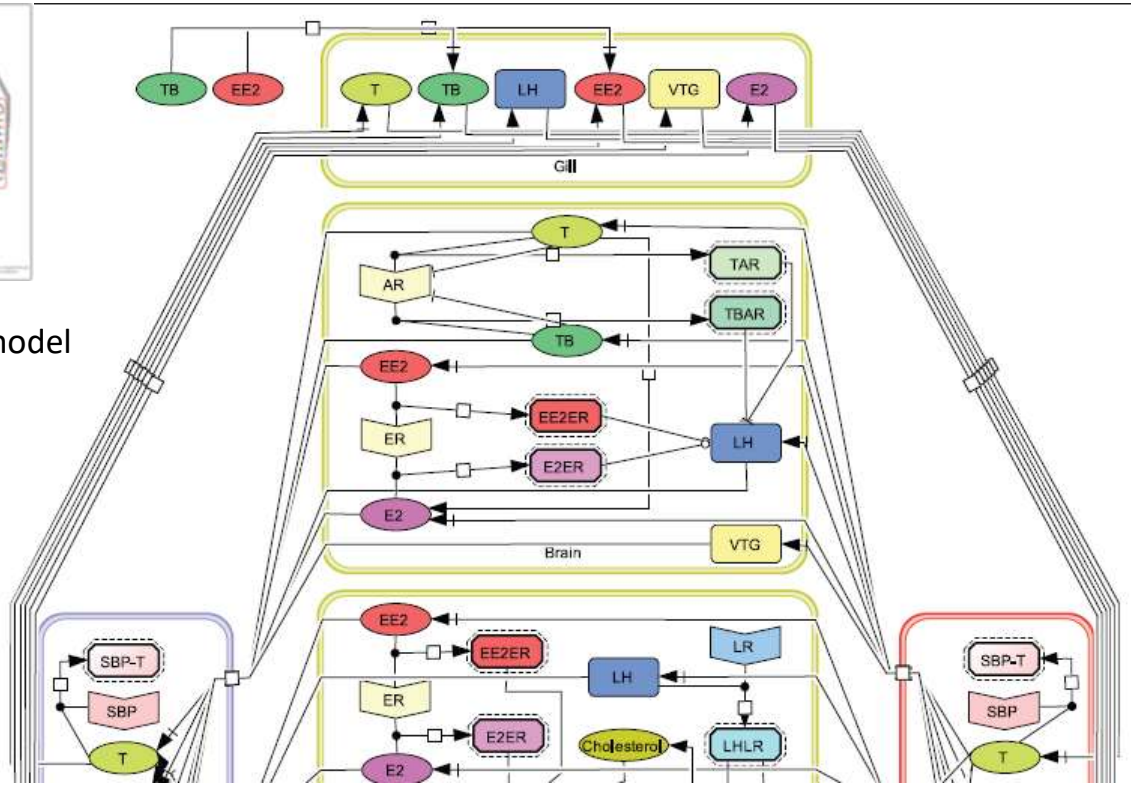


Koncepční model
→ ZOOM



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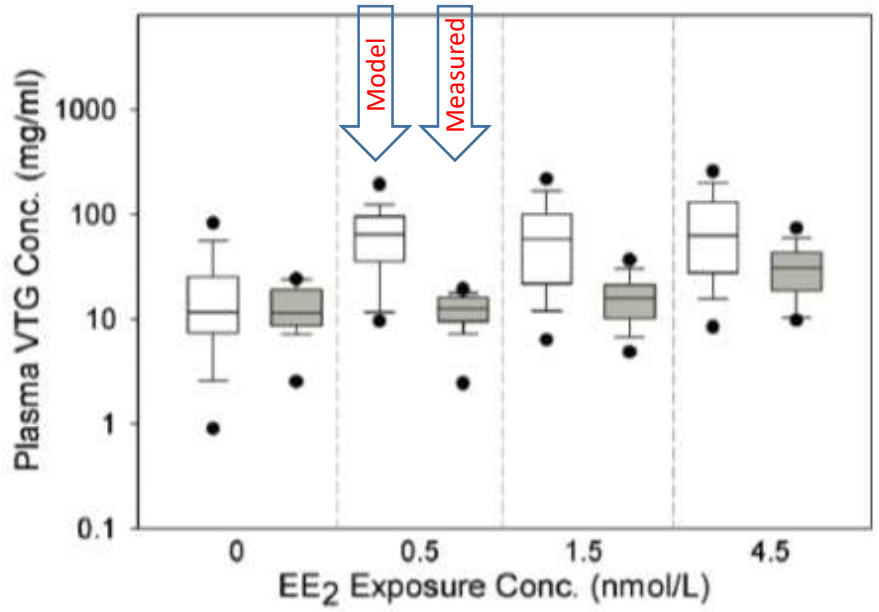

Figure 6 Comparison of model predictions with measured data in female FHMs exposed to EE_2. n = 28 at each sampling time. White boxes represent model predictions, and grey boxes represent measured data [42]. The x-axis represents EE_2 concentrations in ng/L. The solid line within the box marks the median; the boundary of the box farthest from zero indicates the 75th percentile; the boundary of the box closest to zero indicates the 25th percentile; the whisker (error bar) farthest from zero marks the 90th percentile; whisker (error bar) closest to zero marks the 10th percentile; the circle farthest from zero marks the 95th percentile; and the circle closest to zero marks the 5th percentile.

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RESEARCH ARTICLE

A Computational Model of the Rainbow Trout Hypothalamus-Pituitary-Ovary-Liver Axis

Kendall Gillies, Stephen M. Krone, James J. Nagler, Irvin R. Schultz

Published: April 20, 2016 • https://doi.org/10.1371/journal.pcbi.1004874

Abstract

Reproduction in fishes and other vertebrates represents the timely coordination of many endocrine factors that culminate in the production of mature, viable gametes. In recent years

PLoS Comput Biol. 2016 Apr 20;12(4):e1004874.

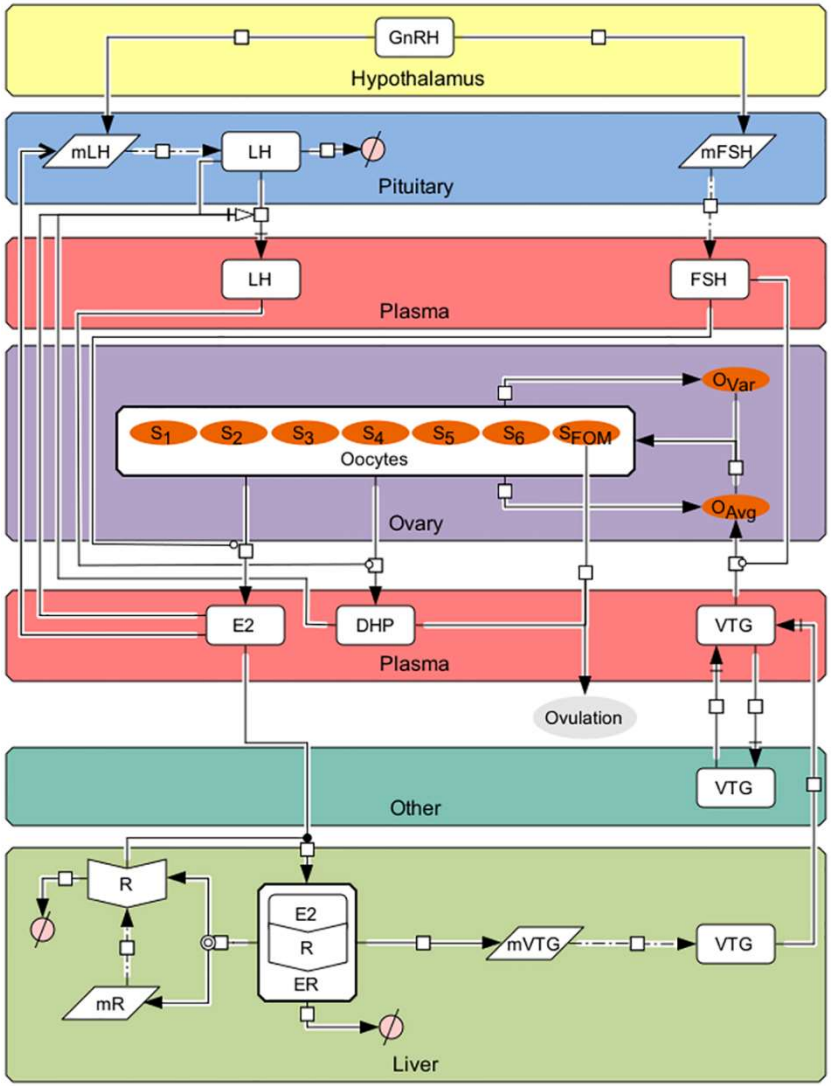

Fig 1. The HPOL signaling network in rainbow trout as formulated in our model.

Arrows and symbols on graph follow CellDesigner vs. 4.4 notation (www.celldesigner.org). GnRH is secreted from the hypothalamus into the pituitary stimulating the production of mFSH and mLH, which then leads to formation of FSH and LH, respectively. FSH, which is being continuously secreted from the pituitary, travels to the ovaries to stimulate production of E2. E2 then travels to the liver to bind with E2 receptors (R; translated from mR) to form ER. ER then stimulates the production of mVTG, which produces VTG_L. Secreted VTG then travels from the liver to the ovaries via the plasma (VTG_P) where it is absorbed by follicles in stages 3 through 6 (the proportion of follicles in these stages are denoted by S_j, j = 3, 4, 5, and 6) during vitellogenesis, the rate of which is affected by FSH_P, to promote oocyte growth (O_{Avg}). Oocyte growth then progresses the oocytes through the stages using a Weibull distribution created from O_{Avg} together with O_{Var}. In the later stages LH_P stimulates the oocytes to produce DHP. Finally, oocytes undergo final maturation (S_{FOM}) and combined with DHP, determine when the fish ovulates

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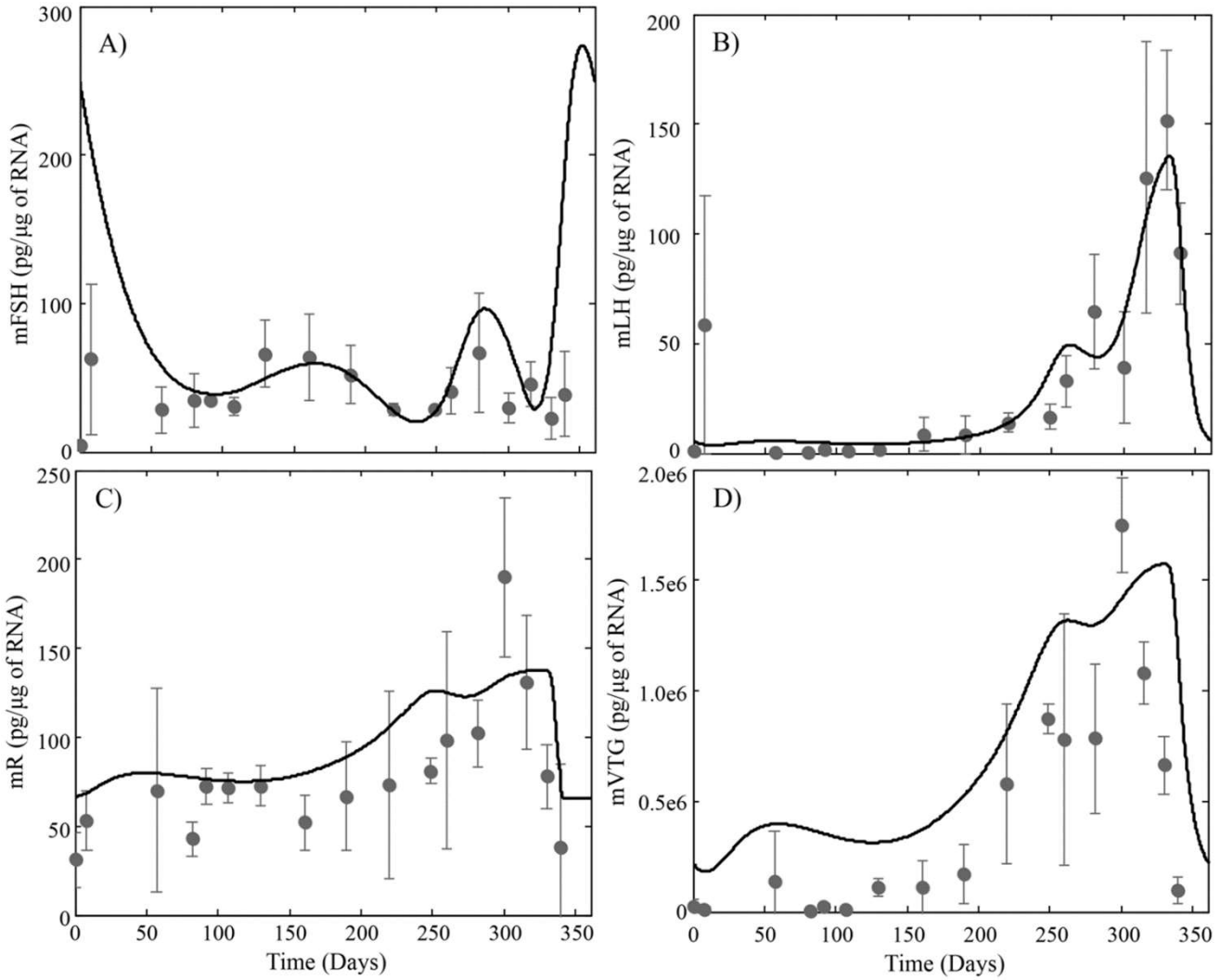
Fig 3. HPOL **model predictions** for (A) pituitary levels of FSH_β subunit mRNA, (B) pituitary levels of LH_β subunit mRNA, (C) Hepatic levels of E2 receptor mRNA and (D) Hepatic levels of VTG mRNA

Observed data (dark grey circles; mean ±TG mR*n* = 3)



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AOP Knowledge Base (AOP-KB)

AOP Knowledge Base and Tools

Effectopedia is part of the OECD's AOP Knowledge Base suite of tools. Constantly developed and refined, AOP-KB is web- based platform which aims to bring together all knowledge on how chemicals can induce adverse effects, therefore providing a focal point for AOP development and dissemination.

The e AOP Portal is the main entry point of the AOP Knowledge Base. A search engine, the Portal enables search by key words in AOP titles and key events in the AOP Wiki and Effectopedia platforms. It houses the status of all AOPs in the OECD Work Plan and the official copy of OECD endorsed AOPs.

The AOP Wiki provides a system that organises, via crowd-sourcing, the available knowledge and published research into a verbal description of individual pathways, using a user friendly Wiki interface. Information on AOP is collected in a qualitative, narrative way.

AOPXplorer drives biological understanding by coupling AOP networks with biological data. Using AOPXplorer, AOPs can be visualized using the AOP Ontology, a community resource updated with AOPs from the AOP-Wiki as well as putative AOPs and disease pathways.

The Intermediate Effects Database (IEDB) provides a platform where real-life data on Intermediate Effects, triggered by *actual chemicals*, underpin a *chemical agnostic* AOP and its Key Events. Data is stored in the internal OECD Harmonised Template for Intermediate Effects (OHT 201).

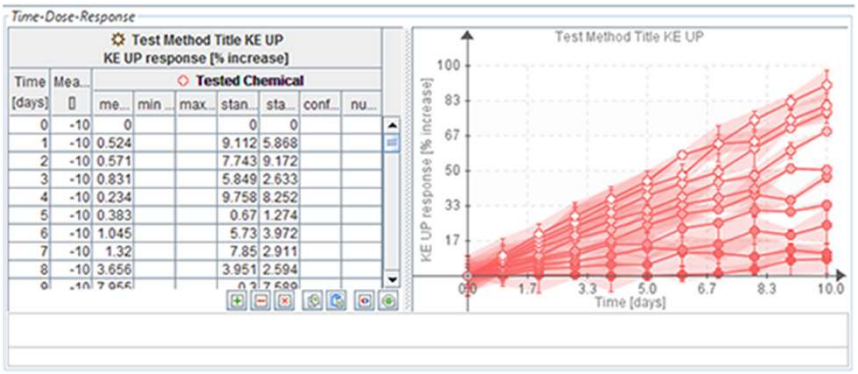
International QSAR Foundation

Effectopedia

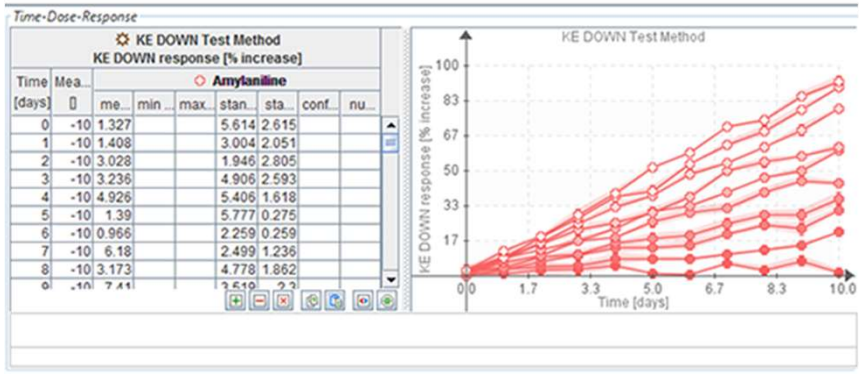
The Online Encyclopedia of Adverse Effect Pathways

- http://www.effectopedia.org/ → **Quantitative Relationships**

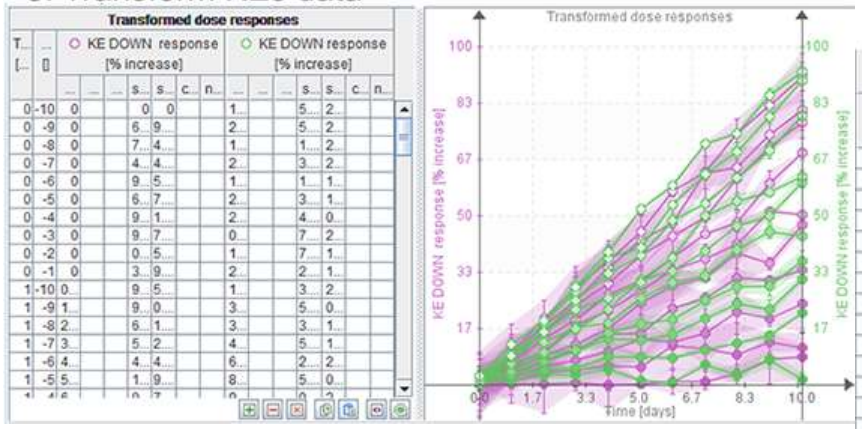
1. Add time-dose-response data for upstream KE



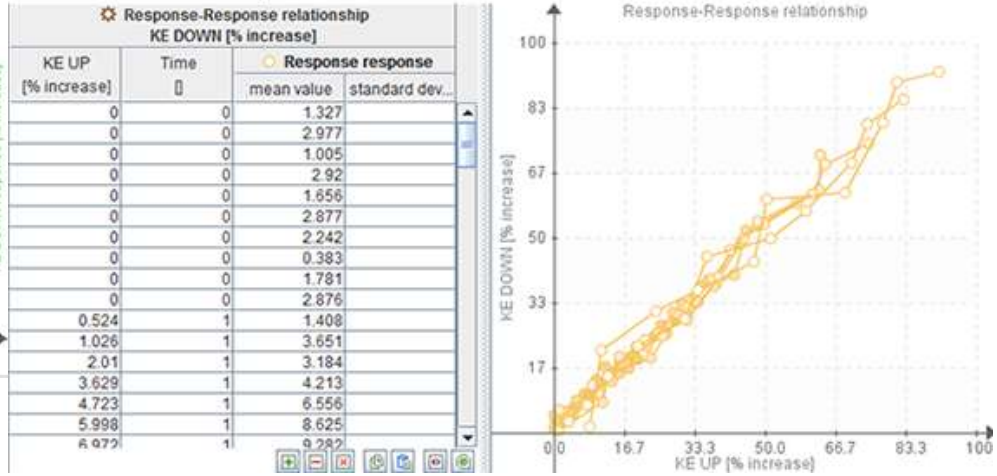
2. Add time-dose-response data for downstream KE



3. Transform KEs data



4. Derive response - response relationship



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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.