ICE Tools for Aligning Assay Endpoints to Adverse Outcome Pathways

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Toward Non-animal Methods to Address Chemical Safety

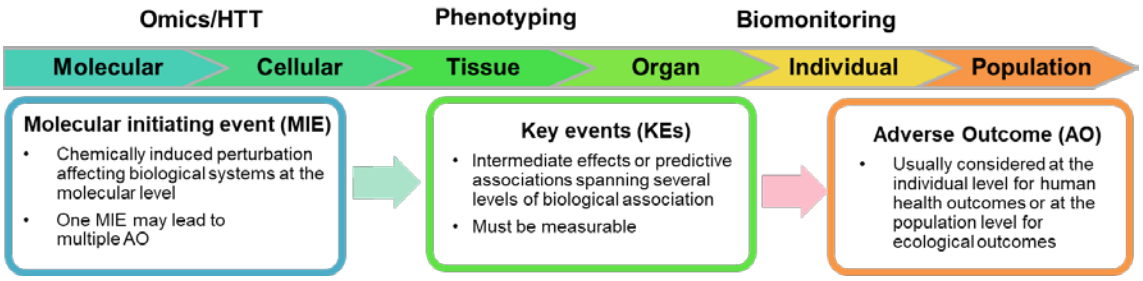
Implementing non-animal approaches in regulatory toxicology testing poses challenges

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:

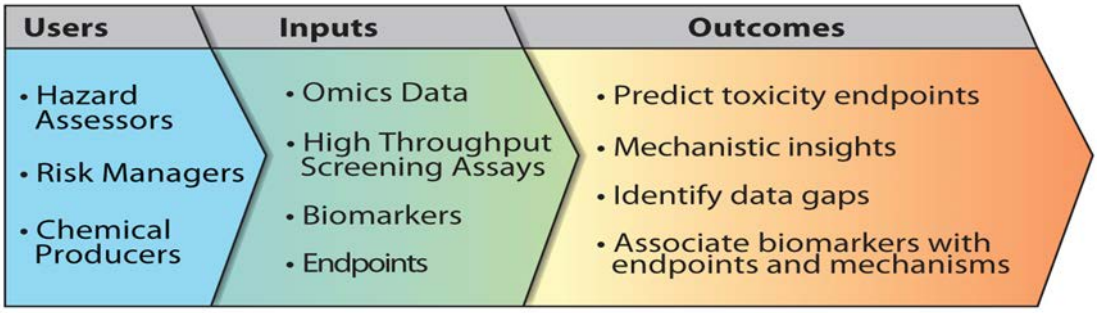
- Understanding end-user needs
- Defining context of use for non-animal approaches
- Establishing confidence in these approaches

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

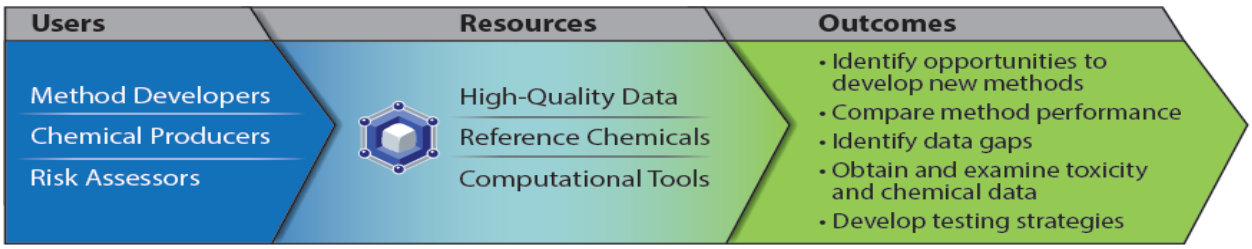
- A plugin for the open source network visualization software Cytoscape (www.cytoscape.org) that allows visualization of users' data onto AOP networks (AOPNs)
- Enables overlaying of high-throughput screening and omics data onto AOPNs
- Supports mechanistic causal analysis
- Available at http://apps.cytoscape.org/apps/aopxplorer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

AOPXplorer

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



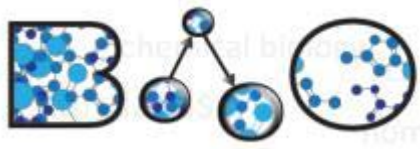
What can ICE do?

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.



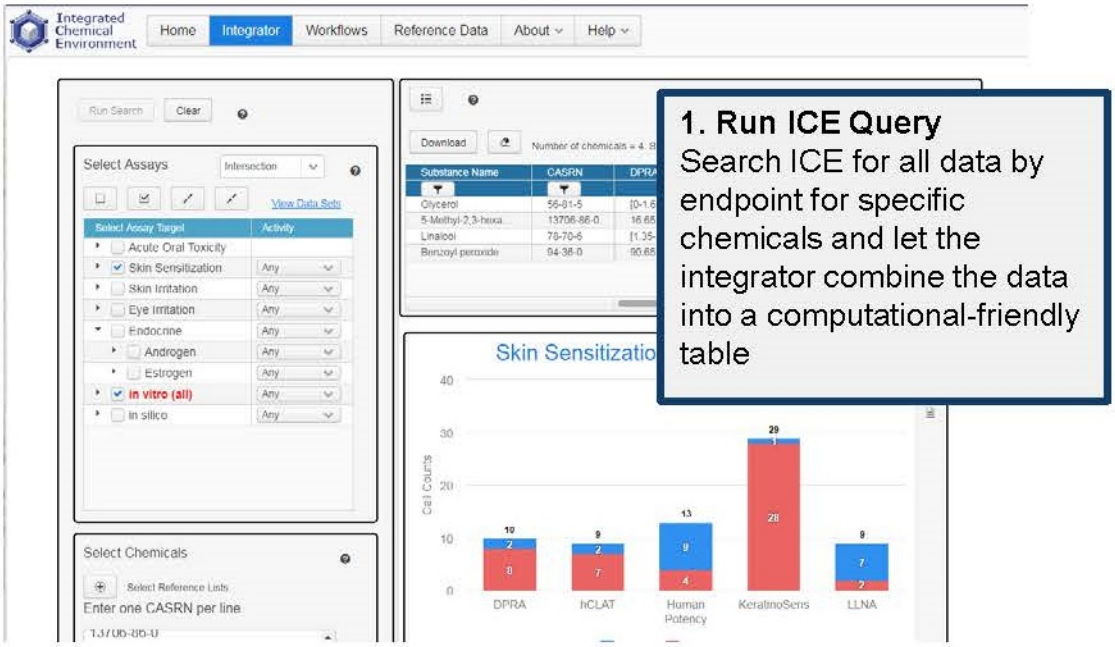
ICE Ontology and AOP Mapping

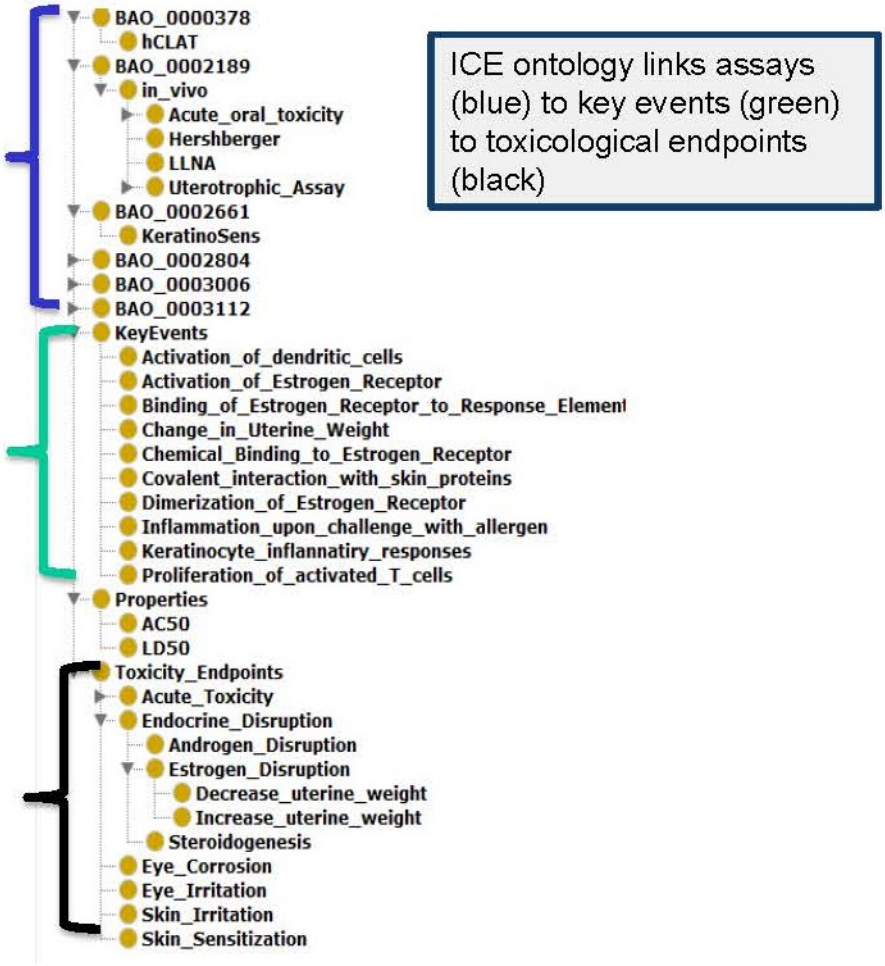
ICE Ontology allows alignment of ICE assays with key events by:

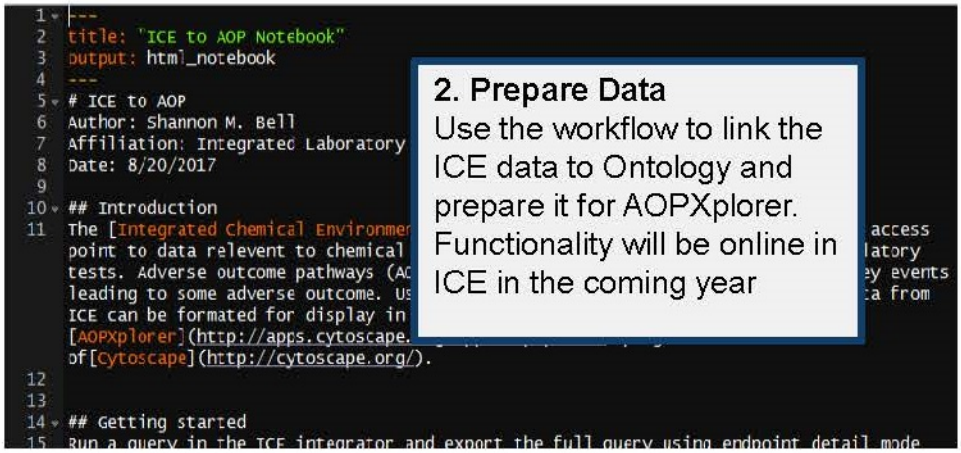
- Adding ontological support for in vivo and low throughput assays
  - Extends BioAssay Ontology
- Complementing the AOP ontology and facilitating AOP mapping of ICE data
- Linking assays to toxicity endpoints used by regulators

Overlaying of ICE data onto AOPNs

The follow series of images give a high-level overview of how to go from ICE query to AOPXplorer network. Look for tutorials and within-ICE support coming soon.




BAO_0000378
hCLAT
BAO_0002189
in_vivo
Acute_oral_toxicity
Hershberger
LLNA
Uterotrophic_Assay
BAO_0002661
KeratinoSens
BAO_0002804
BAO_0003006
BAO_0003112
KeyEvents
Activation_of_dendritic_cells
Activation_of_Estrogen_Receptor
Binding_of_Estrogen_Receptor_to_Response_Elemen
Change_in_Uterine_Weight
Chemical_Binding_to_Estrogen_Receptor
Covalent_interaction_with_skin_proteins
Dimerization_of_Estrogen_Receptor
Inflammation_upon_challenge_with_allergen
Keratinocyte_inflannatiry_responses
Proliferation_of_activated_T_cells
Properties
AC50
LD50
Toxicity_Endpoints
Acute_Toxicity
Endocrine_Disruption
Androgen_Disruption
Estrogen_Disruption
Decrease_uterine_weight
Increase_uterine_weight
Steroidogenesis
Eye_Corrosion
Eye_Irritation
Skin_Irritation
Skin_Sensitization
ICE ontology links assays (blue) to key events (green) to toxicological endpoints (black)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title: "ICE to AOP Notebook"
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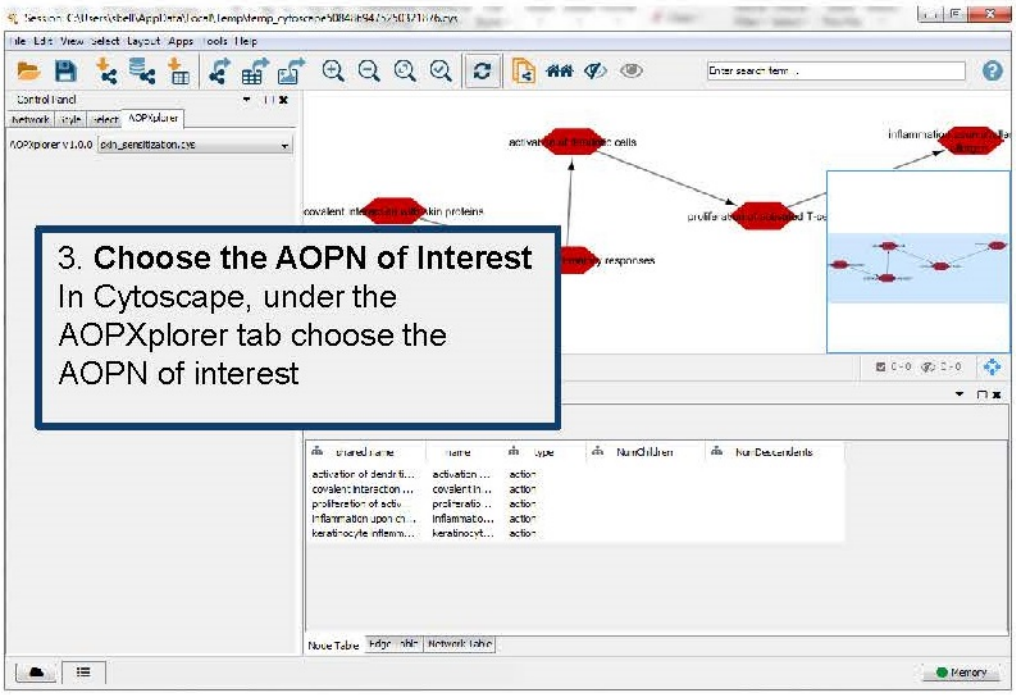
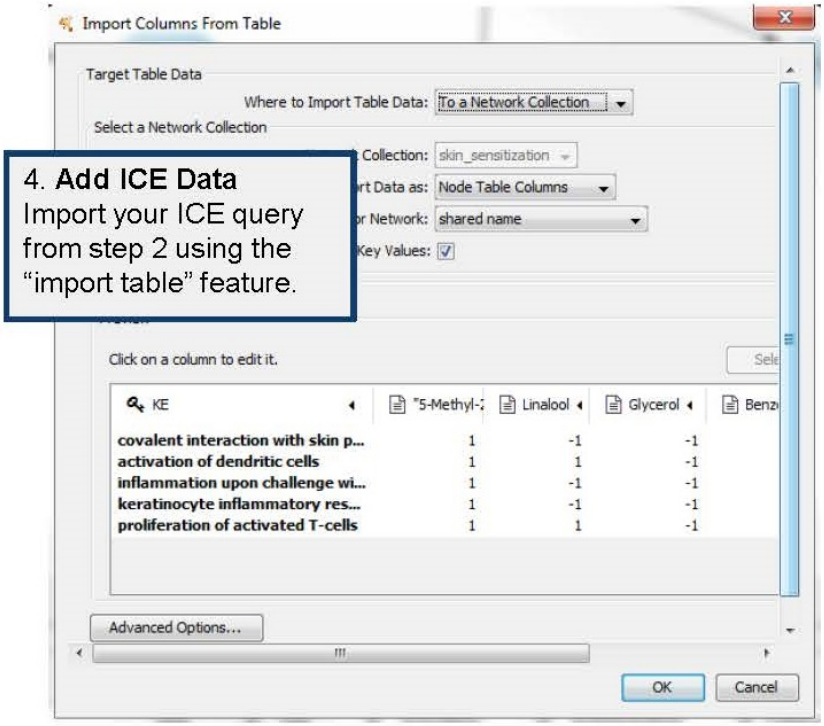
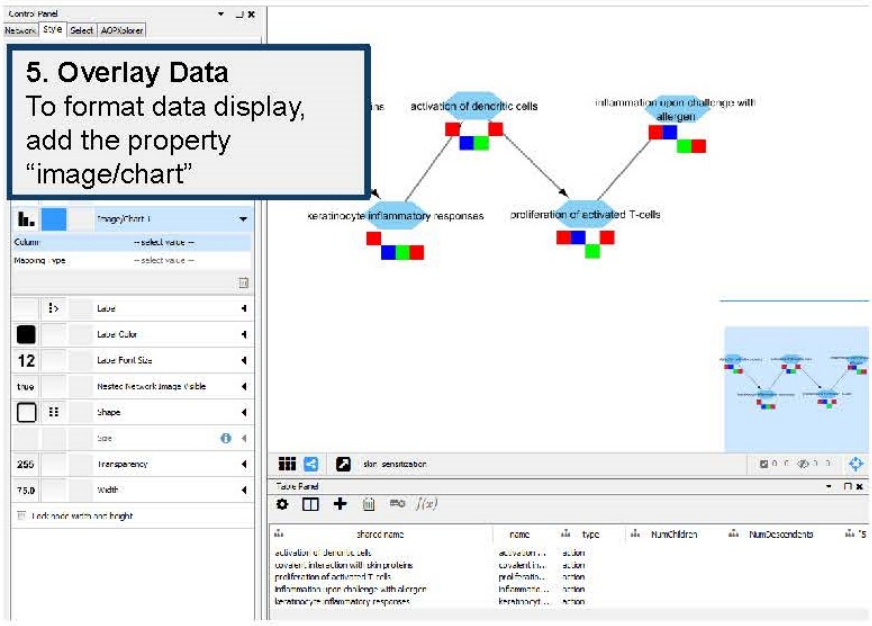
ICE to AOP
Author: Shannon M. Bell
Affiliation: Integrated Laboratory
Date: 8/20/2017
Introduction
The [Integrated Chemical Environmer
point to data relevent to chemical
tests. Adverse outcome pathways (AC
leading to some adverse outcome. Us
ICE can be formated for display in
[AOPXplorer](http://apps.cytoscape.
of[Cytoscape](http://cytoscape.org/).
Getting started
Run a query in the ICE integrator and export the full query using endpoint detail mode
2. Prepare Data
Use the workflow to link the ICE data to Ontology and prepare it for AOPXplorer. Functionality will be online in ICE in the coming year


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


Import Columns From Table
Target Table Data
Where to Import Table Data: To a Network Collection
Select a Network Collection
Collection: skin_sensitization
Data as: Node Table Columns
Network: shared name
Key Values:
4. **Add ICE Data**
Import your ICE query from step 2 using the "import table" feature.
Click on a column to edit it.
KE
Linalool
Glycerol
covalent interaction with skin p... 1 -1 -1
activation of dendritic cells 1 1 -1
inflammation upon challenge wi... 1 -1 -1
keratinocyte inflammatory res... 1 -1 -1
proliferation of activated T-cells 1 1 -1
Advanced Options...
OK
Cancel



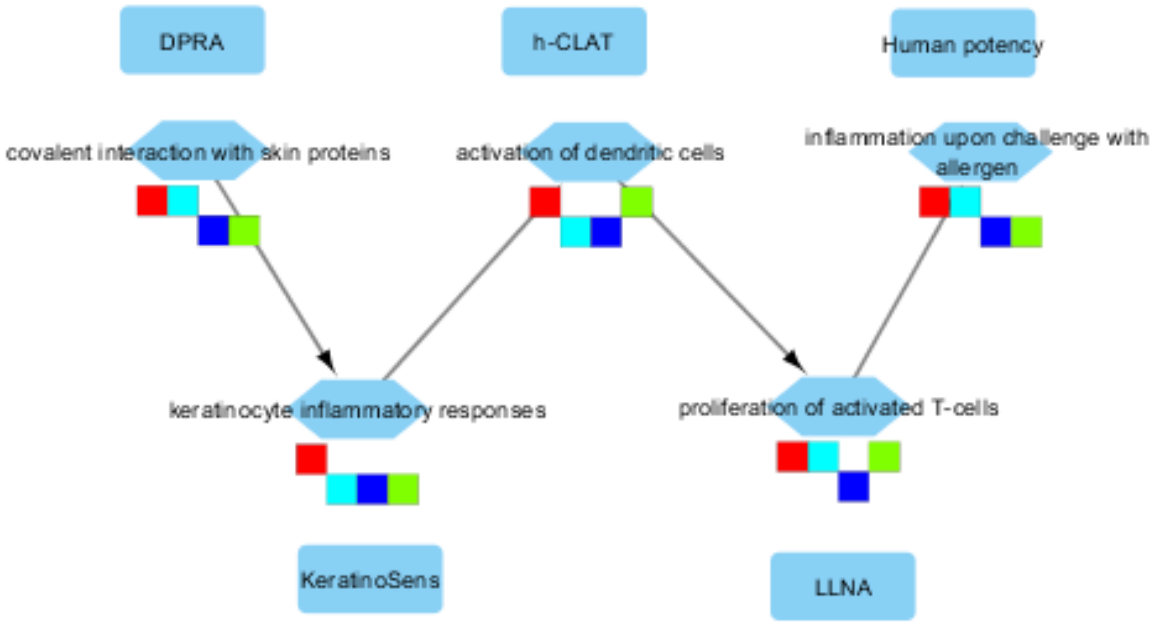
View a video with more detailed instructions on using AOPXplorer at https://www.youtube.com/watch?v=vS3J6OuScQU.

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.

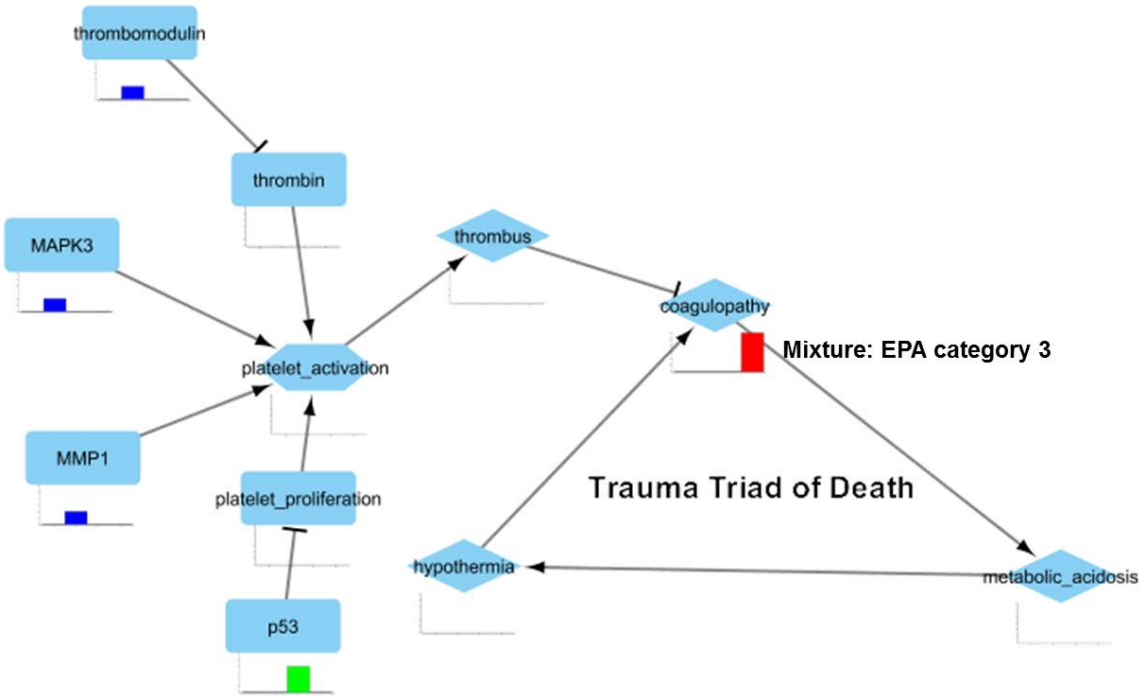
What is the concordance of my data?

- 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.



Acknowledgements

This project was funded in whole or in part with federal funds from the National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN273201500010C.

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