CONSIDERATIONS FOR INCREASING QUANTITATIVE AOP (QAOP) REGULATORY UPTAKE

Magda Sachana
ECETOC Workshop on Quantitative Response-Response Relationships (qAOPs)
(Hybrid, 18-19 October 2022)

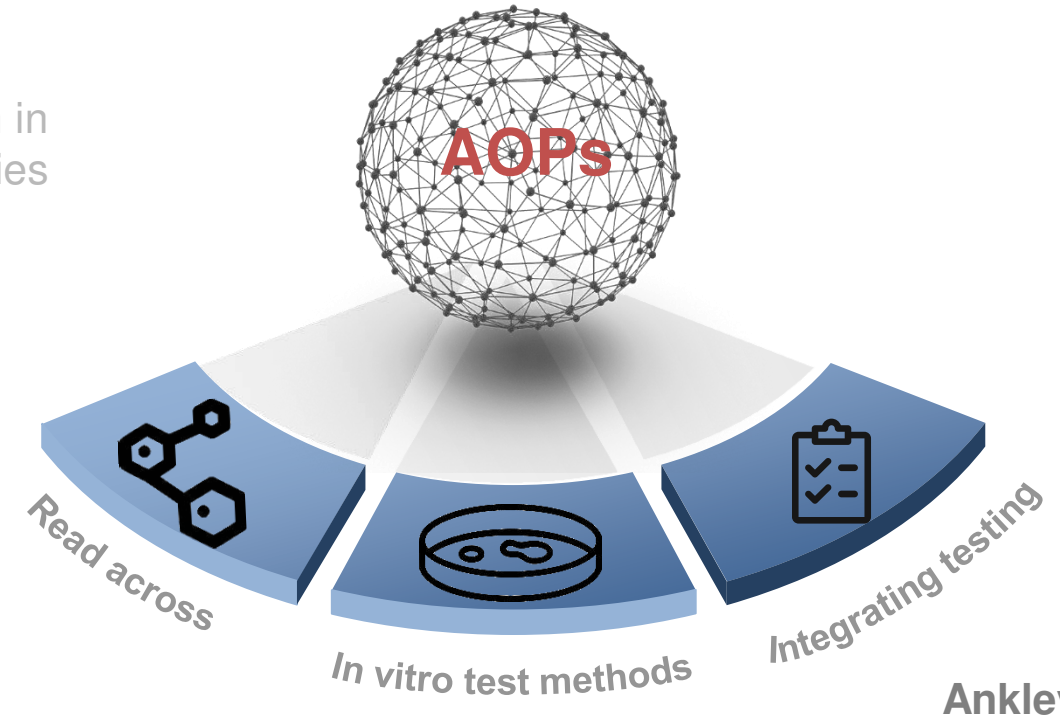
BETTER POLICIES FOR BETTER LIVES

BACKGROUND

Adverse Outcome Pathways (AOPs)

OECD Workshop (Dec 2010)

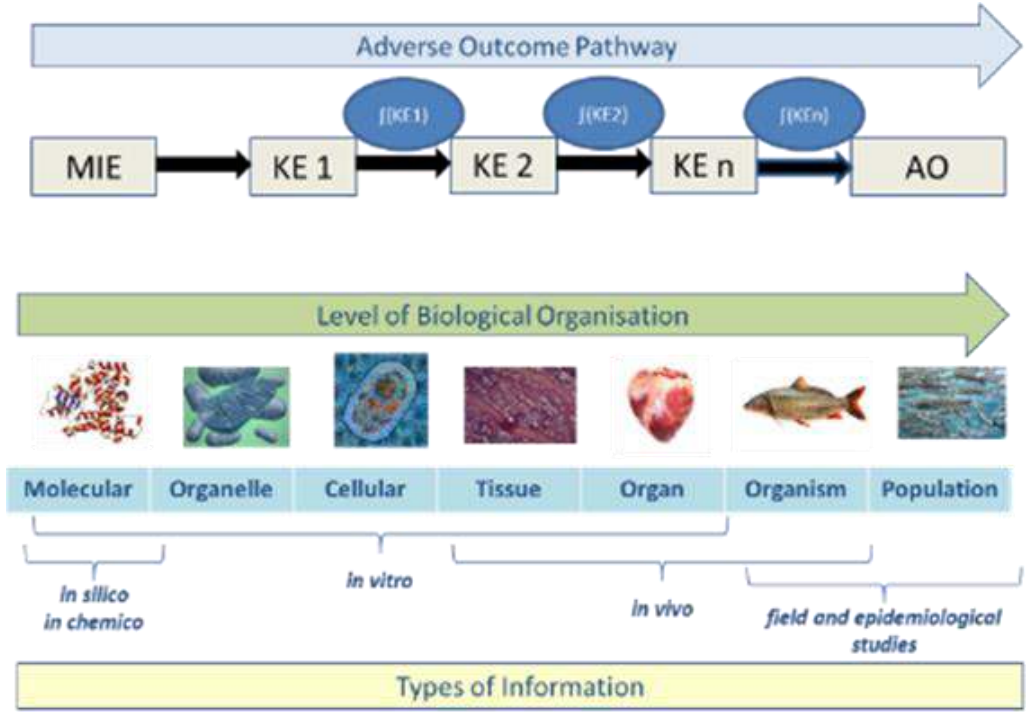
Using Mechanistic Information in Forming Chemical Categories



Ankley et al. 2010 (March 2010)

Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment.

Adverse Outcome Pathway Framework



- AOPs were always envisioned as organising frameworks for:
  - building predictive methods (including test guidelines)
  - building integrated testing strategies
  - guiding next steps for chemical safety testing
  - identifying gaps in information

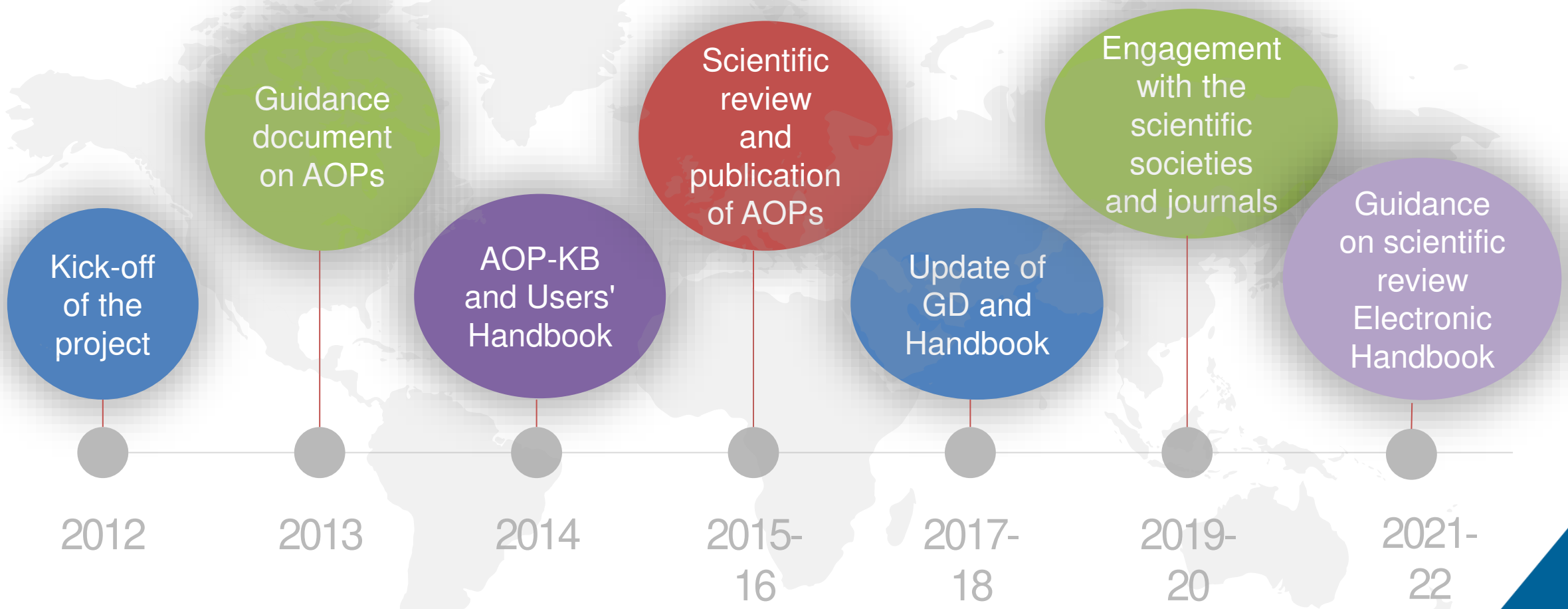
OECD AOP Development Programme

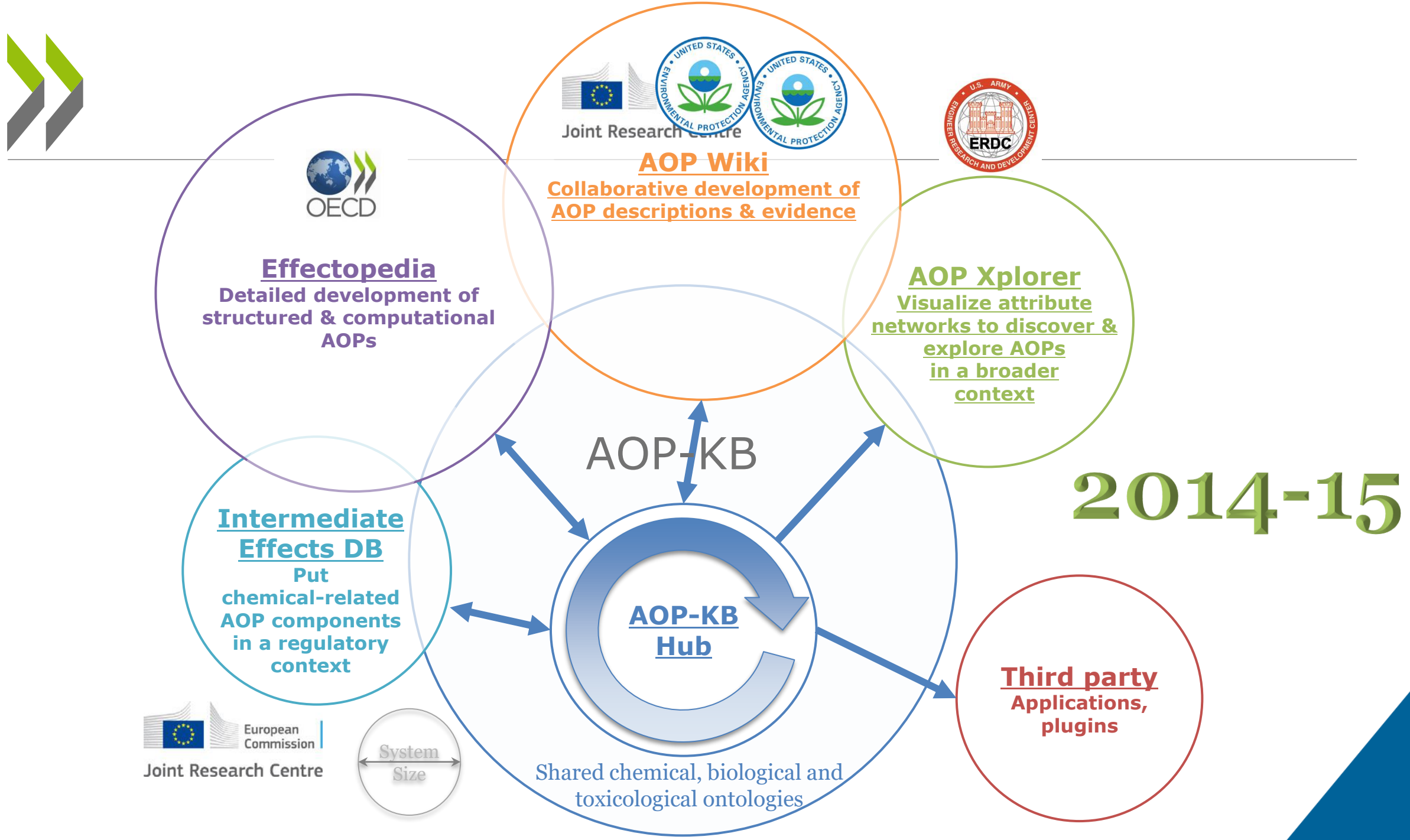
Extended Advisory Group on Molecular Screening

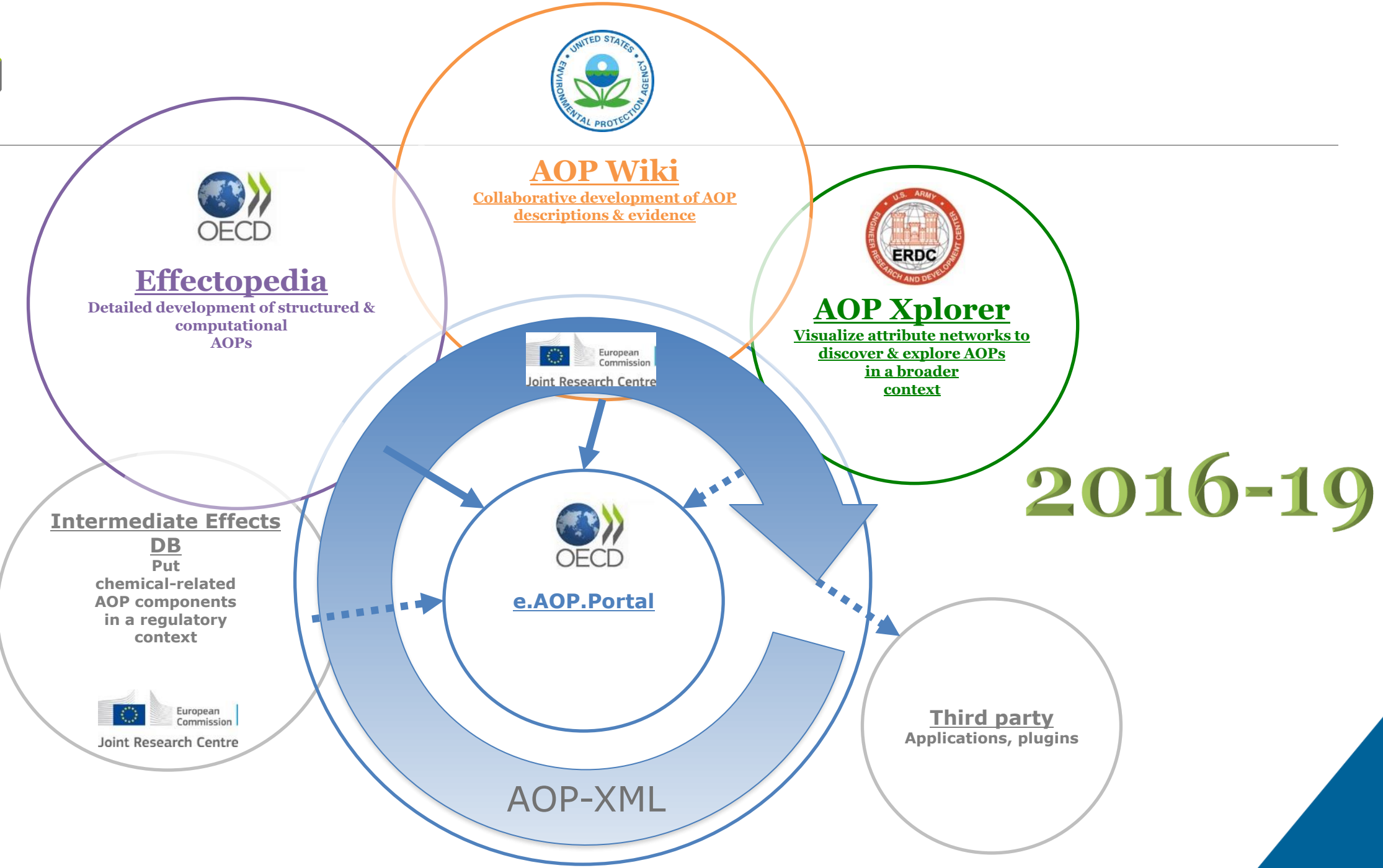
*since taking responsibility in 2012

EAGMST meeting OECD, Paris.

AOP programme: Achievements




Joint Research Centre
AOP Wiki
Collaborative development of AOP descriptions & evidence
OECD
Effectopedia
Detailed development of structured & computational AOPs
ERDC
AOP Xplorer
Visualize attribute networks to discover & explore AOPs in a broader context
AOP-KB
Intermediate Effects DB
Put chemical-related AOP components in a regulatory context
AOP-KB Hub
Third party
Applications, plugins
2014-15
European Commission
Joint Research Centre
System Size
Shared chemical, biological and toxicological ontologies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Intermediate Effects DB
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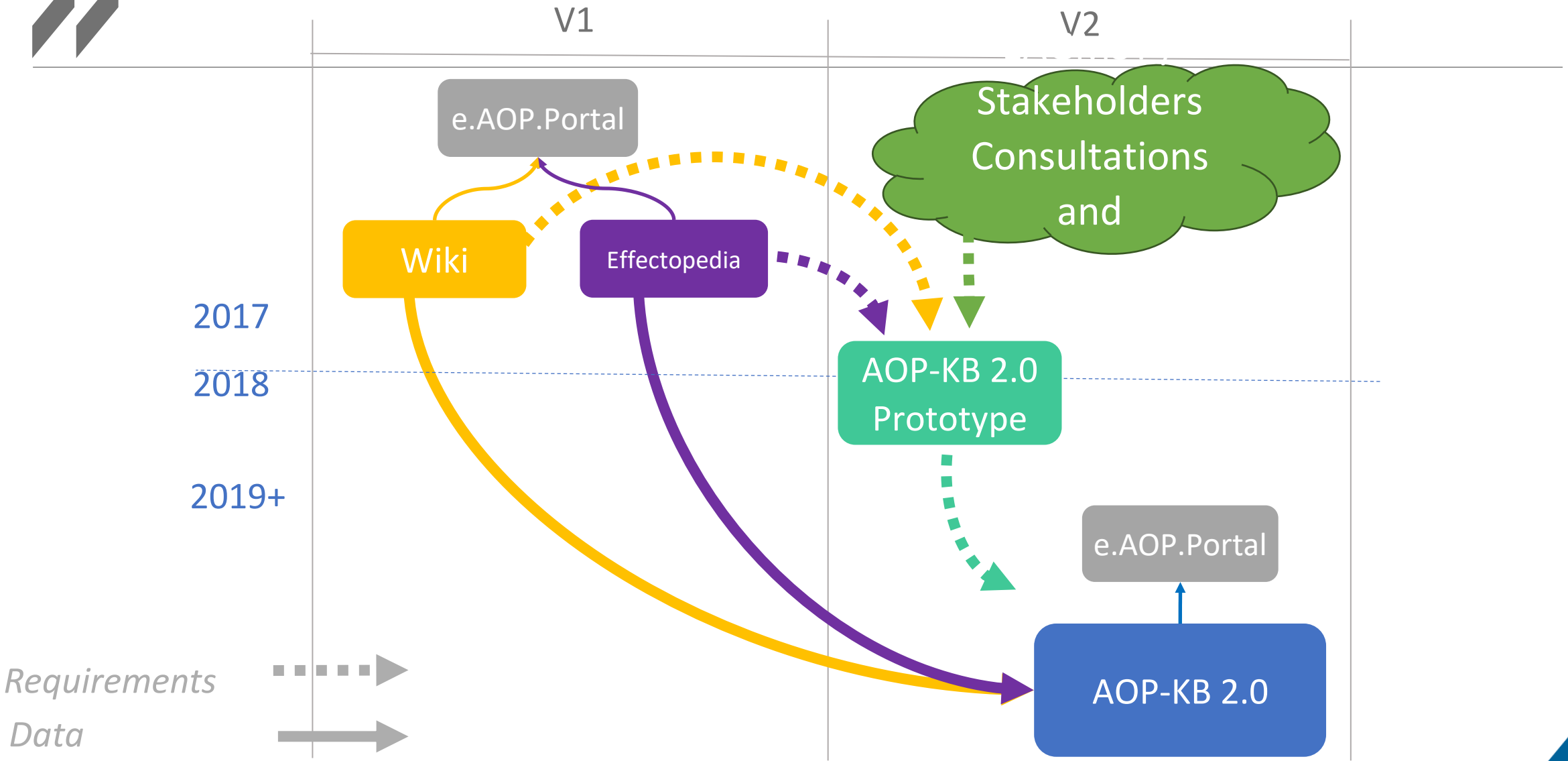
Joint Research Centre
e.AOP.Portal
AOP-XML
Third party
Applications, plugins
2016-19

AOP-KB 1.0 -> AOP-KB 2.0



2019-20

AOP Knowledge Base

portal

https://aopkb.oecd.org/

- Main entry point for the AOP-KB
- Search engine for all AOPs
- Houses the status of all AOPs and links to the official copies
- Allows browsing of review reports

Adverse Outcome Pathway WIKI

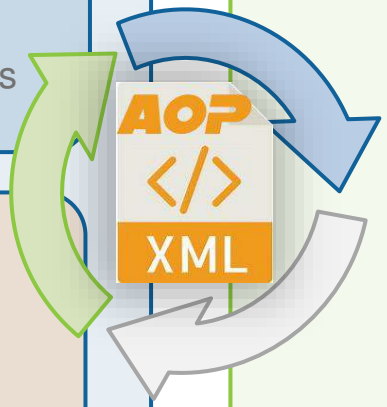
https://aopwiki.org/

- Entry level module for evaluating an AOP's scientific evidence
- Supports OECD review of AOPs
- Default go-to module for all qualitative AOPs

Effectopedia

https://www.effectopedia.org/

- Captures quantitative information and models
- Provides standard visual representation of AOPs and associated test methods



Third Party Tools

AOPXplorer

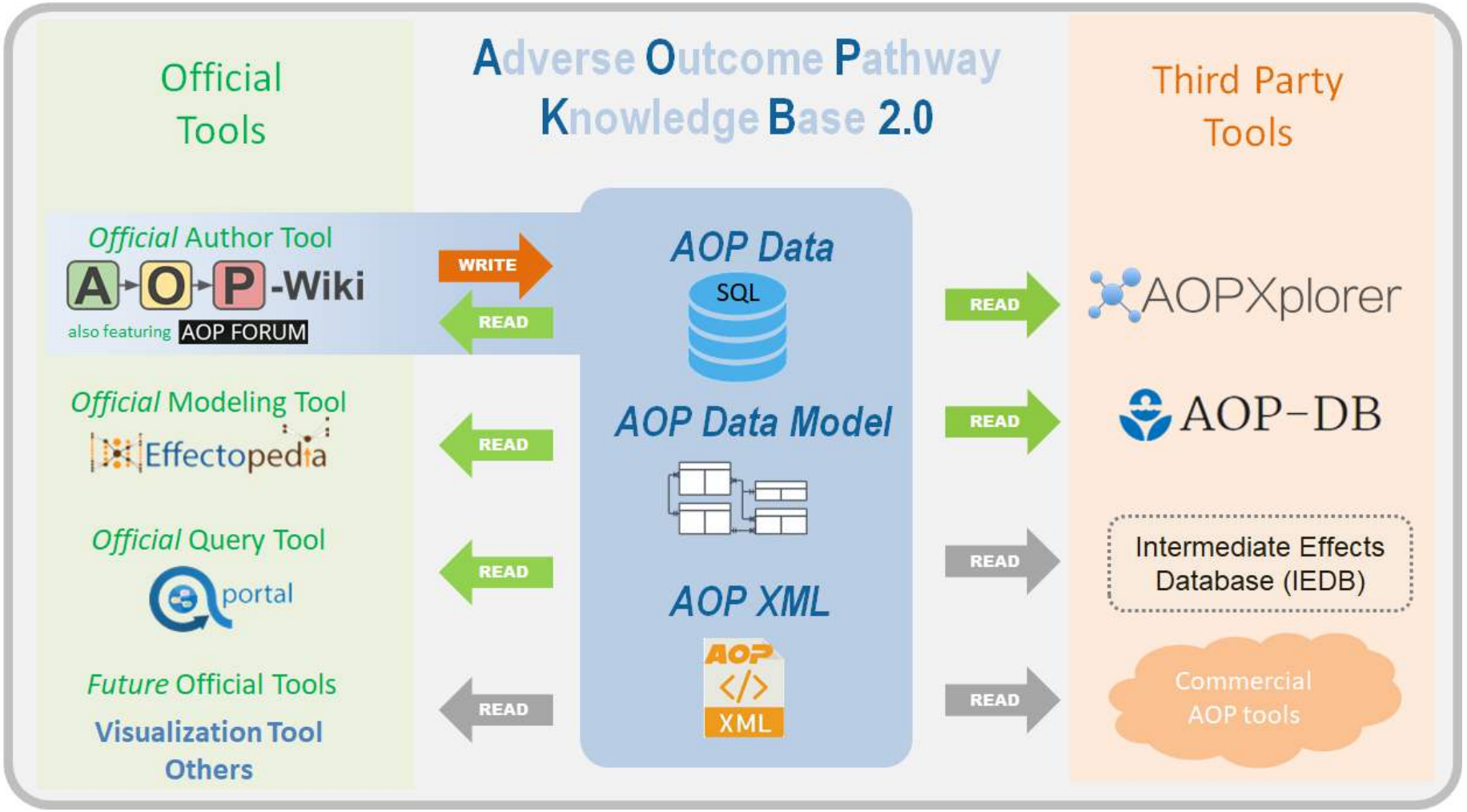
http://apps.cytoscape.org/apps/aopxplorer

AOP-DB

On the Web from Summer 2020!

Intermediate Effects Database (IEDB)

2021


Official Tools
Adverse Outcome Pathway Knowledge Base 2.0
Third Party Tools
Official Author Tool
AOP-Wiki
also featuring AOP FORUM
Official Modeling Tool
Effectopedia
Official Query Tool
portal
Future Official Tools
Visualization Tool
Others
WRITE
READ
READ
READ
READ
AOP Data
SQL
AOP Data Model
AOP XML
AOP
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READ
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Commercial AOP tools

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WRITE

READ

READ

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AOP Data

SQL

AOP Data Model

AOP XML

AOP XML

READ

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READ

READ

READ

Third Party Tools

AOPXplorer

AOP-DB

AOP-helpFinder

Intermediate Effects Database (IEDB)

Commercial AOP tools

Kaptis

Biovista

Versions

2.5

- Assign role of a KE (MIE, KE, AO) automatically in the AOP table
- Filter and sort tables
- Incorporation of third party tools
- Handbook publication (versioning etc.)
- Strategy Fields and Modulating Factors
- Stressors

current

2.6

- Getting ready for upcoming changes
- Stressors
- Improved License model
- Data Model changes

end 2022

3.0

- Systematic Approaches features
  - More machine-readable information
  - Provenance!
- Test methods
  - “How it is measured or detected” – revisited and improved
- Ontologies!

2023-2024

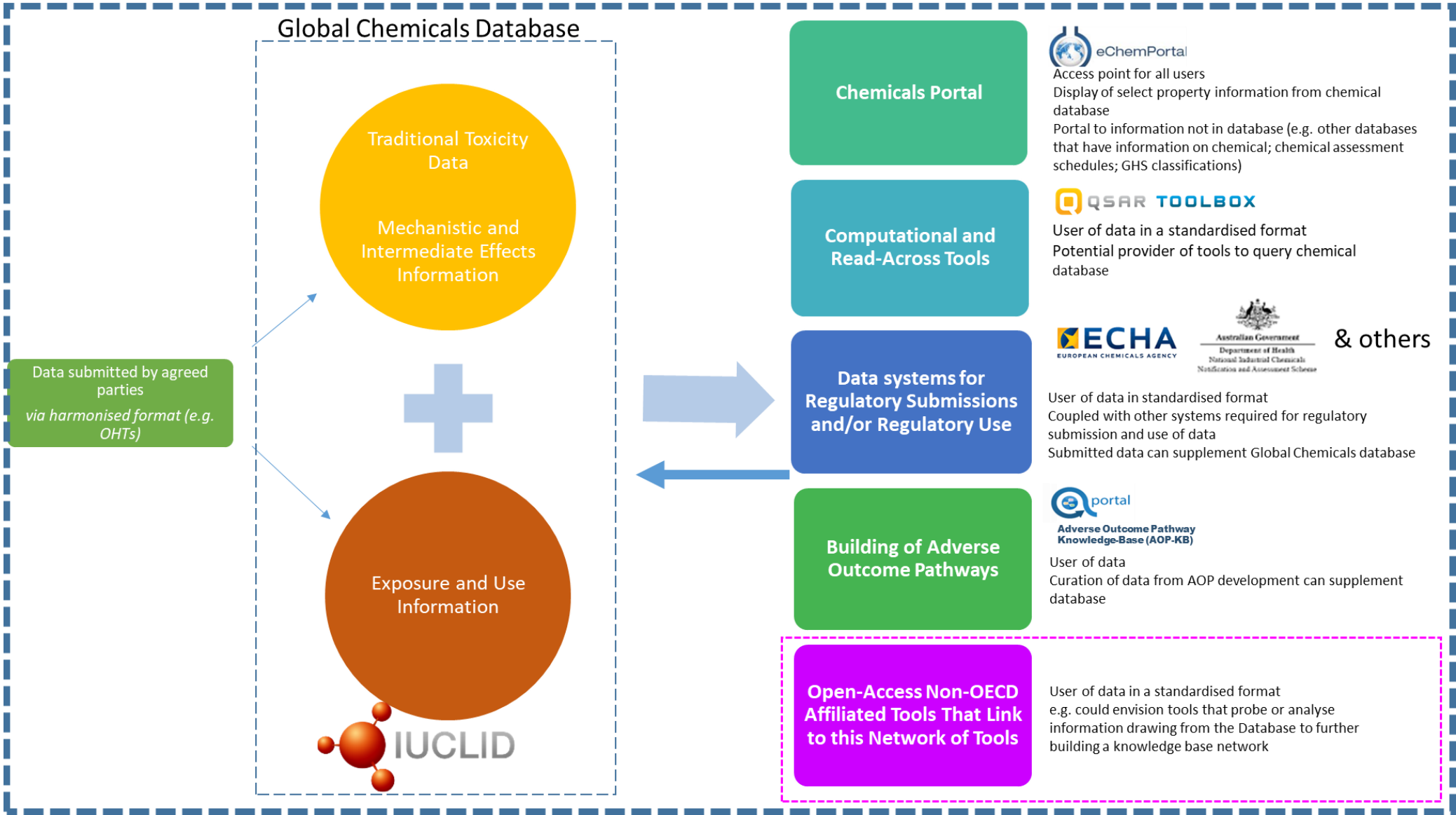
What to expect in the near future

- Effectopedia and eAOP Portal will be gradually retired from the AOP-KB ecosystem
  - There won't be any official tool capturing quantitative information and models
- New AOP-Wiki data model is envisioned to allow
  - Method description
  - Experimental data storage

Data sharing in an Electronic Ecosystem: OECD Global Chemical Knowledge Base

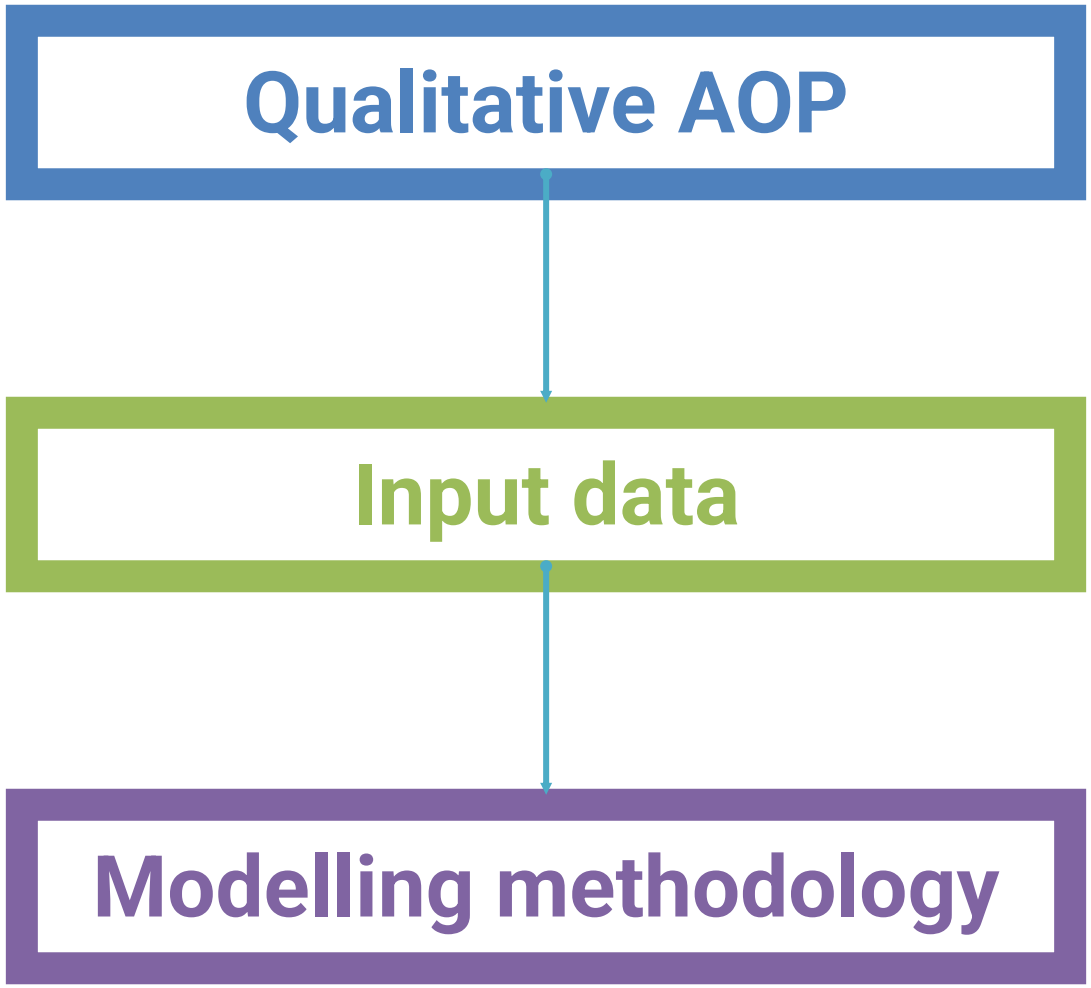
Promotes the **interlinkage** of tools to support regulatory decisions on chemicals

Encourages use of **OHTs** to increase the ability to share data.



CONSIDERATIONS FOR REGULATORY UPTAKE

qAOP elements



Considerations

AOP

- Level of detail (which stage or development/putative vs qualitative AOPs)
- Level of reviewing
- Level of confidence
- One linear AOP vs interacting AOPs (networks) leading to an AO

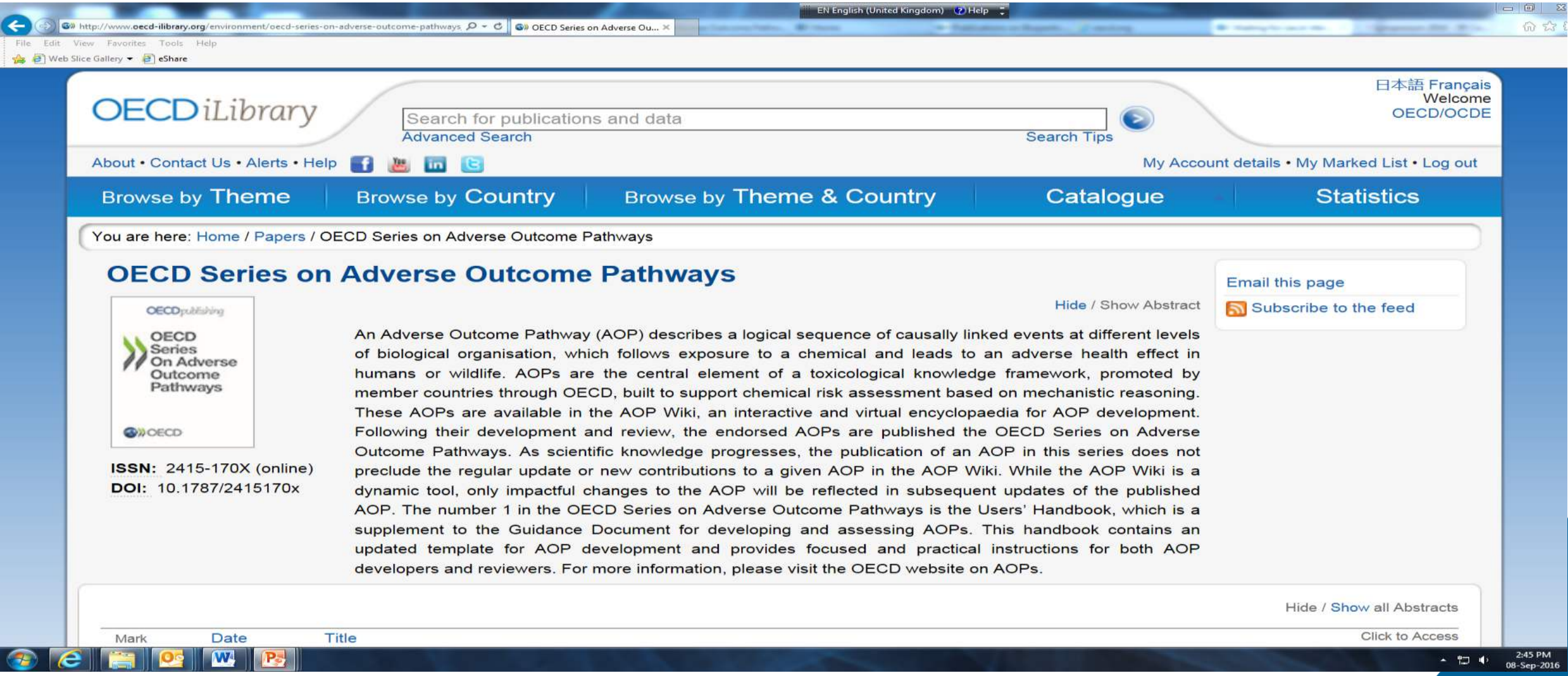
Input Data

- Amount and quality of data supporting of KERs/response-response relationships (number of chemicals and methods)
- Assays used to measure the KEs (status of development/standardization/validation/ GIVIMP)
- Reliability and coverage of methods used to measure or predict the MIE or the KEs
- Technology driven datasets (omics, high throughput)
- QSAR predictions

Modelling methodology

- Limitations and the uncertainties related to the model
- Consideration and incorporation of critical factors that modulate the KERs

Series on Adverse Outcome Pathways

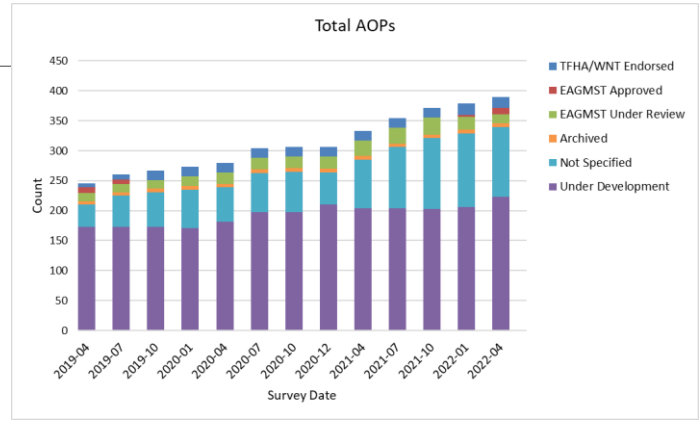


https://www.oecd-ilibrary.org/environment/oecd-series-on-adverse-outcome-pathways_2415170x

☆	No. 19	15 Oct 2021	Adverse Outcome Pathway on Cyp2E1 activation leading to liver cancer **Francina Webster, Iain B. Lambert and Carole L. Yauk**	PDF
☆	No. 18	15 Oct 2021	Adverse Outcome Pathway on inhibition of calcineurin activity leading to impaired T-cell dependent antibody response **Hiroyuki Komatsu, Junichiro Sugimoto, Ken Goto, Kiyoshi Kushima, Naohisa Tsutsui, Shigeru Hisada, Shiho Ito, Tadashi Kosaka, Takumi Ohishi, Yasuharu Otsubo and Yoshihiro Takahashi**	PDF
☆	No. 17	15 Oct 2021	Adverse Outcome Pathway on histone deacetylase inhibition leading to testicular atrophy **Shihori Tanabe, Akihiko Hirose and Takashi Yamada**	PDF
☆	No. 16	30 Jul 2019	Adverse Outcome Pathway on Aryl hydrocarbon receptor activation leading to early life stage mortality, via reduced VEGF **Amani Farhat and Sean W. Kennedy**	PDF READ
☆	No. 15	30 Jul 2019	Adverse Outcome Pathway on Aryl hydrocarbon receptor activation leading to uroporphyria **Amani Farhat, Gillian Manning, Jason O'Brien and Sean W. Kennedy**	PDF READ
☆	No. 14	30 Jul 2019	Adverse Outcome Pathway on inhibition of Na+/I- symporter (NIS) leads to learning and memory impairment **Alexandra Rolaki, Francesca Pistollato, Sharon Munn and Anna Bal-Price**	PDF READ
☆	No. 13	30 Jul 2019	Adverse Outcome Pathway on inhibition of Thyroperoxidase and subsequent adverse neurodevelopmental outcomes in mammals **Kevin M. Crofton, Mary Gilbert, Katie Paul Friedman, Barbara Demeneix, Mary Sue Marty and R. Thomas Zoeller**	PDF READ
☆	No. 12	30 Jul 2019	Adverse Outcome Pathway on aryl hydrocarbon receptor activation leading to early life stage mortality, via increased COX-2 **Jon Doering, Markus Hecker, Dan Villeneuve and Xiaowei Zhang**	PDF READ
☆	No. 11	30 Jul 2019	Adverse Outcome Pathway on binding to the picrotoxin site of ionotropic GABA receptors leading to epileptic seizures in adult brain **Ping Gong and Edward J. Perkins**	PDF READ
☆	No. 10	30 Jul 2019	Adverse Outcome Pathway on antagonist binding to PPARα leading to body-weight loss **Kurt A. Gust, Mitchell S. Wilbanks, Zachary A. Collier, Lyle D. Burgoon and Edward J. Perkins**	PDF READ
☆	No. 9	12 Oct 2018	Adverse Outcome Pathway on Androgen receptor agonism leading to reproductive dysfunction (in repeat-spawning fish) **Dan Villeneuve**	PDF READ
☆	No. 8	12 Oct 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**	PDF READ
☆	No. 7	12 Oct 2018	Adverse Outcome Pathway on Inhibition of the mitochondrial complex I of nigro-striatal neurons leading to parkinsonian motor deficits **Anna Bal-Price, Marcel Leist, Stefan Schildknecht, Florianne Tschudi-Monnet, Alicia Paini and Andrea Terron**	PDF READ
☆	No. 6	09 Sept 2016	Adverse Outcome Pathway on binding of agonists to ionotropic glutamate receptors in adult brain leading to excitotoxicity that mediates neuronal cell death, contributing to learning and memory impairment **Magdalini Sachana, Sharon Munn and Anna Bal-Price**	PDF READ

Other AOP sources

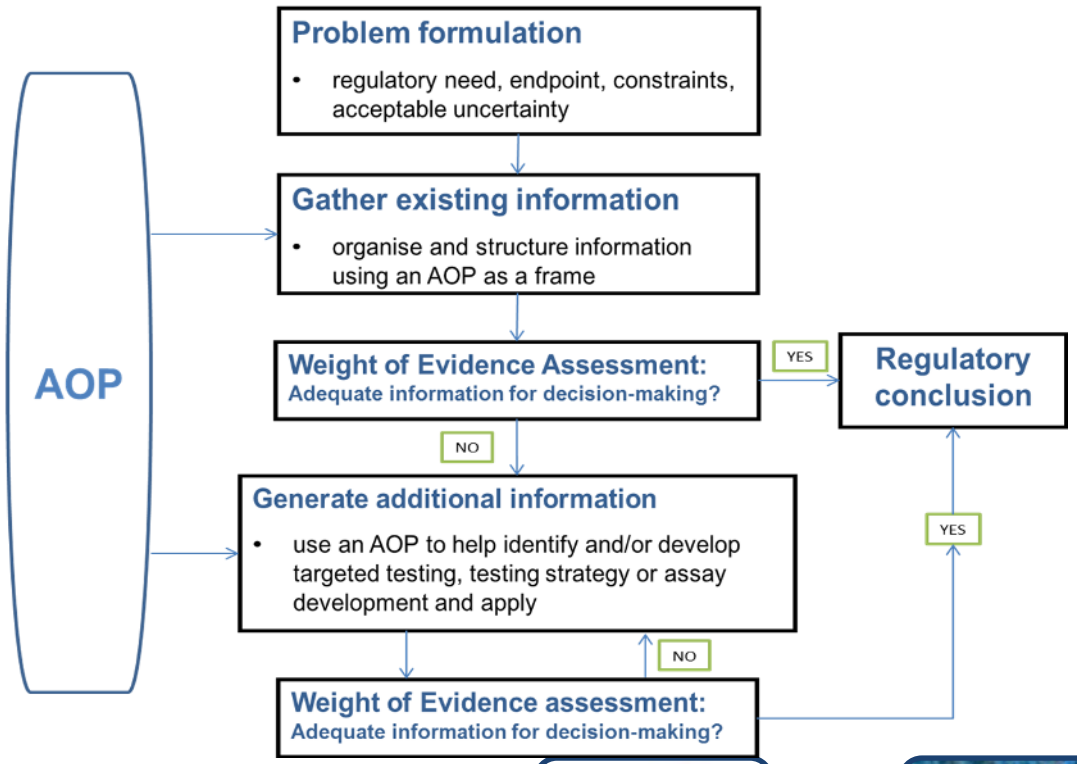
- AOP-Wiki: 390 AOPs

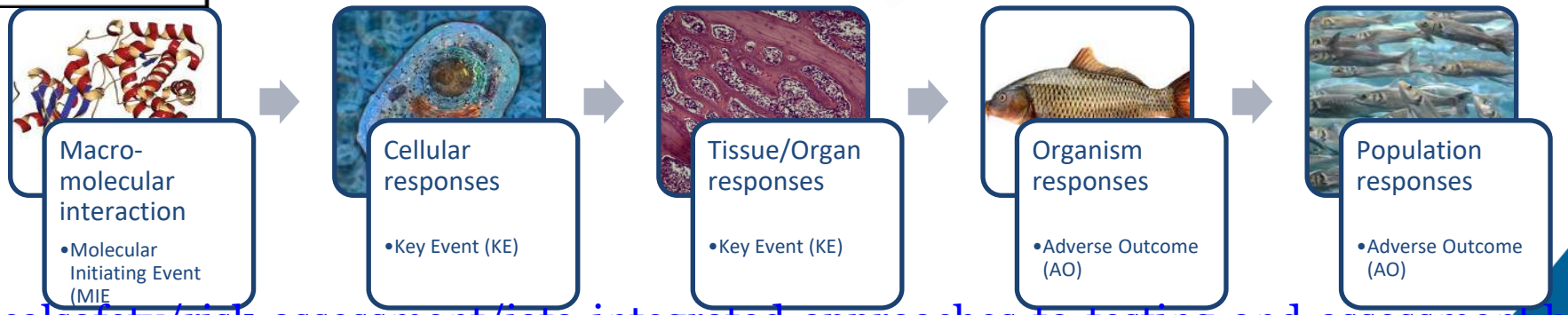


- Pubmed: 530

- Commercial AOP tools

AOPs and IATAs





https://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

Methods

- OECD Test Guidelines

- Guidance Document for Describing Non-Guideline In Vitro Test Methods

- Scientific validation
  - SCIENTIFIC BASIS
  - REPRODUCIBILITY
  - PREDICTIVE CAPACITY

Evolving practice around validation

- Opportunity to evolve the concept of (performance) standards, e.g. functional validation
- Validation of batteries of methods (rather than individual components)
- Validation of systems that are not for transfer to other labs
- Systems that may be “difficult” to transfer as a block

OECD workshop in December 2022:
“How to prepare for emerging technologies ?“ looks at adaptations needed to the TG Programme for their uptake

Standardized Templates and Reporting Formats

- Omics
  - Transcriptomics Reporting Framework
  - Metabolomics Reporting Framework https://www.oecd.org/chemicalsafety/testing/omics.htm
- OECD Harmonised Templates (OHTs) for chemical safety data
  - ~130 standard reporting formats for information used in risk assessment
  - GL and non-GL studies
  - Chemically agnostic

https://www.oecd.org/ehs/templates/

Standardized Templates and Reporting Formats

- Defined Approaches
  - to be used in IATA
  - New TG includes elements to stand-alone DA use
- QSARs
  - QSAR Model Reporting Formats
  - QSAR Prediction Reporting Formats
  - Expanding to be generalizable to in silico models
- PBK
  - PBK Model Reporting Template
  - PBK Model Evaluation Checklist

The goal is to make chemical safety data standardized, sharable, and interoperable

How to build confidence in NAMs, including qAOP

Communication	• Forum to share experiences • Consider **challenges** and **opportunities** for acceptance
Uncertainty	• Transparent description of **domain of applicability** • **Limitations** (technical + lack of information)
Reproducibility	• Standardisation of method • Demonstration of consistency over time / between labs
Relevance	• Performance against **appropriate benchmark** data • Consideration of **relevance** to target species (biology)
Reviews	• Method and data documentation • Use of reporting standards for evaluation

- Waiting for the first qAOP submission
  - SARA model in the TG programme

And/or

- Development of a Guidance on qAOPs

Thanks For Listening

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http://www.oecd.org/chemicalsafety/

acknowledgments

AOP-KB team

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