Effectopedia- an open collaborative platform for AOP development and application

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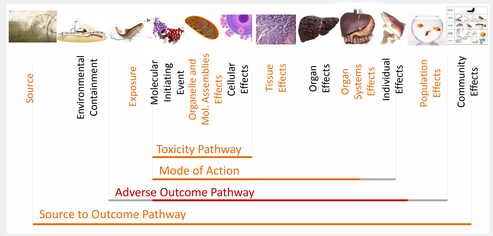
International QSAR Foundation
Effectopedia
The Online Encyclopedia of Adverse Effect Pathways

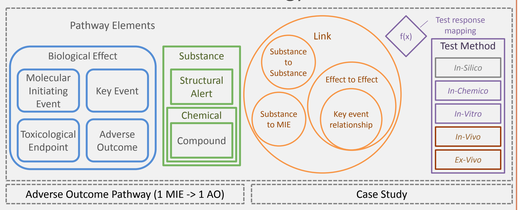
Abstract

Effectopedia is a knowledge aggregation and modeling platform designed for collaborative development and utilization of Adverse Outcome Pathways (AOPs). Aimed at a broad range of users, Effectopedia has a visually expressed modular structure which captures semantically annotated knowledge, computational models, algorithms, and supporting evidence. Knowledge is organized in nested layers. Some descriptions are stored internally (e.g. test method descriptions) and some as references to external systems (e.g. computational modules, databases). Knowledge is structured by its biological context. The context is represented as multidimensional organizational space, which can visualize AOPs against a chosen pair of dimensions (e.g. time to effect vs. level of biological organization or sex vs. life stage). The proximity of different effects and test methods in the pathway space reflects the similarities in their biological context. Thus, pathway space governs scientists with different backgrounds to establish where their knowledge belongs, and aids them in identifying the larger scope of their research and experts who might be interested in it. New contributions are immediately distributed to interested parties, keeping all information current, documented and open for discussion, whilst giving credit to original authors and reviewers. Biological responses and test methods are defined once and shared across pathways that include them. The goal of the system is to provide access to transparent executable AOPs which can be used to improve toxicity predictions by maintaining a single body of knowledge with multifaceted interfaces for users with different backgrounds, including scientists, regulators, industry, and the general public. Quantitative knowledge for two AOPs in fish (estrogen binding and aromatase inhibition mediated population reduction) and one in humans (skin sensitization) serve as proofs of concept and demonstration of the platform's utility.

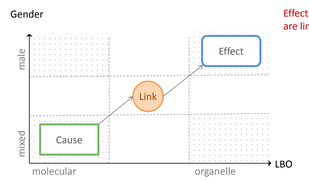
Adverse Outcome Pathways



Terminology



Visual Expression of Biological Context



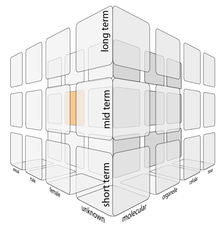
Effects at each level of observation (LOE) are linked to "causes" at lower LOEs

- Quantitative linkages include
  - Thresholds for effects
  - Dose-Response relationships
  - Response-Response relationships
- Qualitative linkages
  - Provide explanation of plausible underlying molecular mechanisms

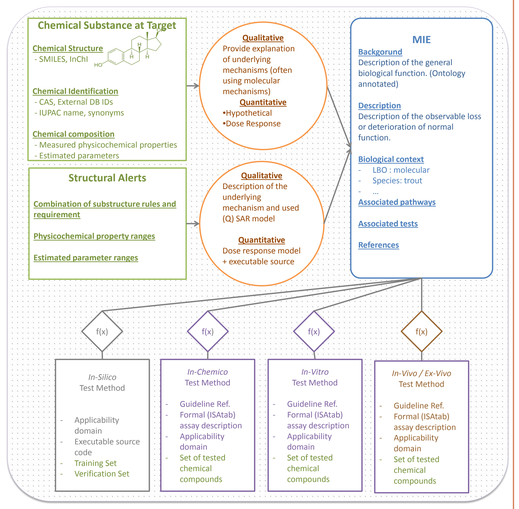
Adverse Effects are observable loss or deterioration of normal function

Pathway Space

- Pathway space defines the biological context in which effects can be explained/described by specialists.
- Pathway space is multidimensional and requires the knowledge of disciplines that do not normally collaborate
  - Life stage
  - Taxonomy
  - Gender
  - Time to effect
  - Level of biological organization
  - ...
  - User defined
- Effect definitions are provided just once and shared across all pathways that include them.
- Shared effects become common nodes in the network of connected pathways stored in Effectopedia.

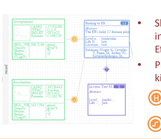


Pathway Elements



Knowledge Representation Layers

Visual Summary Flow Chart



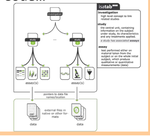
- Show the pathway structure in chosen projection of Effectopedia space
- Provide visual clues of what kind of details are available
  - Hypothetical – no support evidences
  - Dose response data available

Summary Information and Interpretation

- Provide separate structured pages for each type of pathway element shown in the visual diagram
- The level of provided details is similar to the one given in journal publication

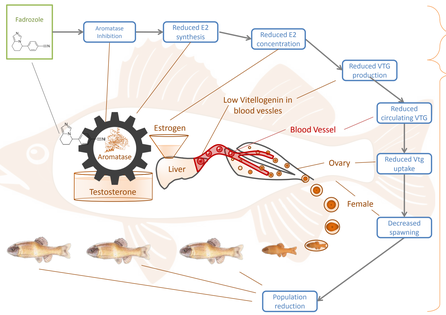
Raw Data, Model Equations, Source Code…

- Detailed metadata description (ISATab compatible) of test methods
- *In silico* model descriptions / equations / source code
- References to external systems and modules



```
[Override]
public double value(double x)
{
  double logKn = logEC50 + (1 / Hillslope) * Math.Log10(Math.pow(2, (1 / symmetry))) - 1);
  double numerator = top - bottom;
  double denominator = Math.pow(1 + Math.pow(10, ((logKn - x) * Hillslope)), symmetry);
  return Bottom + (numerator / denominator);
}
```

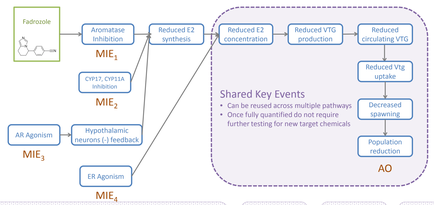
Aromatase Inhibition Leading to Population Reduction

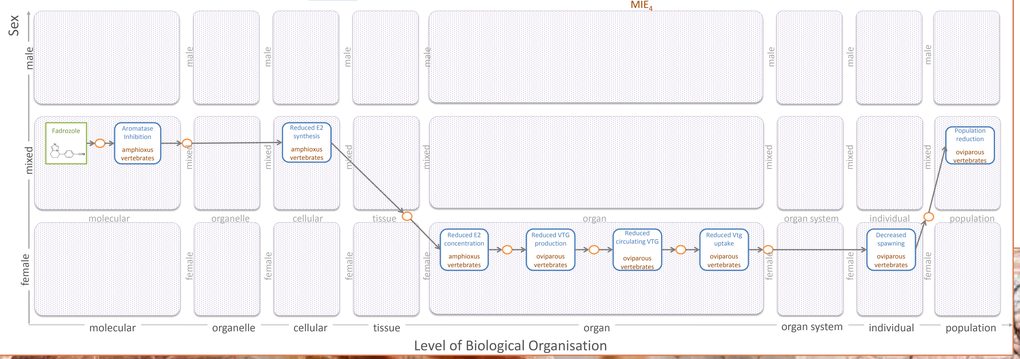


Taxonomic Relevance

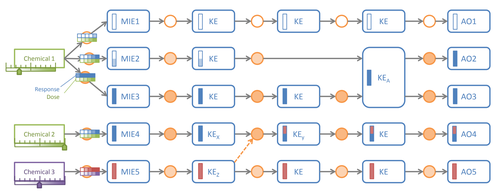
- Aromatase is common between amphioxus and vertebrates
- Vitellogenesis potentially applicable to oviparous vertebrates

Other ways to cause reduced E2 concentration





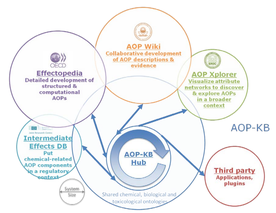
Pathway Networks



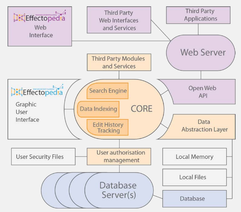
- Vulnerability analysis (e.g. Chemical 1 initiate AOP1 at lower, AOP2 at medium and AOP3 at high concentrations)
- Toxicity of mixtures (e.g. KE_B modulate the processes linking KE_A to KE_n in such a way that only combined exposure to Chemical 2 and Chemical 3 can produce AO4)
- Identify key events that are common across multiple pathways (e.g. $KE_{2.}$) and prioritize the development of robust low cost non animal alternative test methods.
- Identify tests that are required but rarely used in decision making and risk assessment processes.

Integration with AOP-KB

- Conceived at the International QSAR Foundation, Effectopedia has been in development since 2006, source code published under GPL v3.0 in 2008, pre alpha until 2010, multiple alpha releases since 2010
- Since Feb 2014 Effectopedia is developed at OECD, Paris as part of AOP-KB project in close collaboration with EC, JRC and US-EPA



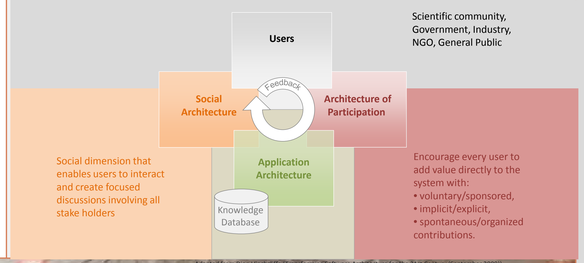
Software Architecture



Effectopedia has modular architecture which allows different usage patterns.

- Gray shaded boxes represent modules that can be executed on local machine as part of standalone application.
- Orange shaded modules provide the core Effectopedia functionality. They have mixed usage: as server side and / or as application embedded modules.
- Blue shaded modules provide access to database (local or remote) functionality.
- Purple shaded modules provide web interface to the Effectopedia core functionalities.

Architecture of Participation



Adapted from Dion Hinchcliffe ("Transforming Software Architecture for the 21st Century (September 2009))

Applications in Toxicology

- Collate the descriptive mechanistic information and quantitative potency data for well-studied chemical case studies which have been spread across the many disciplines by our growing specializations.
- QSAR models describe possible molecular interactions which can be linked to all known molecular initiating events and AOPs that lead to the adverse outcomes being assessed.
- Integrating *in-silico* models to AOPs permits large lists of untested chemicals to be screened and prioritized for their potential to cause specific hazards and generate hypotheses for chemical specific testing requirements.
- Precisely define the context in which observations are made to allow the unique behaviors of thousands of chemicals to be interpreted for many species and test conditions.

Effectopedia as a Tool for AOP Development

- Effectopedia approach for delineating AOPs is visual and semantic – aiming to organize information in custom build reusable components.
- Designed to maintain **live version controlled AOPs**
  - Containing all the relevant information – descriptions, experimental data and executable models in one place;
  - Always open for review and collaboration;
  - Decoupled editing and review/approval processes;
  - Citable, traceable and fully credited;
  - Use the same system/standard for private and public data;
  - Recognized as publications? (when pier review system is established).
- Alpha release available on effectopedia.org (and SOURCEFORGE.NET®)
- Quantitative features are the current development focus – early adopters encouraged to join us in building better platform.

Acknowledgments

Effectopedia appreciates the generous support provided by

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