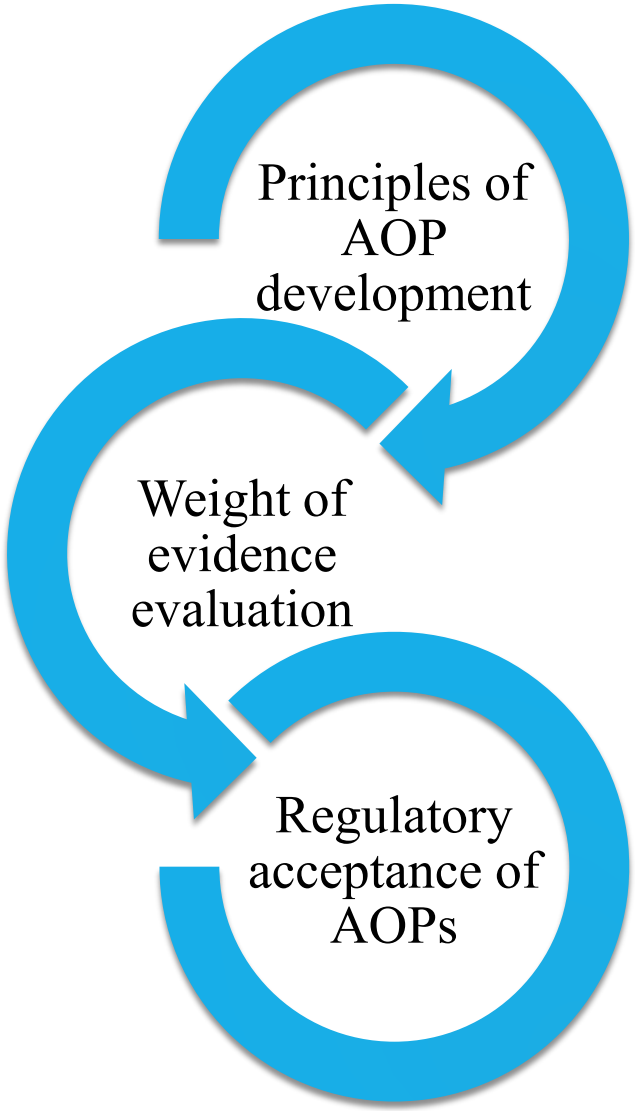
# AOPS IN PRACTICE:

## A Tools to Support AOP Development and Application

# AOP-WIKI

Crowd-source AOP development

# Formalization



# The AOP-KB

Adverse Outcome Pathway WIKI https://aopwiki.org/

Effectopedia https://www.effectopedia.org

portal https://aopkb.oecd.org/

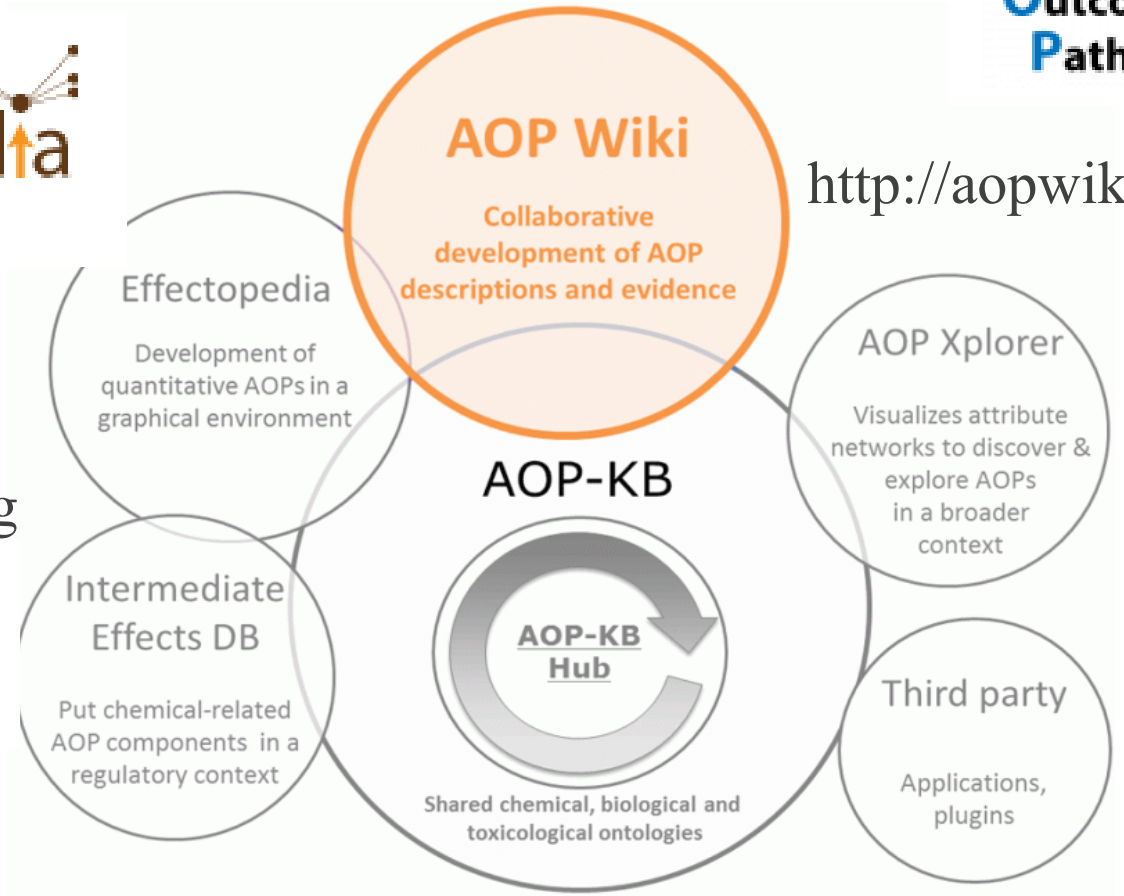
# AOP-knowledgebase

Adverse Outcome Pathway WIKI

Effectopedia

http://aopwiki.org

http://aopkb.org



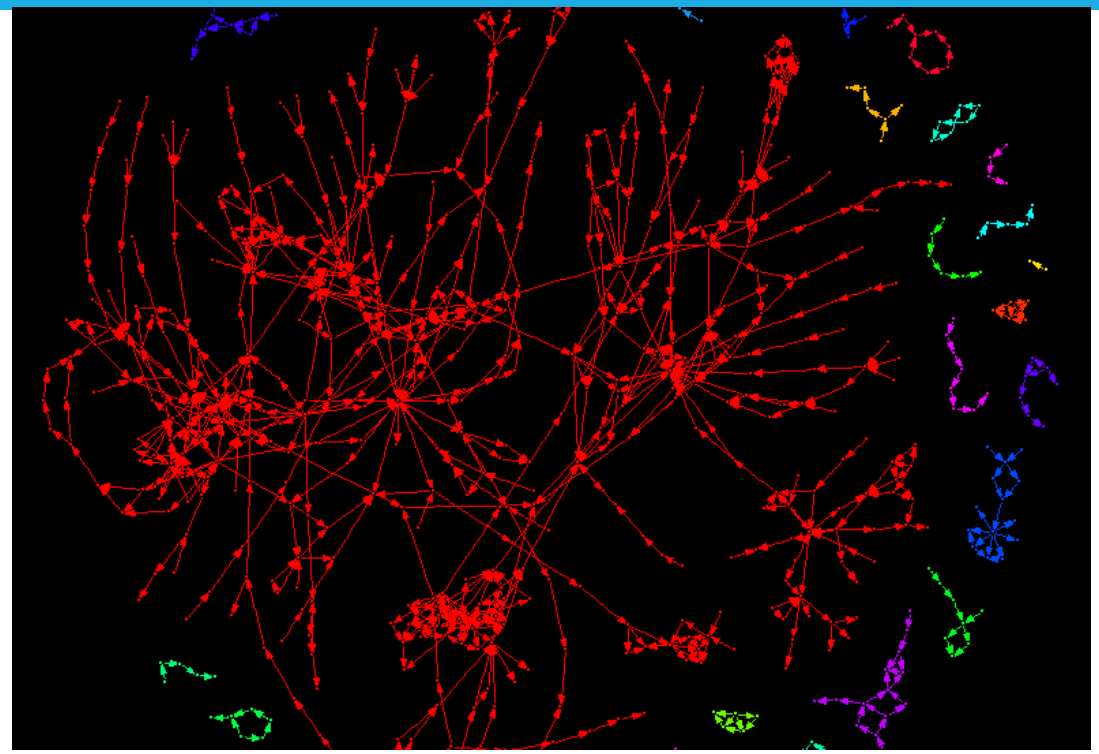

portal

OECD
BETTER POLICIES FOR BETTER LIVES

European Commission

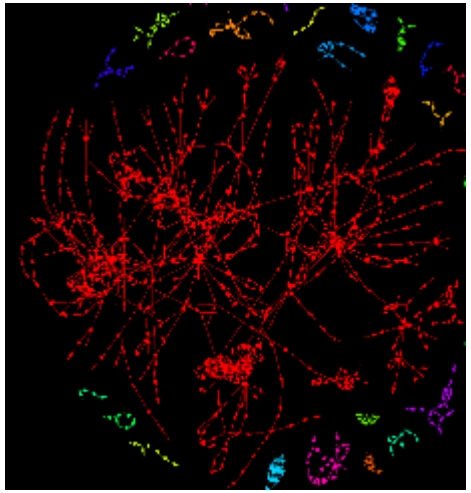
ERDC

# Introduction to the AOP-Wiki



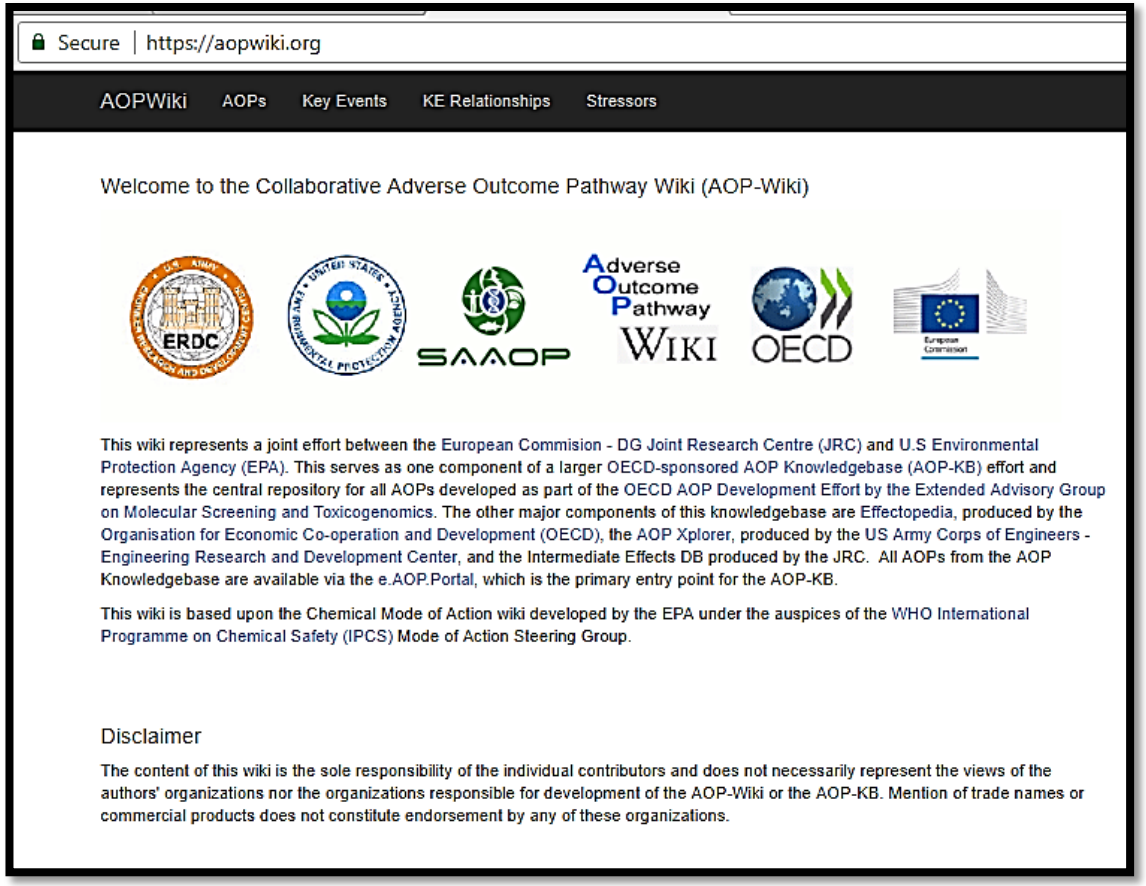
- GLOBAL AOP NETWORK (AS OF SEPT 2020)
  - 299 USER-DEFINED AOPS
  - 1362 KES
  - 1764 KERS

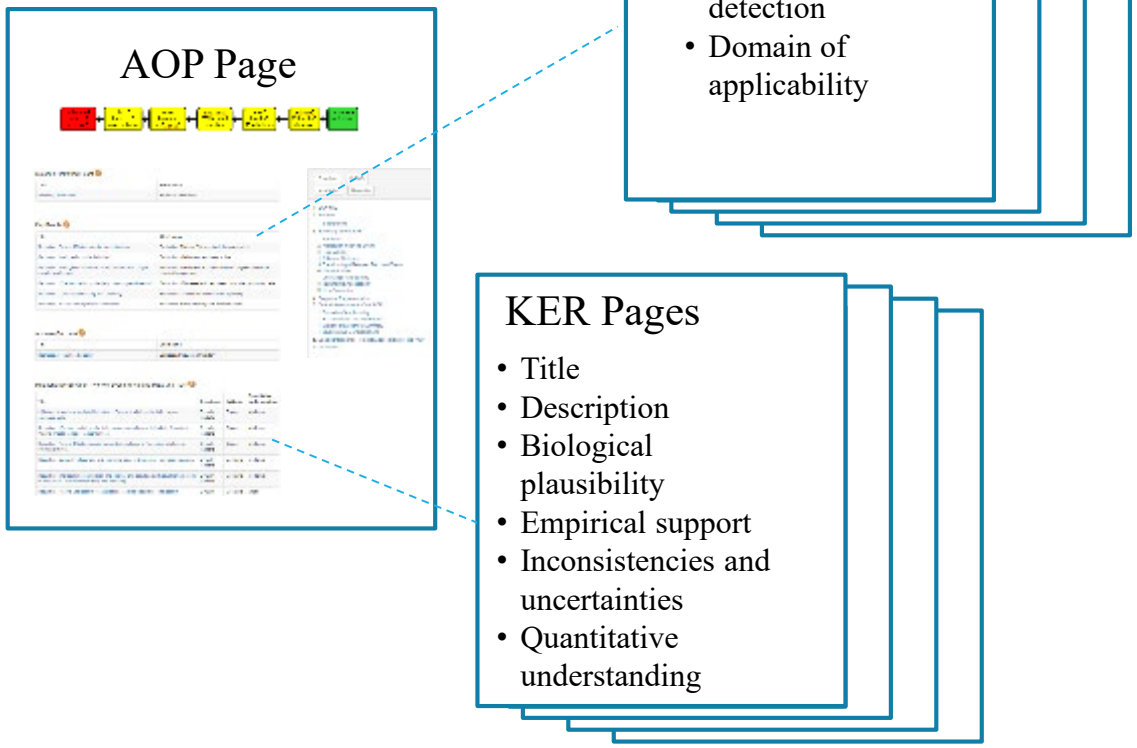
Adverse Outcome Pathway WIKI



# Content of an AOP Description

## Aopwiki.org

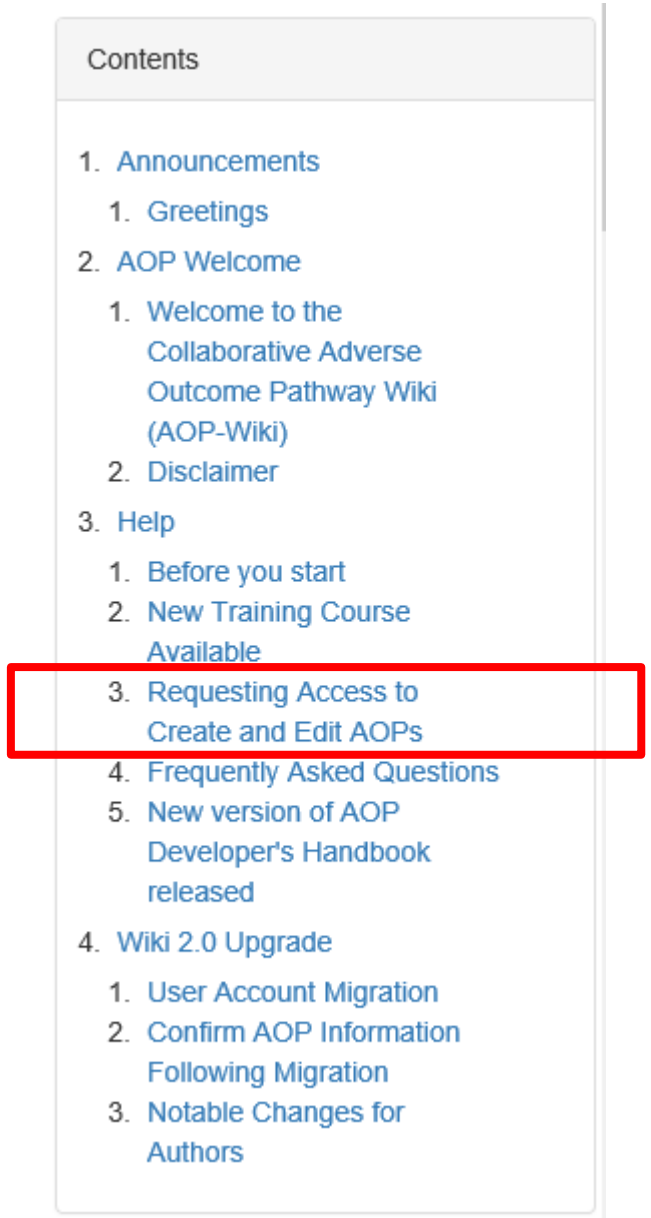


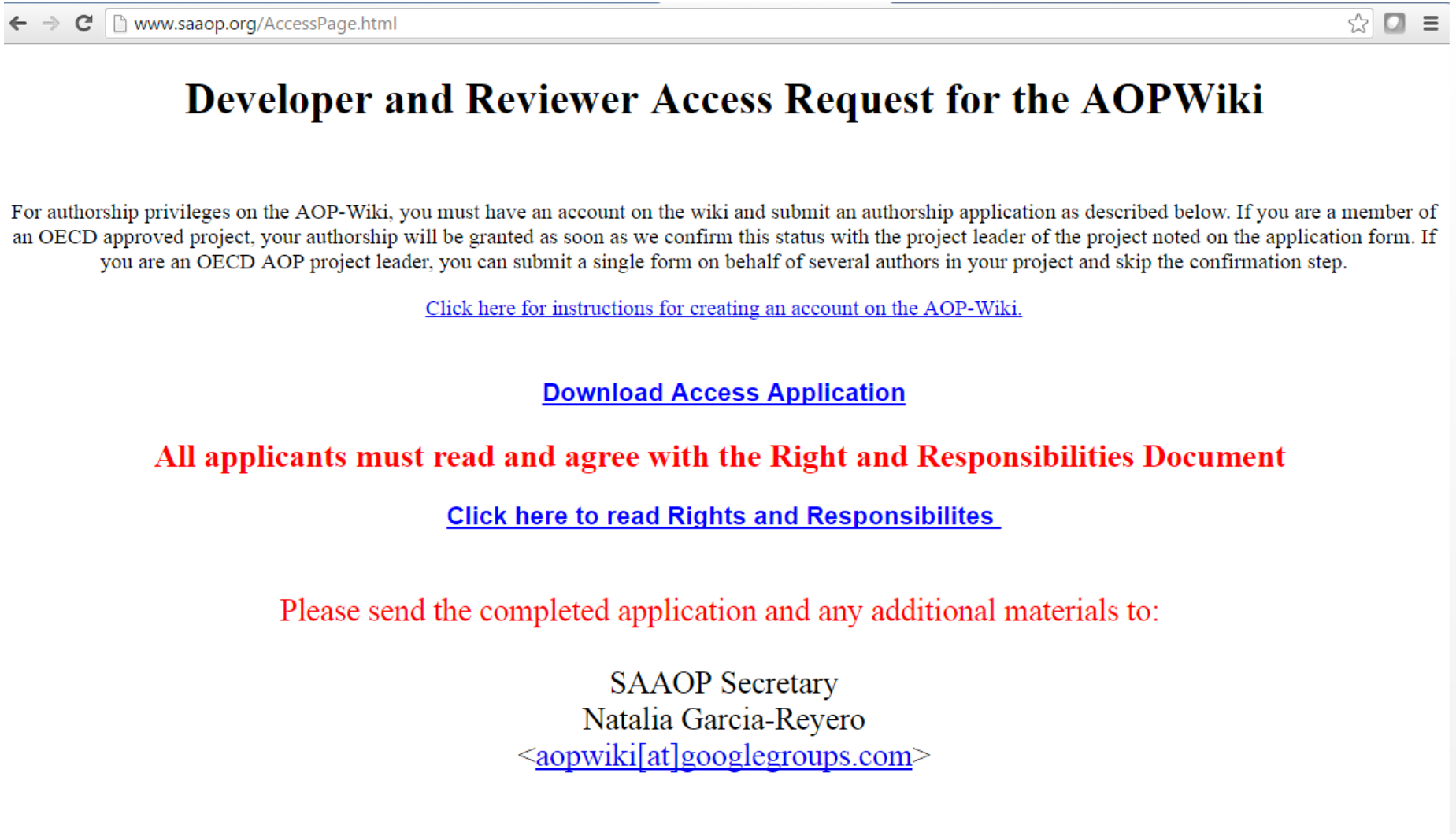
# Accessing the AOP-Wiki

https://aopwiki.org/#Requesting Access to Create and Edit AOPs

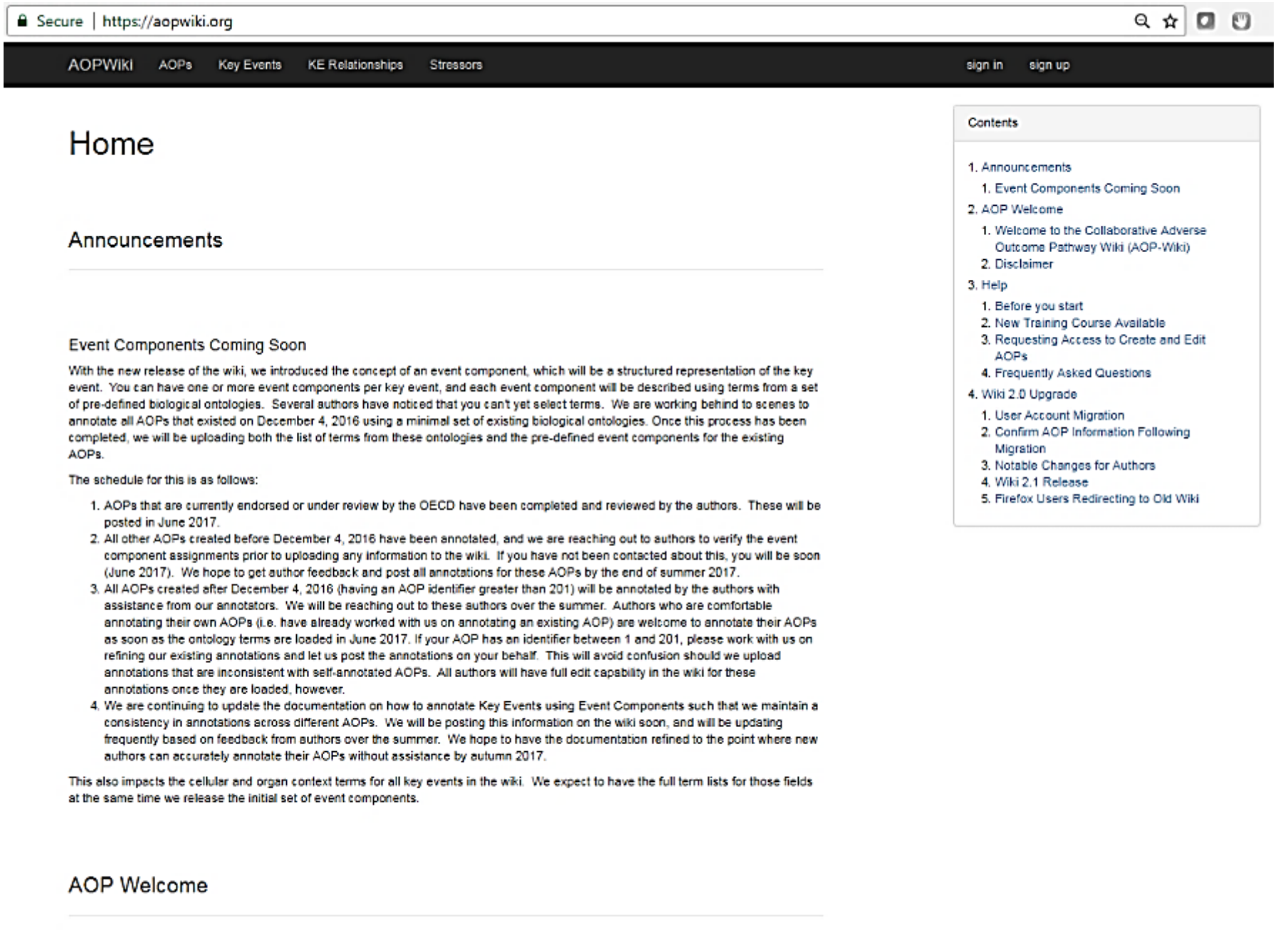
| | |
|---|---|
| Read access | • Open to anyone, no account required |
| Commenting | • Create account, no approvals required<br>sign in sign up |
| Development/write access | • Create account<br>• Submit brief developer application for approval<br>• http://www.saaop.org/AccessPage.html. |



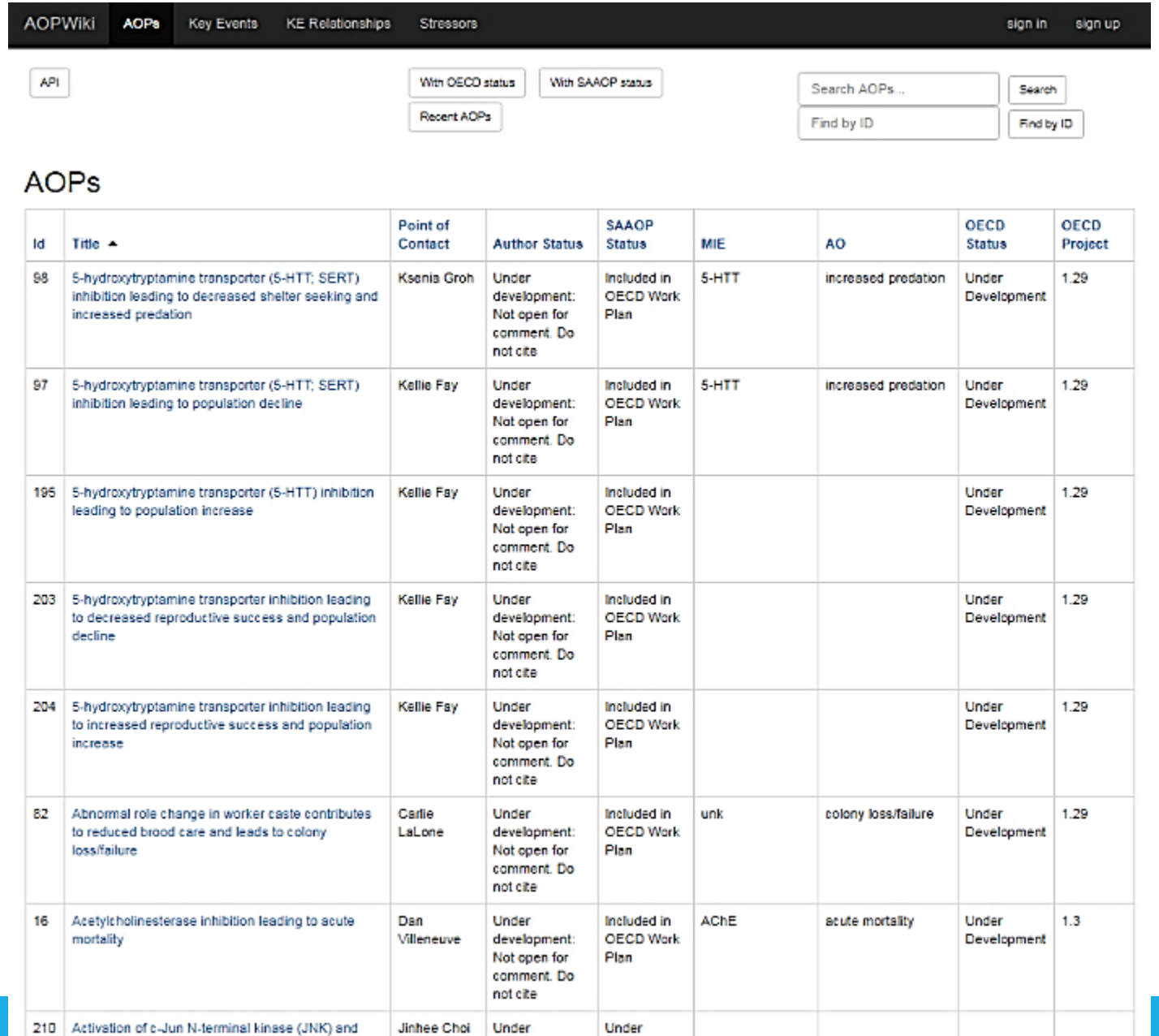
# Accessing the AOP-Wiki



Aopwiki.org


Secure | https://aopwiki.org
AOPWiki
AOPs
Key Events
KE Relationships
Stressors
sign in
sign up
Home
Announcements
Event Components Coming Soon
With the new release of the wiki, we introduced the concept of an event component, which will be a structured representation of the key event. You can have one or more event components per key event, and each event component will be described using terms from a set of pre-defined biological ontologies. Several authors have noticed that you can't yet select terms. We are working behind to scenes to annotate all AOPs that existed on December 4, 2016 using a minimal set of existing biological ontologies. Once this process has been completed, we will be uploading both the list of terms from these ontologies and the pre-defined event components for the existing AOPs.
The schedule for this is as follows:
1. AOPs that are currently endorsed or under review by the OECD have been completed and reviewed by the authors. These will be posted in June 2017.
2. All other AOPs created before December 4, 2016 have been annotated, and we are reaching out to authors to verify the event component assignments prior to uplosding any information to the wiki. If you have not been contacted about this, you will be soon (June 2017). We hope to get author feedback and post all annotations for these AOPs by the end of summer 2017.
3. All AOPs created after December 4, 2016 (having an AOP identifier greater than 201) will be annotated by the authors with assistance from our annotators. We will be reaching out to these authors over the summer. Authors who are comfortable annotating their own AOPs (i.e. have already worked with us on annotating an existing AOP) are welcome to annotate their AOPs as soon as the ontology terms are loaded in June 2017. If your AOP has an identifier between 1 and 201, please work with us on refining our existing annotations and let us post the annotations on your behalf. This will avoid confusion should we upload annotations that are inconsistent with self-annotated AOPs. All authors will have full edit capability in the wiki for these annotations once they are loaded, however.
4. We are continuing to update the documentation on how to annotate Key Events using Event Components such that we maintain a consistency in annotations across different AOPs. We will be posting this information on the wiki soon, and will be updating frequently based on feedback from authors over the summer. We hope to have the documentation refined to the point where new authors can accurately annotate their AOPs without assistance by autumn 2017.
This also impacts the cellular and organ context terms for all key events in the wiki. We expect to have the full term lists for those fields at the same time we release the initial set of event components.
AOP Welcome
Contents
1. Announcements
1. Event Components Coming Soon
2. AOP Welcome
1. Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)
2. Disclaimer
3. Help
1. Before you start
2. New Training Course Available
3. Requesting Access to Create and Edit AOPs
4. Frequently Asked Questions
4. Wiki 2.0 Upgrade
1. User Account Migration
2. Confirm AOP Information Following Migration
3. Notable Changes for Authors
4. Wiki 2.1 Release
5. Firefox Users Redirecting to Old Wiki

# Search AOPs




AOPs

| Id | Title ▲ | Point of Contact | Author Status | SAAOP Status | MIE | AO | OECD Status | OECD Project |
|---|---|---|---|---|---|---|---|---|
| 98 | 5-hydroxytryptamine transporter (5-HTT; SERT) inhibition leading to decreased shelter seeking and increased predation | Ksenia Groh | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | 5-HTT | increased predation | Under Development | 1.29 |
| 97 | 5-hydroxytryptamine transporter (5-HTT; SERT) inhibition leading to population decline | Kellie Fay | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | 5-HTT | increased predation | Under Development | 1.29 |
| 195 | 5-hydroxytryptamine transporter (5-HTT) inhibition leading to population increase | Kellie Fay | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | | | Under Development | 1.29 |
| 203 | 5-hydroxytryptamine transporter inhibition leading to decreased reproductive success and population decline | Kellie Fay | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | | | Under Development | 1.29 |
| 204 | 5-hydroxytryptamine transporter inhibition leading to increased reproductive success and population increase | Kellie Fay | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | | | Under Development | 1.29 |
| 82 | Abnormal role change in worker caste contributes to reduced brood care and leads to colony loss/failure | Carlie LaLone | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | unk | colony loss/failure | Under Development | 1.29 |
| 16 | Acetylcholinesterase inhibition leading to acute mortality | Dan Villeneuve | Under development: Not open for comment. Do not cite | Included in OECD Work Plan | AChE | acute mortality | Under Development | 1.3 |
| 210 | Activation of c-Jun N-terminal kinase (JNK) and | Jinhee Choi | Under | Under | | | | |

Search by

Author

Key words

Status

# Properties of AOPs

## 1. Naming convention


AOP Title

**Covalent Protein binding leading to Skin Sensitisation**

AOP Title

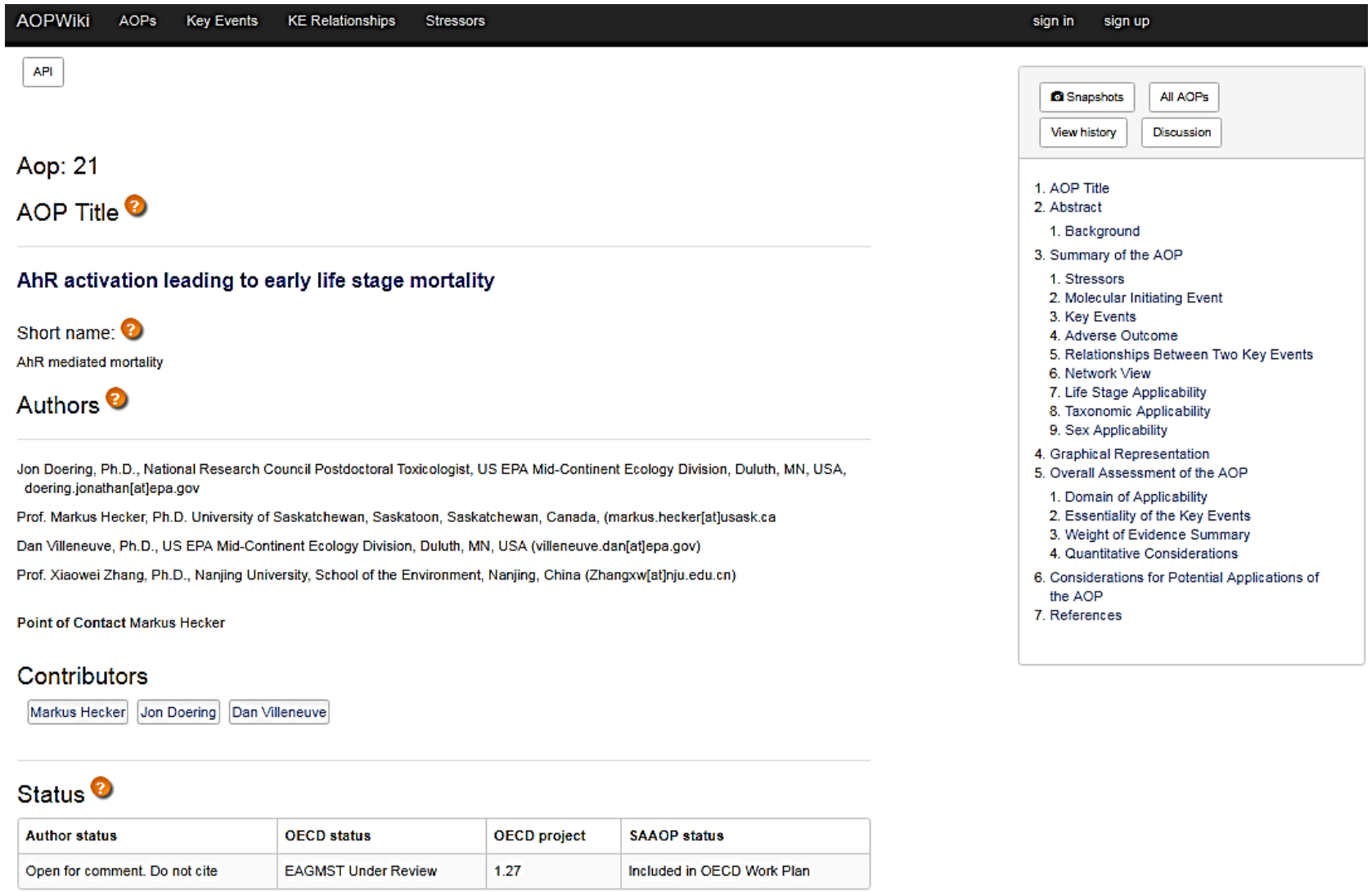
**Protein Alkylation leading to Liver Fibrosis**

AOP Title

**Androgen receptor agonism leading to reproductive dysfunction**

Villeneuve et al., Toxicological Sciences, 142(2), 2014, 321–330

# AOP Page Overview



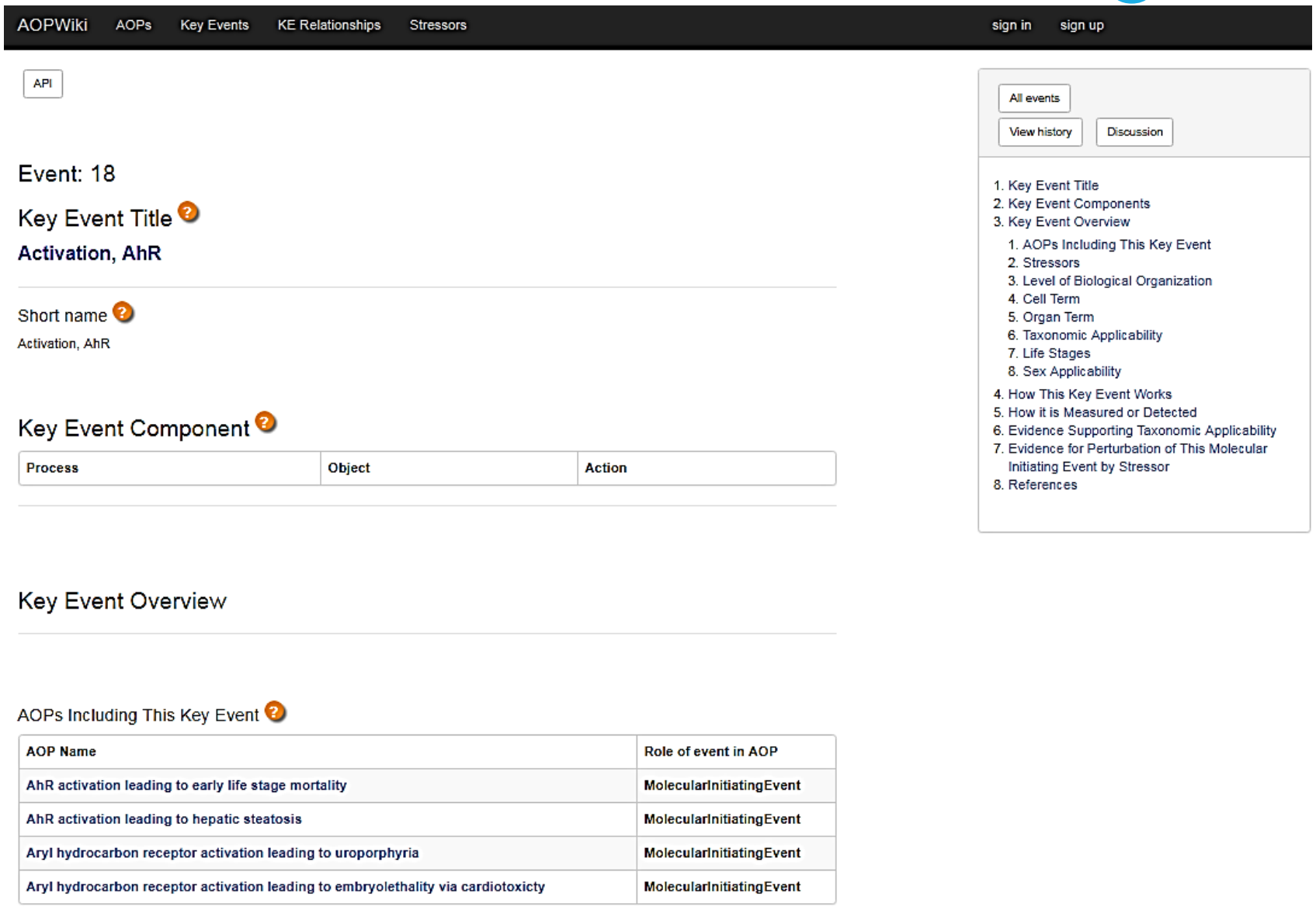

Structured fields

- Summary of AOP
- Applicability

Overall Assessment

- Applicability
- WoE
- Potential appl.

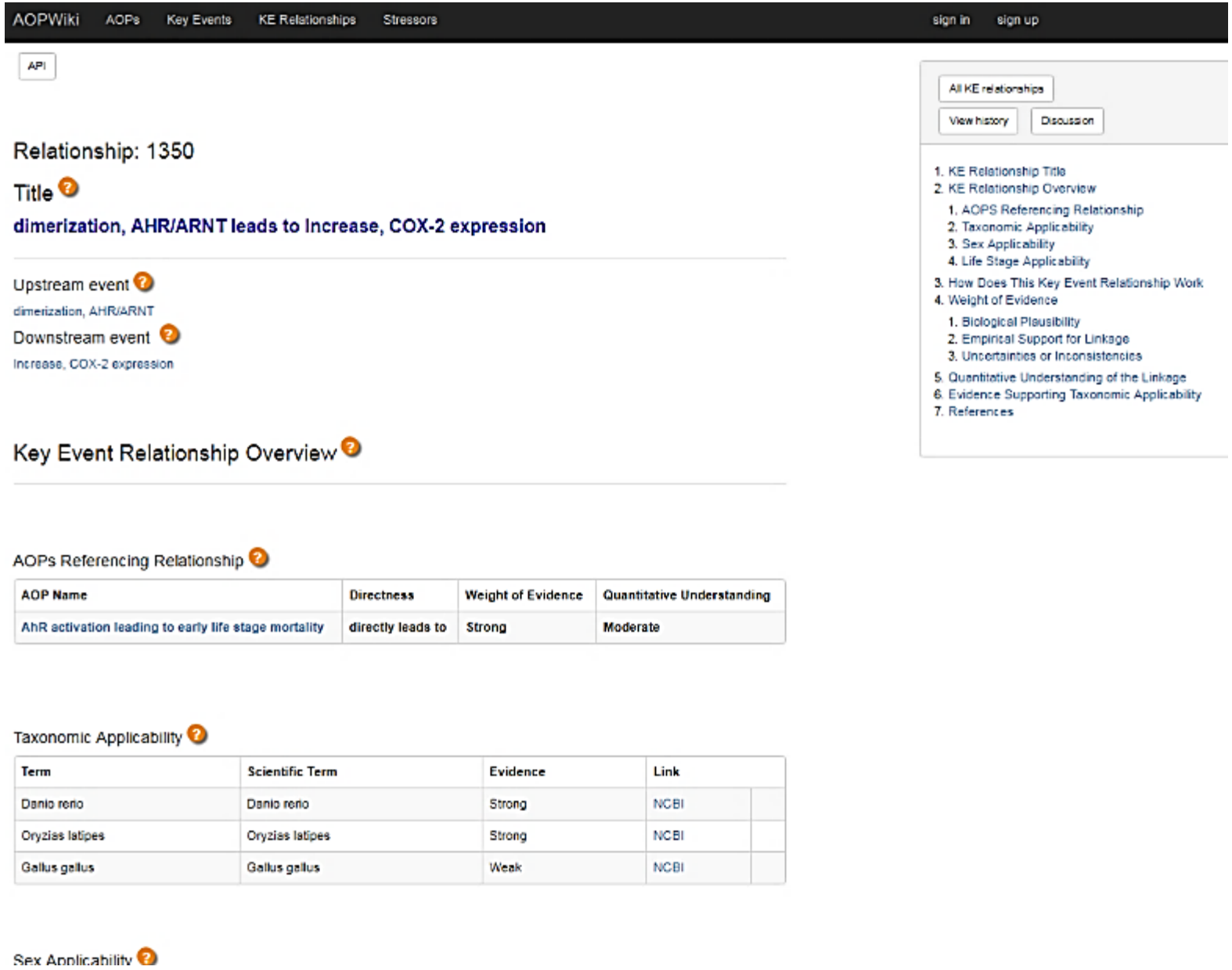
# EVENT Page Overview




Structured fields
- Ontologies
- Stressors
- Applicability

Free text
- Description
- Methods for measuring
- Applicability

# RELATIONSHIP PAGE OVERVIEW




Structured fields
- Applicability

Free text
- Description
- WoE
  - Plausibility
  - Empirical
  - Un / In
- Quantitative understanding
- Applicability

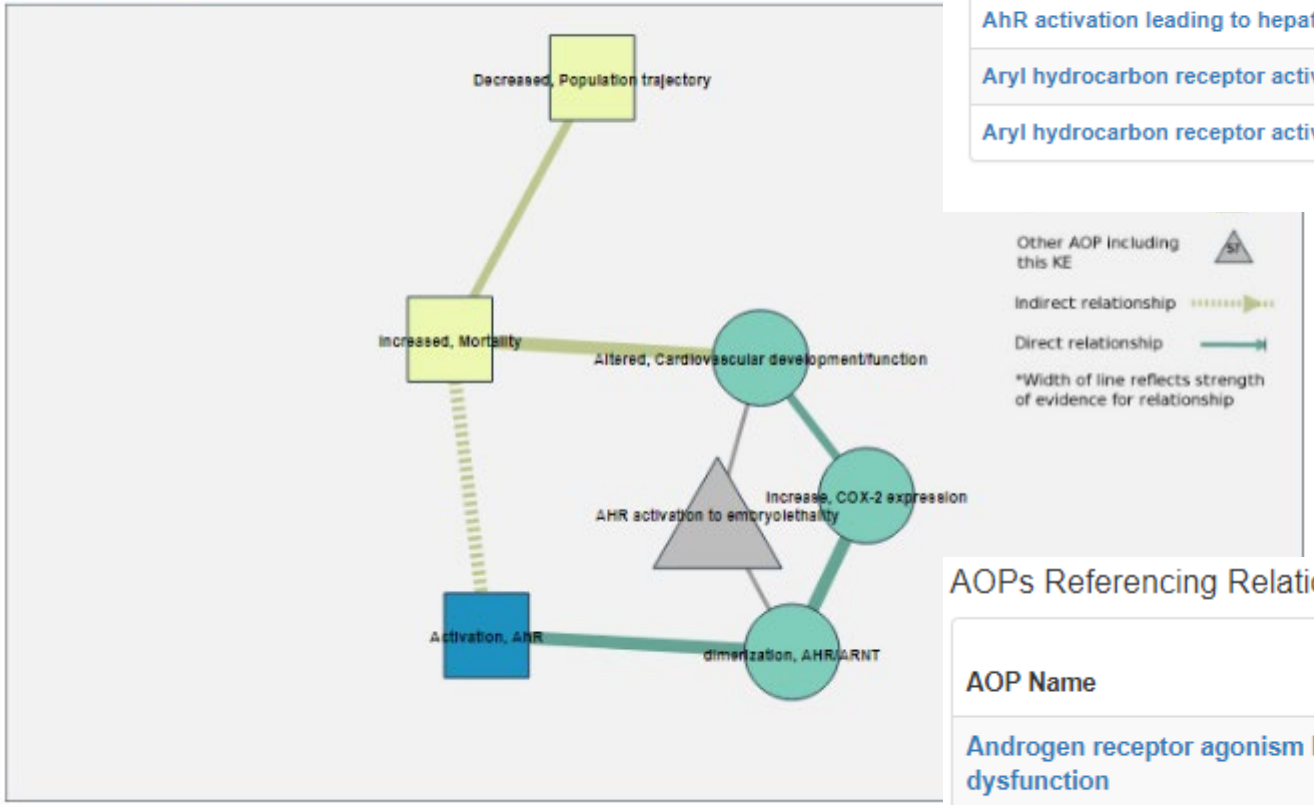

# STRESSOR PAGES

AOPs are chemical agnostic

There is interest in linking AOPs to relevant chemical categories/domains

# AOP NETWORKS

Network View




Event:251 Increased, Mortality

AOPs Including This Key Event

| AOP Name | Role of event in AOP |
|---|---|
| AhR activation leading to early life stage mortality | MolecularInitiatingEvent |
| AhR activation leading to hepatic steatosis | MolecularInitiatingEvent |
| Aryl hydrocarbon receptor activation leading to uroporphyria | MolecularInitiatingEvent |
| Aryl hydrocarbon receptor activation leading to embryolethality via cardiotoxicty | MolecularInitiatingEvent |

AOPs Referencing Relationship

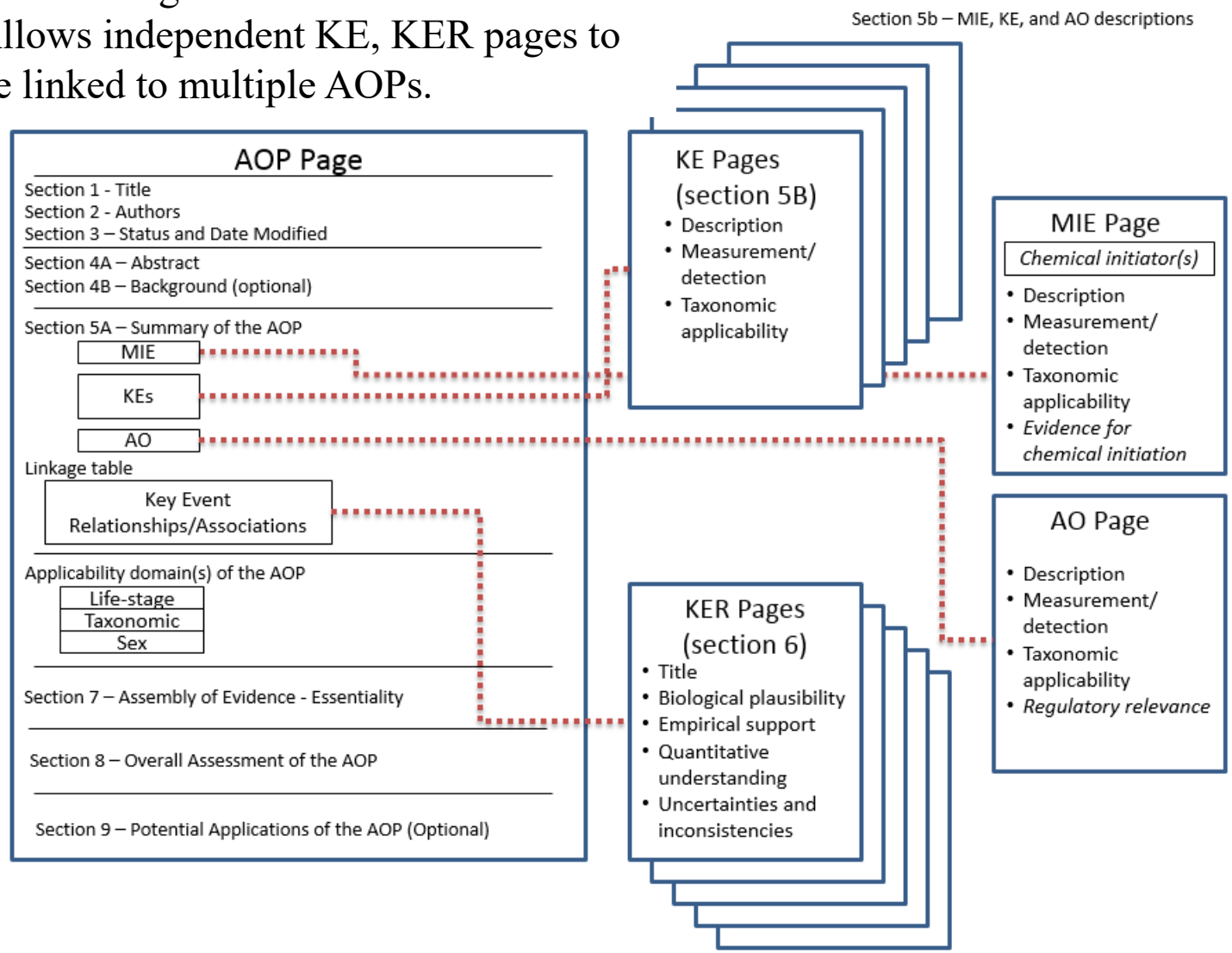
| AOP Name | Directness | Weight of Evidence | Quantitative Understanding |
|---|---|---|---|
| Androgen receptor agonism leading to reproductive dysfunction | indirectly leads to | Strong | Moderate |
| Aromatase inhibition leading to reproductive dysfunction | indirectly leads to | Strong | Moderate |

# AOP Description

Adverse Outcome Pathway WIKI

https://aopwiki.org/

Modular organization.
Allows independent KE, KER pages to be linked to multiple AOPs.




Page contents align with sections of the "User's Handbook"

# Getting Oriented

## AOP Title

**Aromatase inhibition leading to reproductive dysfunction**

## Abstract

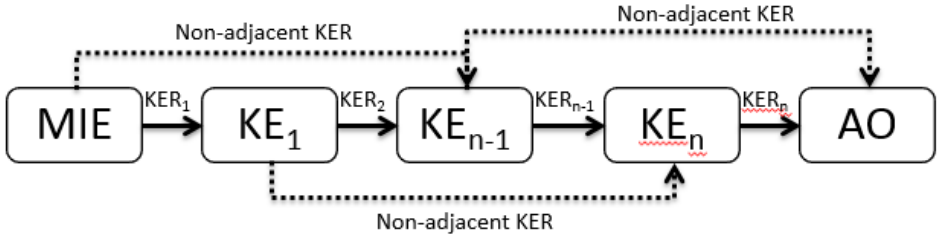
This adverse outcome pathway details the linkage between inhibition of gonadal aromatase activity in females and reproductive dysfunction, as measured through the adverse effect of reduced cumulative fecundity and spawning. Initial development of this AOP draws heavily on evidence collected using repeat-spawning fish species. Cumulative fecundity is the most apical endpoint considered in the OECD 229 Fish Short Term Reproduction Assay. The OECD 229 assay serves as screening assay for endocrine disruption and associated reproductive impairment (OECD 2012). Cumulative fecundity is one of several variables known to be of demographic significance in forecasting fish population trends. Therefore, this AOP has utility in supporting the application of measures of aromatase, or in silico predictions of the ability to inhibit aromatase, as a means to identify chemicals with known potential to adversely affect fish populations and potentially other oviparous vertebrates.

Get an overview of what the AOP is about

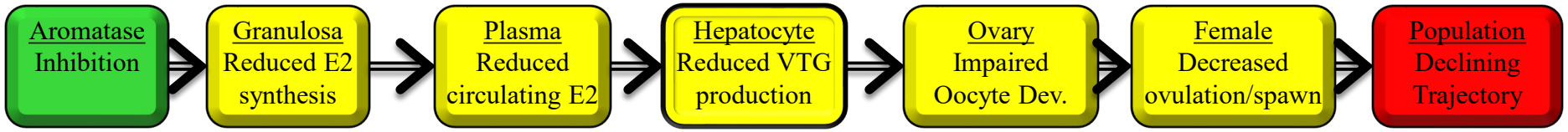
*Found on the AOP page in the AOP-Wiki; first page or two of pdf snap shot*

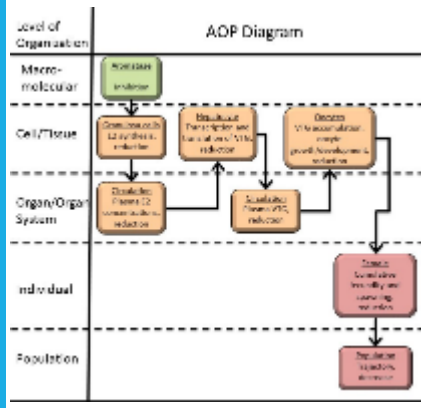
# Getting Oriented

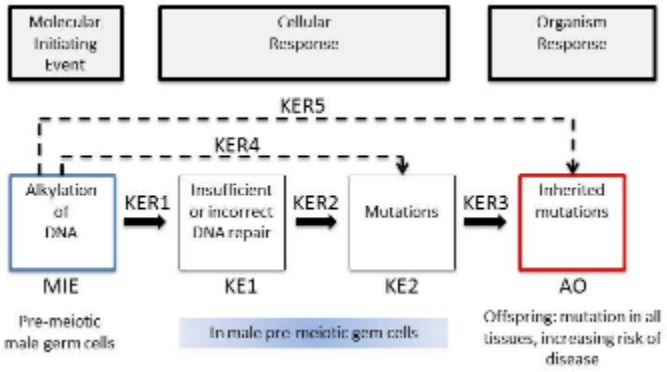
## Grab a road map

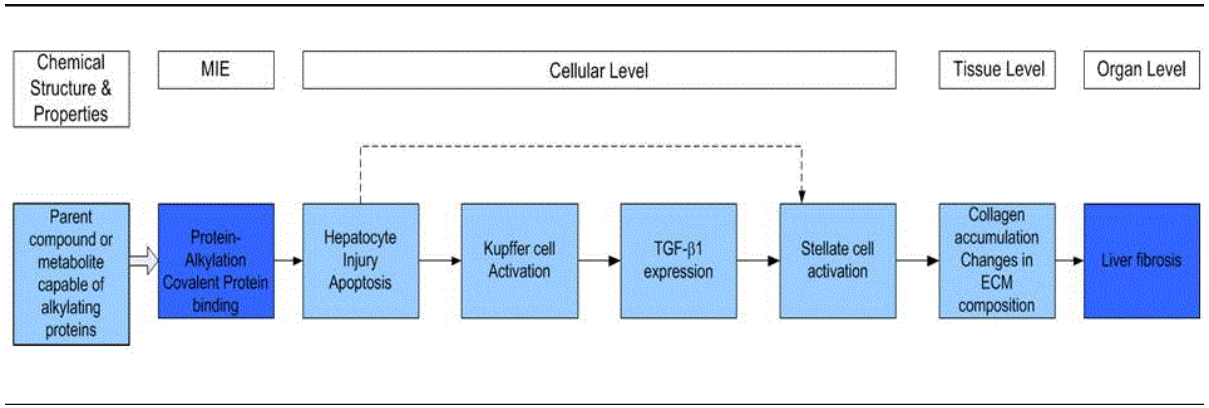



## Graphical Representation ?



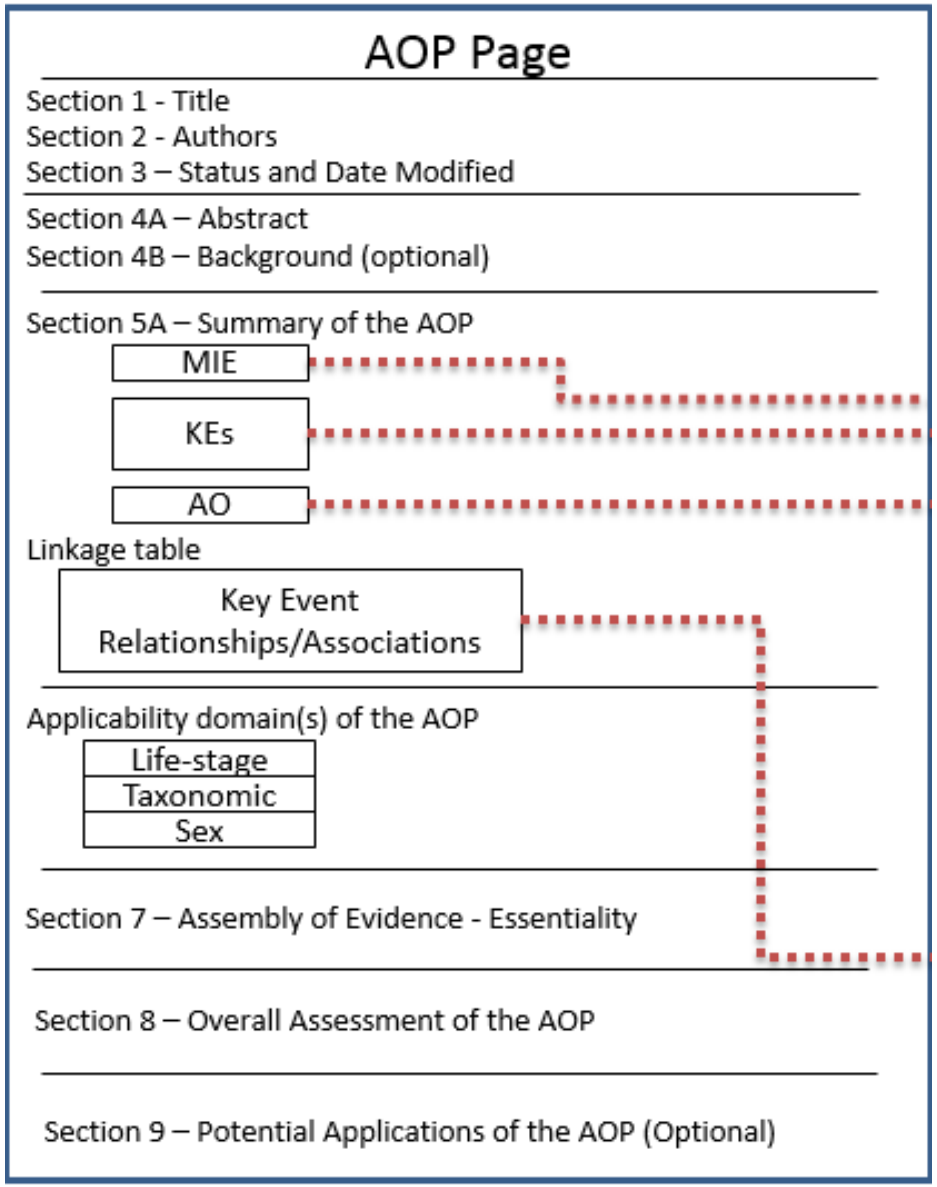




*Easiest to find on the AOP-Wiki page; often buried or absent from the pdf snap shot*

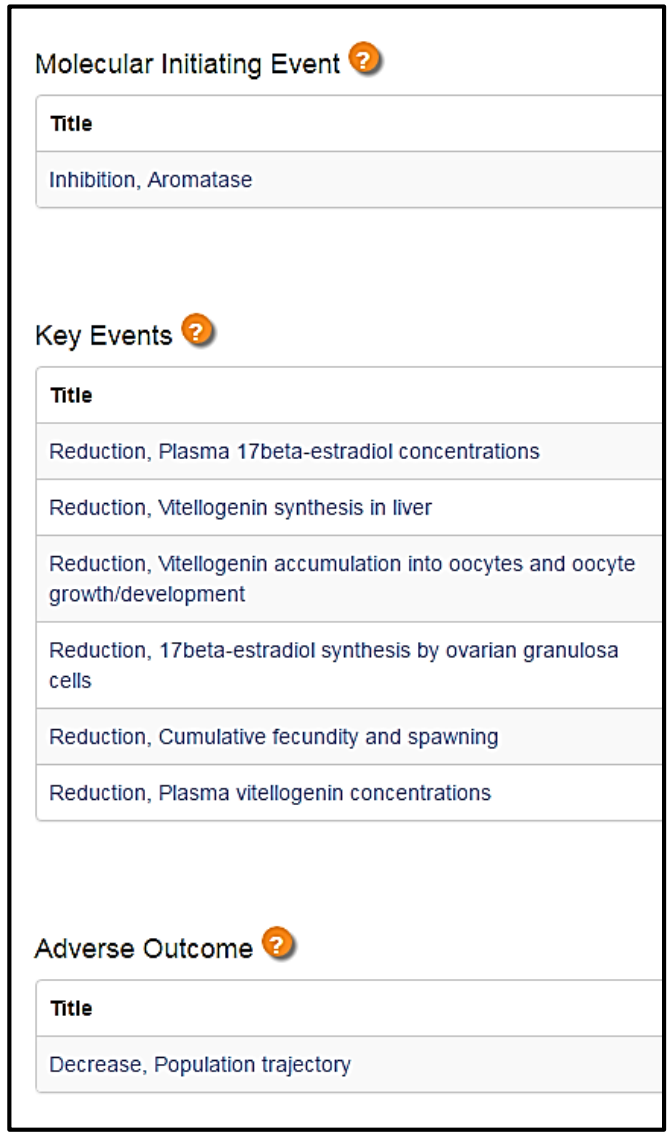
# Getting Oriented




Snap shots will be laid out basically as shown:

- Title, abstract, background
- KE content pages
- KER content pages
- Overall assessment of the AOP
  - Domain of applicability and rationale
  - Support for essentiality
  - Weight of evidence summary

# Getting Oriented - Event Pages



Molecular Initiating Event

| Title |
| --- |
| Inhibition, Aromatase |

Key Events

| Title |
| --- |
| Reduction, Plasma 17beta-estradiol concentrations |
| Reduction, Vitellogenin synthesis in liver |
| Reduction, Vitellogenin accumulation into oocytes and oocyte growth/development |
| Reduction, 17beta-estradiol synthesis by ovarian granulosa cells |
| Reduction, Cumulative fecundity and spawning |
| Reduction, Plasma vitellogenin concentrations |

Adverse Outcome

| Title |
| --- |
| Decrease, Population trajectory |

Click on Event Links from AOP page to navigate to corresponding KE page

## Four most important sections

### Key Event Description

- Is it clear what biology the KE refers to?
- What is the “sign post”

### How It Is Measured or Detected

### Domain of Applicability

### References

# Getting Oriented - Event Pages

- Should refer to an observable/measurable change, how to measure or observe it, and in what taxa, life-stage, and sex it can be observed

- By intent, the contents should be stand-alone without reference to other KEs in the AOP

- Event pages do not provide evidence that measureable entity is impacted by a specific stressor or other biological change – except in the case of the MIE

# Getting Oriented – Relationship Pages

- Each KER represents a predictive relationship between a pair of key events that can be supported by weight of evidence.
- Relationship is causal – one KE causes the other
- Much of the content pertaining to scientific quality will be found on the individual relationship pages.
- By intent, they include only support that references that specific pair of KEs – generally will not reference other KEs in the pathway

# Getting Oriented – Relationship Pages

Relationships Between Two Key Events (Including MIEs and AOs)

| Title |
| --- |
| Inhibition, Aromatase leads to Reduction, 17beta-estradiol synthesis by ovarian granulosa cells |
| Reduction, 17beta-estradiol synthesis by ovarian granulosa cells leads to Reduction, Plasma 17beta-estradiol concentrations |
| Reduction, Plasma 17beta-estradiol concentrations leads to Reduction, Vitellogenin synthesis in liver |
| Reduction, Cumulative fecundity and spawning leads to Decrease, Population trajectory |
| Reduction, Vitellogenin accumulation into oocytes and oocyte growth/development leads to Reduction, Cumulative fecundity and spawning |
| Reduction, Plasma vitellogenin concentrations leads to Reduction, Vitellogenin accumulation into oocytes and oocyte growth/development |
| Reduction, Vitellogenin synthesis in liver leads to Reduction, Plasma vitellogenin concentrations |

Click Links in the Relationship Table found on the AOP page

Key Event Relationship Description

Evidence Supporting this KER

Biological Plausibility

Empirical Evidence

Uncertainties or Inconsistencies

Quantitative Understanding of the Linkage

- Response-response Relationship
- Time-scale
- Known modulating factors
- Known Feedforward/Feedback loops influencing this KER

Domain of Applicability

References

# Getting Oriented – Relationship Pages

## Key Event Relationship Description

- Should describe the conditions/biological context in which this KER operates
  - A specific tissue context
  - Duration of impact at KEup

- May also detail biology that is operable but not represented at KEs in the pathway

# Support for KERs

## Biological Plausibility 

- Define the biological rationale for a connection between $KE_{upstream}$ and $KE_{downstream}$
- What are the structural or functional relationships between the KEs?

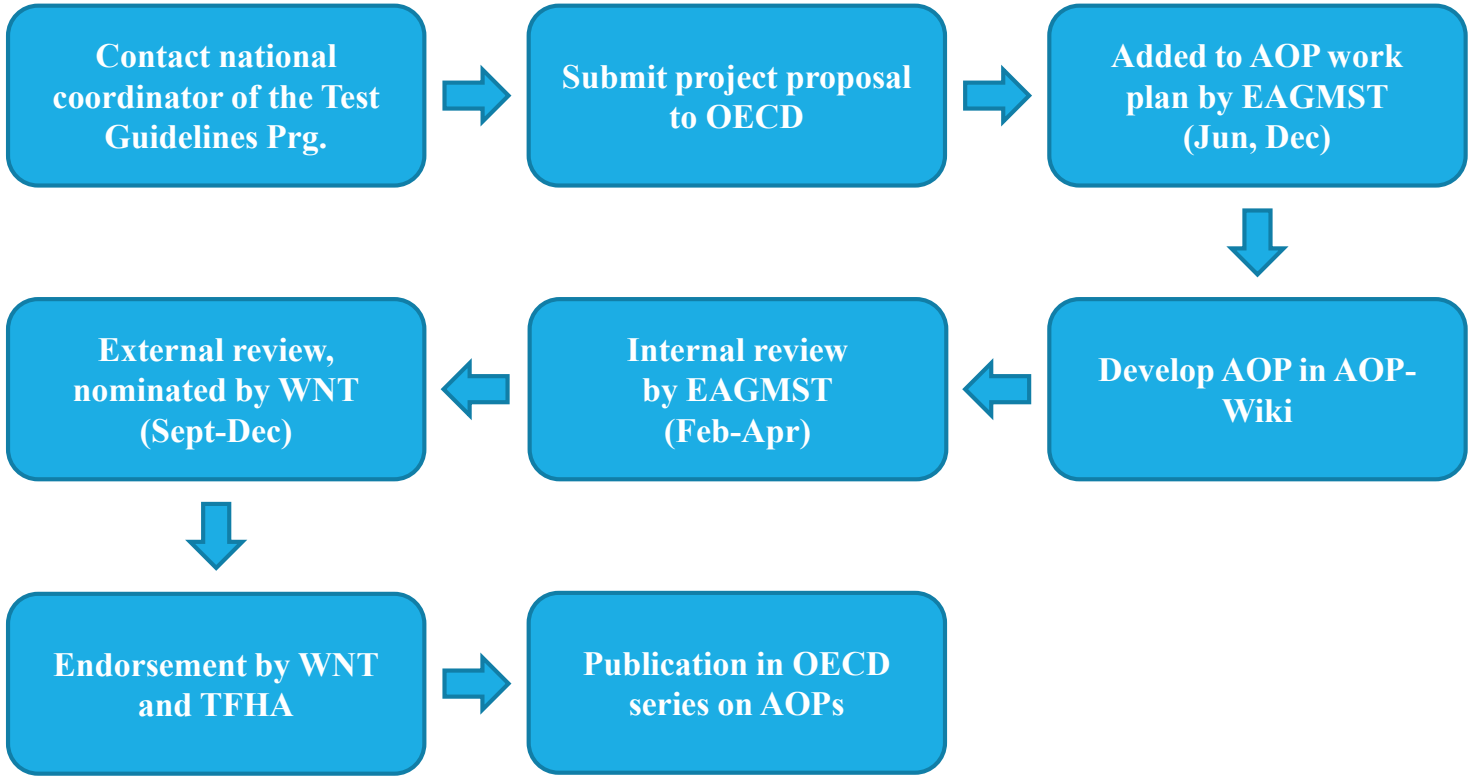
# Support for KERs

## Empirical Evidence 

- Evidence that supports the idea that a change in the upstream KE ($KE_{upstream}$) will lead to, or is associated with, a subsequent change in the downstream KE ($KE_{downstream}$), assuming the perturbation of $KE_{upstream}$ is sufficient.
- Helpful to provide as much detail about the toxicological and biological context in which the measurements were made, as is feasible, including the stressor(s) tested, the effective doses at each KE, etc.

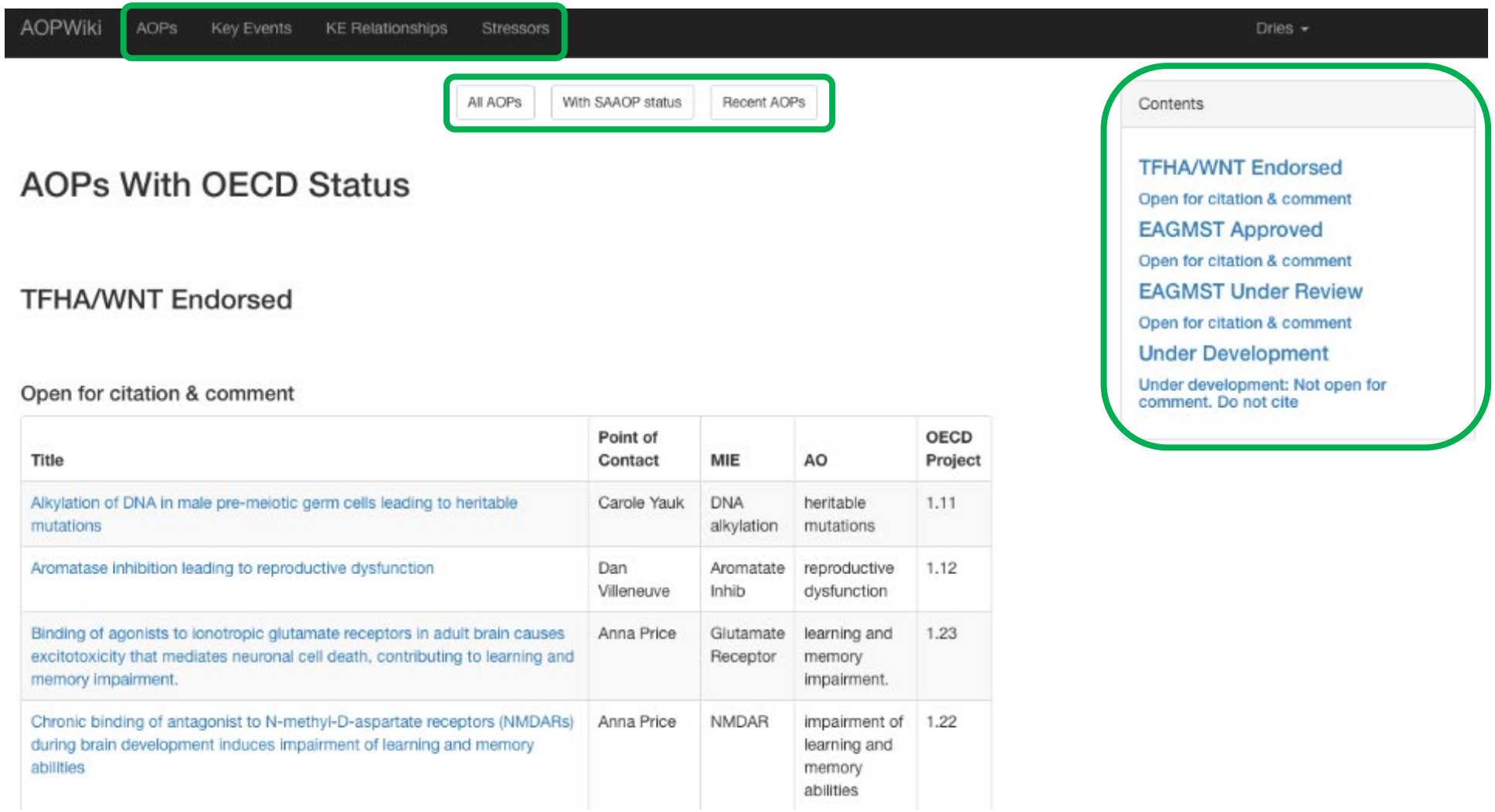
# OECD AOP development program

# Submission and review process



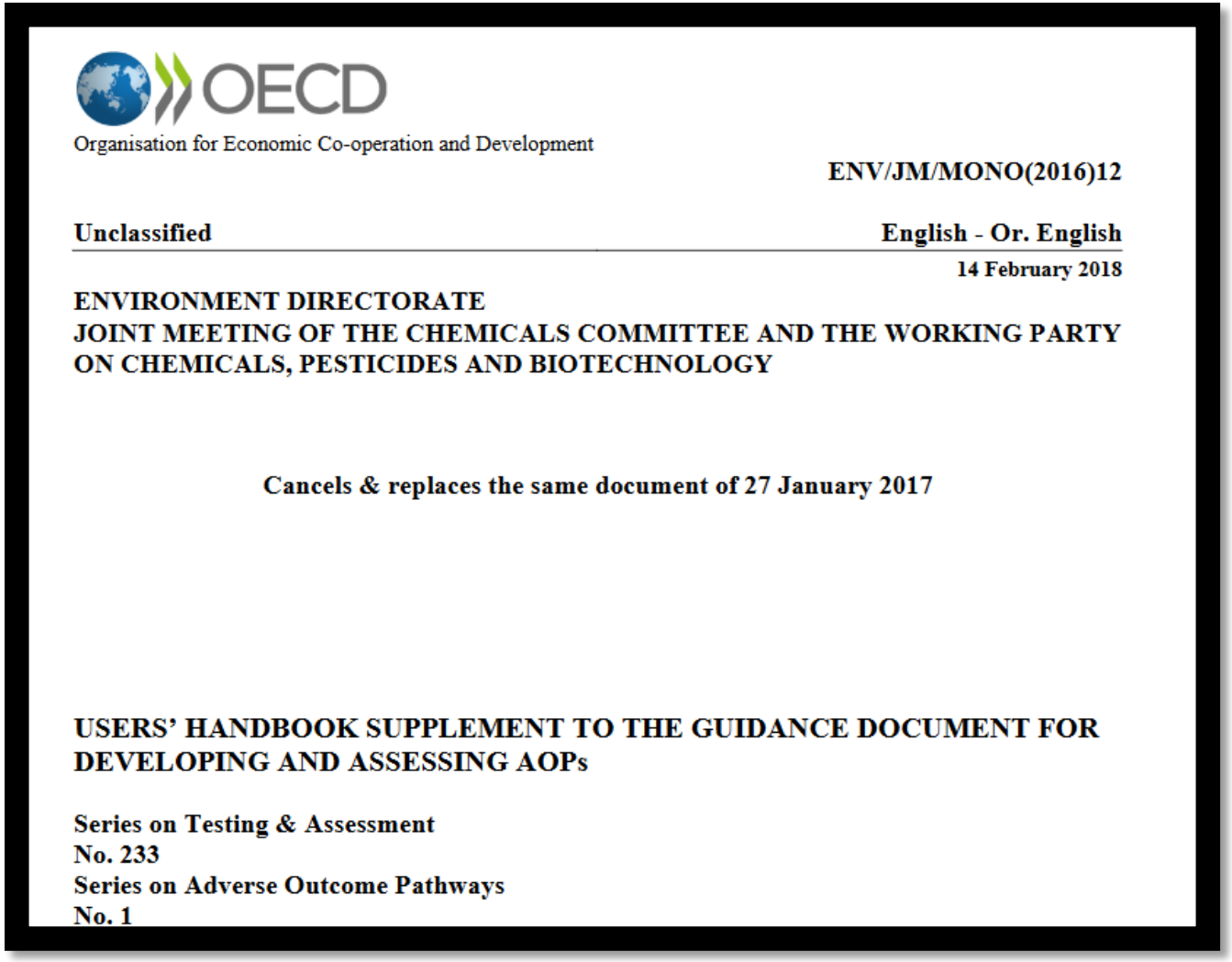

EAGMST: Extended Advisory Group on Molecular Screening and Toxicogenomics
WNT: Working Group of the National Coordinators of the Test Guidelines Programme
TFHA: Task Force on Hazard Assessment

# AOP-Wiki: navigation



# Resources

## 1. Guidance document on developing and assessing AOPs



OECD

Organisation for Economic Co-operation and Development

ENV/JM/MONO(2016)12

Unclassified

English - Or. English

14 February 2018

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

Cancels & replaces the same document of 27 January 2017

USERS' HANDBOOK SUPPLEMENT TO THE GUIDANCE DOCUMENT FOR DEVELOPING AND ASSESSING AOPs

Series on Testing & Assessment
No. 233
Series on Adverse Outcome Pathways
No. 1

# AOP-Wiki

https://aopwiki.org/

# ECOTOX KNOWLEDGEBASE

Identify KEs, Gather evidence for KERs, and Define the domain of applicability

EPA United States Environmental Protection Agency

# ECOTOXicology Knowledgebase:


US EPA ECOTOX Project Team:

*Colleen Elonen*
*Jennifer Olker*
*Dale Hoff*
*Rong-Lin Wang*

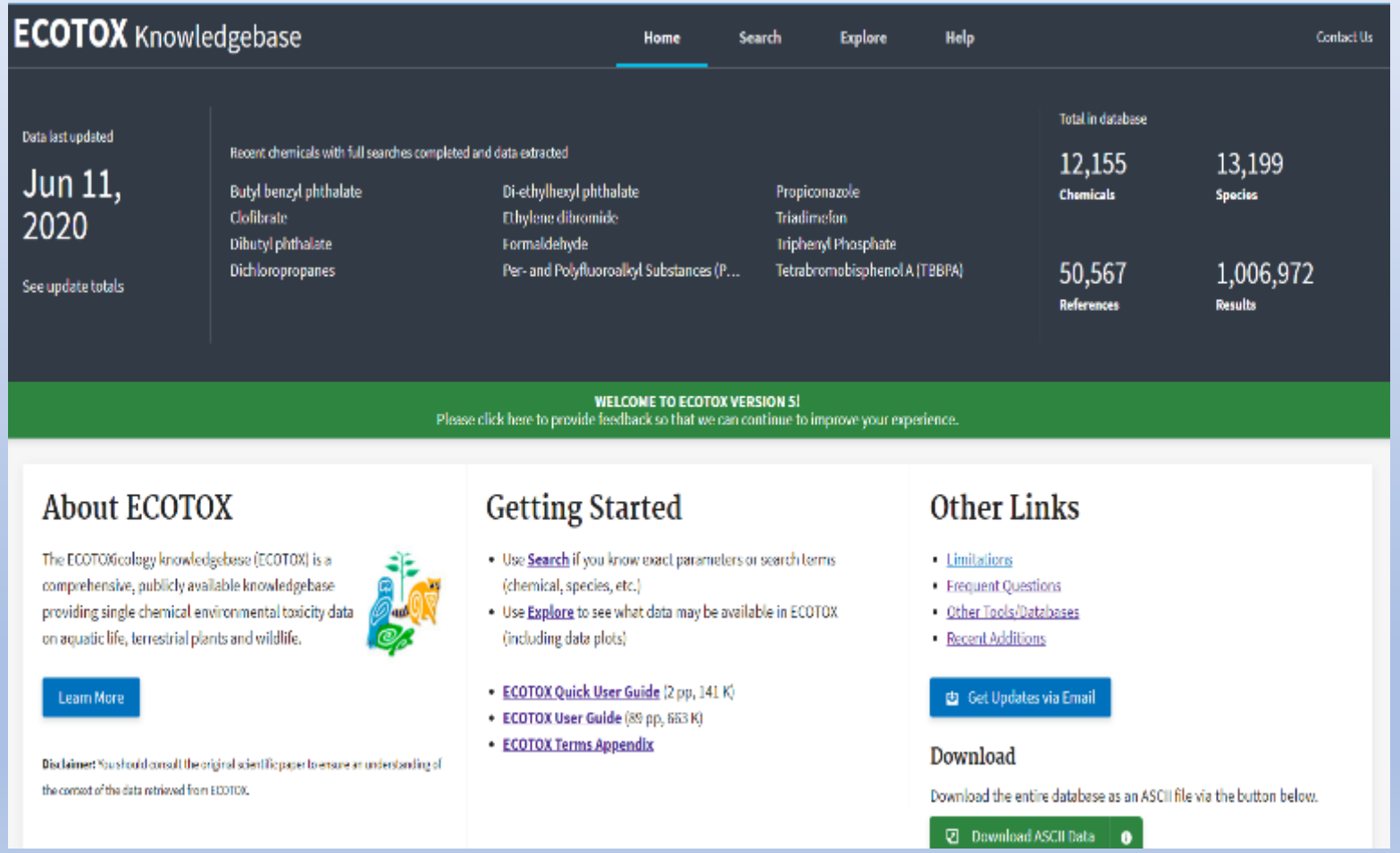
*GDIT contract staff*
*SEE staff*


www.epa.gov/ecotox

# What is the ECOTOX Knowledgebase?

Publicly available, curated database providing toxicity data from single-chemical exposure studies to aquatic life, terrestrial plants, and wildlife

- From comprehensive search and review of open and grey literature
  - Data extracted from acceptable studies, with up to 250 fields
  - Updated quarterly
- 30+ year history
  - Originated in the early 1980s
  - Developed at US EPA's Office of Research and Development in Duluth
- Current user statistics
  - 8,000 distinct hosts search the Knowledgebase each month



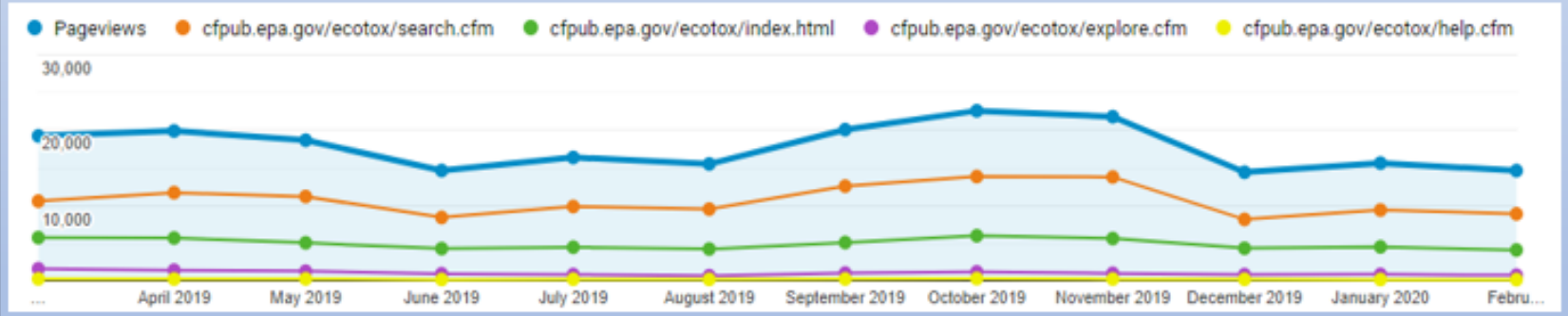
# ECOTOX by the numbers

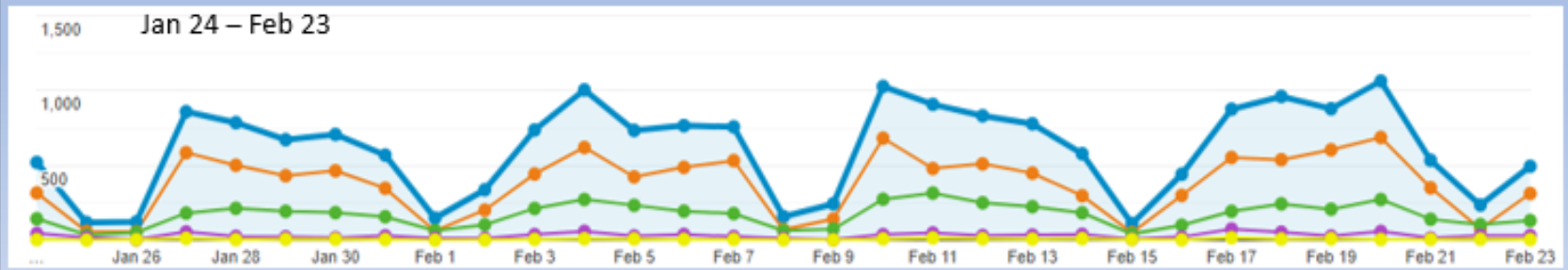
Curated ecological data from ~50,000 papers, with >12,000 chemicals and >13,000 species.

March 2019 – February 2020:

17,800 page views per month

8,400 unique page views per month



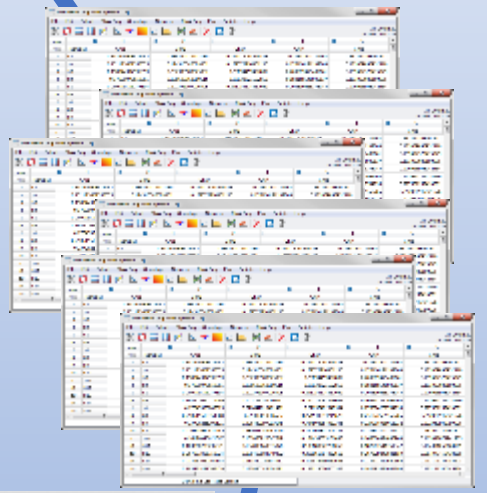
# ECOTOX Literature Searches

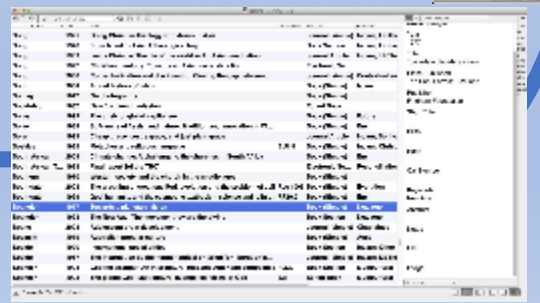
- **Identification**
  - Chemical verification and development of search terms
  - Conduct literature searches
- **Screening**
  - Identify and acquire potentially applicable studies
- **Eligibility**
  - Review literature for applicability to ECOTOX
- **Included**
  - Data extraction
  - Study quality evaluation

Chemical specific searches
(using terms from chemical verification step)
OR
Monthly electronic searches
of 11 highly relevant journals

<u>Search Engines</u>

1. Science Direct
2. AGRICOLA
3. TOXNET
4. ProQuest ESPM
5. ProQuest Dissertation Abstracts
6. Web of Science/ Current Contents





Collate data and remove duplicates

In 2019: 159,727 references were manually skimmed for applicability

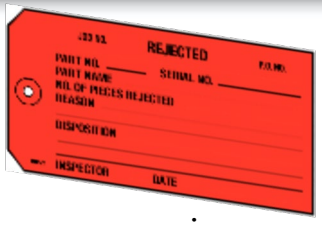
# ECOTOX Applicability Criteria

- Paper must meet these criteria
  - Single chemical exposure
  - Ecologically-relevant species
  - Must be able to verify CAS registry numbers
  - Must be able to verify taxonomic information for test species
  - Exposure to live organism, viable tissue or cells
  - Report concurrent exposure concentration, dose or application rate
  - Report duration of exposure
  - Must have a control treatment
  - Primary source of the data
  - Study must be a full article in English
- The following studies are excluded
  - Air pollution studies related to CO2 and ozone
  - Studies on humans, monkeys, bacteria, viruses and yeast
  - Review and summary articles
  - Terrestrial studies with an inhalation route of exposure
  - Non-English publications and abstracts

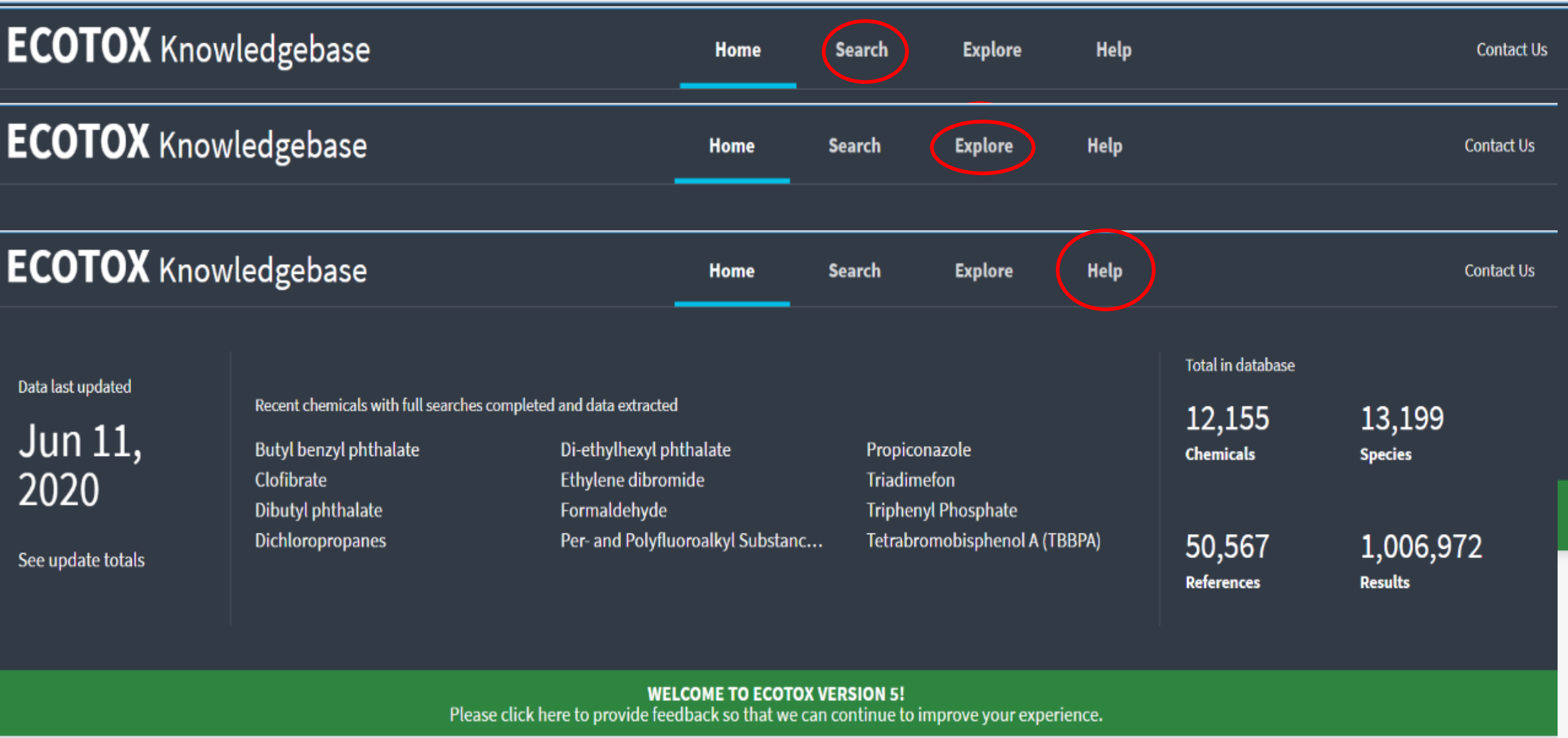
Review literature for applicability to ECOTOX

# ECOTOX Applicability Criteria

All Excluded and Non-Applicable studies are Tagged with the reason for rejection




- Abstract – Published as an abstract
- Bacteria – only test organism is a Bacteria
- CAS # Unavailable – could not verify/locate chemical CAS Registry number
- Chemical method – description of chemical analysis procedures
- Fate – only report chemical distribution in media
- Human Health – data on human subjects of surrogate animal subjects for human health risk assessment
- Incident – reports death of animal by poison, but does not provide concentration/duration of exposure
- Method – paper only reports methods for conducting a toxicity test or other aspect of an experiment
- Mixture – paper reports results from mixture of chemicals; no single chemical exposure results
- Modeling – results of the development of a model; no primary data available
- No Conc – the authors report a response in an organism but do not provide conc/dose/app rate
- No Duration – duration of exposure is not presented
- No Effect – paper does not report observed responses adverse of otherwise
- No Toxicant (ozone, CO2)
- Non-English
- Nutrient – in situ chemical tested as nutrient
- PUBL AS – duplicate data published elsewhere
- Retracted – paper retracted by Journal
- Review – primary data published elsewhere
- Sediment – only sediment concentration presented
- Survey – chemical measured in organism, but lack quantification of exposure (dose/duration)
- Virus – virus is only test organism
- Yeast – yeast is only test organism




## About ECOTOX

The ECOTOXicology knowledgebase (ECOTOX)

## Getting Started

- Use **Search** if you know exact parameters or search terms

## Other Links

- Limitations

All Chemicals +

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

## Chemicals

Name(s) or CAS number(s)

Contains | Exact Match

*Enter each chemical name and/or CAS registry number on separate lines.*

See US EPA CompTox Chemicals Dashboard.

**Any Chemical Group**

**Metal or Organometal Compounds**

- Aluminum
- Antimony
- Arsenic
- Barium
- Beryllium
- Cadmium
- Chromium
- Cobalt
- Lead
- Manganese
- Mercury
- Nickel
- Silver
- Organotin
- Selenium
- Vanadium

Customize Output Fields

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

All Chemicals +

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

# Effect Measurements

Effect(s) (eg. food, vitellogenin, acetylcholine)

Contains | Exact Match

*Enter each effect measurement on separate lines.*

Exclude Post-exposure Measurements

**Any Effect Group**

- **Accumulation Group**
- **Behavior Group**
  - Avoidance
  - Behavior
  - Feeding Behavior
- **Biochemical Group**
- **Growth Group**
  - Development
  - Growth
  - Morphology
- **Mortality Group**
- **Multiple Group**

Customize Output Fields

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

Parameters

Aquatic | Terrestrial

All Chemicals +

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

## Endpoints

Customize Output Fields

**Any Endpoints**

**Concentration Based Endpoints**

- AC xx (all % values)
  - AC50
- LC/LD xx (all % values)
  - LC50
  - LD50
- LL xx (all % values)
  - LL10
  - LL50
- EC/ED xx (all % values)
  - EC50
  - ED50
- EL xx (all % values)
  - EL10
- IC/ID xx (all % values)
  - IC50
  - ID50
- LOEC
- LOEL
- LOELR
- NOEC
- NOEL
- NOELR
- MATC
- LETC/ATCN

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

All Chemicals +

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

‹ Species

Customize Output Fields

## Specific Species

*Enter each species name on separate lines.*

Species name(s)

Contains | Exact Match

**Kingdom**

Animals

Plants

Both

**For Name Searches**

Genus/Species Name

Common Name

Other Taxonomic Names

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

*OR: Select from Species Groups below, with the option to limit results by Special Interest groups.*

## Any Species Group

**Animals**

Amphibians

Other Invertebrates

Parameters

Aquatic | Terrestrial

All Chemicals +

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

## Test Conditions

**Any Test Locations**

- Lab
- Not Reported
- All Field Tests
  - Field, Artificial
  - Field, Natural
  - Field, Undeterminable

**Any Exposure Media**

**Water**

- Fresh Water
- Salt Water
- Fresh or Saltwater Not Specified

**Soil**

- Artificial
- Humus
- Litter
- Mineral Soil
- Soil Mixture
- Natural Soil

Customize Output Fields

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

All Chemicals +

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

## Publication Options

**Publication Years**

1915 to 2020

**Author(s):** *All*

**Ref Num(s):** *All*

*Enter each author and/or reference number on separate lines.*

**Any Independently Compiled Data**

- EPA: Fathead Minnow Acute Toxicity Database (MED-Duluth)
- EPA: Office of Pesticides Program Database
- Dutch Dataset
- French Dataset
- German Dataset
- Russian Dataset

Customize Output Fields

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

Chemicals
- nitrapyrin

All Effects

All Endpoints

All Species

All Test Conditions

All Publication Options

Reset All

Update Search

# Chemicals

Reset

nitrapyrin

Contains | Exact Match

*Enter each chemical name and/or CAS registry number on separate lines.*

See US EPA CompTox Chemicals Dashboard.

**Any Chemical Group**

**Metal or Organometal Compounds**

- Aluminum
- Antimony
- Arsenic
- Barium
- Beryllium
- Cadmium
- Chromium
- Cobalt
- Lead
- Manganese
- Mercury
- Nickel
- Silver
- Organotin
- Selenium
- Vanadium

ate your search.

Customize Output Fields

ata from the ECOTOX Knowledgebase if you know the

t method to retrieve data that can be refined by limiting
ters including but not limited to: Chemical, Species,
Once you have selected your search options, you are able
xport to an Excel spreadsheet or delimited text format.

# ECOTOX Knowledgebase

Home | Search | Explore | Help | Contact Us

Parameters

Aquatic | Terrestrial

Chemicals +

- nitrapyrin

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

× Reset All

View All Applied

**48** results

Customize Output Fields | Export as... | ⚙

*Results shown in condensed table. Use "Customize Output Fields" to view expanded data results.*

| CAS NUM / CHEM. NAME | CHEM. GRADE | CHEM. ANAL. | CHEM. PUR. | SPEC. SCI. NAME / SPEC. COMMON NAME | SPEC. GROUP | ORG. LIFESTG. | ORG. AGE |
|---|---|---|---|---|---|---|---|
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | Unmeasured | | Algae / Algae | Algae | | |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | Unmeasured | | Algae / Algae | Algae | | |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | Unmeasured | | Algae / Algae | Algae | | |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | Unmeasured | | Algae / Algae | Algae | | |

Chemicals +

- nitrapyrin

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

× Reset All

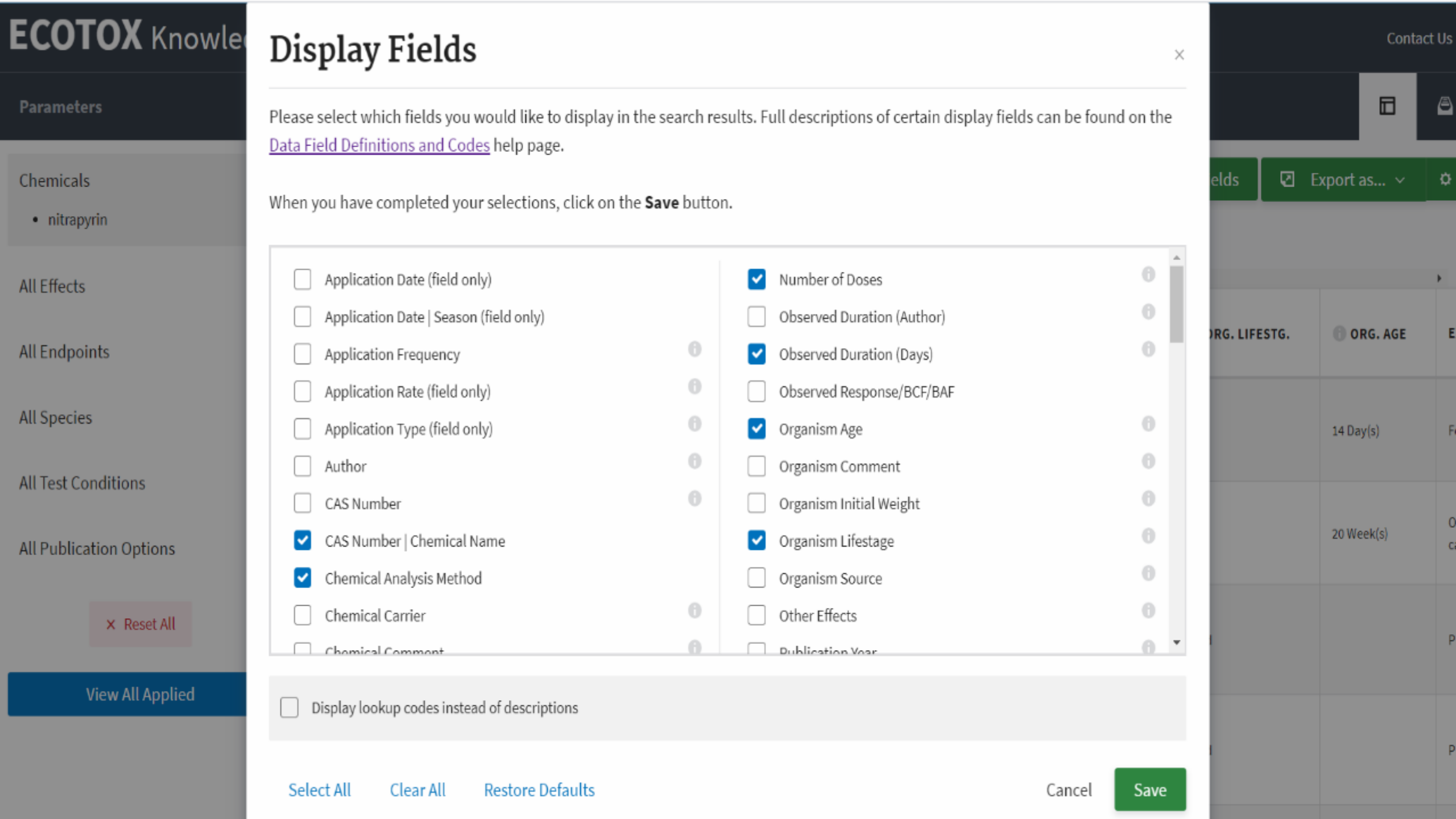
View All Applied

**304** results

Customize Output Fields | Export as... | ⚙

*Results shown in condensed table. Use "Customize Output Fields" to view expanded data results.*

| CAS# / CHEM. NAME | CHEM. GRADE | CHEM. ANAL. | CHEM. PUR. | SPEC. SCI. NAME / SPEC. COMMON NAME | SPEC. GROUP | ORG. LIFESTG. | ORG. AGE |
|---|---|---|---|---|---|---|---|
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | 96 | Anas platyrhynchos / Mallard Duck | Birds; Standard Test Species | | 14 Day(s) |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | 92.6 | Anas platyrhynchos / Mallard Duck | Birds; Standard Test Species | | 20 Week(s) |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | | Beta vulgaris / Sugar Beet | Flowers, Trees, Shrubs, Ferns; Standard Test Species | Seed | |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | | Beta vulgaris / Sugar Beet | Flowers, Trees, Shrubs, Ferns; Standard Test Species | Seed | |


ECOTOX Knowle
Contact Us
Parameters
Chemicals
• nitrapyrin
All Effects
All Endpoints
All Species
All Test Conditions
All Publication Options
× Reset All
View All Applied
elds
Export as...
ORG. LIFESTG.
ORG. AGE
14 Day(s)
20 Week(s)
Display Fields
Please select which fields you would like to display in the search results. Full descriptions of certain display fields can be found on the Data Field Definitions and Codes help page.
When you have completed your selections, click on the Save button.
Application Date (field only)
Application Date | Season (field only)
Application Frequency
Application Rate (field only)
Application Type (field only)
Author
CAS Number
CAS Number | Chemical Name
Chemical Analysis Method
Chemical Carrier
Number of Doses
Observed Duration (Author)
Observed Duration (Days)
Observed Response/BCF/BAF
Organism Age
Organism Comment
Organism Initial Weight
Organism Lifestage
Organism Source
Other Effects
Display lookup codes instead of descriptions
Select All
Clear All
Restore Defaults
Cancel
Save

Chemicals +

- nitrapyrin

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

× Reset All

View All Applied

**304** results

Customize Output Fields | Export as... | ⚙

Excel

Delimited

*Results shown in condensed table. Use "Customize Output Fields" to view expanded data results.*

| CAS# / CHEM. NAME | CHEM. GRADE | CHEM. ANAL. | CHEM. PUR. | SPEC. SCI. NAME / SPEC. COMMON NAME | SPEC. GROUP | ORG. LIFESTG. | ORG. AGE |
|---|---|---|---|---|---|---|---|
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| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | 92.6 | Anas platyrhynchos / Mallard Duck | Birds; Standard Test Species | | 20 Week(s) |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | | Beta vulgaris / Sugar Beet | Flowers, Trees, Shrubs, Ferns; Standard Test Species | Seed | |
| 1929824 / 2-Chloro-6-(trichloromethyl)pyridine | | | | Beta vulgaris / Sugar Beet | Flowers, Trees, Shrubs, Ferns; Standard Test Species | Seed | |

Chemicals +

- nitrapyrin

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

× Reset All

View All Applied

**35** references

Export as...

type to find...

Al-Uqaili,J.K.. *The Influence of Rates and Sources of Nitrogen with and Without a Nitrification Inhibitor on Corn Nutrition and Soil Nitrogen*. Ph.D. Thesis, University of Nebraska, Lincoln, NE:202 p., 1981. ECOREF #96928

Search Google Scholar EXIT

Bailey,L.D.. *The Effects of 2-Chloro-6 (Trichloromethyl)-Pyridine ('N-Serve') and N Fertilizers on Productivity and Quality of Canadian Oilseed Rape*. Can. J. Plant Sci.70(4): 979-986, 1990. ECOREF #171338

Search Google Scholar EXIT

Berdasco,N.M., L.G. Lomax, M.A. Zimmer, and T.R.,Jr. Hanley. *Teratologic Evaluation of Orally Administered Nitrapyrin in Rats and Rabbits*. Fundam. Appl. Toxicol.11:464-471, 1988. ECOREF #171197

Search Google Scholar EXIT

Chemicals +
- nitrapyrin

All Effects +

All Endpoints +

All Species +

All Test Conditions +

All Publication Options +

× Reset All

View All Applied

35 ref

type to f

Al-Uqaili,J.H
Nitroge

Search Goo

Bailey,L.D..
Oilseed

Search Goo

Berdasco,N
Rabbits

Search Goo

# All Applied Parameters

×

**Habitat**

*Terrestrial*

**Chemicals**

Name(s) / Number(s)

nitrapyrin

**Effect Measurements**

**Endpoints**

**Species**

**Test Conditions**

**Publication Options**

Export Close

# ECOTOX Knowledgebase



Data last updated

Jun 11, 2020

See update totals

Recent chemicals with full searches completed and data extracted

- Butyl benzyl phthalate
- Clofibrate
- Dibutyl phthalate
- Dichloropropanes
- Di-ethylhexyl phthalate
- Ethylene dibromide
- Formaldehyde
- Per- and Polyfluoroalkyl Substanc...
- Propiconazole
- Triadimefon
- Triphenyl Phosphate
- Tetrabromobisphenol A (TBBPA)

Total in database

| | |
|---|---|
| 12,155 **Chemicals** | 13,199 **Species** |
| 50,567 **References** | 1,006,972 **Results** |

**WELCOME TO ECOTOX VERSION 5!**
Please click here to provide feedback so that we can continue to improve your experience.

## About ECOTOX

The ECOTOXicology knowledgebase (ECOTOX) is a comprehensive, publicly available knowledgebase providing single chemical environmental toxicity data on aquatic life, terrestrial plants and wildlife.

Learn More

## Getting Started

- Use **Search** if you know exact parameters or search terms (chemical, species, etc.)
- Use **Explore** to see what data may be available in ECOTOX (including data plots)

- **ECOTOX Quick User Guide** (2 pp, 141 K)
- **ECOTOX User Guide** (89 pp, 663 K)

## Other Links

- Limitations
- Frequent Questions
- Other Tools/Databases
- Recent Additions

Get Updates via Email

*Choose a starting point below.*




# About Explore

**Explore** is a great tool for searching the ECOTOX Knowledgebase if you do not know the exact parameters you want to search, or would like a visual representation of general and specific data trends.

The ECOTOX Knowledgebase **Explore** function is an interactive way to examine search paths by Chemical, Species, and Effects. Once you've selected the path to explore, additional data fields will be displayed to filter your data, e.g. Effects, Endpoints, Publication Year.

During the exploration there are also options to examine the data visually via plotting functions. Once you have completed your exploration, you are able to select different options for exporting the data.

## Custom Group

*Create a custom chemical group by browsing available chemicals or entering a list of CAS numbers.*

Create Custom Group...

## Defined Groups

*Select one or more categories from the graph to filter groups in the table.*

# 35 Chemical Groups

**Chemical groups are solely intended for the purposes of searching multiple chemicals efficiently and do not reflect the view(s) or the policy(cies) of the U.S. Environmental Protection Agency.**

Some of the Chemical groups are currently being re-evaluated. They will be refreshed and restored in future ECOTOX updates.

*Select one or more groups then click "Explore Data" to continue.*

× Reset All  Export CSV  Explore Data ›

| CHEMICAL GROUP | RECORDS | PUBLICATIONS | YEAR MIN | YEAR MAX |
|---|---|---|---|---|
| Aluminum | 3928 | 469 | 1915 | 2014 |
| Antimony | 557 | 75 | 1948 | 2013 |
| Arsenic | 5037 | 528 | 1927 | 2020 |
| Barium | 409 | 91 | 1939 | 2012 |
| Beryllium | 357 | 54 | 1925 | 2012 |
| Cadmium | 24660 | 3208 | 1915 | 2019 |
| Chromium | 7974 | 1007 | 1915 | 2018 |
| Cobalt | 1898 | 301 | 1915 | 2019 |

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*Create a custom chemical group by browsing available chemicals or entering a list of CAS numbers.*

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| ☑ | Aluminum | 3928 | 469 | 1915 | 2014 |
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| ☐ | Barium | 409 | 91 | 1939 | 2012 |
| ☐ | Beryllium | 357 | 54 | 1925 | 2012 |
| ☐ | Cadmium | 24660 | 3208 | 1915 | 2019 |
| ☐ | Chromium | 7974 | 1007 | 1915 | 2018 |
| ☐ | Cobalt | 1898 | 301 | 1915 | 2019 |

Aquatic Terrestrial

Group Summary Records Plot View

Send Query Filters to Search

## Query Filters

*Select one or more* of each filter to reduce the records.

Chemicals

Loading...

Species Group

Loading...

Class

Loading...

Order (128)

All

# 23 Chemicals

Export CSV

Chemicals are ordered by **CAS Number**.

*Showing **all** 23 chemicals from **1302427** to **103616177***

| CAS | CHEMICAL NAME | RECORDS | PUBLICATIONS | YEAR MIN | YEAR MAX |
|---|---|---|---|---|---|
| type to filter... | ... | ... | ... | ... | ... |
| 1302427 | Sodium aluminate (NaAlO2) | 10 | 3 | 1957 | 1990 |
| 1327419 | PAX 18 | 50 | 6 | 1969 | 2011 |
| 1344009 | Sodium aluminosilicate | 27 | 3 | 1977 | 1999 |
| 1344281 | Alumina | 57 | 12 | 2008 | 2012 |
| 7429905 | Aluminium | 546 | 64 | 1965 | 2011 |
| 7446700 | Aluminum chloride | 917 | 122 | 1937 | 2014 |

Aquatic | Terrestrial

Group Summary | Records | Plot View

Send Query Filters to Search

## Query Filters

*Select one or more of each filter to reduce the records.*

Chemicals (23)

All

Species Group (14)

All

Class (50)

All

Order (128)

All

# 1,961 Distinct Records — 3,928 Total Records

Export CSV

Distinct Records summarized by **Effect & Endpoint** and ordered by **CAS Number (low-high)**.

*Showing **all** 1,961 records from CAS Number **1302427** to **103616177***

| CAS NUMBER | CHEMICAL N... | SPECIES COM... | EFFECT | EFFECT MEAS... | ENDPOINT | YEAR | RECORDS | REFERENCE ... |
|---|---|---|---|---|---|---|---|---|
| type to filter... | ... | ... | ... | ... | ... | ... | ... | ... |
| 1302427 | Sodium aluminate (NaAlO2) | Chicken | Biochemistry | Riboflavin content | NOEL | 1990 | 1 | Rennie,J.S., C.C. Wh... Google Scholar EXIT |
| 1302427 | Sodium aluminate (NaAlO2) | Chicken | Reproduction | Progeny counts/numbers | NOEL | 1990 | 1 | Rennie,J.S., C.C. Wh... Google Scholar EXIT |
| 1302427 | Sodium aluminate | Common Bay | Mortality | Mortality | LC50 | 1977 | 1 | Robinson,D.J.S., and... |

Aquatic | Terrestrial

Group Summary | Records | Plot View

Send Query Filters to Search

## Query Filters

*Select one or more* of each filter to reduce the records.

Chemicals (23)
All

Species Group (14)
All

Class (50)
All

Order (128)
All

Family (207)
All

# 2,319 Plottable Records — 3,928 Total Records

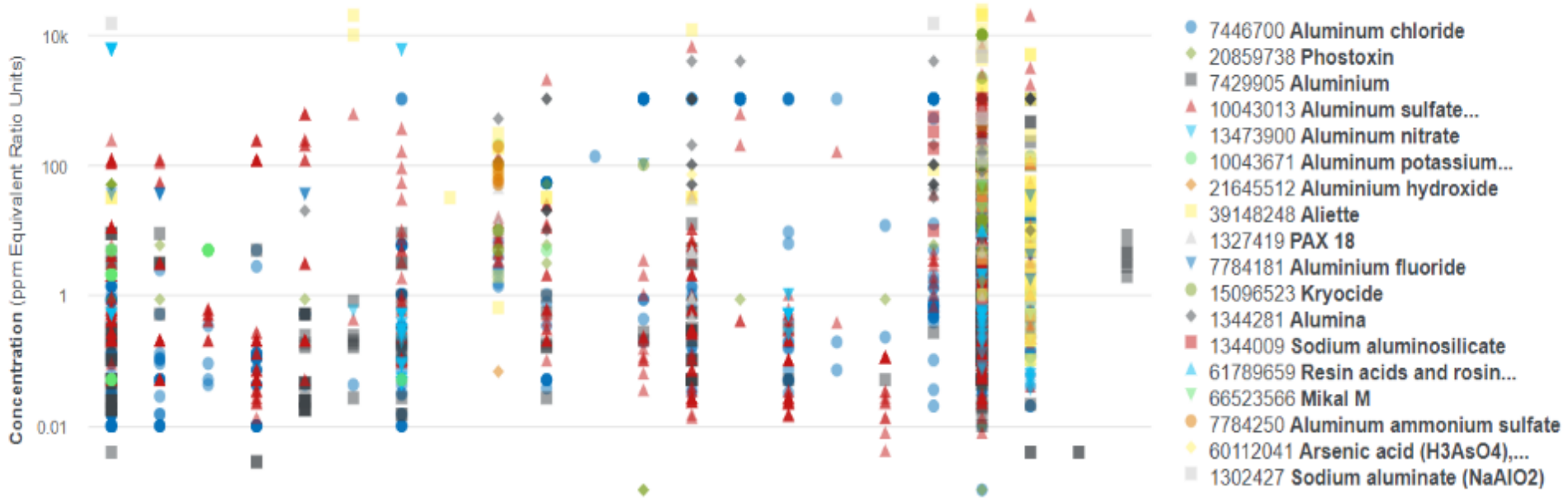
Records are **plotted** if they can be converted to **Standardized Concentration Units**. Ordered by **Concentration (low-high)**.

Effect × Chem | Dur × Chem | Dur × Endpt

Export

Y-axis scale: Linear Logarithmic

*Click and drag to zoom in. Hold down shift key to pan.*



# SEQAPASS

Define the Taxonomic Domain of Applicability Across Species

EPA
United States
Environmental Protection
Agency

# Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) Tool

Carlie A. LaLone


**Office of Research and Development**
Center for Computational Toxicology and Exposure, Great Lakes Toxicology and Ecology Division

**January 28th, 2020**

# Transformation of Toxicity Testing

**Historically:**

**Whole animal test**

- **Observe Toxic Outcome**
  - **Examples**
    - **tumor development**
    - **mortality**

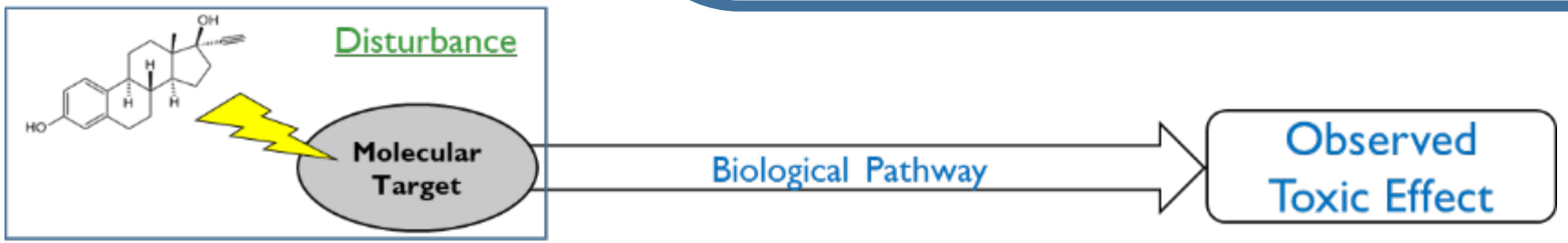
  **Resource intensive**


**Toxicity Testing in the 21st Century:**

- ***In vitro* and *in silico* methods**
  - **Pathway-based approaches**
  - **Focus on disturbance of the biological pathway**
    - **Predictive of the observable toxic effects**

**New Approach Methods (NAMs)**

- Informatics
- High throughput
- Systems biology
- OMICs

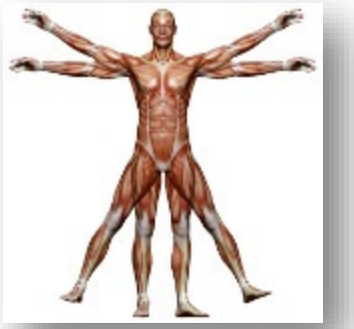



Enabled by evolution of the science and technology

# Model Organisms for Toxicity Testing

- **Assumed** that sensitivity of species to a chemical is a function of their relatedness

- **Human Health Risk Assessment**



Cannot Test

≈




- **Ecological Risk Assessment**

Use of Surrogates

Cannot Test

≈

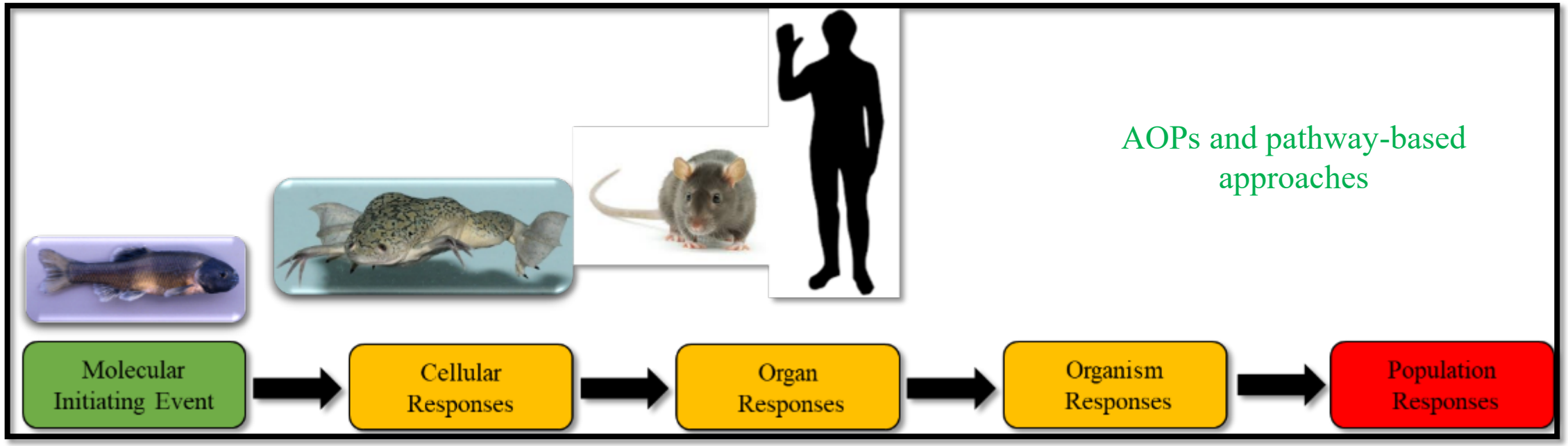






Representative species across a diversity of organism classes

# Surrogates in 21st Century Chemical Safety

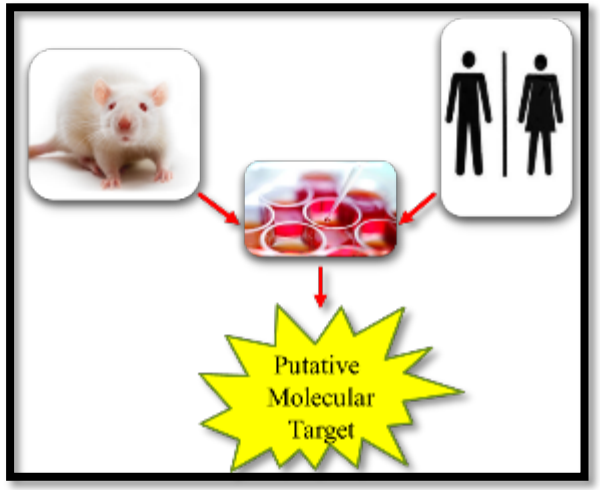



AOPs and pathway-based approaches

HTS

Is the model organism
A good surrogate for the
Species we are trying to protect?
Maybe

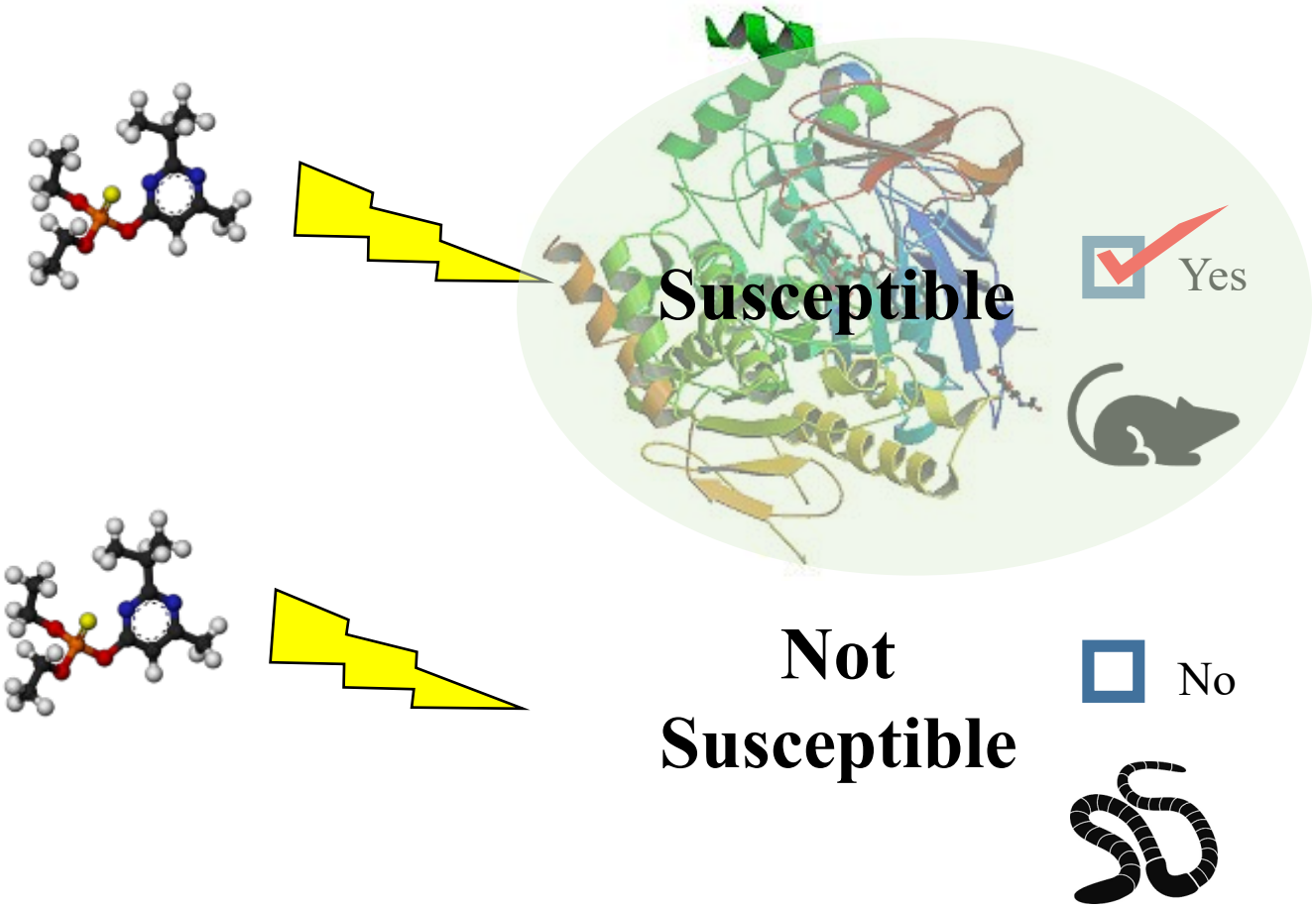
Could we gather evidence rapidly
to help us understand this question?
Absolutely!!!



# Considering chemical sensitivity?

Factors that make a species sensitive

- Exposure
- Dose
- ADME
- Target receptor availability
- Life stage
- Life history
- etc.
- etc.




Simple question to address:

Is the known chemical target available in a species for a chemical to act upon?

Yes or No

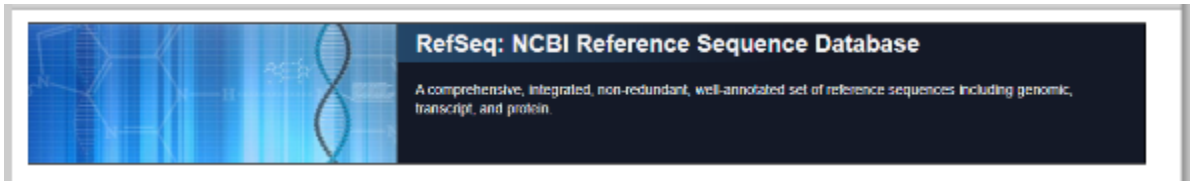
Likely susceptible or Not likely susceptible (at least through the known mechanism)

# New Approach Methods: Species Extrapolation

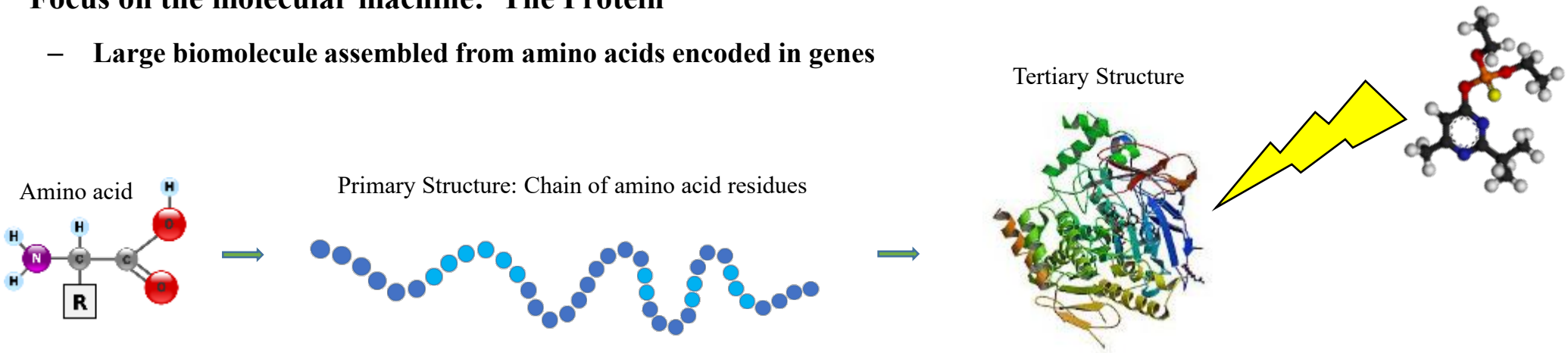
**Continued advances in OMICs and informatics**

- Improved sequencing technologies
- Large databases of sequence data

**As of this week**
**~161 million Proteins**
**~98 thousand Species**




- **Focus on the molecular machine: The Protein**
  - **Large biomolecule assembled from amino acids encoded in genes**




  - **Many functions (e.g., catalyze reactions, structural/mechanical functions, cell signaling, immune response, etc.)**

- **Evaluate protein similarity between species**
  - **Moving away from empirical testing and qualitative understanding of molecular target (protein) conservation to quantitative measures**

EPA
United States
Environmental Protection
Agency

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

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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

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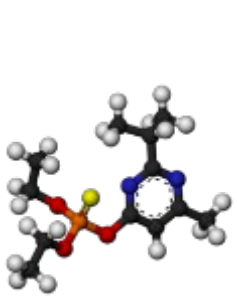
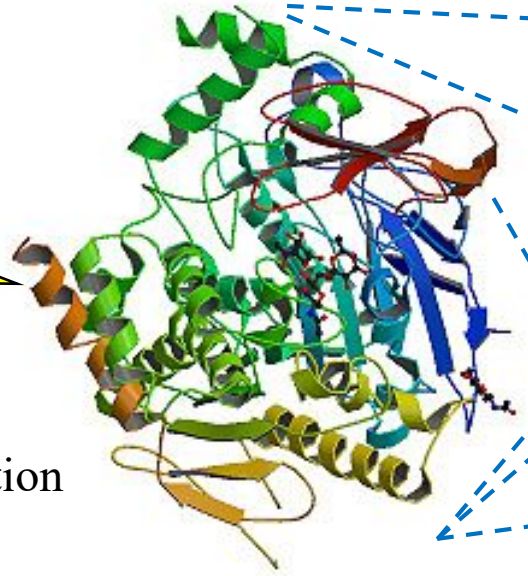
https://seqapass.epa.gov/seqapass/

# Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS)

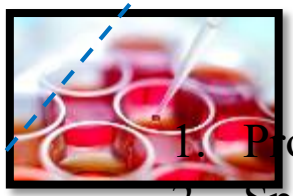
# What information is required for a SeqAPASS query?





Chemical-Protein Interaction

Knowledge of a sensitive or targeted species

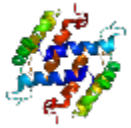


Knowledge of the model organism used in an *in vitro* assay

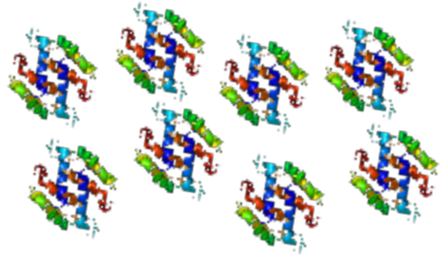
1. Protein
2. Species


Knowledge of the species for which the Key Event was developed

Chemical Molecular Target in Target Species



≅

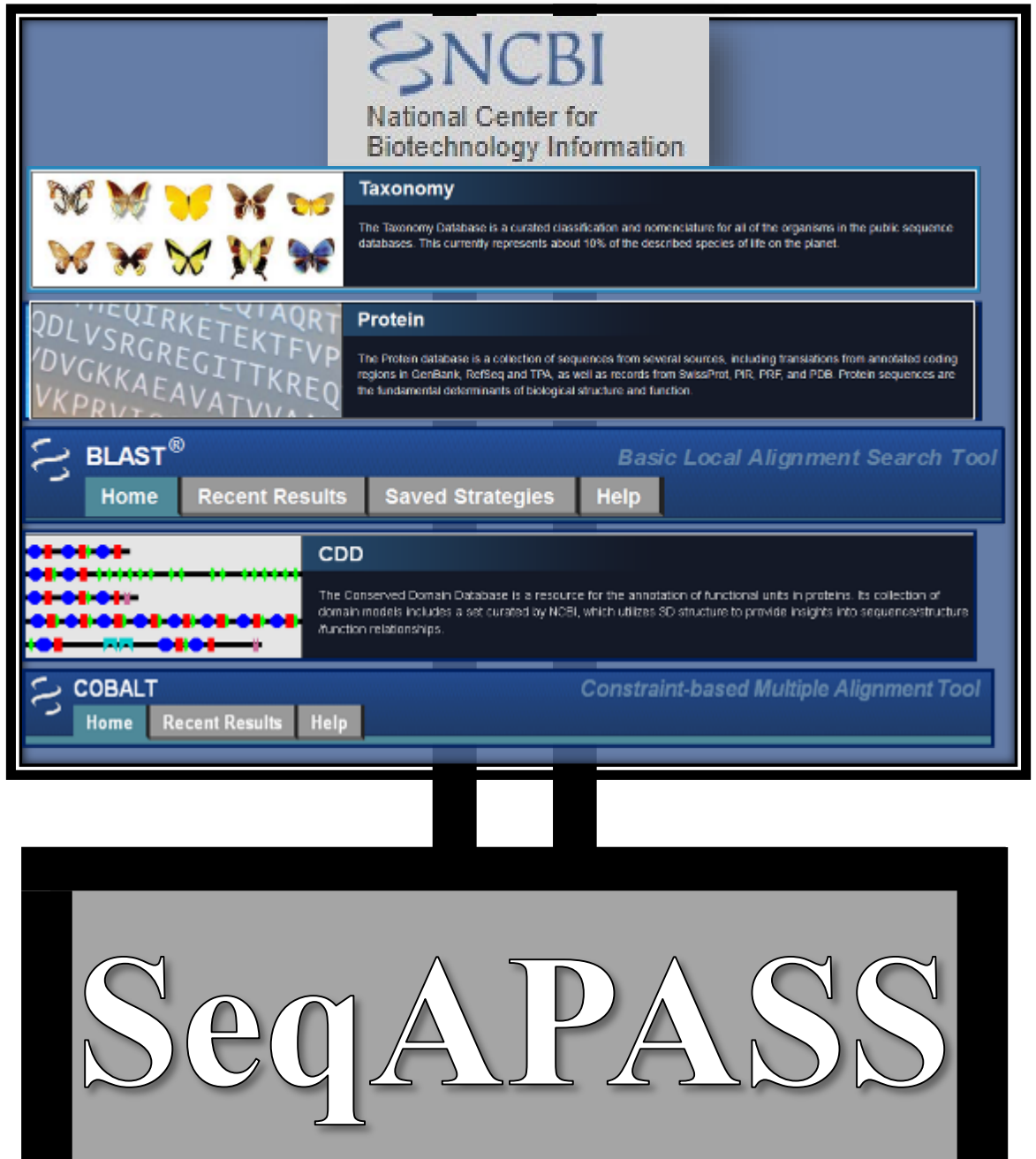


**Compare to Millions of Proteins**
**From Thousands of Species**

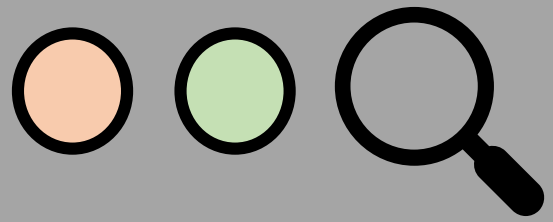
**Greater similarity = Greater likelihood that chemical can act on the protein**
**Line of Evidence: Predict Potential Chemical Susceptibility Across Species**

Animation by: Miguel Moravec (EPA CSS) & Andrew Patterson

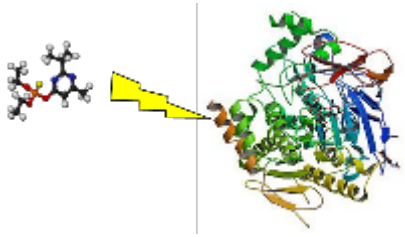
# SeqAPASS


NCBI
National Center for
Biotechnology Information
Taxonomy
The Taxonomy Database is a curated classification and nomenclature for all of the organisms in the public sequence databases. This currently represents about 10% of the described species of life on the planet.
Protein
The Protein database is a collection of sequences from several sources, including translations from annotated coding regions in GenBank, RefSeq and TPA, as well as records from SwissProt, PIR, PRF, and PDB. Protein sequences are the fundamental determinants of biological structure and function.
BLAST®
Basic Local Alignment Search Tool
Home
Recent Results
Saved Strategies
Help
CDD
The Conserved Domain Database is a resource for the annotation of functional units in proteins. Its collection of domain models includes a set curated by NCBI, which utilizes 3D structure to provide insights into sequence/structure /function relationships.
COBALT
Constraint-based Multiple Alignment Tool
Home
Recent Results
Help
SeqAPASS

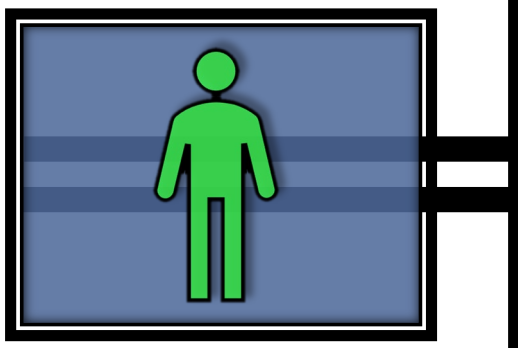
# SeqAPASS Level 1

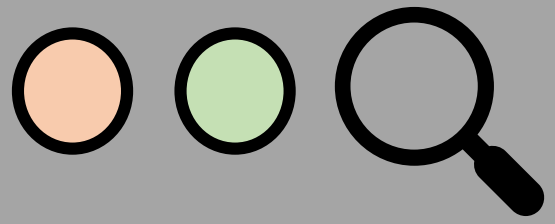


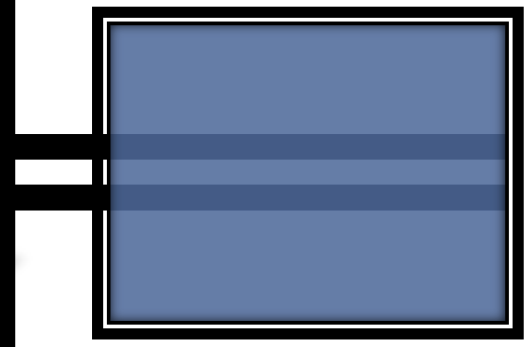
Human Protein Target



# SeqAPASS Level 1

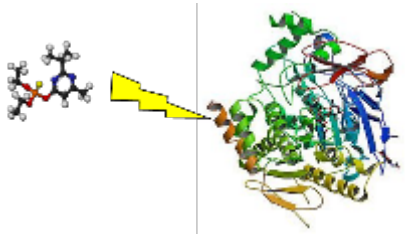


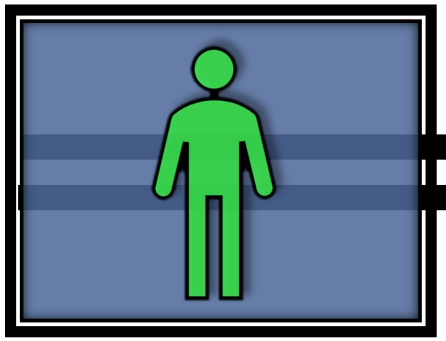


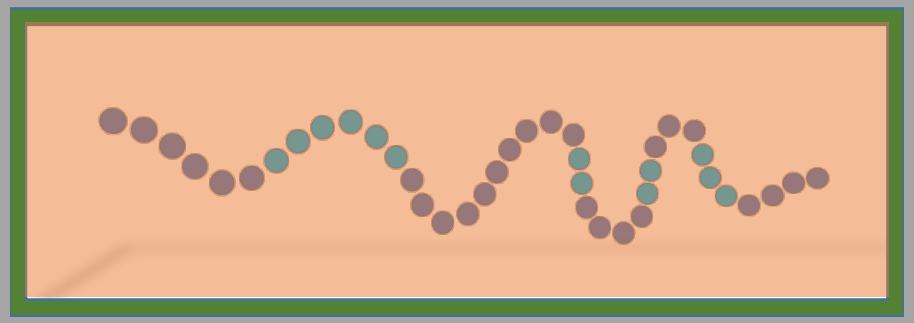


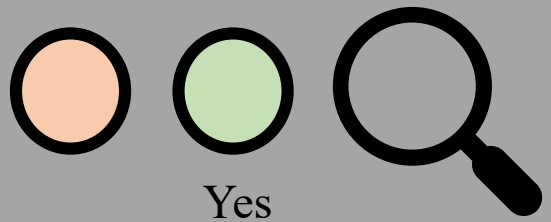
# SeqAPASS Level 1

Human Protein Target







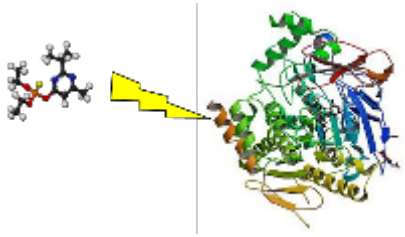


Yes

Line of Evidence:
Primary amino acid sequence
Conserved

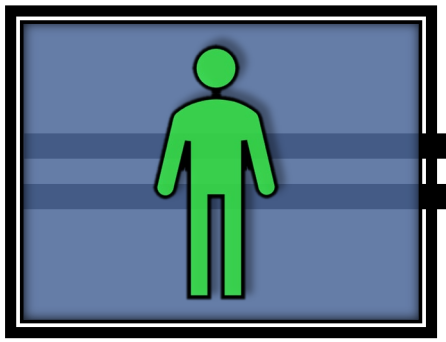
Percent similarity

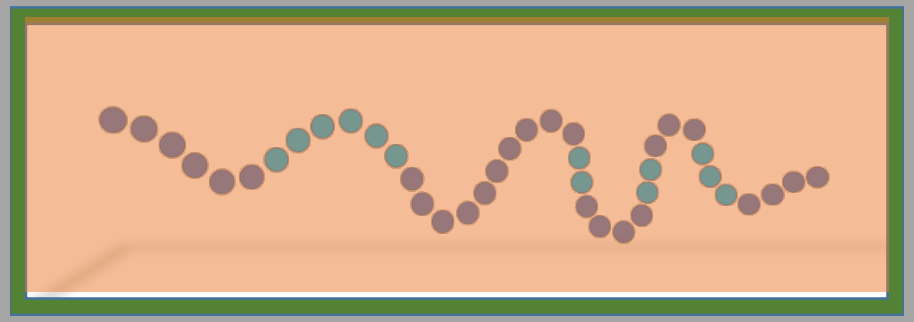
Human Protein Target

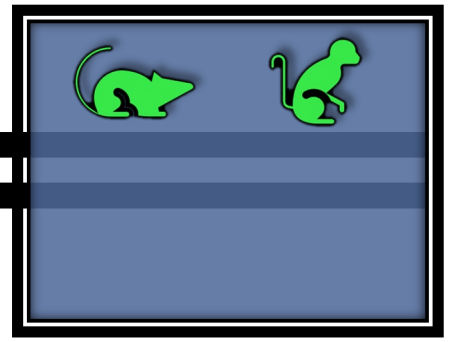


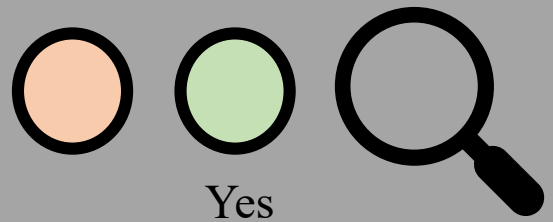
# SeqAPASS Level 1

Line of Evidence:
Primary amino acid sequence
Conserved





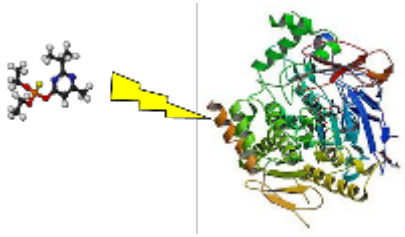


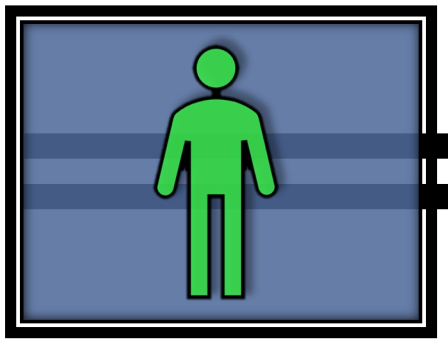


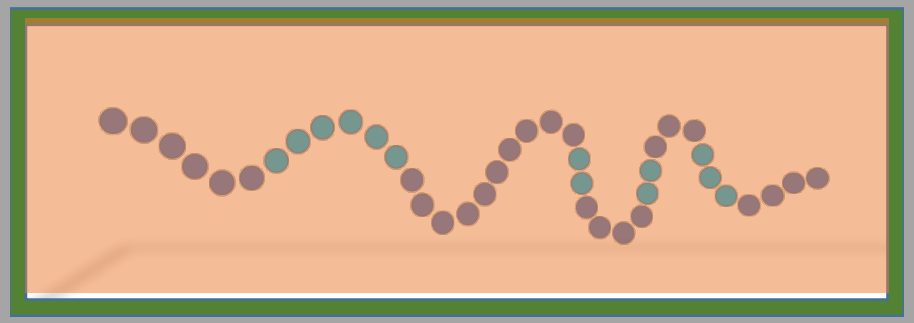
Yes

# SeqAPASS Level 1

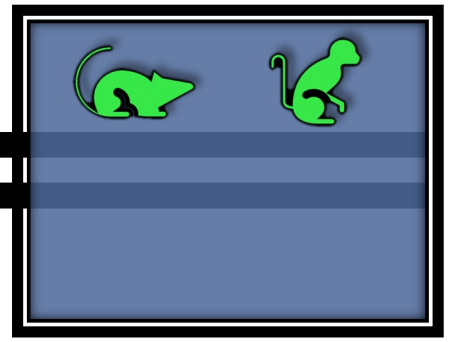
Human Protein Target

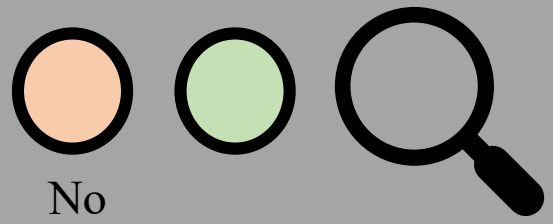




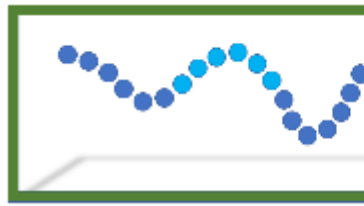


Line of Evidence:
Primary amino acid sequence
Conserved





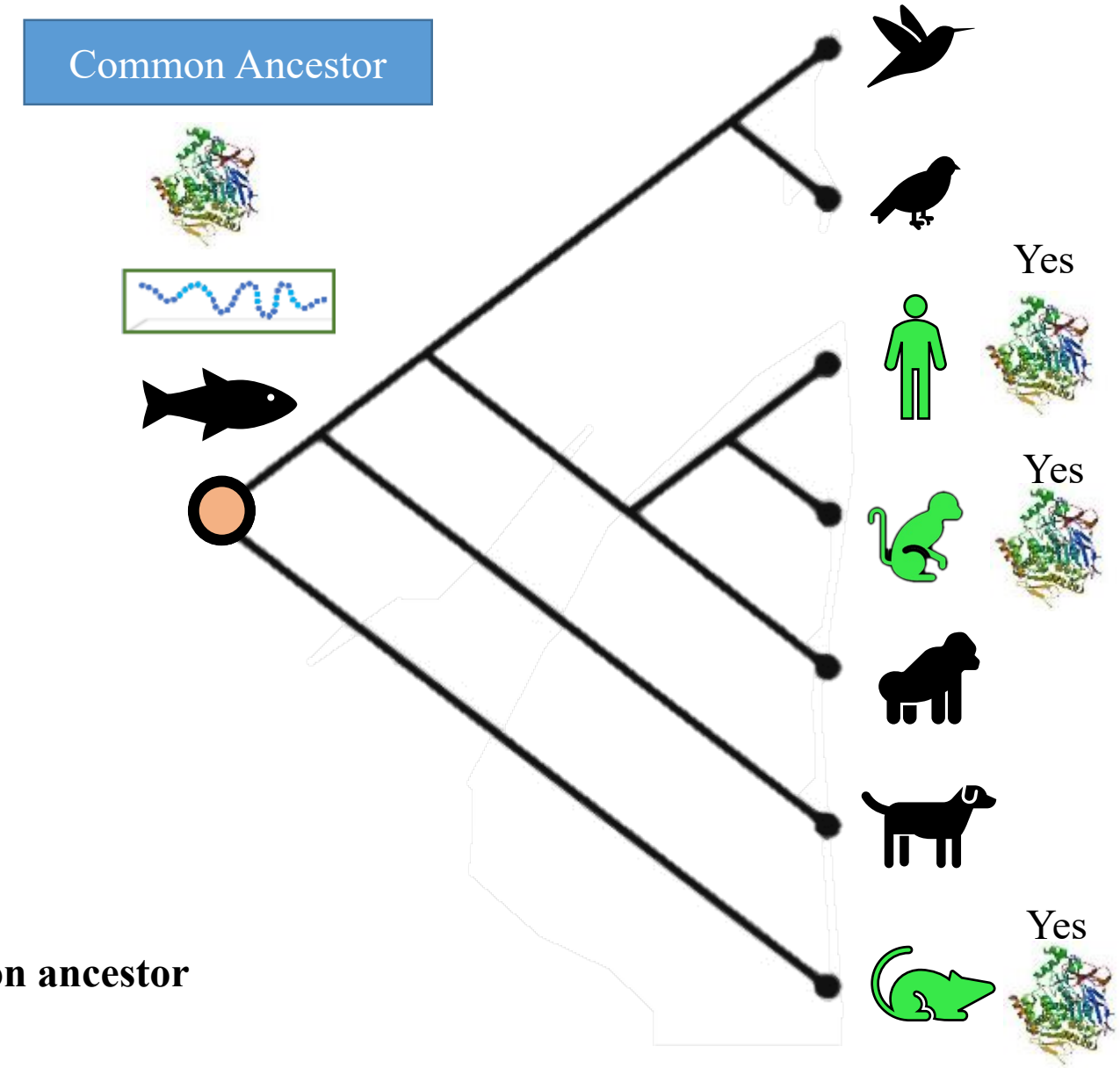
No



# SeqAPASS Level 1

## Ortholog Candidate Identification

Yes




**Proteins in different species that evolved from a common ancestor**

Typically maintain similar function

# SeqAPASS Level 1

## Ortholog Candidate Identification

No

Common Ancestor

No

# SeqAPASS Level 1

| Common Name | Ortholog Candidate | Cut-off | Percent Similarity |
|---|---|---|---|
| Human | Y | 33.15 | 100 |
| Florida manatee | Y | 33.15 | 98.8 |
| Mallard | Y | 33.15 | 82.29 |
| Rock pigeon | Y | 33.15 | 80.93 |
| Green anole | Y | 33.15 | 80.65 |
| Pacific transparent sea squirt | Y | 33.15 | 33.15 |
| Yesso scallop | N | 33.15 | 32.87 |
| Purple sea urchin | N | 33.15 | 26.05 |
| Human whipworm | N | 33.15 | 23.53 |
| Bed bug | N | 33.15 | 21.62 |

Lowest % Similarity that is still an ortholog

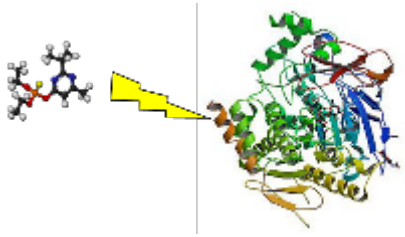
Example:

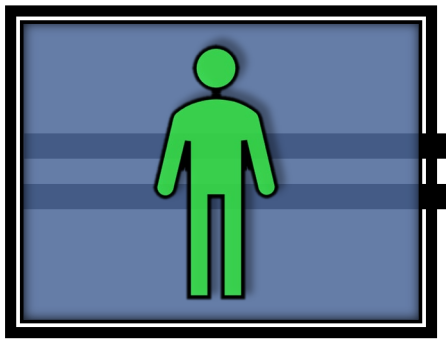
Susceptibility Cut-off: Set at 33.15

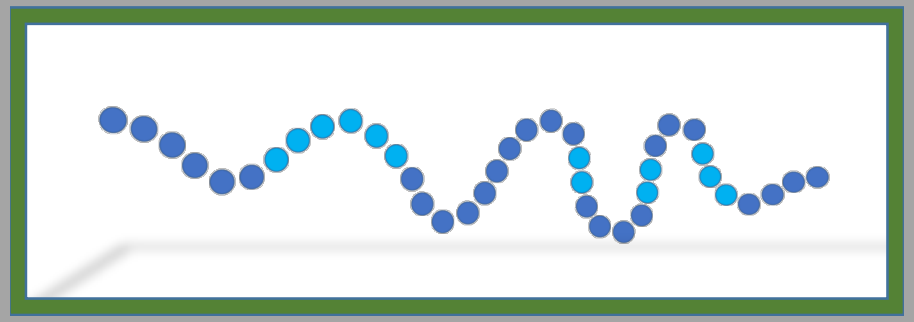
Above cut-off: More likely to be susceptible base on similar **FUNCTION**

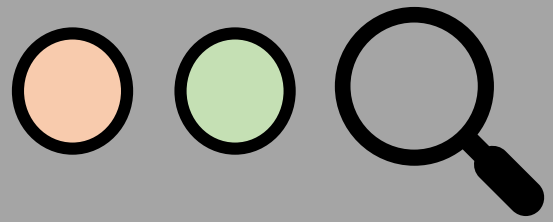
# SeqAPASS Level 1

Human Protein Target

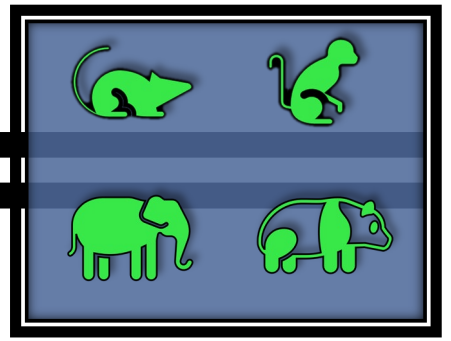








Line of Evidence:
Primary amino acid sequence
Conserved



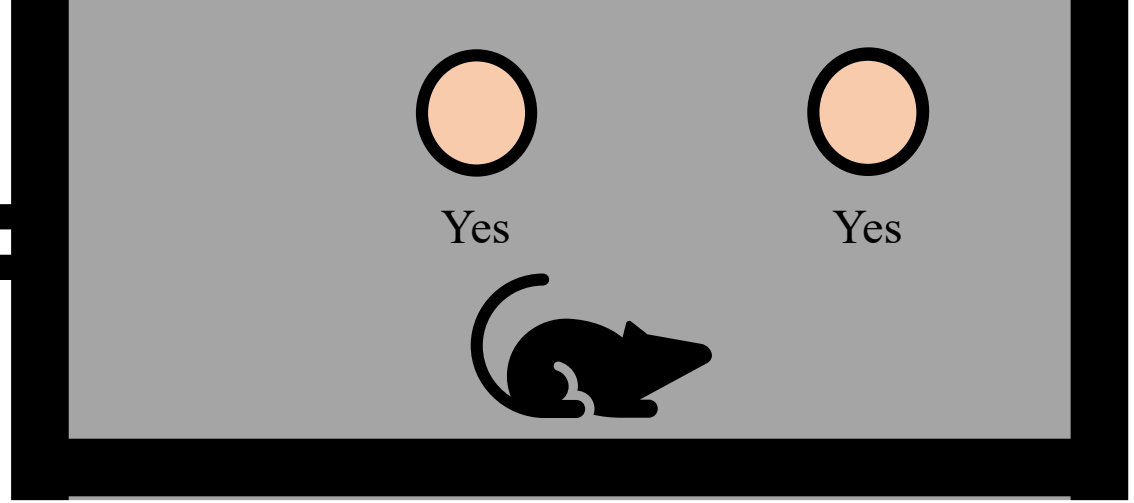
Hundreds to Thousands of Species

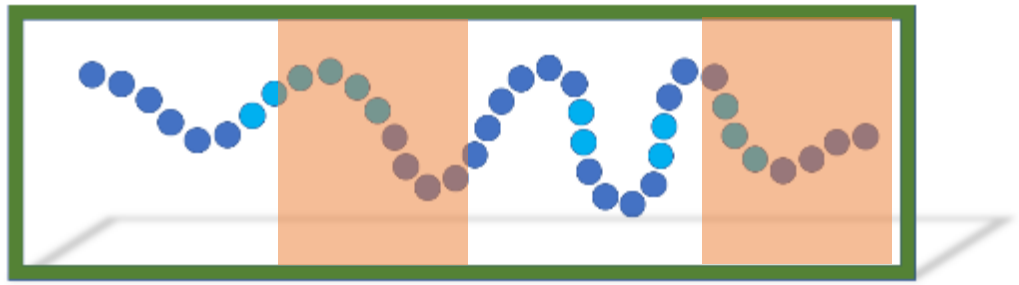
Level 2

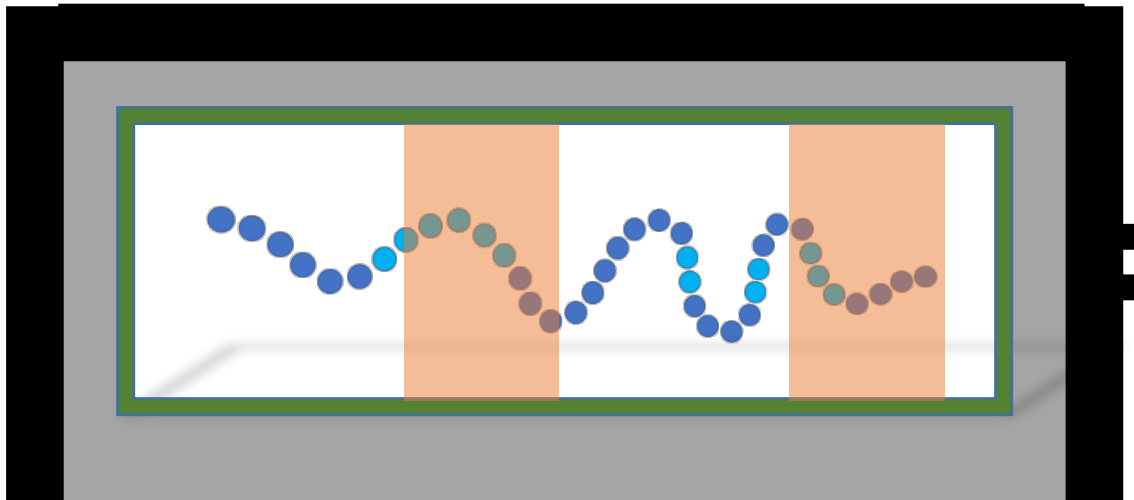
Line of Evidence:

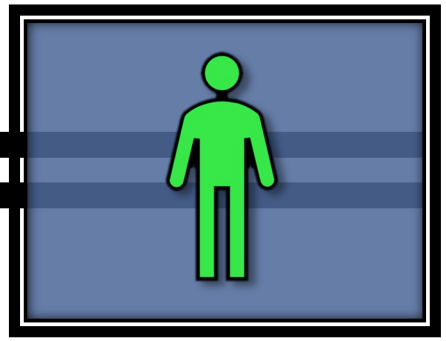
Domain

Conserved

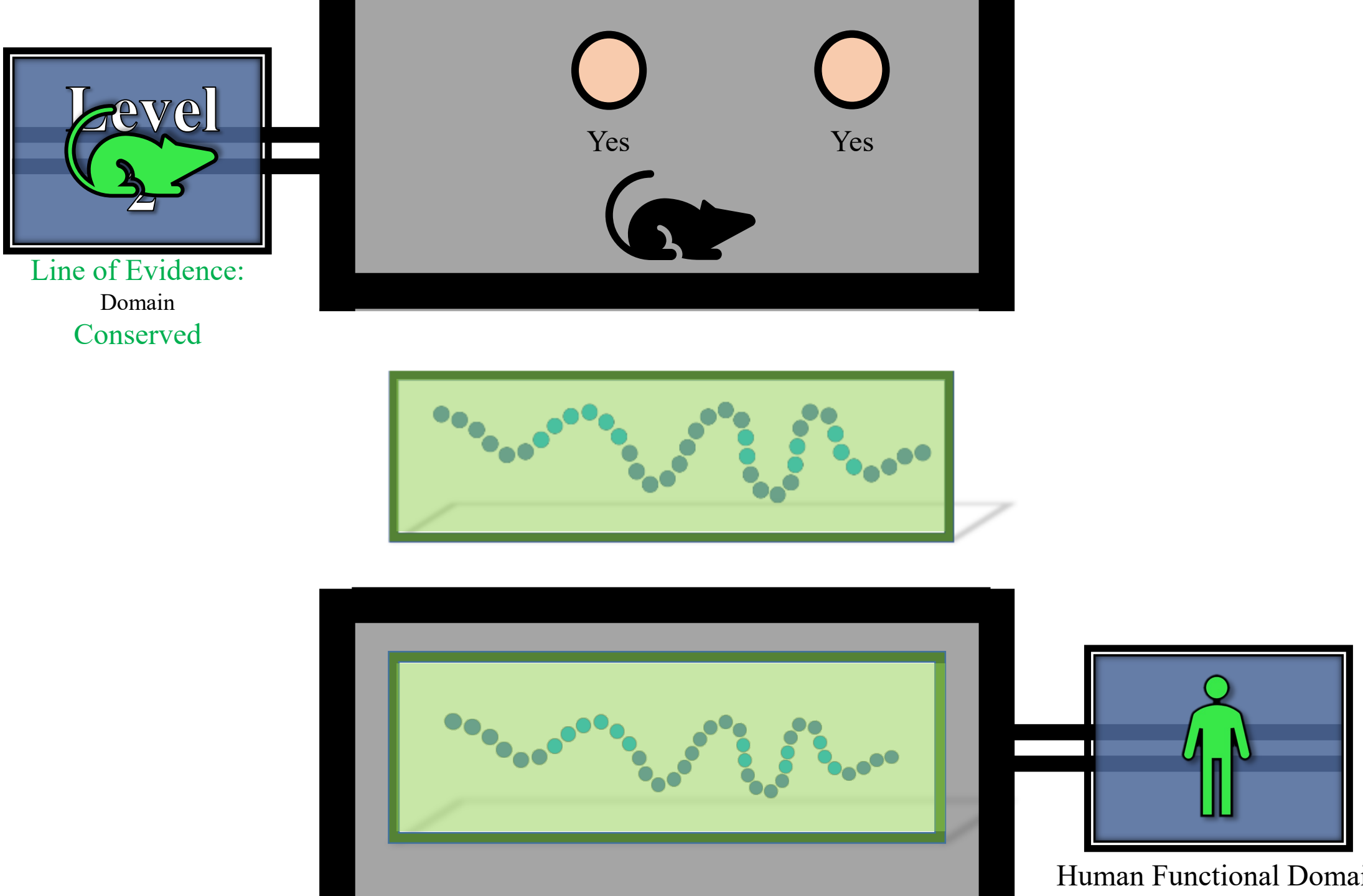






Human Functional Domain(s)

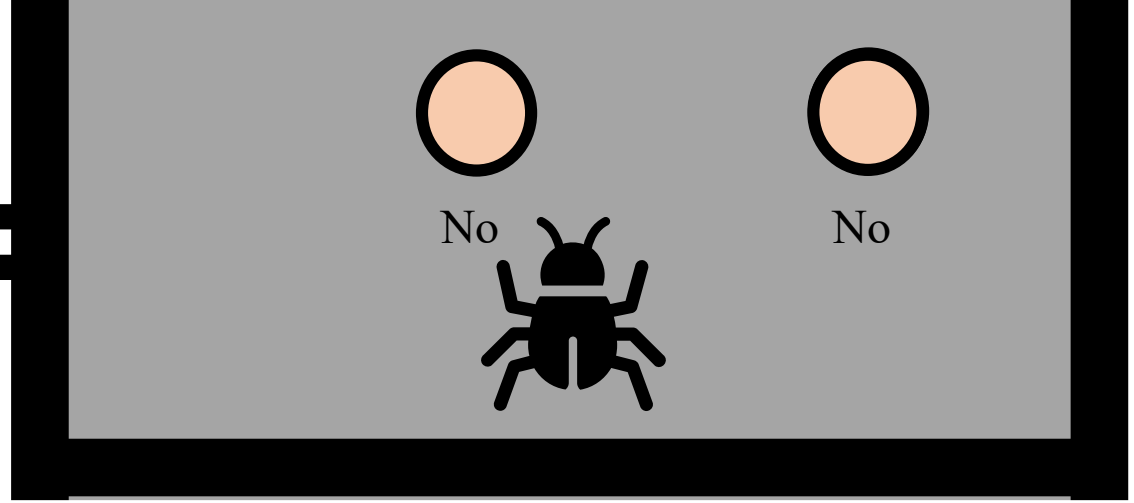

Level
2
Yes
Yes
Line of Evidence:
Domain
Conserved
Human Functional Domain(s)

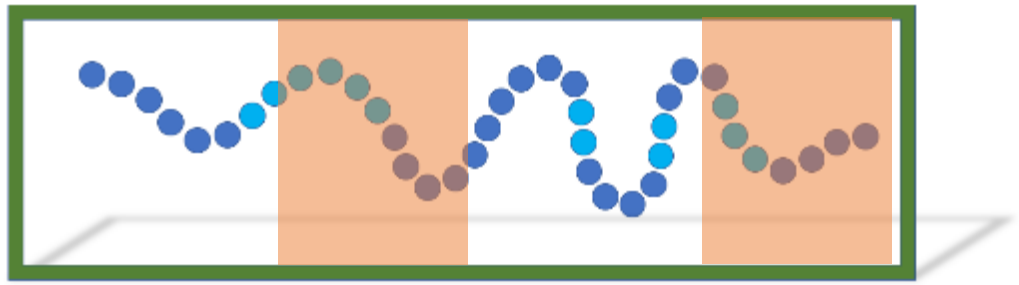
# Level 2

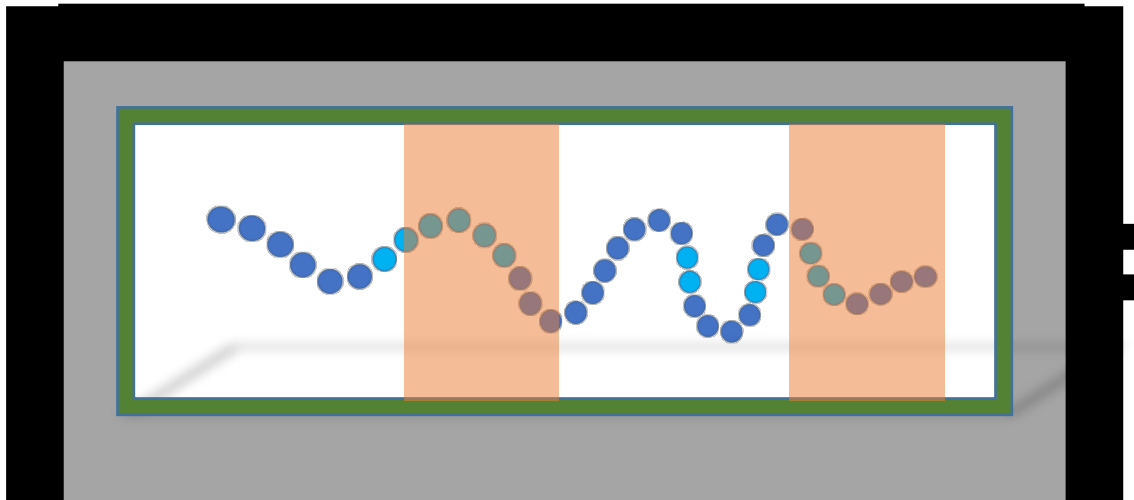
Line of Evidence:

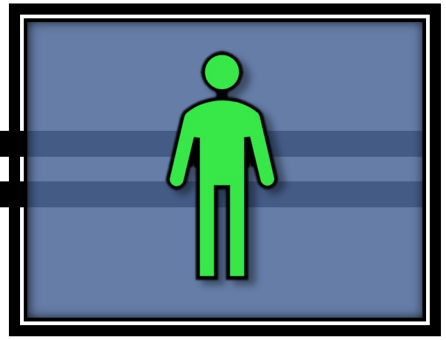
Domain

Conserved

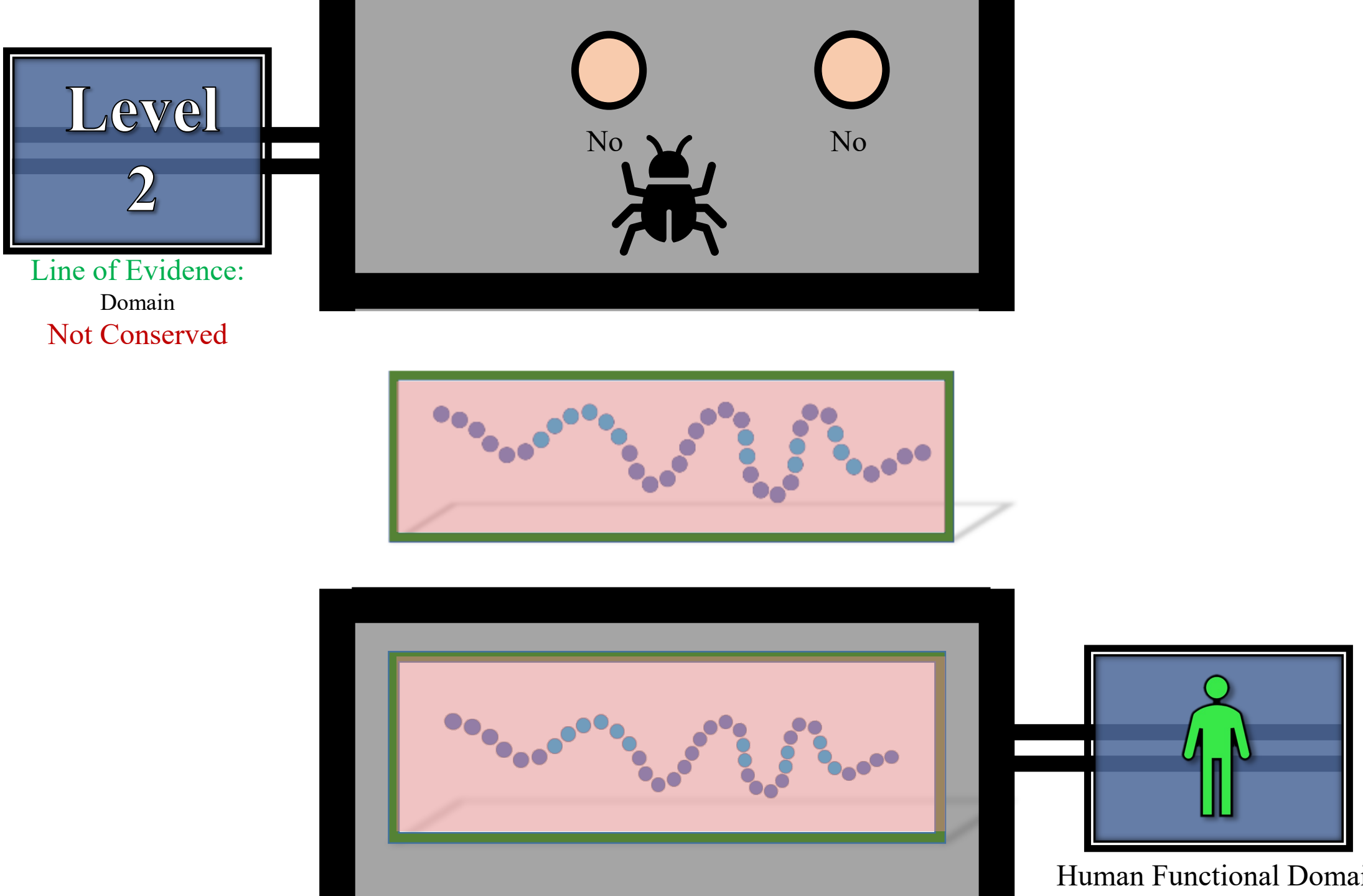


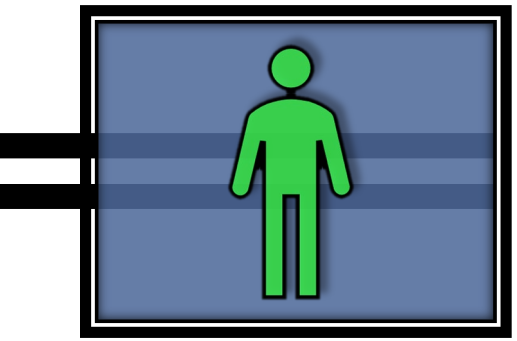





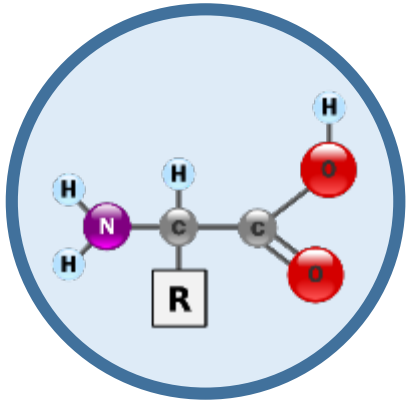


Human Functional Domain(s)

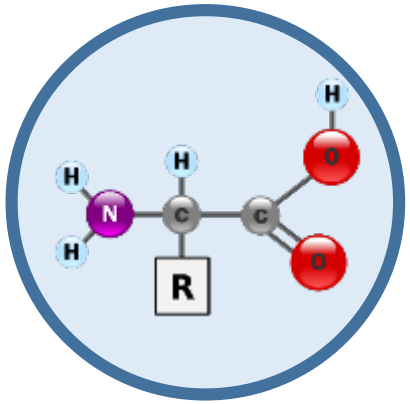

Level
2
No
No
Line of Evidence:
Domain
Not Conserved
Human Functional Domain(s)

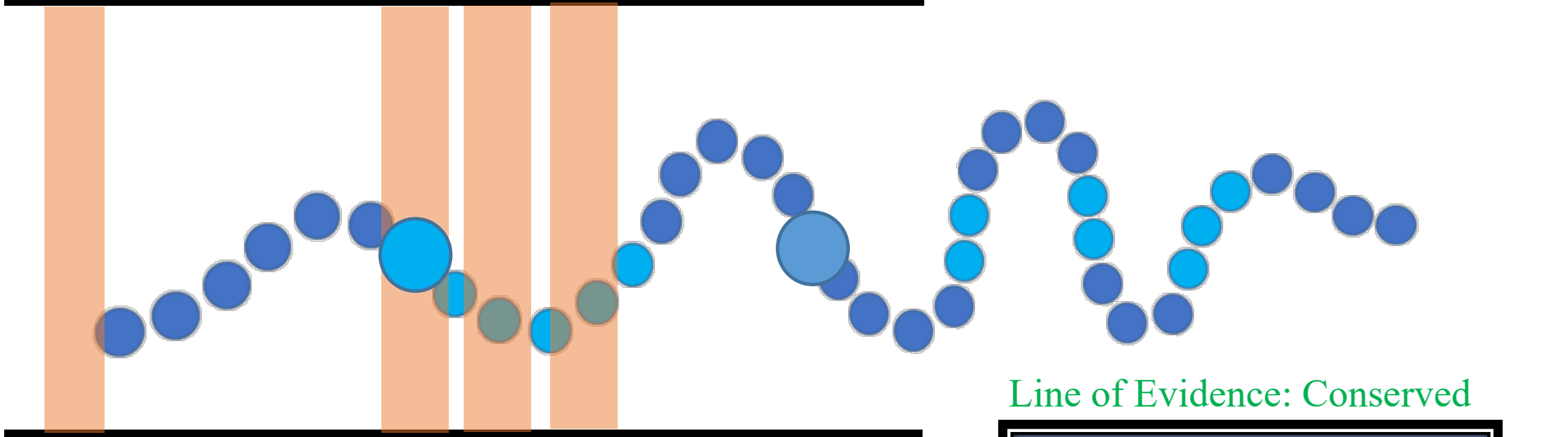


Human Critical Amino Acids

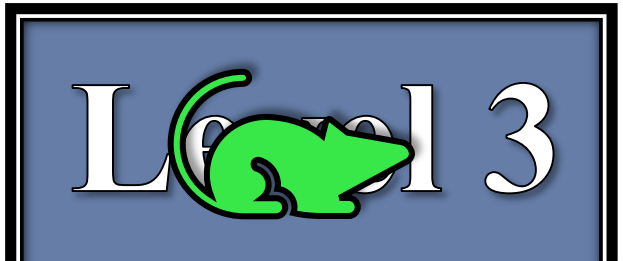


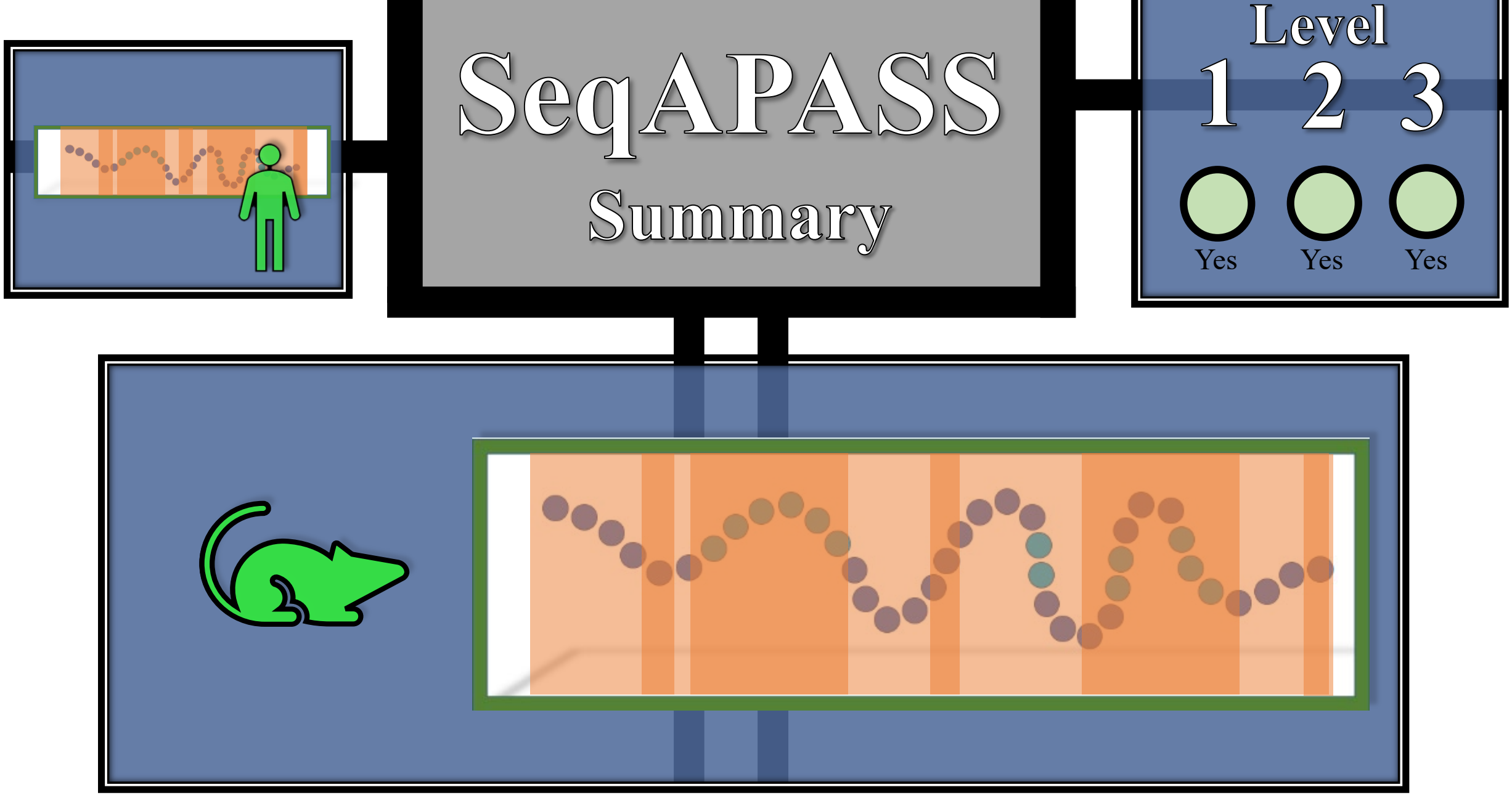


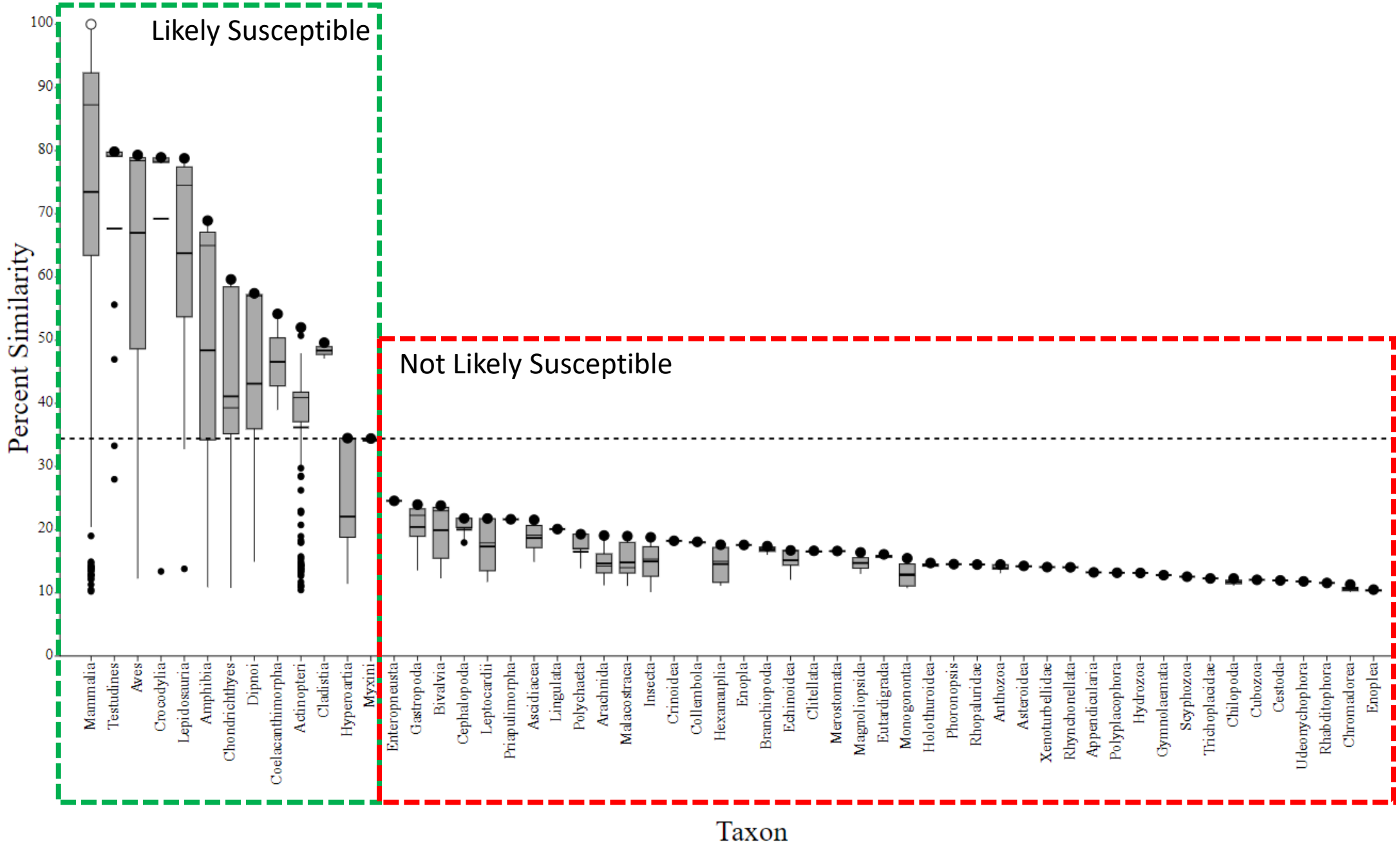



Line of Evidence: Conserved



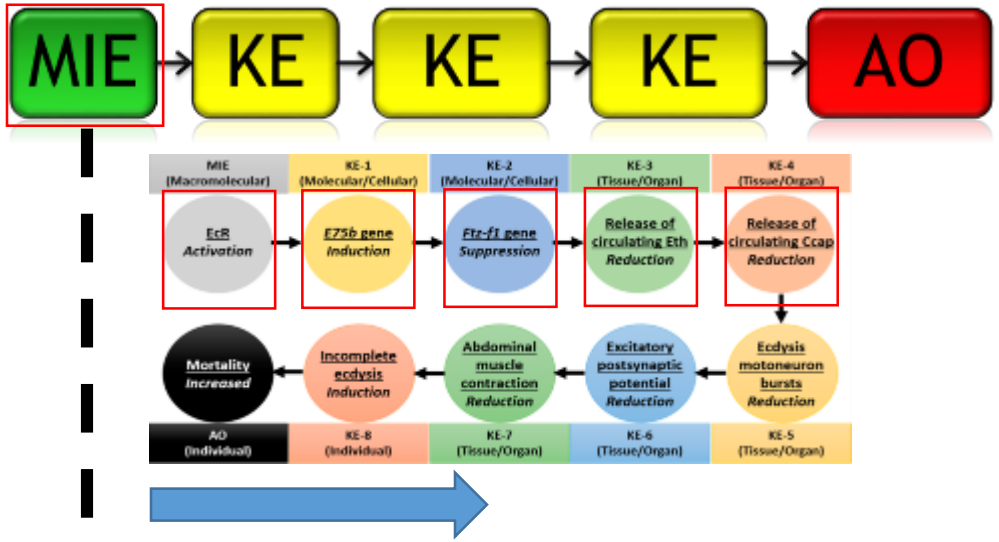



**Gather Lines of Evidence for Conservation of Protein Target:**
**Susceptibility Prediction: Yes or No**


Likely Susceptible
Not Likely Susceptible
Percent Similarity
100
90
80
70
60
50
40
30
20
10
0
Mammalia
Testudines
Aves
Crocodylia
Lepidosauria
Amphibia
Chondrichthyes
Dipnoi
Coelacanthimorpha
Actinopteri
Cladistia
Hyperoartia
Myxini
Enteropneusta
Gastropoda
Bivalvia
Cephalopoda
Leptocardii
Priapulimorpha
Ascidiacea
Lingulata
Polychaeta
Arachnida
Malacostraca
Insecta
Crinoidea
Collembola
Hexanauplia
Enopla
Branchiopoda
Echinoidea
Clitellata
Merostomata
Magnoliopsida
Eutardigrada
Monogononta
Holothuroidea
Phoronopsis
Rhopaluridae
Anthozoa
Asteroidea
Xenoturbellidae
Rhynchonellata
Appendicularia
Polyplacophora
Hydrozoa
Gymnolaemata
Scyphozoa
Trichoplacidae
Chilopoda
Cubozoa
Cestoda
Udeomychophora
Rhabditophora
Chromadorea
Enoplea
Taxon

# 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)

Taxonomic domain of applicability