Handbook Guidance, Gardening, and Internal Review (HGGIR) Task 6:

GUIDANCE DOCUMENTATION FOR DEFINING THE DOMAIN OF APPLICABILITY

Objectives

Describe the Domain of Applicability in AOP Development

- Handbook Guidance

Introduce how this information is captured in the AOP-Wiki

- Current Status of Domain of Applicability fields

Challenges with current guidance

Recruit expert participants to draft guidance

Domain of Applicability and Intended application

- Taxonomic applicability
- Life-stage applicability
- Sex applicability

- Why fill in the DOA field on an AOP?
  - Support extrapolation
  - Maximize use of existing knowledge

- Domain of Applicability on AOP-Wiki
  - AOP page
  - KE page
  - KER page

OECD Series on Adverse Outcome Pathways No. 1

Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways

OECD

https://dx.doi.org/10.1787/5jlv1m9d1g32-en

Defining the taxonomic, life stage and sex relevance of each KE helps to bound the domain of applicability of the AOP as a whole and provides an understanding of how broadly data represented by a KE measurement may be extrapolated, including potential human relevance. As a general guide, there are two primary considerations associated with defining the applicability domain of a KE:

1. Structure: Is the biological object being measured/observed present/conserved in the taxa/sex/life-stage of interest? Here biological object may refer to a protein, a cell type, an organ, etc.

2. Function: Is the function of that biological object and the process being measured via the KE conserved and relevant in the taxa/sex/life-stage of interest. Does it play the same role?

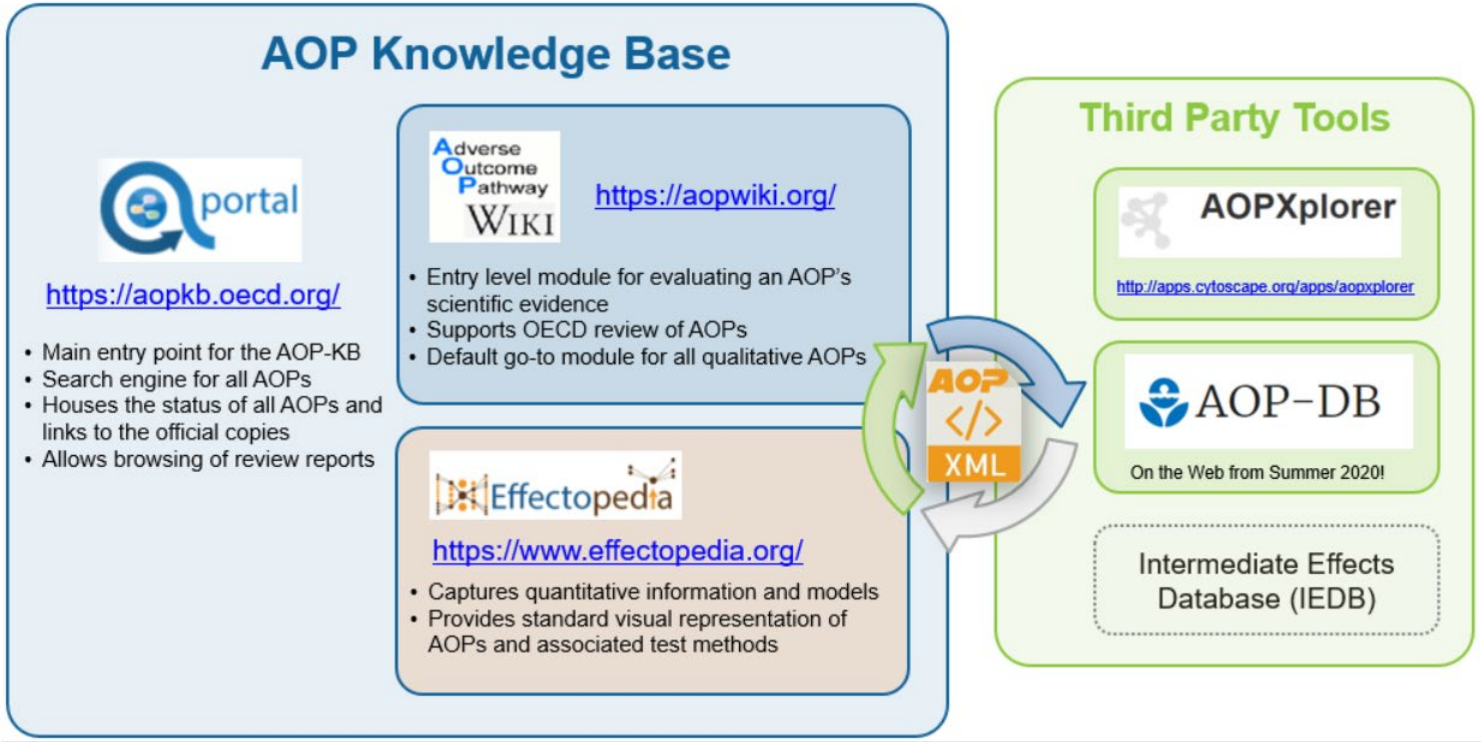
Evidence calls should be based on **expert knowledge of the biology and the extent of supporting experimental evidence**.
Recommendations for these calls are:

- **Low:** With the understanding that by definition a KE must be measurable in the species/taxonomic group/lifestage/sex defined, no such measurements have been reported or shown experimentally to date;

- **Moderate:** The measurement associated with the KE can plausibly be made for the species/taxonomic group/lifestage/sex, and there is at least some supporting experimental evidence, although that may be something other than direct measurement of the KE;

- **High:** The measurement associated with the KE has been made repeatedly or frequently and/or with multiple orthogonal methods for the species/taxonomic group/lifestage/sex.

AOP-knowledgebase



OECD
BETTER POLICIES FOR BETTER LIVES

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

European Commission

U.S. ARMY ENGINEER RESEARCH AND DEVELOPMENT CENTER
ERDC

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

This wiki is hosted by the Society for the Advancement of Adverse Outcome Pathways (SAAOP) and serves as one component of a larger OECD-sponsored AOP Knowledgebase (AOP-KB) effort. The AOP-KB 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. All AOPs from the AOP Knowledgebase are available via the e.AOP.Portal, which is the primary entry point for the AOP-KB. More information about the AOP-KB efforts, the organizations supporting these efforts, and the other modules of the AOP-KB are available on the About page.

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

Taxonomic Applicability

Term	Scientific Term	Evidence	Link
human	Homo sapiens	High	NCBI
rat	Rattus norvegicus	High	NCBI
mouse	Mus musculus	High	NCBI
chicken	Gallus gallus	Moderate	NCBI
Xenopus laevis	Xenopus laevis	Moderate	NCBI
Pig	Pig	High	NCBI

NCBI Taxonomy Browser

Entrez PubMed Nucleotide Protein Genome Structure PMC Taxonomy BioCollections

Search for [ ] as [complete name] lock [Go] [Clear]

Display [3] levels using filter: [none]

Homo sapiens

Taxonomy ID: 9606 (for references in articles please use NCBI:txid9606)

current name

Homo sapiens Linnaeus, 1758

Genbank common name: **human**
NCBI BLAST name: **primates**
Rank: **species**
Genetic code: Translation table 1 (Standard)
Mitochondrial genetic code: Translation table 2 (Vertebrate Mitochondrial)
Other names:

common name(s)

man

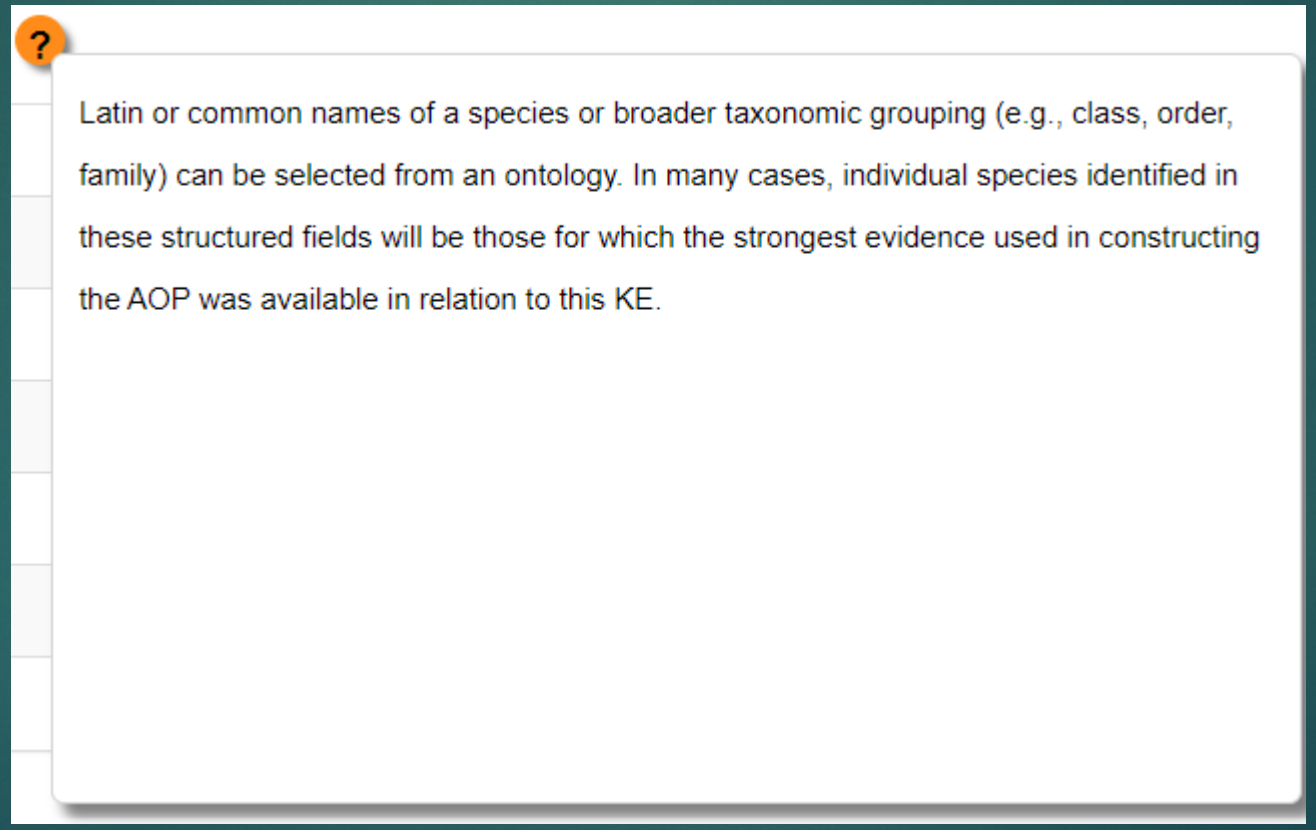
Lineage *(full)*

cellular organisms; Eukaryota; Opisthokonta; Metazoa; Eumetazoa; Bilateria; Deuterostomia; Chordata; Craniata; Vertebrata; Gnathostomata; Teleostomi; Euteleostomi; Sarcopterygii; Dipnotetrapodomorpha; Tetrapoda; Amniota; Mammalia; Theria; Eutheria; Boreoeutheria; Euarchontoglires; Primates; Haplorrhini; Simiiformes; Catarrhini; Hominoidea; Hominidae; Homininae; Homo

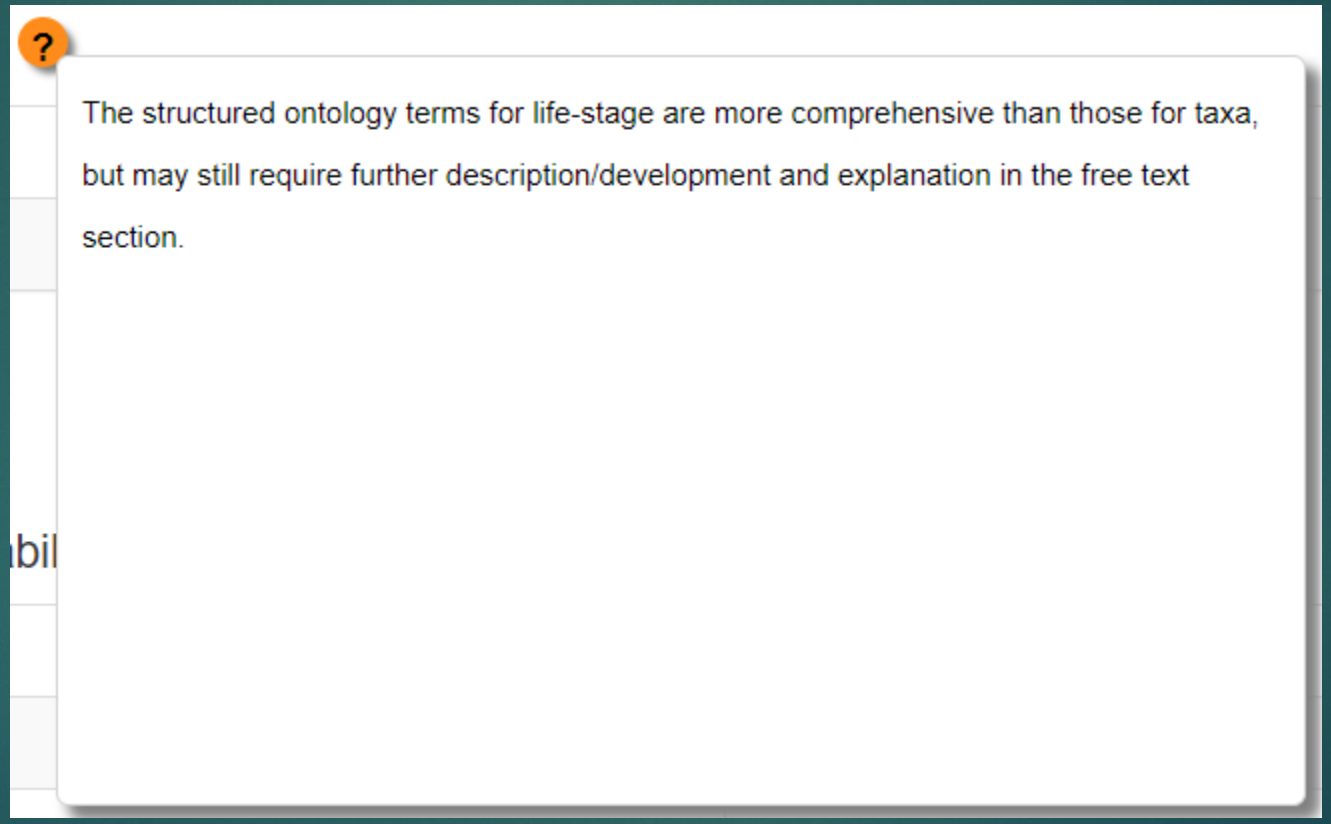
Entrez records

Database name	Subtree links	Direct links
Nucleotide	27,682,287	27,680,906
Protein	1,423,829	1,423,387
Structure	48,783	48,779
Genome	1	1
Popset	24,537	24,536
SNP	719,647,137	719,647,137
Conserved Domains	53	53
GEO Datasets	2,129,352	2,129,352
PubMed Central	38,850	38,795
Gene	225,526	225,453
HomoloGene	18,713	18,713
SRA Experiments	2,209,019	2,208,442
GEO Profiles	61,958,910	61,958,910
Protein Clusters	13	13
Identical Protein Groups	1,430,671	1,430,613

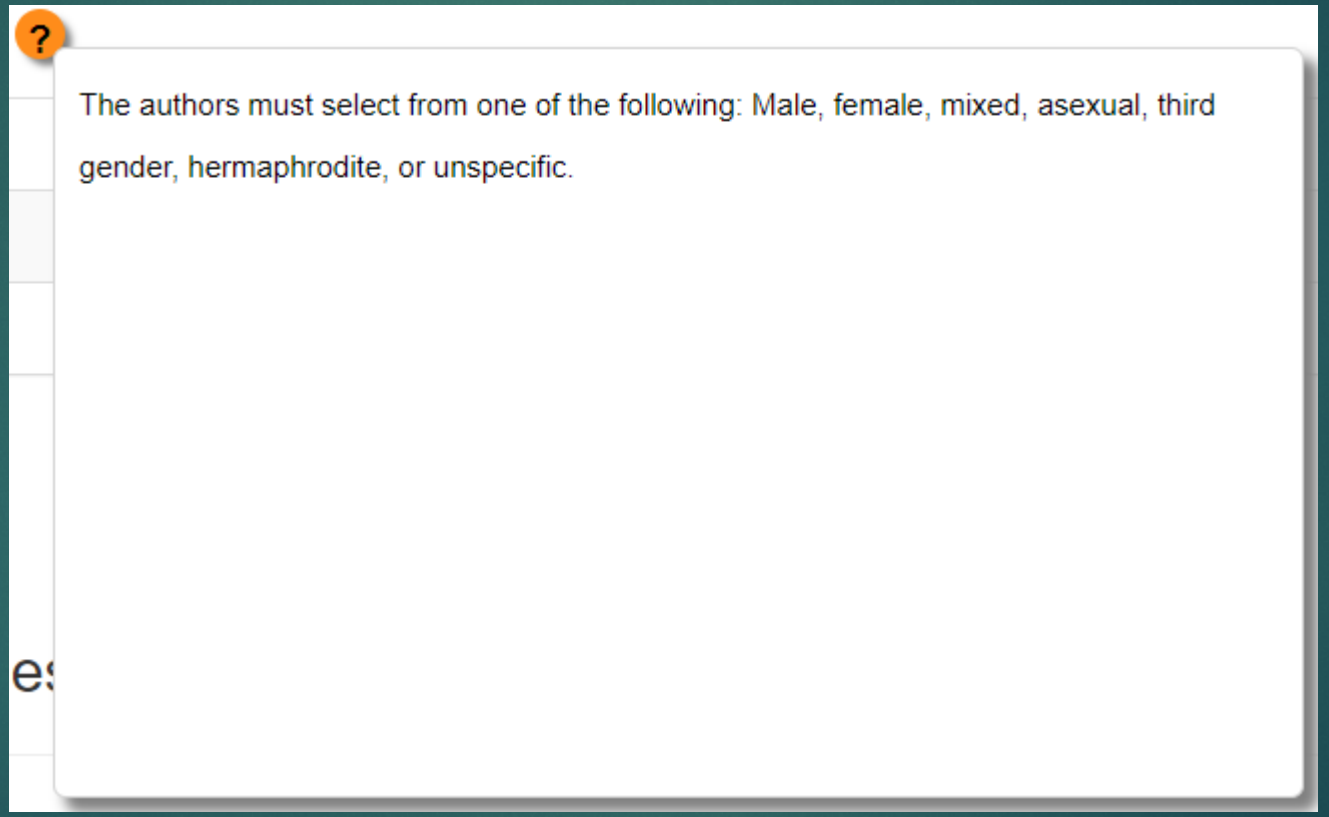
Taxonomic Applicability



Life Stage


?
The structured ontology terms for life-stage are more comprehensive than those for taxa, but may still require further description/development and explanation in the free text section.

Sex Applicability



Specific Identified Need:

- It has been recognized that **fields for the Domain of Applicability** for AOPs, which include separate pages and sections for Key events and Key Event Relationships, **are typically blank or inadequately described** in the current version of the AOP-Wiki.
- It is plausible that AOP developers are not populating these fields because of a **lack of specific guidance regarding what information is appropriate**.
- The descriptors of the taxonomic domain, life stage, and sex are **not linked in the AOP-Wiki which make interpretation of the AOP challenging** for those looking to apply the pathway for research or decision-making.

Task 6 – Guidance on domains of applicability

Identified Issue for Further Investigation

General Guidance Issues for DoA:

- Do authors indicate all relevant domains VS only domains for which data exists
- Relevant VS NOT relevant (i.e. is it possible/desirable to NEGATIVELY identify a specific domain as NOT relevant)
- Best practices for developing domain-specific AOPs (e.g. for establishing human relevance)

Taxonomic Domain:

- Short term: Discuss the benefits/drawbacks to integrating the taxonomic lineage in the AOP-Wiki
- Medium term: Consider what guidance would look like for extrapolating from one species to others
- Long term: A Consortium surrounding using existing bioinformatic approaches for defining the domain of applicability for AOPs is developing and could be used to inform this field in AOP KB v2.0 either directly or as a 3rd party tool

Linkages Among Domains:

Currently the domain of applicability fields are not linked therefore it is not possible to capture Life Stage and Sex for each species defined in the Taxonomic Domain, etc. These linkages are needed.

- Propose, through example and a write up, how these linkage would be implemented in the AOP-Wiki, as depending on short term priorities it may be able to integrated prior to AOP KB v2.0
- Develop guidance to the developer on linking the Domain of Applicability fields

Ontologies

The domain of applicability fields in the AOP-Wiki have not undergone a great deal of modification in the last 5 years relative to ontology integration and there are areas where existing ontology efforts, particularly on the Ecotoxicology side could inform life stage in particular relative to the AOP KB v2.0.

- Identify existing controlled vocabularies or ontologies relative to Life Stage as a Starting Point

How to begin?

- Bioinformatics
- Ontologies
  - Systematic review
- Hierarchical frameworks for integrating across data streams
  - In silico, in vitro, in vivo

This Helps the Program by:

- Identifying available data to fill knowledge gaps
  - e.g., SeqAPASS
- Allows for filters and layers
  - Extract data from the AOP-Wiki
  - e.g., Ontologies
- Create guidance to define domain
  - Currently no guidance on Weight of Evidence calls

https://seqapass.epa.gov/seqapass/

OXFORD
SOT Society of Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 153(2), 2016, 228–245

doi: 10.1093/toxsci/kfw119
Advance Access Publication Date: June 30, 2016
Research article

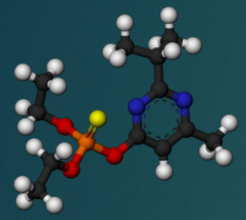
Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS): A Web-Based Tool for Addressing the Challenges of Cross-Species Extrapolation of Chemical Toxicity

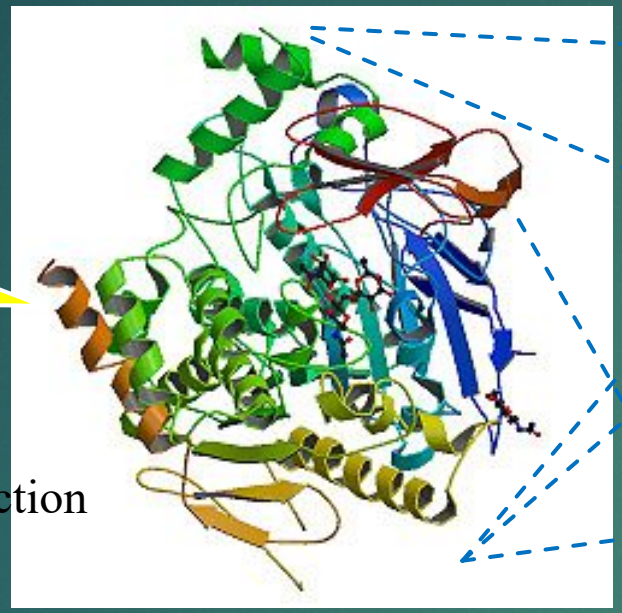
Carlie A. LaLone,*,[1] Daniel L. Villeneuve,* David Lyons,† Henry W. Helgen,‡ Serina L. Robinson,§,[2] Joseph A. Swintek,¶ Travis W. Saari,* and Gerald T. Ankley*

For Example:

Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS)

What information is required for a SeqAPASS query?





Chemical-Protein Interaction

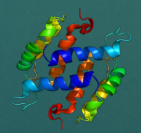
Knowledge of a sensitive or targeted species

Knowledge of the model organism used in an *in vitro* assay

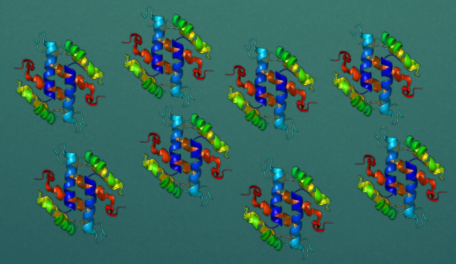
1. Protein
2. Species

Knowledge of the species for which the Key Event was developed

Chemical Molecular Target in Target Species



≈

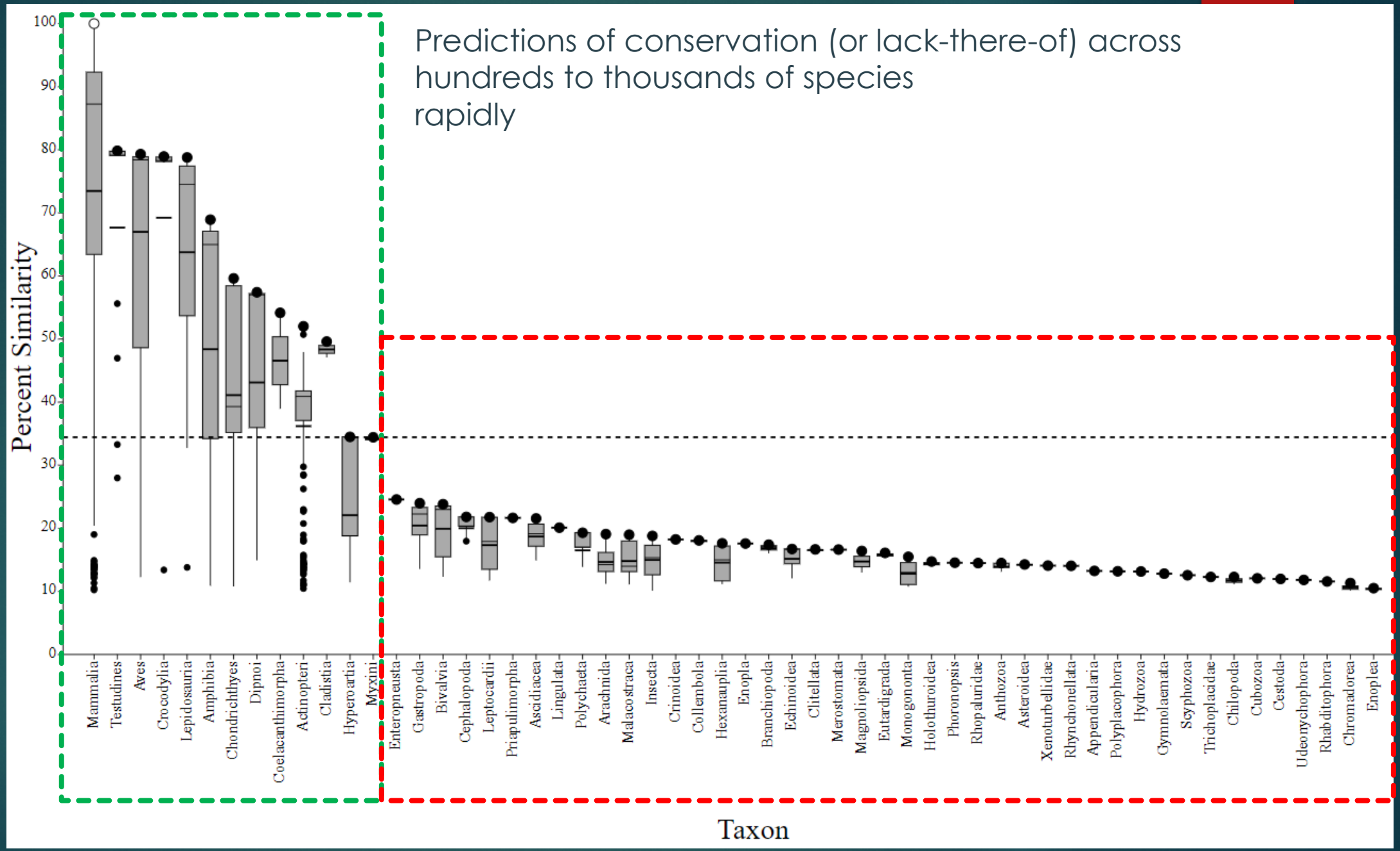


Compare to Millions of Proteins
From Thousands of Species

Greater similarity = Greater likelihood that chemical can act on the protein

Line of Evidence: Predict Potential Chemical Susceptibility Across Species

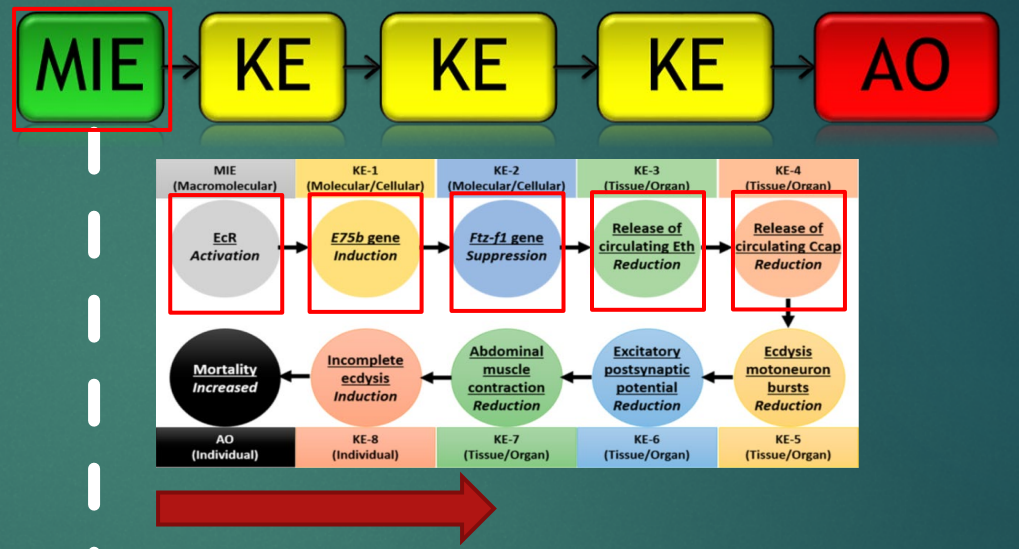
Predictions of conservation (or lack-there-of) across hundreds to thousands of species
rapidly



SeqAPASS in practice

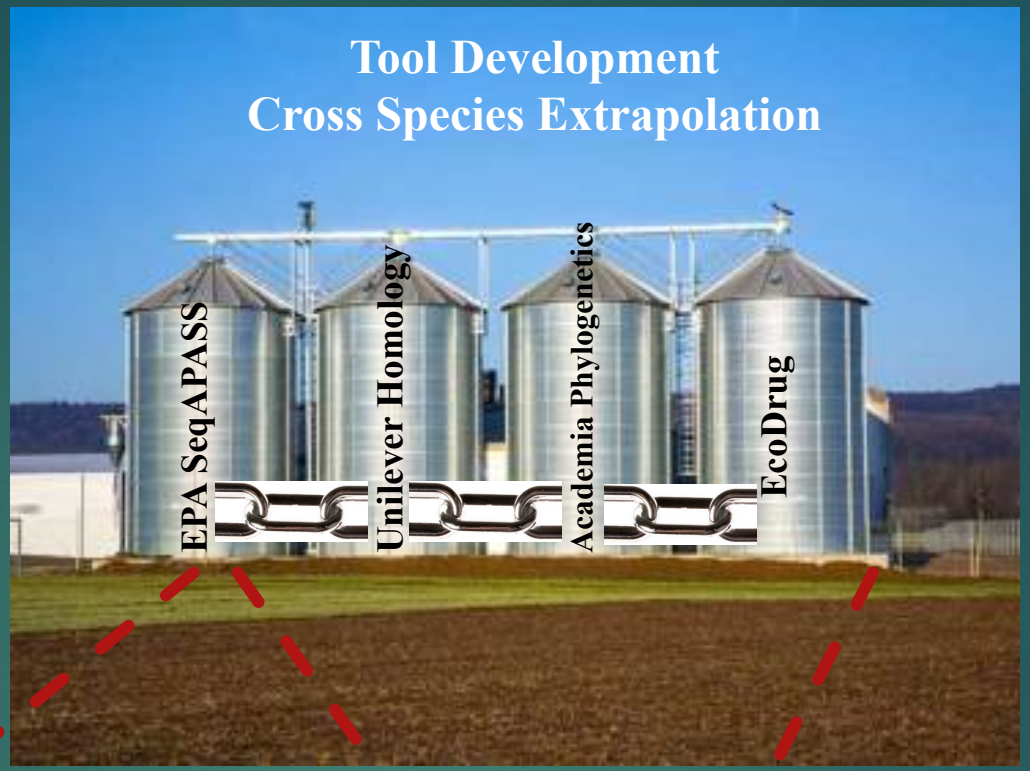
EcR sequence and structural conservation: MIE likely relevant

- Branchiopoda
- Malacostraca
- Insecta
- Chilopoda
- Merostomata
- Arachnida
- Maxillopoda



Next steps: "Walk down" the AOP using SeqAPASS

- Ultraspiracle
- Ecdysone-induced protein 75B (E75b)
- Nuclear hormone receptor (Ftz-f1)
- Ecdysis triggering hormone (Eth)
- Crustacean cardioactive peptide (Ccap)



AOP: Domain of Applicability

OECD AOP Knowledgebase: Consistency in evaluation by expert consortium

Proposed Milestones:

- OECD Webinar to introduce Domain of Applicability objectives and recruit participants to the task team.
- Propose list of "minimum effort" modifications to AOP-Wiki domain of applicability to improve utility of information
- Develop draft guidance on empirical evidence-based vs. biological plausibility-based descriptions of the domain of applicability (including a draft proposal for integration of third-party bioinformatic tools/results to assist in defining the taxonomic domain of applicability)

Develop Team

Task Lead
Carlie LaLone

Team Member
Jason O'Brien

- If your experience and expertise would allow you to meaningfully contribute to this task, please consider volunteering your time:
  - Seeking 2-3 team members
  - Contact LaLone.Carlie@epa.gov

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the US EPA