

ICE Tools for Aligning Assay Endpoints to Adverse Outcome Pathways

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Toward Non-animal Methods to Address Chemical Safety

Implementing non-animal approaches in regulatory toxicology testing poses challenges

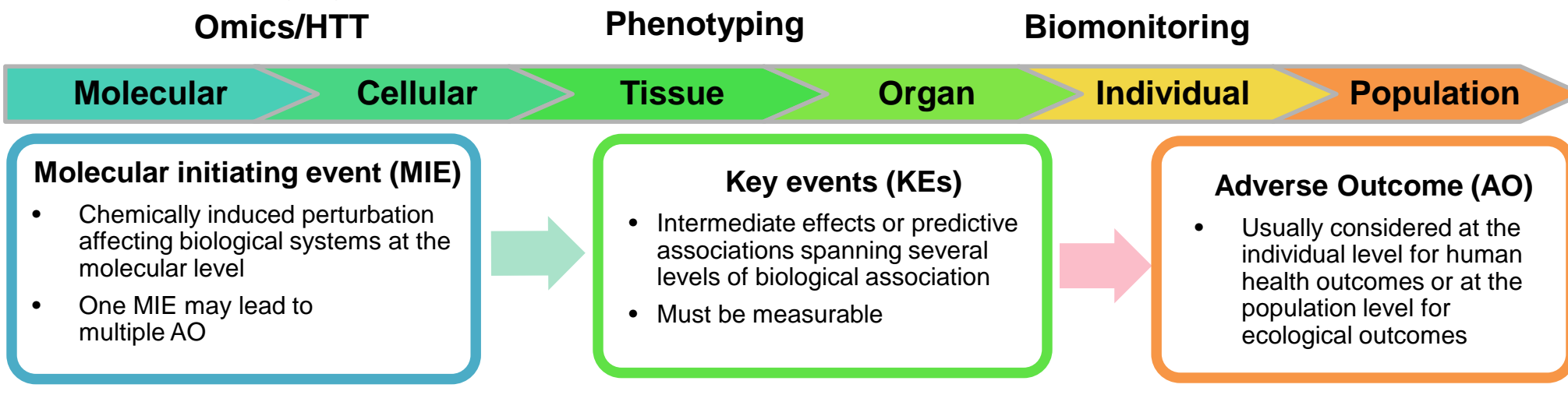
The recent U.S. roadmap (<https://ntp.niehs.nih.gov/go/natl-strategy>) for establishing new approaches to evaluate the safety of chemicals and medical products described three challenges to implementing non-animal approaches:

- Understanding end-user needs
- Defining context of use for non-animal approaches
- Establishing confidence in these approaches



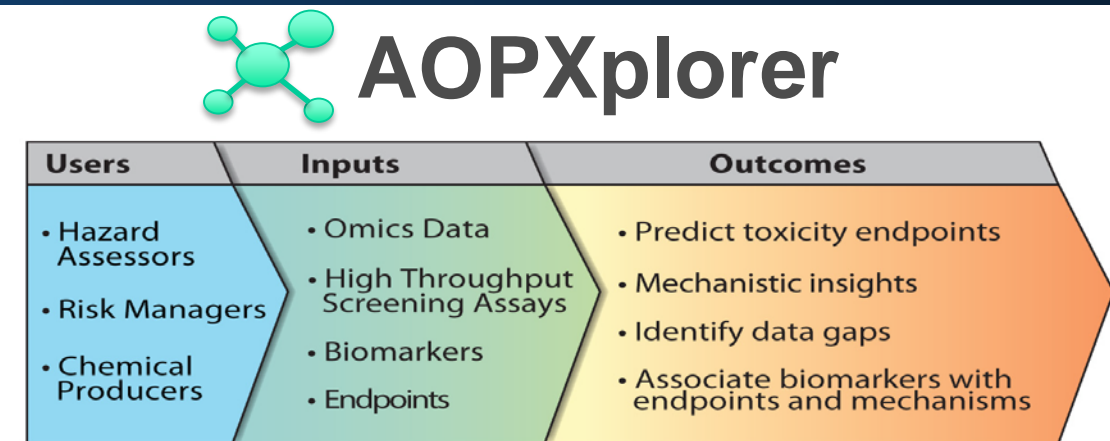
Adverse outcome pathways (AOPs) help address these challenges

- Adverse outcomes (AOs) relate to regulatory endpoints
- Key events (KEs) describe the critical biological interactions leading to the AO
- Assays and non-animal methods, including high throughput testing (HTT), can be developed targeting the KEs
- Assays relevant to the biology defined by the AOP can be integrated into defined approaches
- Tools and resources going from assay to KE are needed to help facilitate this process



AOPXplorer

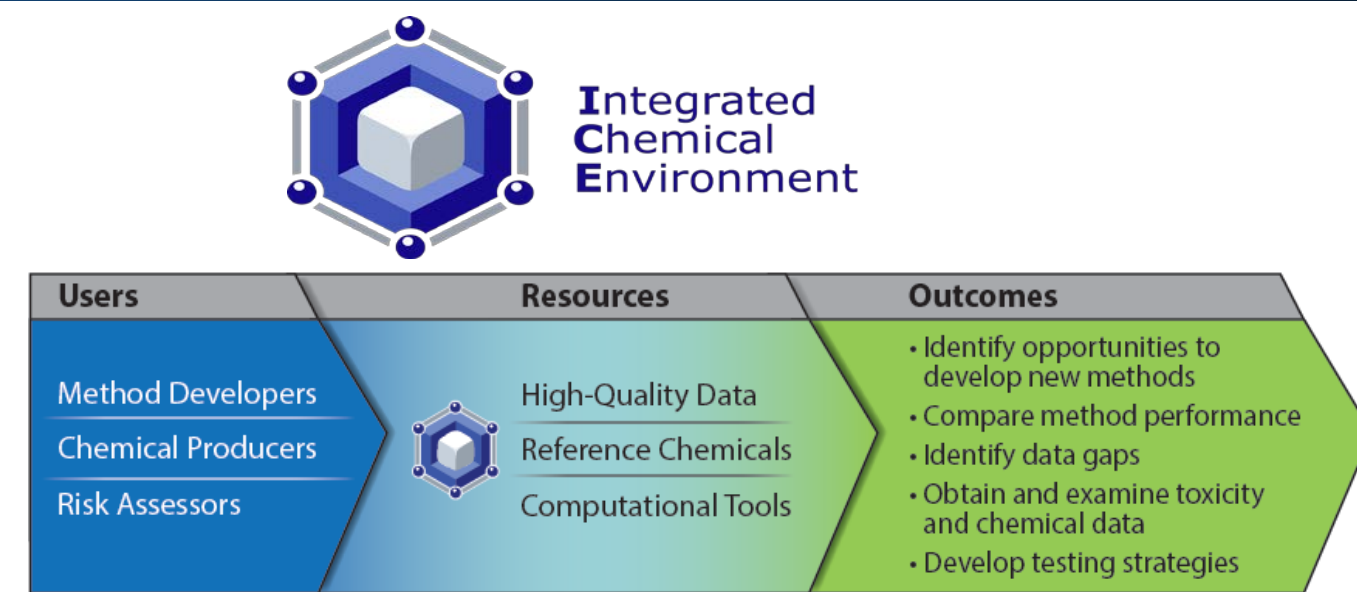
- A plugin for the open source network visualization software Cytoscape (www.cytoscape.org) that allows visualization of users' data onto AOP networks (AOPNs)
- Enables overlaying of high-throughput screening and omics data onto AOPNs
- Supports mechanistic causal analysis
- Available at <http://apps.cytoscape.org/apps/aopexplorer>



Integrated Chemical Environment

The National Toxicology Program's Integrated Chemical Environment (ICE) is a data resource that includes:

- In vivo, in vitro, and in silico data from NICEATM and partners, curated and formatted to support exploration and use in computational workflows
- Reference chemical lists (for a given assay or endpoint) and associated data
- Computational tools and workflows



What can ICE do?

- ICE supports:
- Data integration: bringing together data from different endpoints and experiments for comparison and exploration
 - Results exploration: dynamic, graphical exploration of query results with capability to refine
 - Data accession: obtaining reference chemical lists and supporting data
 - Data analysis: downloadable computational tools and workflows to support test method assessment and development

Need for an Ontology

- Ontologies facilitate organization of information so it can be easily shared and reused by machines.
- An ontology incorporating biological context, assay context, and AOP information is necessary to link the data to the tools that work on different data types.
- BioAssay Ontology (BAO, <http://bioassayontology.org>) is a commonly used ontology to describe screening assays.
 - Does not include coverage for in vivo and low throughput assays
- AOP ontology describes key event relationships and is part of AOPXplorer.



ICE Ontology and AOP Mapping

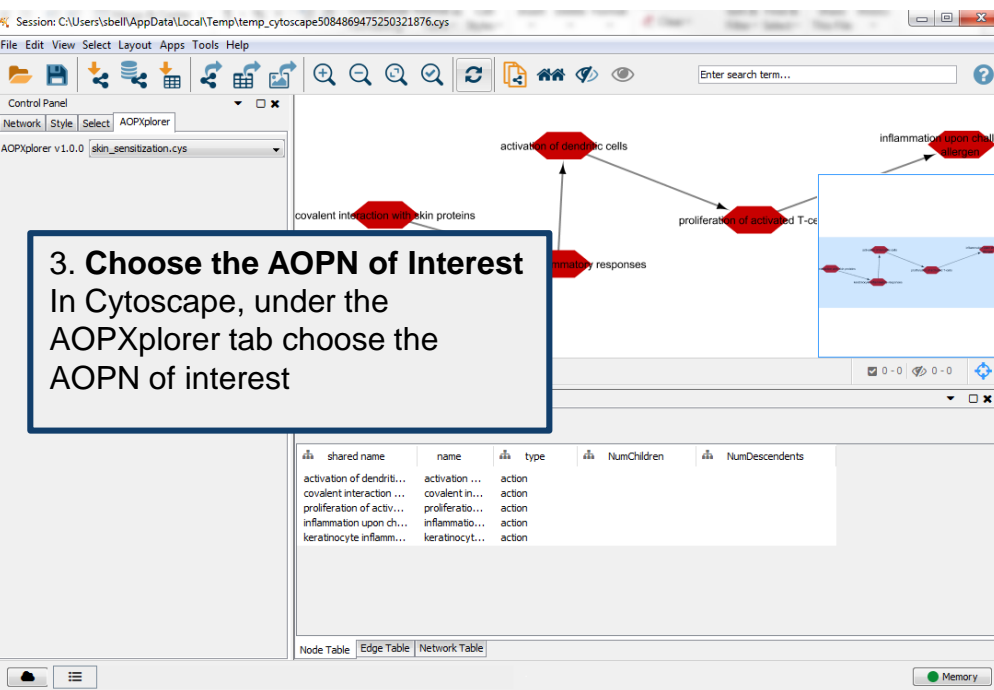
ICE Ontology allows alignment of ICE assays with key events by:

- Adding ontological support for in vivo and low throughput assays
 - Extends BioAssay Ontology
- Complementing the AOP ontology and facilitating AOP mapping of ICE data
- Links assays to toxicity endpoints used by regulators

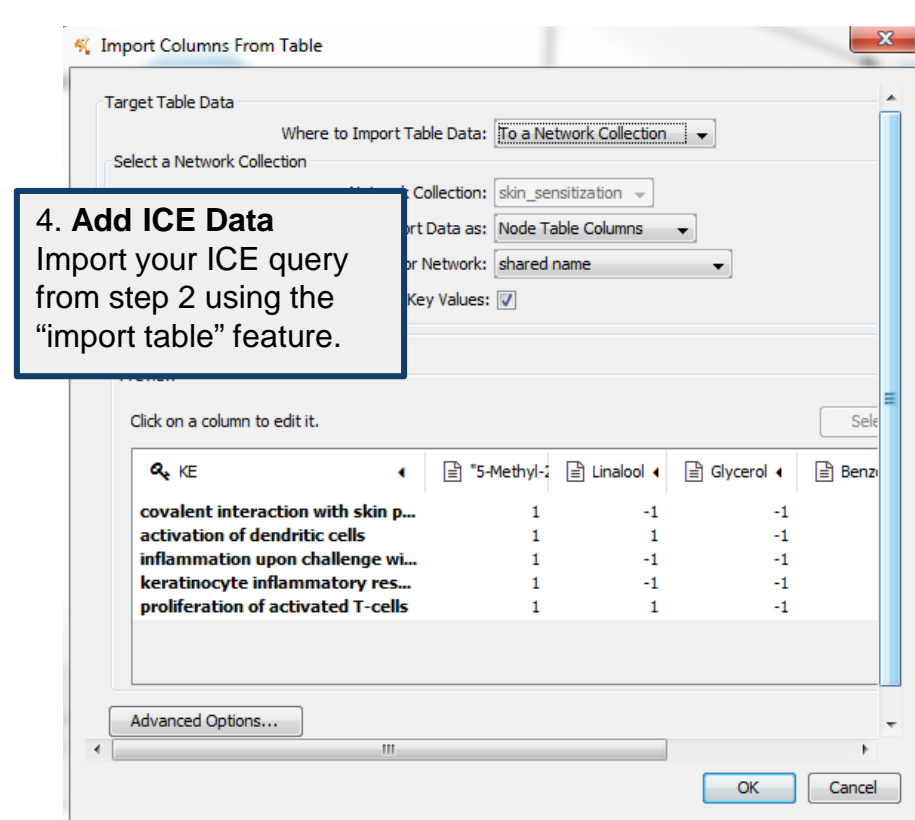
Overlaying of ICE data onto AOPNs

This series of images gives a high-level overview of how to go from ICE query to an AOPN view in AOPXplorer. Look for tutorials and within-ICE support coming soon.

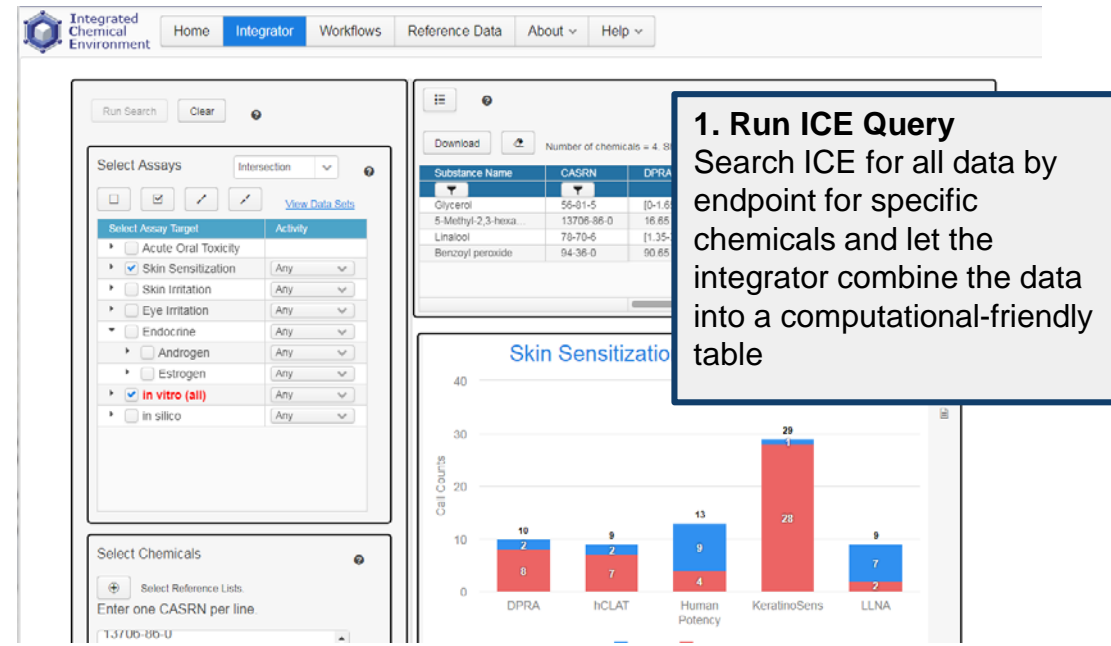
```
1: # ICE to AOP
2: title: "ICE to AOP notebook"
3: output: html_notebook
4:
5: # ICE to AOP
6: Author: Shannon M. Bell
7: Affiliations: Integrated Laboratory
8: Date: 8/20/2017
9:
10: ## Introduction
11: The Integrated Chemical Environment
12: point to data relevant to chemical
13: tests, adverse outcome pathways (AOP)
14: leading to some adverse outcome. ICE
15: can be formatted for display in
16: [AOPXplorer] (http://apps.cytoscape.org/aopexplorer)
17: or [Cytoscape] (http://www.cytoscape.org/).
18:
19: ## Getting started
20: Run a query in the ICE Integrator and export the full observation endpoint details mode
```



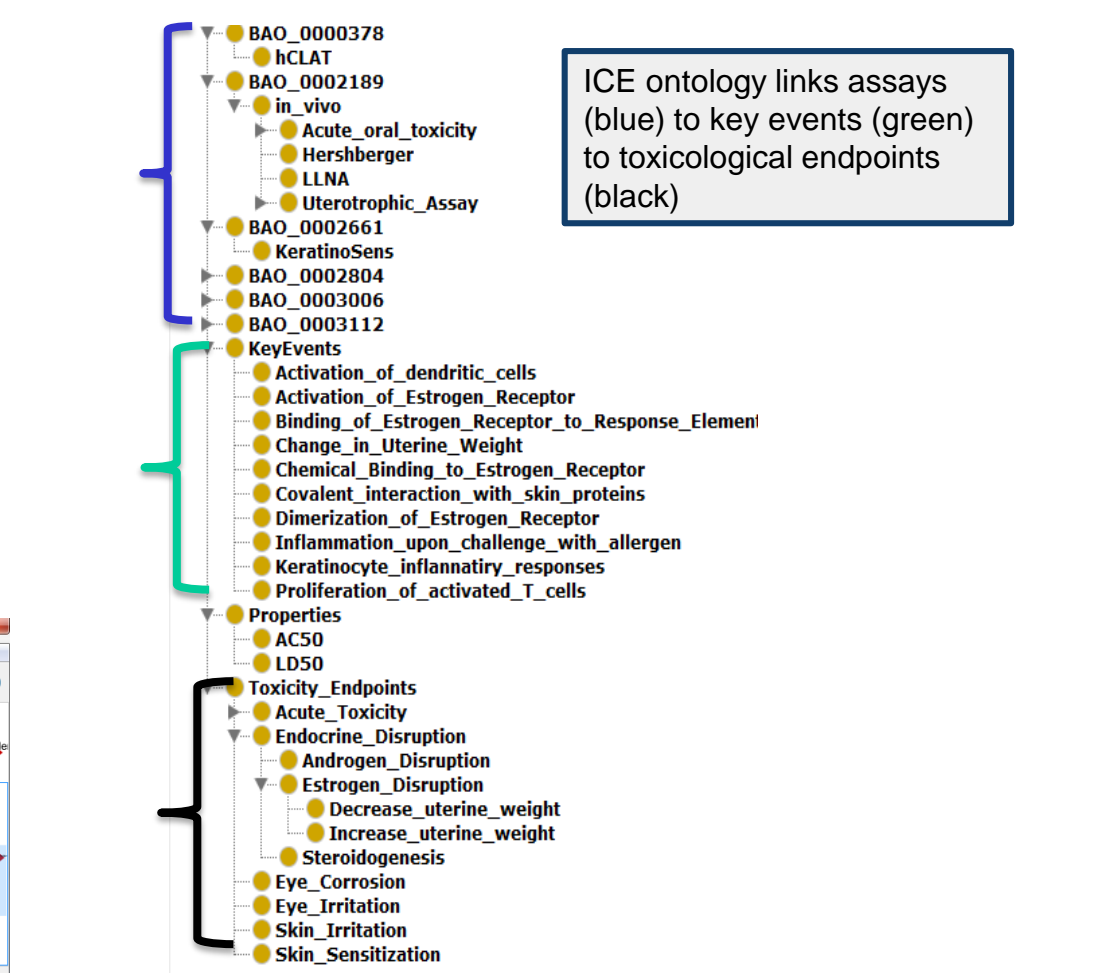
3. Choose the AOPN of Interest
In Cytoscape, under the AOPXplorer tab choose the AOPN of interest



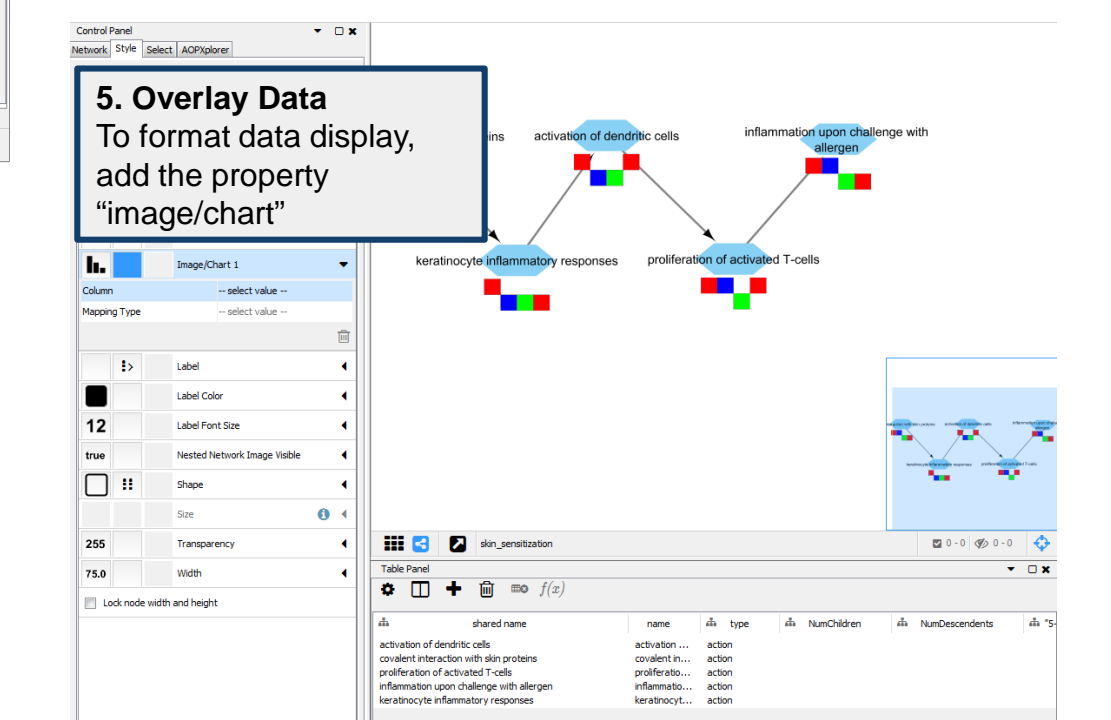
4. Add ICE Data
Import your ICE query from step 2 using the "import table" feature.



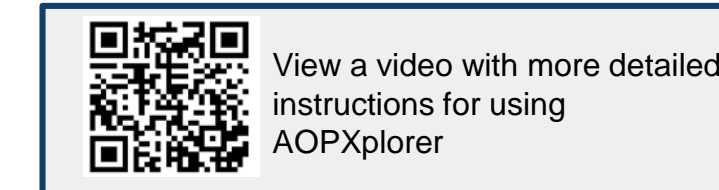
1. Run ICE Query
Search ICE for all data by endpoint for specific chemicals and let the integrator combine the data into a computational-friendly table



ICE ontology links assays (blue) to key events (green) to toxicological endpoints (black)



5. Overlay Data
To format data display, add the property "image/chart"

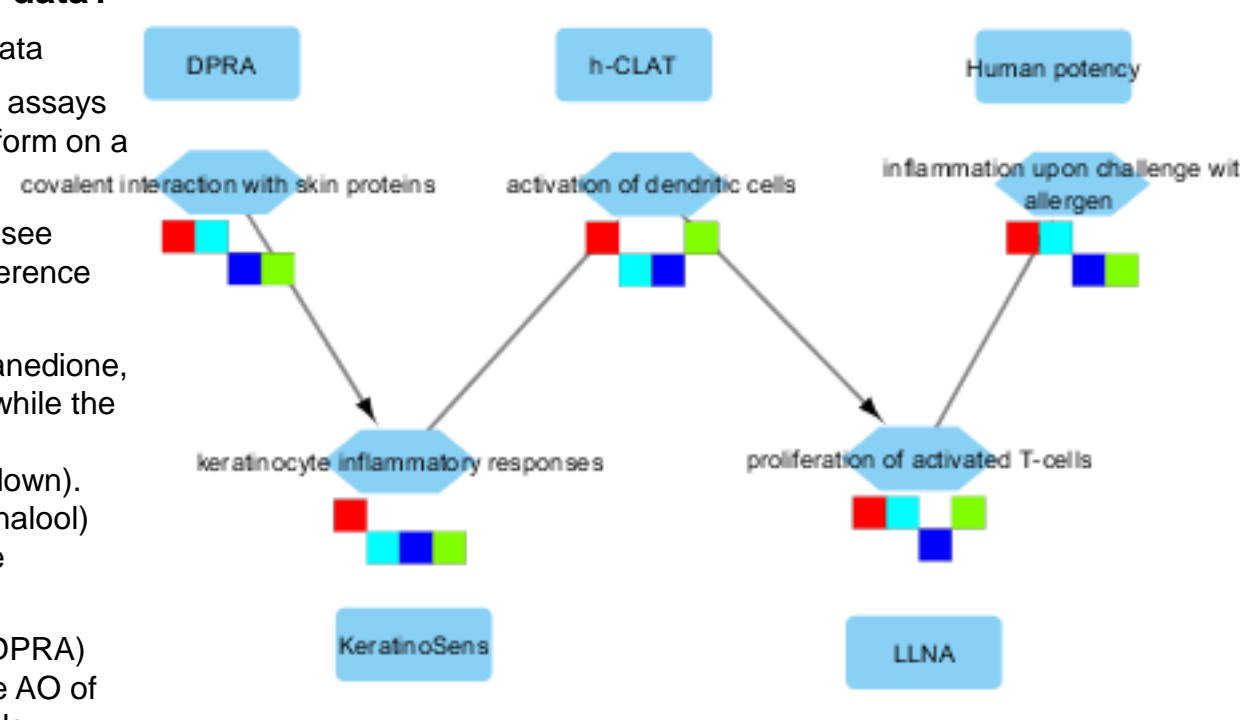


Case Studies

Exported ICE queries can be easily uploaded into Cytoscape for use with AOPXplorer. Below are case studies to illustrate questions one can ask with data from ICE (or other sources). The nodes along the AOPNs are KEs; the final KE is the AO.

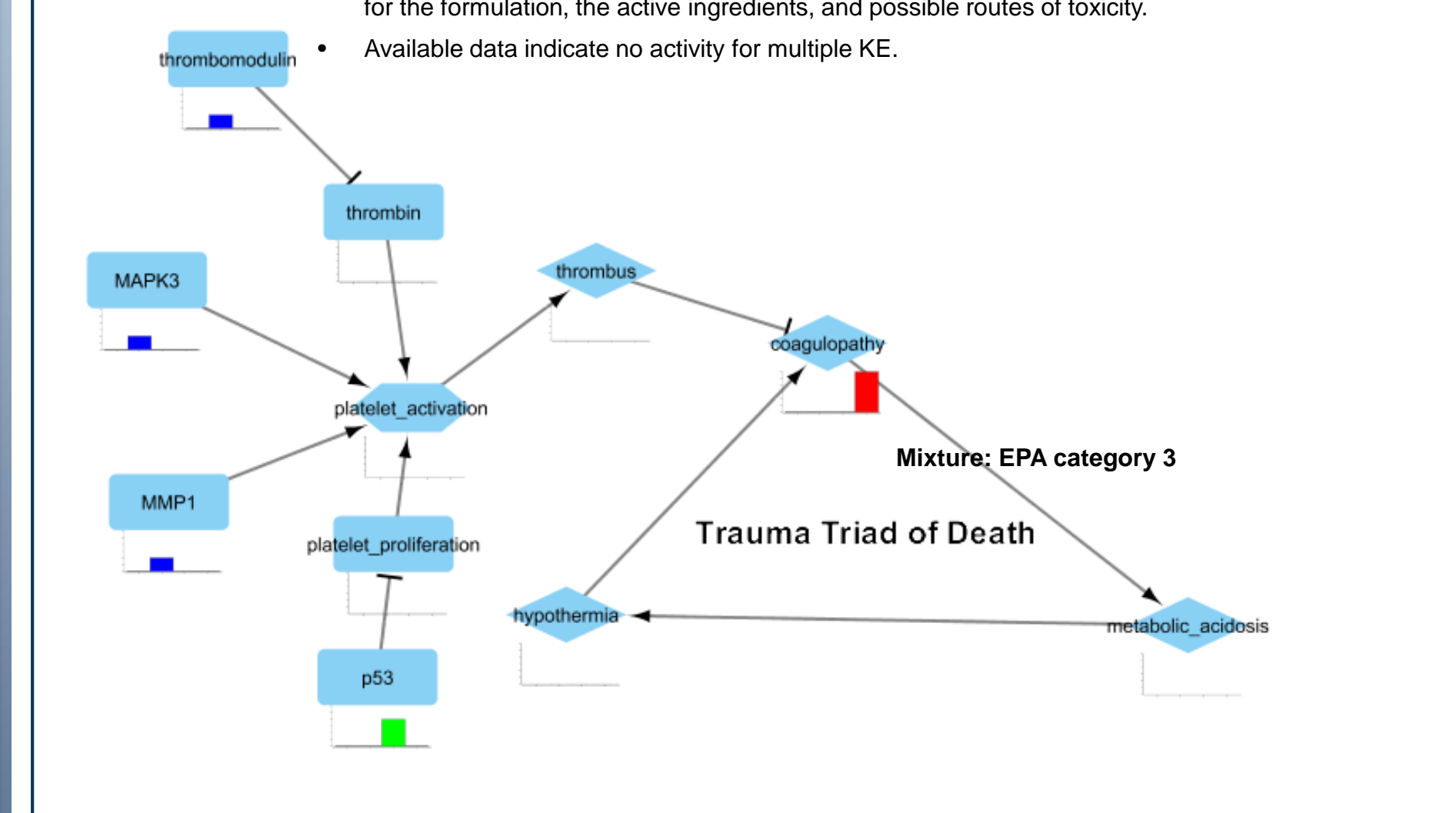
What is the concordance of my data?

- Example using skin sensitization data
- Hexagons are KEs, rectangles are assays that align with each KE and can inform on a chemical's activity (squares).
- Overlay query results on AOPN to see where there is concordance or difference between assays and chemicals.
- Red compound (5-methyl-2,3-hexanedione, a sensitizer) is always active (up) while the dark blue compound (glycerol, a nonsensitizer) is always inactive (down). Chemicals represented by cyan (linalool) and green (benzoyl peroxide) have mixed responses.
- Easy to identify assays (example DPRA) that give consistent results with the AO of human potency across all chemicals.



How do components relate to overall toxicity?

- Example considering a formulation containing propiconazole, tebuconazole, and imidacloprid
- Each color represents results from a different active ingredient in the formulation (EPA Category III for acute systemic toxicity). The formulation contains propiconazole (blue), tebuconazole (green), and imidacloprid (no data), the formulation data is also included in red; height of the colored bars indicate magnitude of the effect.
- Overlaying available ICE data on an AOPN can provide insight as to the relevance of the AOPN for the formulation, the active ingredients, and possible routes of toxicity.
- Available data indicate no activity for multiple KE.



Contact Us

Access ICE

ICE is maintained by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Want to explore ICE? Scan the QR code to the right or go to the ICE landing page at <https://ice.ntp.niehs.nih.gov>



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Read More About ICE!

Bell SM, Phillips J, Sedykh A, Tandon A, Sprinkle C, Morefield SQ, Shapiro A, Allen D, Shah R, Maul EA, Casey WM, Kleinstreuer NC. 2017. An Integrated Chemical Environment to support 21st century toxicology. Environmental Health Perspectives. DOI 10.1289/EHP1759

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