National Institute of Environmental Health Sciences
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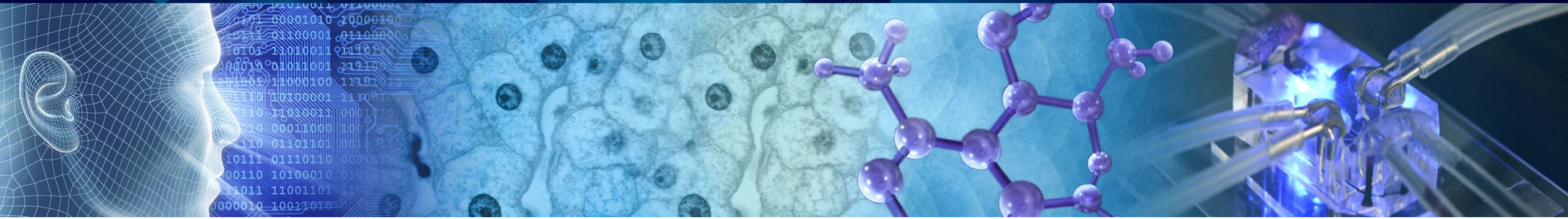

NICEATM Update: ICCVAM Public Forum 2024

Nicole C. Kleinstreuer, PhD

Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

Executive Director, Interagency Coordinating Committee for the Validation of Alternative Methods

ICCVAM Participating Agencies Update
18 Participating Agencies

- Consumer Product Safety Commission
- Department of Agriculture
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- Occupational Safety and Health Administration
- National Institute for Occupational Safety and Health
- Agency for Toxic Substances and Disease Registry
- National Cancer Institute
- **National Center for Advancing Translational Sciences (since 2024)**
- National Inst of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy
- National Institute of Standards and Technology (since 2017)
- Dept of Veterans Affairs Office of Research and Development (since 2020)
- Other participants
  - Tox21
  - NCATS

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Recent NCATS Collaborations

Toxicology in Vitro 91 (2023) 105630

Contents lists available at ScienceDirect

ELSEVIER

Toxicology

Parallel evaluation of a… skin for dermal absorpt…

Alec T. Salminen [a], Kelly J. Da…
Frederick A. Beland [a], Kristy L…
Nicole C. Kleinstreuer [g], Jonat…
Menghang Xia [d], Suzanne C. F…

[a] *Division of Biochemical Toxicology, National Cente…*
[b] *Toxicologic Pathology Associates, Jefferson, AR, U…*
[c] *Office of Scientific Coordination, National Center f…*
[d] *National Center for Advancing Translational Scien…*
[e] *Center for Drug Evaluation and Research, U.S. Foo…*
[f] *Center for Food Safety and Applied Nutrition, U.S.…*
[g] *National Toxicology Program Interagency Center fo… Triangle Park, NC, USA*
[h] *Center for Veterinary Medicine, U.S. Food and Dru…*

frontiers | Frontiers in Toxicology

TYPE Original Research
PUBLISHED 28 February 2024
DOI 10.3389/ftox.2024.1321857

Check for updates

OPEN ACCESS

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Use of *in vitro* methods combined with *in silico* analysis to identify…

EPA

Development and Validation of Enzyme-Based CYP26A1 Inhibition Assay in a High-Throughput Screening Platform

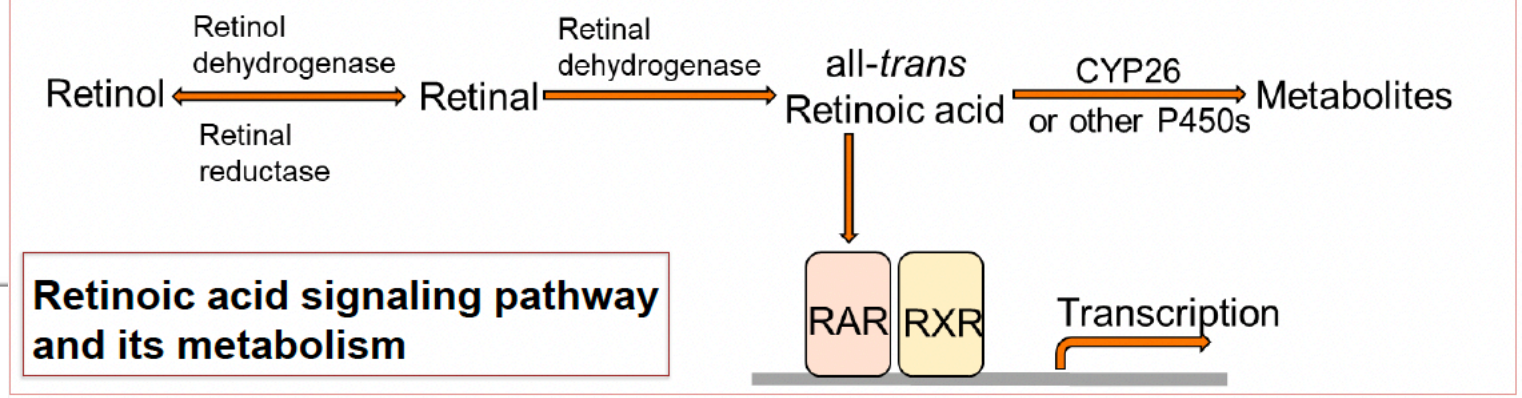
Abstract # 3015

Srilatha Sakamuru[1], Dongping Ma[2], Jocylin D. Pierro[3], Nancy C. Baker[4], Nicole Kleinstreuer[5], James J. Cali[2], Thomas B. Knudsen[3], Menghang Xia[1]

[1] Division of Pre-clinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA.
[2] Promega Corporation, Madison, WI, USA.
[3] Center for Computational Toxicology and Exposure, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, NC, USA.
[4] Leidos, Research Triangle Park, NC, USA.
[5] National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA.

Tox21

NIH National Center for Advancing Translational Sciences



Retinoic acid signaling pathway and its metabolism

FDA

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Integrated Chemical Environment

ICE Data

- Curated in vivo, in vitro, and in silico toxicity data
- Measured and predicted chemical properties
- Predicted exposure
- Reported and predicted chemical use categories

The data are used across ICE tools.

Search | **Chemical Quest** | **Curve Surfer** | **PBPK** | **IVIVE** | **Chemical Characterization**

- Explore ICE data through interactive visualizations
- Identify structurally similar chemicals
- Leverage computational models without coding

Inter-connectivity: Send chemical and assay selections between tools.

Chemical Quick Lists

- Reference and Non-reference chemical lists
- Support the development and evaluation of new test methods

https://ice.ntp.niehs.nih.gov/

ICE v4.0.1 (August 2023)

- Exposure data added to REST API
- Functional use data set and its exploration through chemical characterization tool
- New chemical quick lists: Mixtures and Formulations in ICE and ToxCast Phase I, Phase II, and e1k
- Search tool UI and visualization updates

ICE v4.0.2 (March 2024)

- cHTS updated to invitrodb v3.5
- Technological interference flags added to cHTS pipeline and applied to Curve Surfer tool result cards
- Additional ACC overlay option provided in Curve Surfer tool result visualizations
- Additional Search tool UI and visualization updates

ICE v4.1 (August 2024)

- Update cHTS annotations from NCI Metathesaurus to OBO Foundry
- New PFAS chemical quick list and updated ROC chemical quick list
- ICE REST API updated to include Curve Surfer tool raw data
- Additional data visualizations in Search tool

Future Updates

- Update cHTS pipeline to integrate invitrodb v4.1
- Option to use custom ADME parameters to run PBPK/IVIVE
- Ongoing search visualization updates

Contributors

Subscribe to NICEATM News
https://ntp.niehs.nih.gov/go/niceatm

CEBS

UNITED STATES ICCVAM *Advancing Alternatives to Animal Testing*

SciCome

OPERA OPEn qsaR App

https://github.com/NIEHS/OPERA

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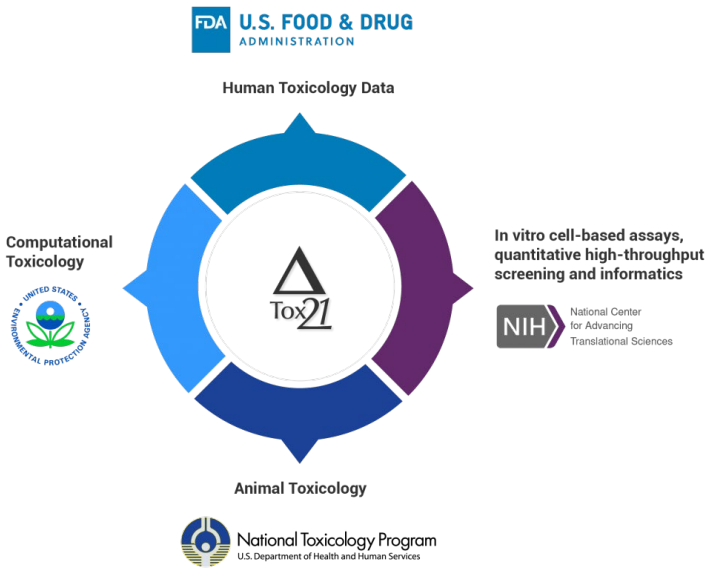
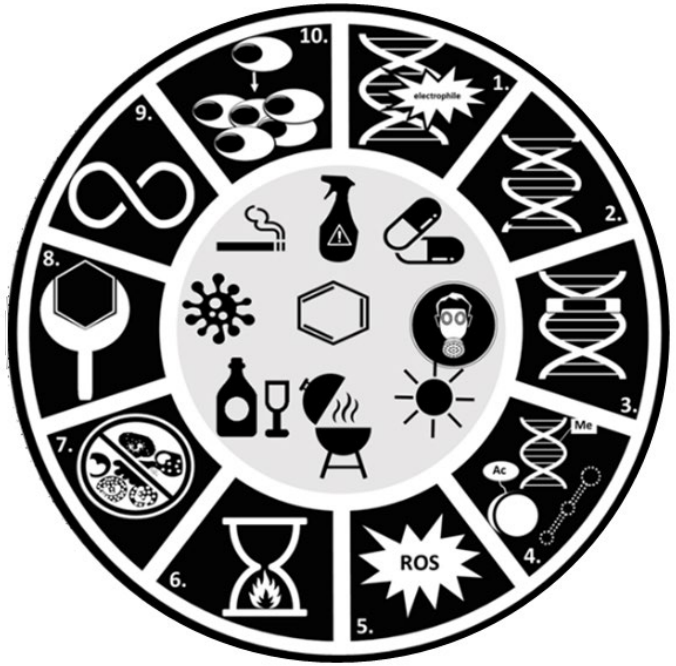
Mapping Tox21/ToxCast assays on Key Characteristics of Carcinogens



Mapping



KCC1: Is Electrophile or can be Activated to Electrophiles
KCC2: Induces DNA Damage response
KCC3: Activates Mutagenic DNA Repair & Promotes Genomic Instability
KCC4: Induces Epigenetic Alterations
KCC5: Induces Oxidative stress
KCC6: Induces Chronic Inflammation
KCC7: Is Immunosuppressive
KCC8: Modulates Receptors-mediated effects
KCC9: Causes Immortalization
KCC10: Alters Cell Proliferation, Cell Death or Nutriment Supply

- ~ 9000 unique chemicals
- ~ 2000 assays

Expert working group including ~20 people from NICEATM, EPA, NIEHS ROC, IARC, U. Berkely, Texas A&M University

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Developing AI workflow for carcinogenicity prediction

Known carcinogens

Regulatory lists of carcinogens

Curated High Throughput Screening (CHTS)

Enrich/impute CHTS results

Build confidence on AI generated data

abstractR (PMI)

Mapping CHTS on KCC

Working group (~20 people)

EPA

IARC

15th Report on Carcinogens 2021

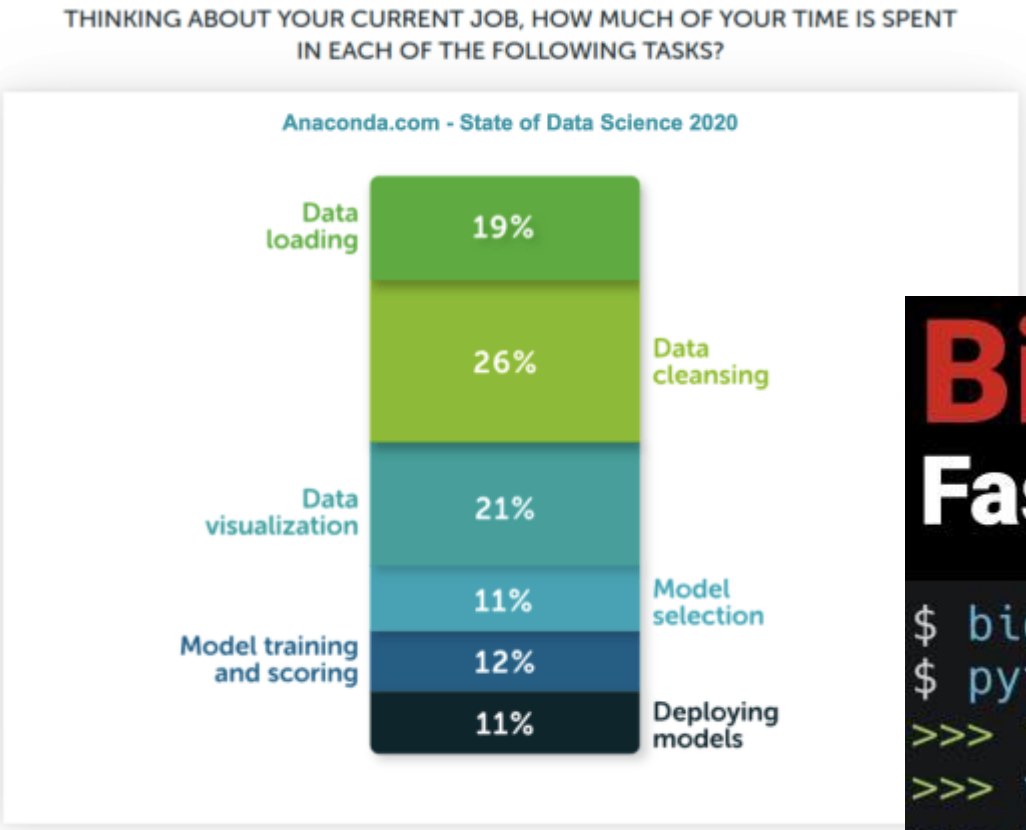
Carcinogenicity score by KCC

toxpiR

Integrated Chemical Environment

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Bio/Chemical Database Assembly



45% of data analysts time is spent loading and cleaning data → **BioBricks: one-line command**

BioBricks.ai
Faster Informatics

```
$ biobricks install tox21
$ python
>>> import biobricks, pandas
>>> tx21 = biobricks.load('tox21')
>>> tx21.tox21.read().load()
#          SAMPLE_ID  PROTOCOL_NAME  ...                SMILES  ...
# NCGC00256074-01  tox21-ache-p3  ...          OCC(=O)OCCCC  ...
# NCGC00255047-01  tox21-ache-p3  ...  Nc1ccc(cc1)C(=O)OCC  ...
# [2075022 rows x 19 columns]
```

NICEATM & BioBricks Partnership: NSF ProtoOKN

National Institute of Environmental Health Sciences
Division of Translational Toxicology

OPERA models (version 2.9)

Physchem properties		Chemicals	Version
BP	**Boiling Point**	**7860**	**2.9**
HL	**Henry's Law Constant**	**2233**	**2.9**
LogP	**Octanol-water Partition Coefficient**	**18154**	**2.9**
MP	**Melting Point**	**22554**	**2.9**
VP	**Vapor Pressure**	**6764**	**2.9**
WS	**Water Solubility**	**9943**	**2.9**
pKa	Acid Dissociation Constant	6503	2.6
KOA	Octanol/Air Partition Coefficient	270	2.6

Environmental fate		Chemicals	Version
AOH	Atmospheric Hydroxylation Rate	692	2.6
BCF	Bioconcentration Factor	626	2.6
BioHL	Biodegradation Half-life	150	2.6
RB	Ready Biodegradability	1603	2.6
KM	Fish Biotransformation Half-life	541	2.6
KOC	Soil Adsorption Coefficient	728	2.6

Toxicity endpoints		Chemicals	Version
ER	Estrogen Receptor Activity	32464	2.6
AR	Androgen Receptor Activity	47673	2.6
AcuteTox	Acute Oral Systemic Toxicity	50660	2.6

ADME properties		Chemicals	Version
FUB	**Fraction unbound**	**3229**	**2.8**
Clint	**Intrinsic clearance**	**1346**	**2.8**
CACO2	**Caco-2 permeability**	**4601**	**2.8**

New/updated since 2021

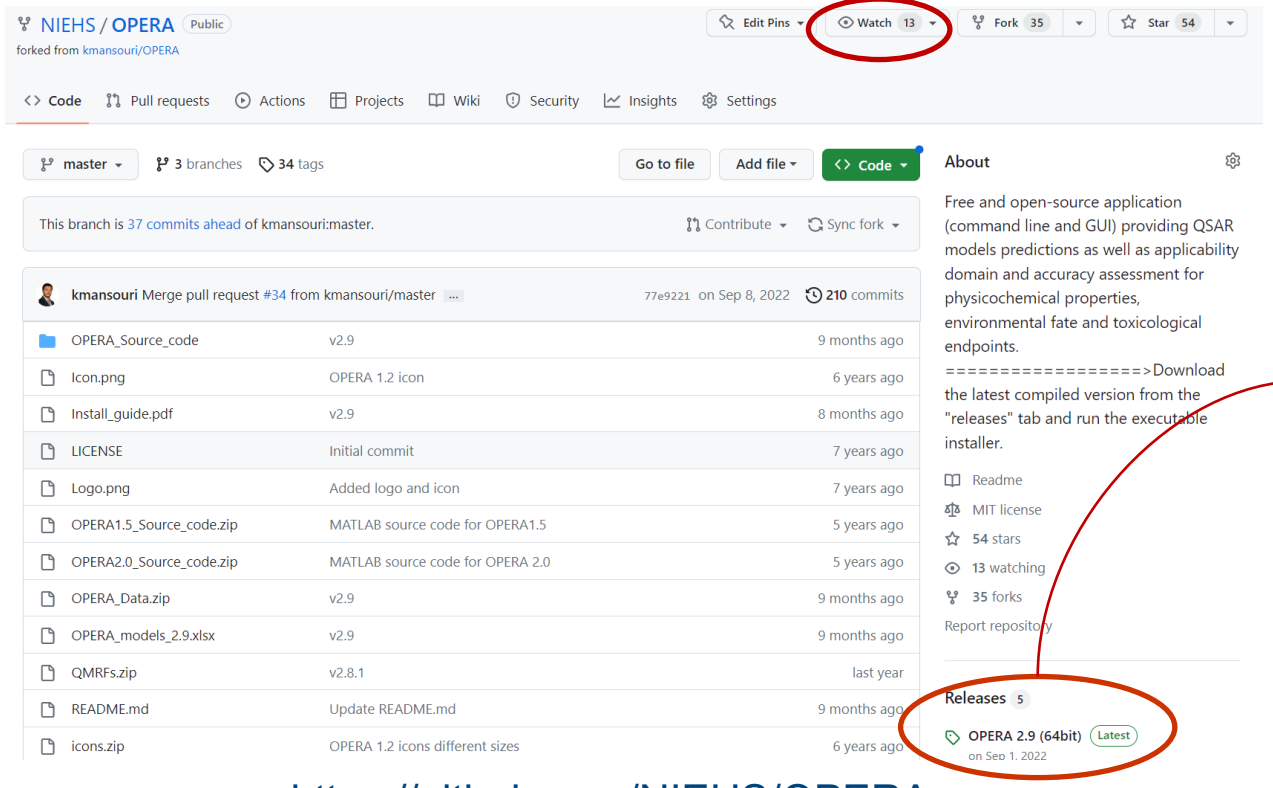
National Institute of Environmental Health Sciences
Division of Translational Toxicology

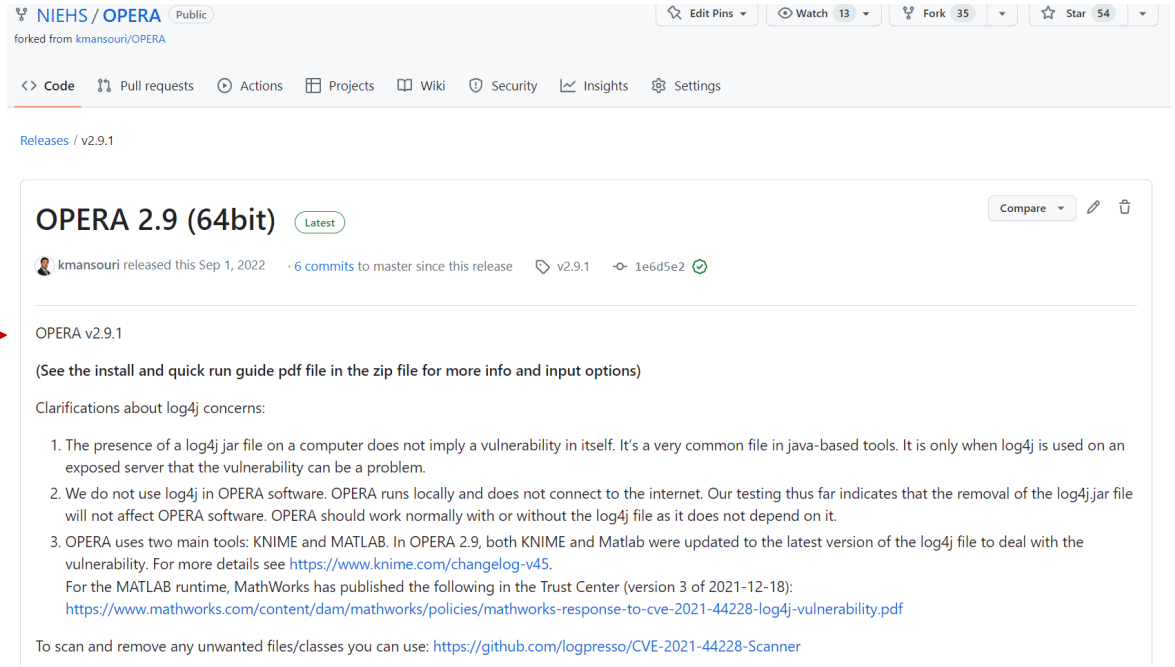
OPERA on GitHub

Source code

Packaged installers

Updates notifications





https://github.com/NIEHS/OPERA

https://github.com/NIEHS/OPERA/releases

Over 7000 downloads

(https://tooomm.github.io/github-release-stats/)

National Institute of Environmental Health Sciences
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OPERA predictions online

National Toxicology Program
U.S. Department of Health and Human Services

QSAR TOOLBOX

Input | Profiling | Data | Category definition | Data Gap Filling | Report

Gap Filling: Trend analysis | Read across | (Q)SAR
Workflow Editor: Automated | Standardized | New | Import | Export | Delete

Documents
Document 1
[C: 1;Md: 0;P: 0] CAS: 58082

Filter endpoint tree...
1 [target]
Structure

- Structure info
- Parameters
- Physical Chemical Properties
  - Autoflammability / Self-ignition tempera...
  - Boiling point
  - Chemical reactivity
  - Density
  - Dissociation Constant (pKa)
  - Explosive properties
  - Flammability
  - Flash point
  - Melting / freezing point
  - Oxidation reduction potential
  - Oxidising properties
  - Particle size
  - Partition Coefficient:
  - Solubility in organic solvents / fat solubil...
  - Stability in organic solvents and identity...
  - Surface tension
  - Vapour pressure
  - Viscosity
  - Water solubility
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards

Data Gap Filling Settings
Only endpoint relevant
At this position:
QSARs 2
Automated workflows 0
Standardized workflows 0

Details for 2 (Q)SAR models

QSAR name	#	Predicted	Domain	QMRF	Test set	Training set
Boiling Point Adapted Stein and Brown Method (EPISUITE) (1.0)						
Opera BP (2.6)						

Executions 1203
Spec | Executions (10) | Readme
DEFAULT INSTANCE TYPE: baseline-4
HAS INTERNET ACCESS: No
INPUTS: string — Input file format — REQUIRED
OUTPUTS: file — OPERA output tarball — REQUIRED

EPA United States Environmental Protection Agency

Endosulfan
115-29-7 | DTXSID1020560
Searched by DSSTox Substance Id.

ToxCast: Models
ToxCast Model Predictions

Toolbox Repository

Tools / QSARs / OPERA models

OPERA models

OPERA
OPEn (q)saR App

Current version:	1.0
Supported Toolbox versions:	4.5
Developer:	NIEHS
Category:	QSARs
Downloads:	57
Rating:	☆☆☆☆☆ 0

Description:

OPERA is a free and open-source/open-data suite (physicochemical properties, environmental fate, ADME a information including applicability domain and accuracy data and standardized QSAR-ready chemical structures. C friendly graphical interface for Windows and Linux operati

OPERA and ICE Used Worldwide

Environmental Science & Technology

Open Access

pubs.acs.org/est

Article

Two-Stage Machine Learning-Based Approach to Predict Points of Departure for Human Noncancer and Developmental/Reproductive Effects

Jacob Kvasnicka, Nicolò Aurisano, Kerstin von Borries, En-Hsuan Lu, Peter Fantke, Olivier Jolliet, Fred A. Wright, and Weihsueh A. Chiu*

Cite This: https://doi.org/10.1021/acs.est.4c00172

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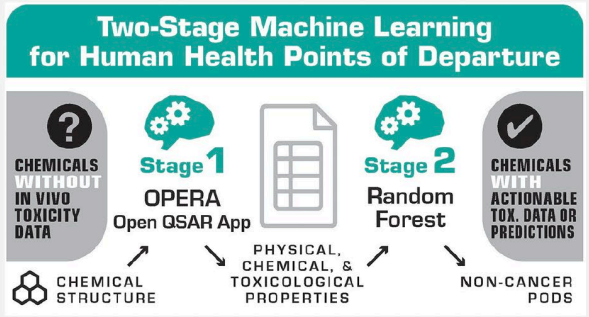
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Chemical points of departure (PODs) for critical health effects are crucial for evaluating and managing human health risks and impacts from exposure. However, PODs are unavailable for most chemicals in commerce due to a lack of *in vivo* toxicity data. We therefore developed a two-stage machine learning (ML) framework to predict human-equivalent PODs for oral exposure to organic chemicals based on chemical structure. Utilizing ML-based predictions for structural/physical/chemical/toxicological properties from OPERA 2.9 as features (Stage 1), ML models using random forest regression were trained with human-equivalent PODs derived from *in vivo* data sets for general noncancer effects (n = 1,791) and reproductive/developmental effects (n = 2,228), with robust cross-validation for feature selection and estimating generalization errors (Stage 2). These two-stage models accurately predicted PODs for both effect categories with cross-validation-based root-mean-squared errors less than an order of magnitude. We then applied one or both models to 34,046 chemicals expected to be in the environment, revealing several thousand chemicals of *moderate* concern and several hundred chemicals of *high* concern for health effects at estimated median population exposure levels. Further application can expand by orders of magnitude the coverage of organic chemicals that can be evaluated for their human health risks and impacts.



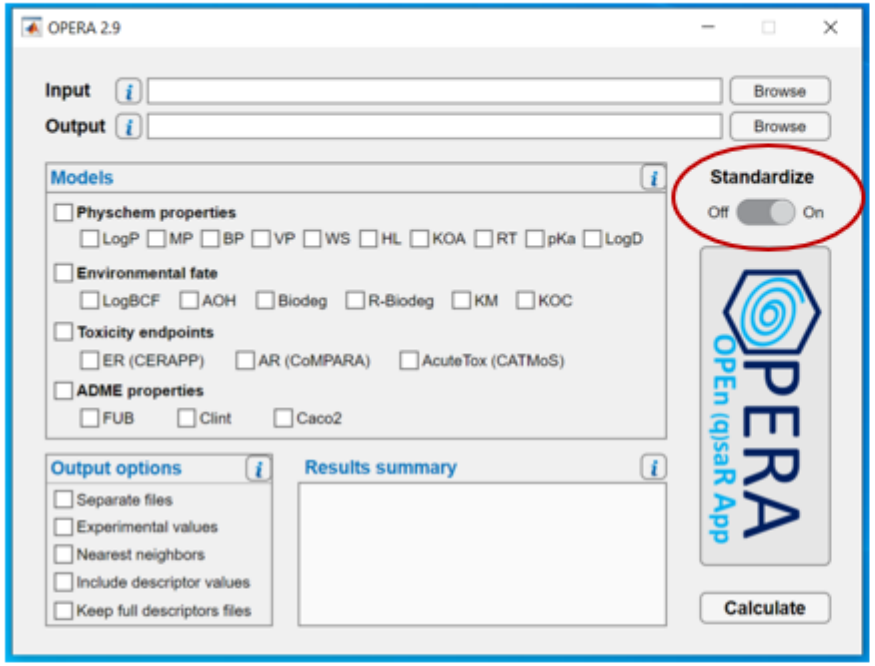
KEYWORDS: *QSAR model, machine learning, toxicity prediction, chemical risk assessment, high-throughput screening, life cycle impact assessment (LCIA)*

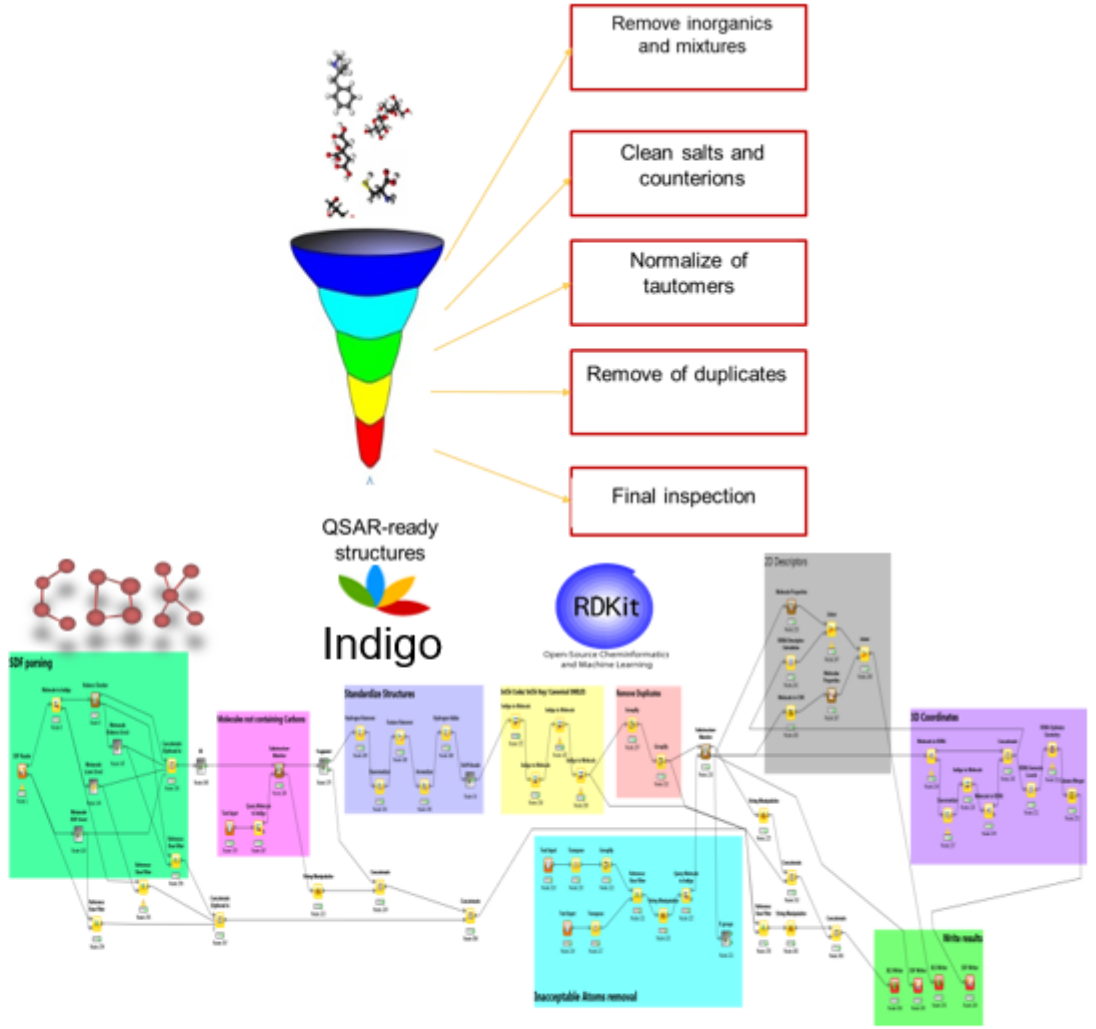
- OPERA predicted properties used as features in ML model to predict PODs for thousands of chemicals
- US EPA SEEM3 exposure data downloaded from ICE to facilitate comparisons

OPERA OPEn (q)saR App

National Institute of Environmental Health Sciences
Division of Translational Toxicology

QSAR-ready standardization tool





GitHub: https://github.com/NIEHS/QSAR-ready/releases
KNIME Hub: https://kni.me/w/_iyTwvXi6U3XTFW1
Docker Hub: https://hub.docker.com/r/kamelmansouri/qsar-ready

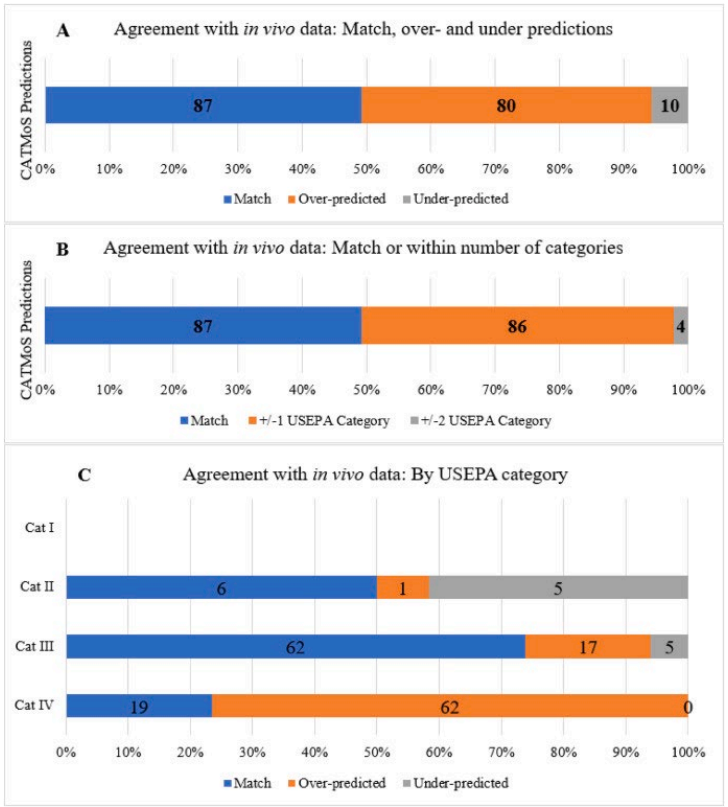
Mansouri, K. *et al.* Free and open-source QSAR-ready workflow for automated standardization of chemical structures in support of QSAR modeling. *J Cheminform* **16**, 19 (2024). https://doi.org/10.1186/s13321-024-00814-3

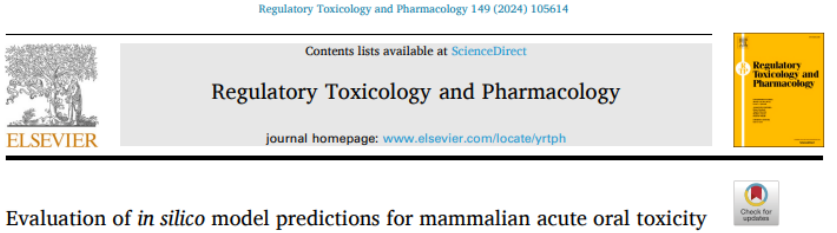
Application of CaTMOS to Pesticide AIs

EPA Case Study

- Comparative analysis of 177 pesticides with LD_{50} data between CaTMOS and EPA database
- 88% categorical concordance for 165 chemicals with empirical *in vivo* LD_{50} values ≥ 500 mg/kg

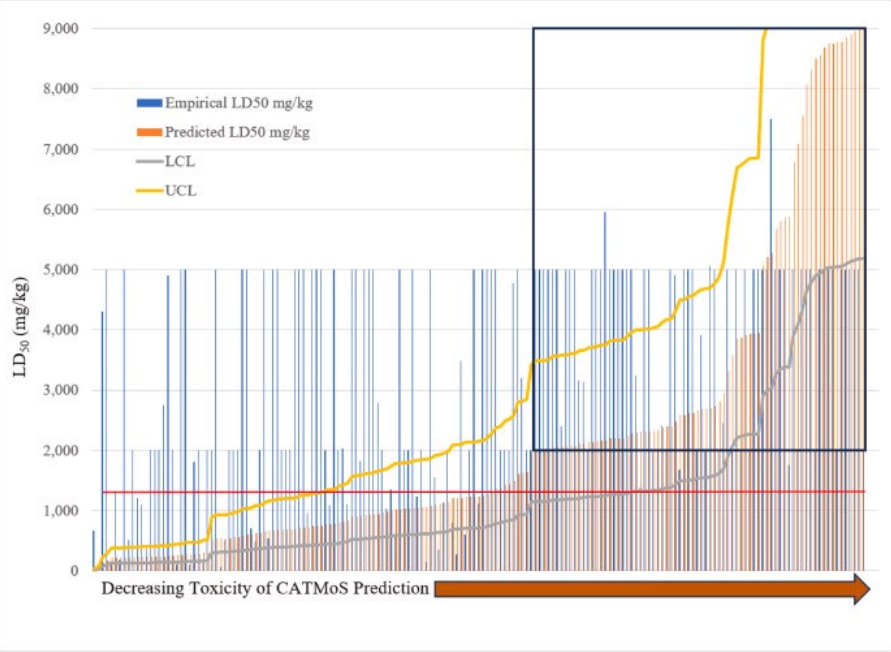
Toxicity Category based on CATMoS Prediction	Number of predictions	Toxicity Category based on Empirical *In Vivo* Test Data			
		I	II	III	IV
I (<50 mg/kg)	2	-	1	1	-
II (50-500 mg/kg)	25	-	**6**	16	3
III (>500-5,000 mg/kg)	126	-	5	**62**	59
IV (>5,000 mg/kg)	24	-	-	5	**19**
III and IV combined	150	-	5	145	




Regulatory Toxicology and Pharmacology 149 (2024) 105614
Contents lists available at ScienceDirect
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph
ELSEVIER

Evaluation of *in silico* model predictions for mammalian acute oral toxicity and regulatory application in pesticide hazard and risk assessment

Patricia L. Bishop [a,*], Kamel Mansouri [b], William P. Eckel [c], Michael B. Lowit [c], David Allen [d,1], Amy Blankinship [c], Anna B. Lowit [e], D. Ethan Harwood [c], Tamara Johnson [c], Nicole C. Kleinstreuer [b]



Bishop et al., Reg. Tox. Pharm., 2024

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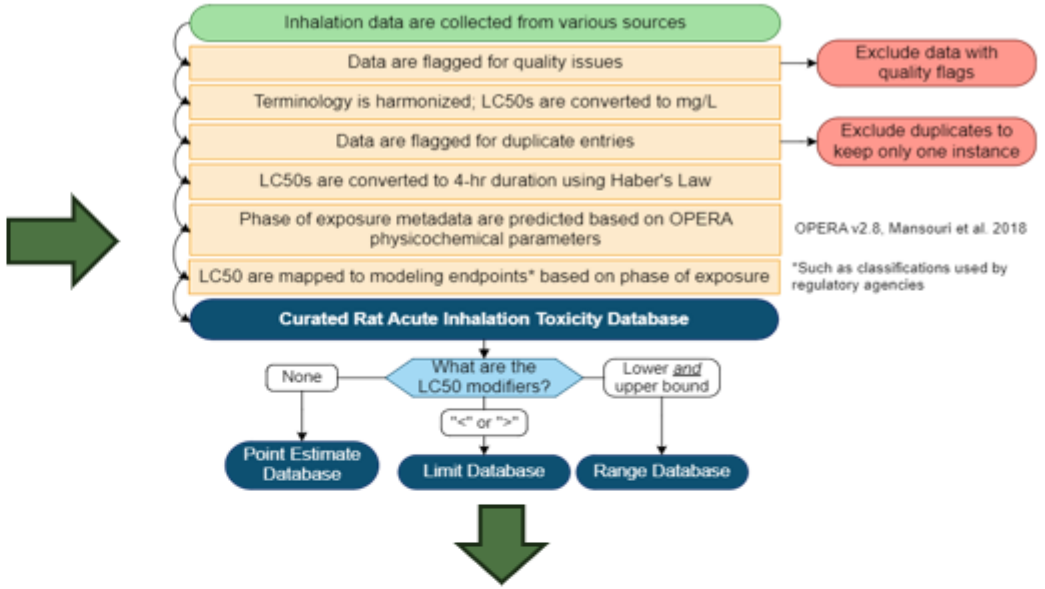
Acute Inhalation Toxicity Database

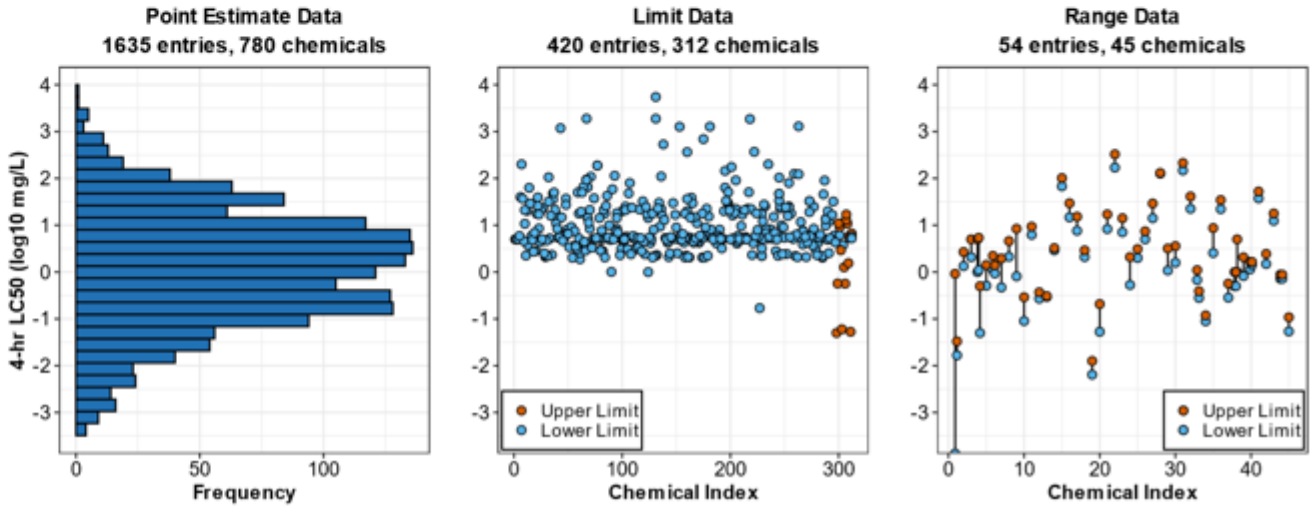
Data Source	Data Records	Unique Substances
Legacy data from ChemIDplus (now integrated into PubChem)	2036	1249
National Institute for Occupational Safety and Health Pocket Guide	136	649
European Chemicals Agency Registration, Evaluation, Authorisation and Restriction of Chemicals Database	3016	611
U.S. Environmental Protection Agency Acute Exposure Guideline Levels	1682	271
U.S. Department of Defense	47	13



Database Summary

- 1025 unique chemicals
- ~760 chemicals will be used to support a collaborative modeling effort
- The database can be downloaded and explored on ICE

Download the Rat Acute Inhalation Database from ICE.
https://ice.ntp.niehs.nih.gov/DATASETDESCRIPTION



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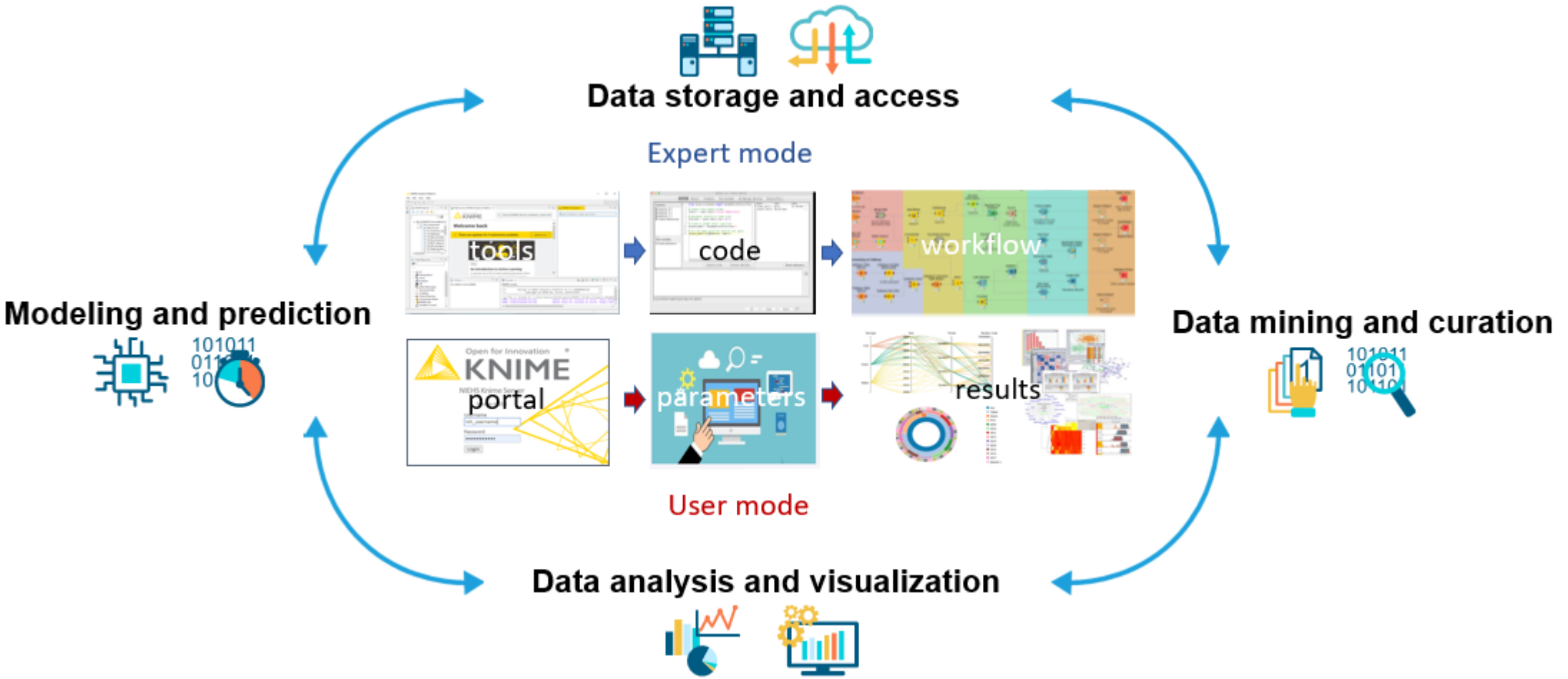
Modeling and Visualization (MoVIZ) Pipeline



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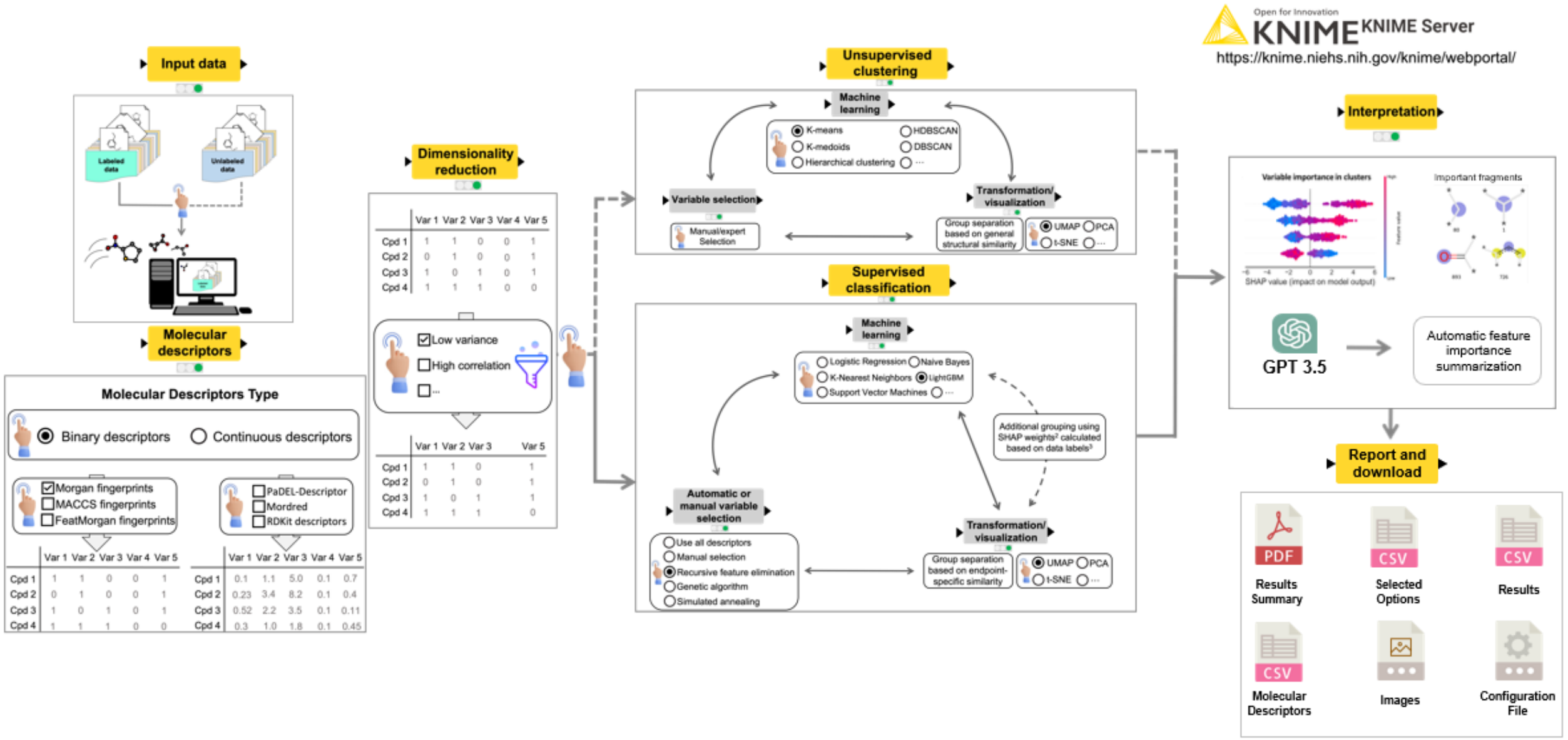
Chemical Grouping Workflow



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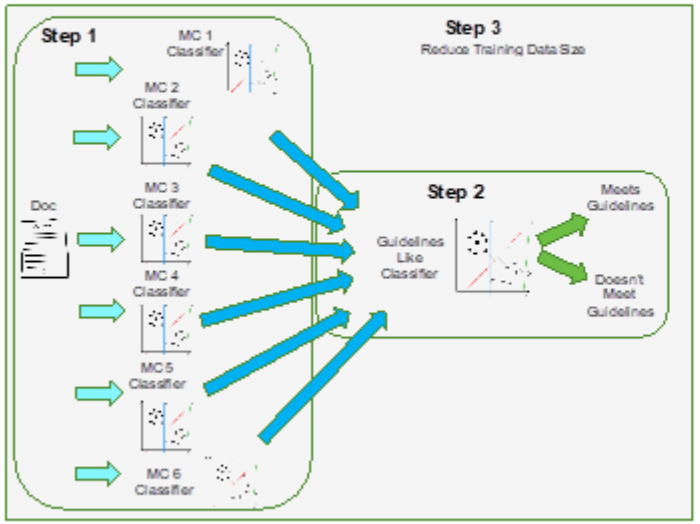
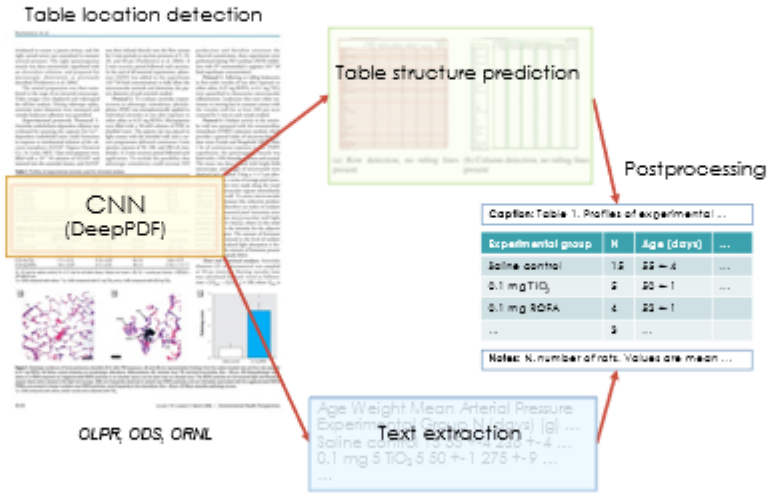
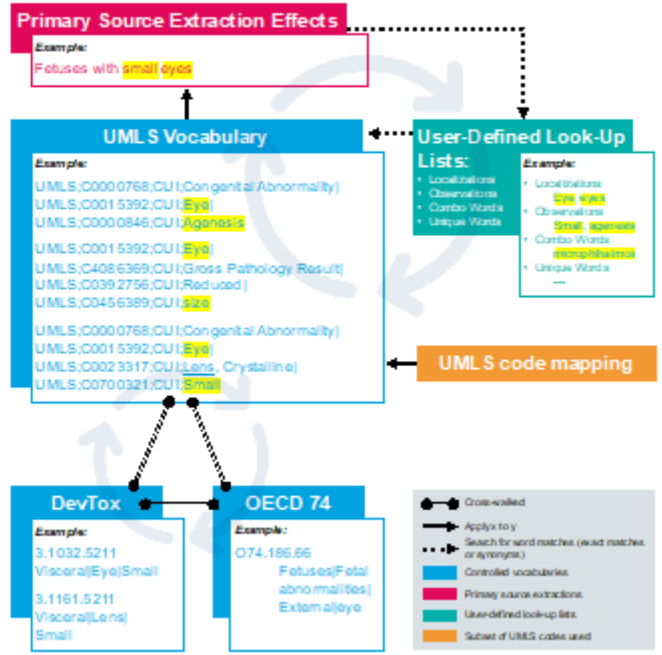
Machine Automating Study Data Curation

Identification → Extraction → Annotation







- Important for leveraging high-quality studies in the published literature
- Applications in systematic review of chemical effects
- Establishing reference datasets for validating new methods

Foster et al. EHP, 2024

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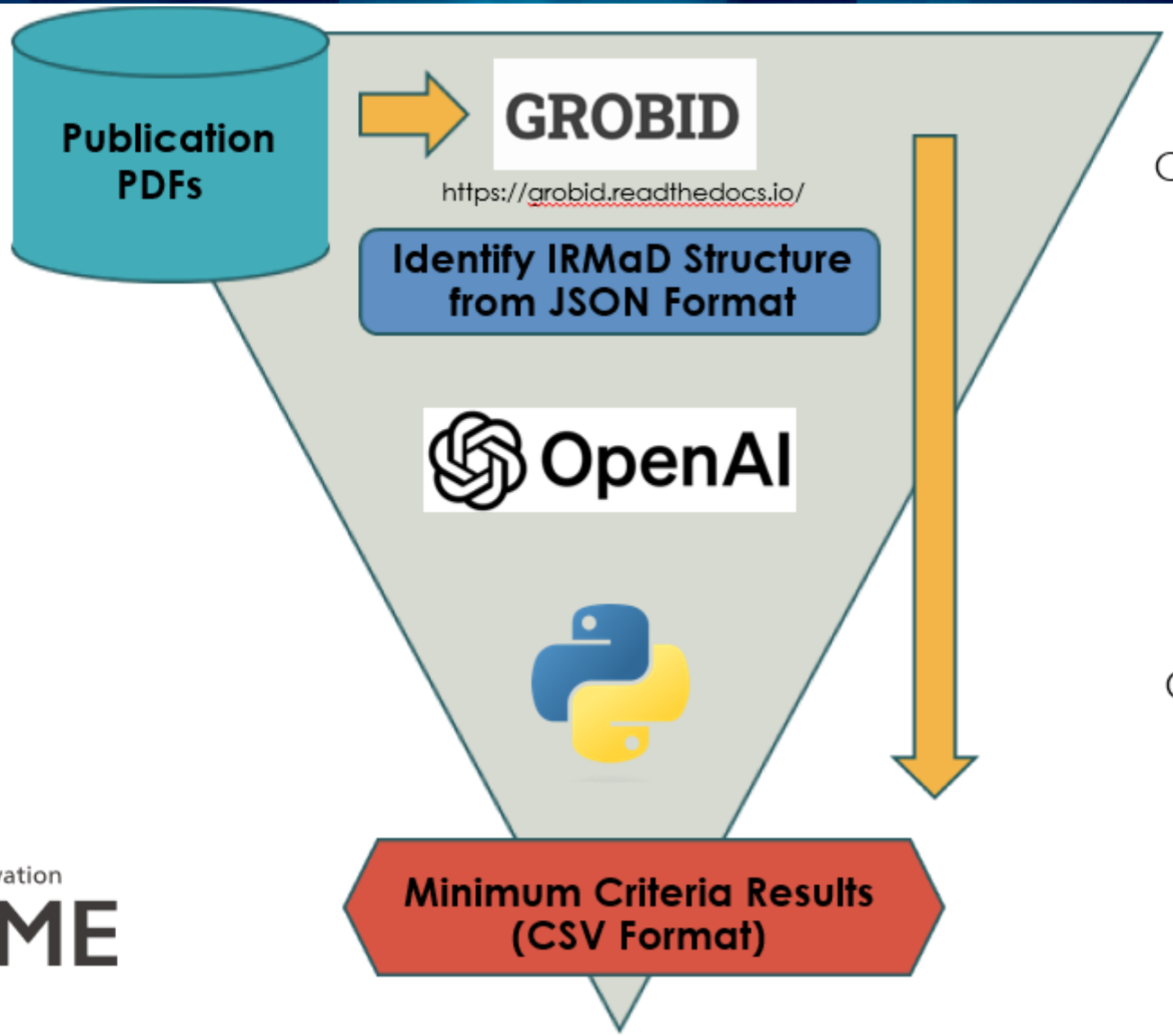
LLMs to Extract Study Information



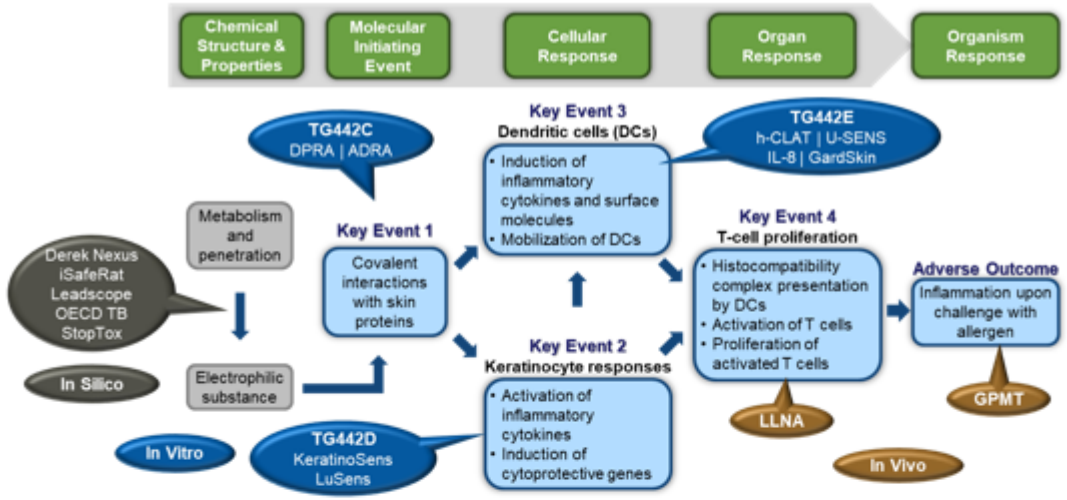
Grobid
Convert PDF to JSON Format

LLM - GPT-3.5 Turbo
Extract info

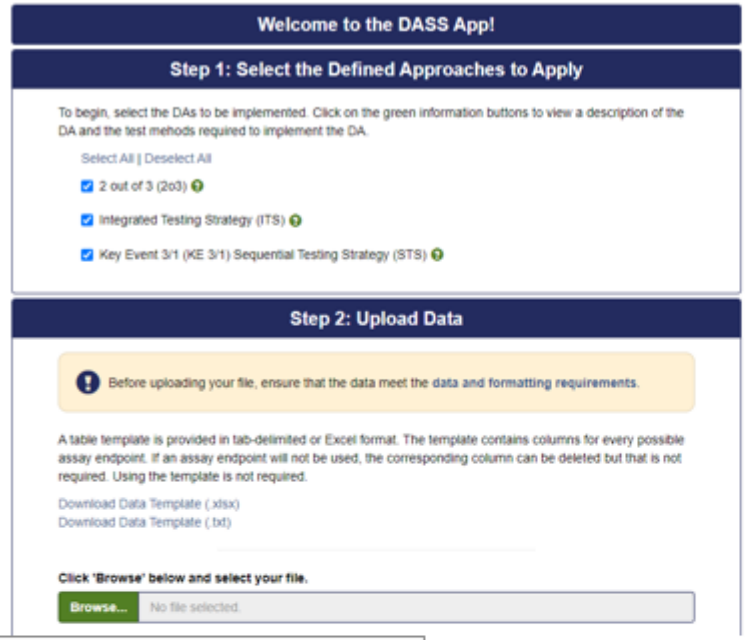
Python
Convert extracted info to table format

Open for Innovation
KNIME

User Friendly DASS App



DA ITS h-CLAT Score	DA ITS DPRA Score	DA ITS in Silico Score	DA ITS Total Score	DA ITS Call	DA ITS Potency
0	3	1	4	1	1B
0	0	NA	0	0	NC
2	0	1	3	1	1B
1	1	1	3	1	1B
0	0	1	1	0	NC
0	0	0	0	0	NC
2	3	1	6	1	1A
2	3	1	6	1	1A
3	3	1	7	1	1A
2	0	1	3	1	1B



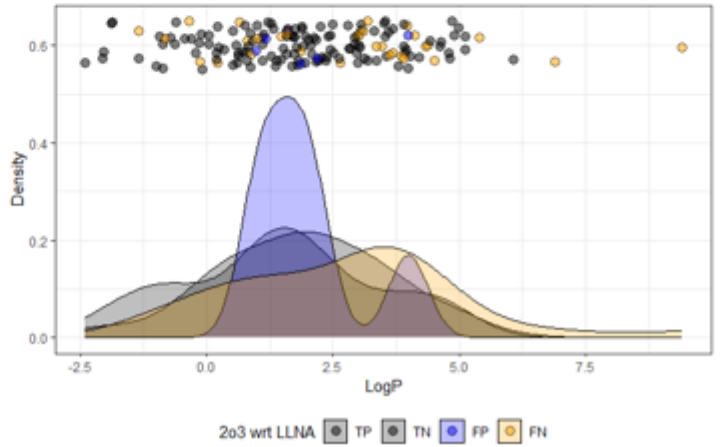
Access the DASS App
https://ntp.niehs.nih.gov/go/952311

Confusion Matrix and Performance Metrics

Reference Column: reference_hppt_call
Prediction Column: DA ITS Call

		Reference	
		Positive	Negative
Predicted	Positive	50	5
	Negative	3	6
	Inconclusive	2	0

Metric	Value
N	66
Accuracy	85%
Balanced Accuracy	73%
F1 Score	93%
True Positive Rate	91%
False Positive Rate	45%
True Negative Rate	55%
False Negative Rate	5%



To et al. BMC Bioinformatics. 2024.

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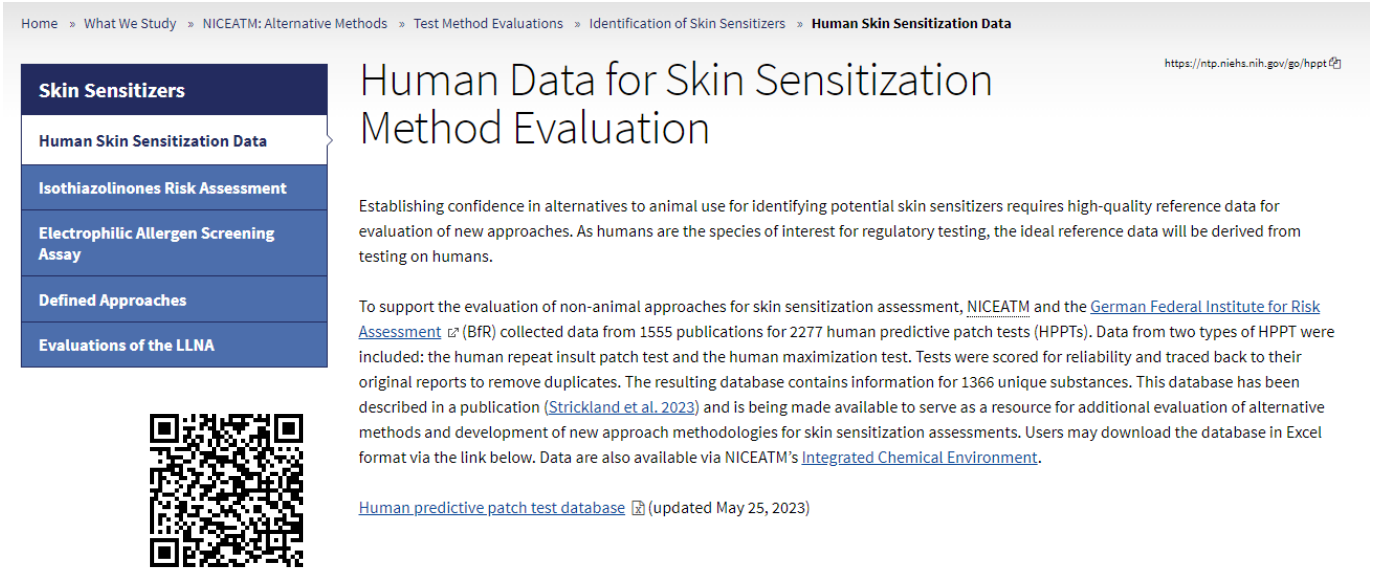
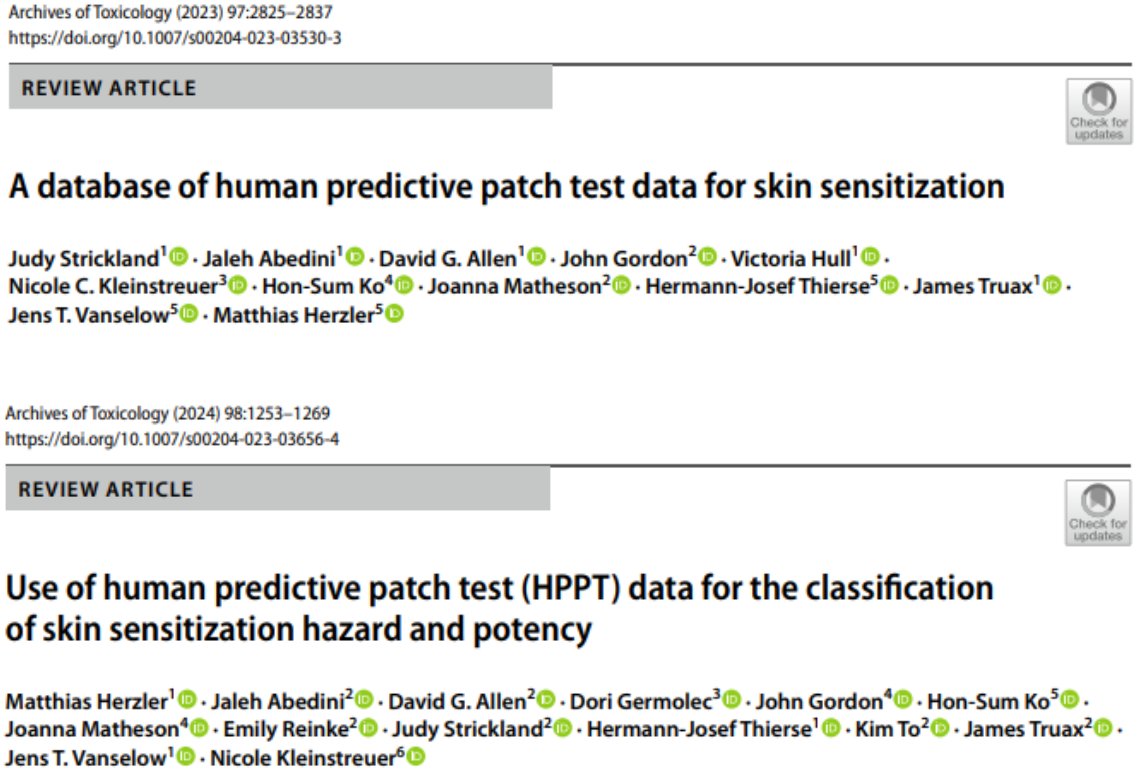
HPPT Database and papers



https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/skin-sens/hppt



- As part of TG 497 development, a highly curated human predictive patch test database was developed
- Database published in 2023, available on NICEATM website
- Proposed HPPT GHS classification approach, utilizing a dose descriptor, published in 2024
- Manuscript evaluating HPPT variability is under development
- HPPT App (Rshiny tool) under development

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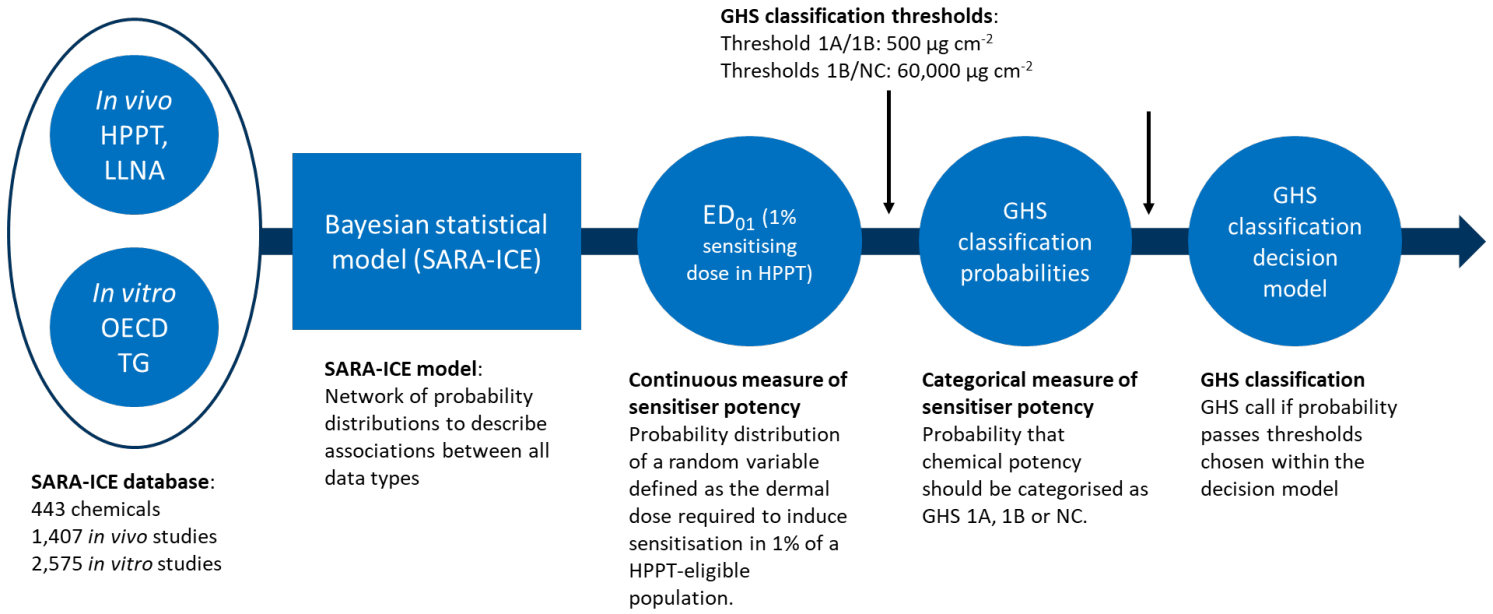
The Skin Allergy Risk Assessment (SARA) – ICE Model

- SARA originally developed by Unilever as a defined approach for skin allergy risk assessment
  - A Bayesian statistical model which infers a human-relevant metric of sensitiser potency (termed ED_{01}), the dose with a 1% chance of human skin sensitisation.
    - Accounts for variability of the input data and explicitly quantifies uncertainty.
  - SARA-ICE is an expansion of the original SARA model, with increased database, input data types and a refined output.
    - Utilises any combination of human repeat insult patch test (HRIPT), LLNA, direct peptide reactivity assay (DPRA), KeratinoSens(TM), h-CLAT, U-SENS(TM) data.
    - Added GHS classification parameters
- SARA-ICE is on the OECD workplan for inclusion in TG 497, the Defined Approaches for Skin Sensitization



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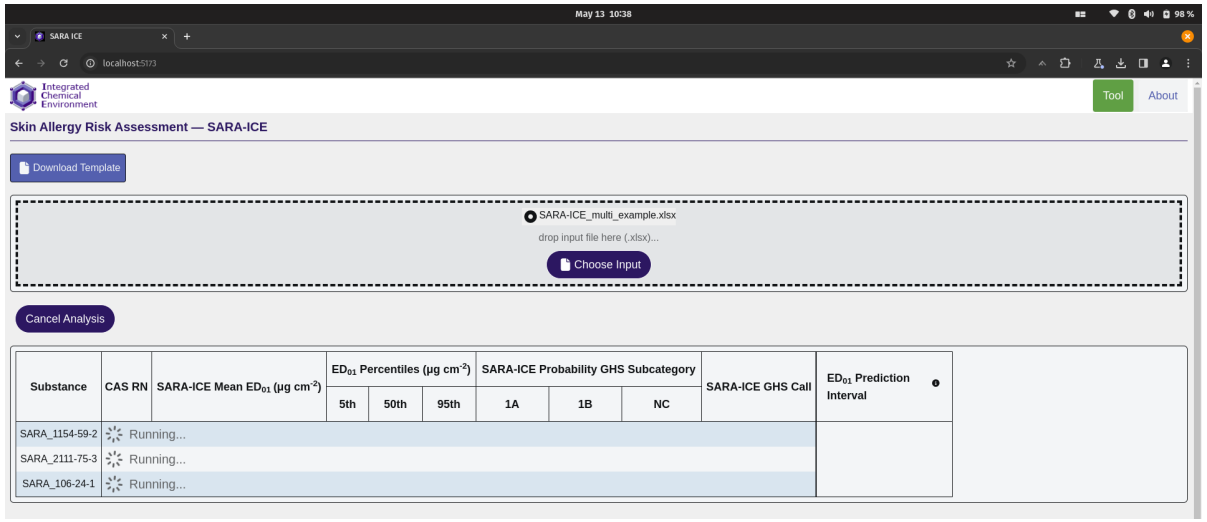
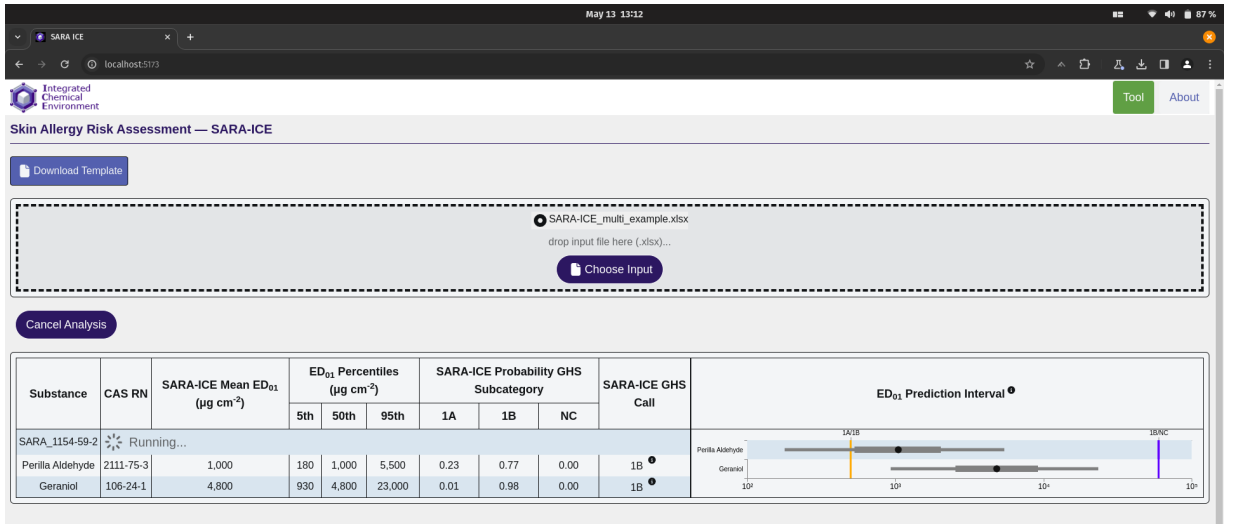
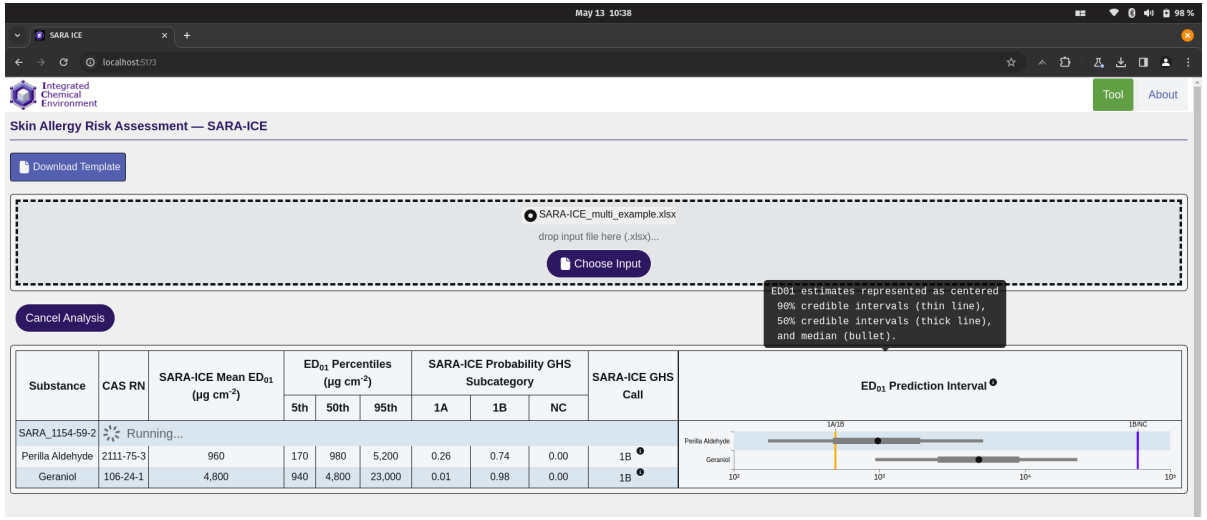
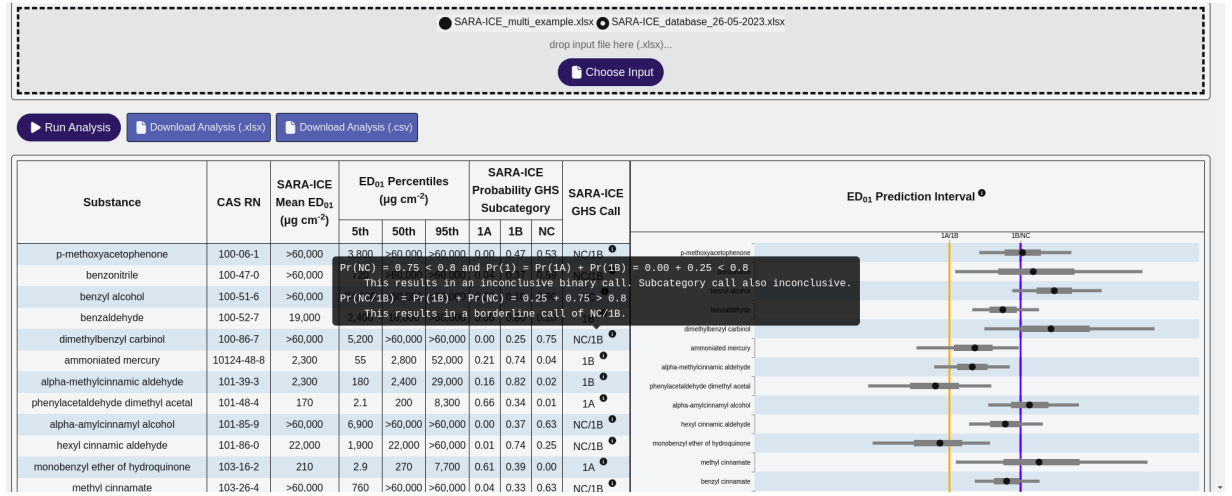
Unilever

The SARA – ICE Model Container







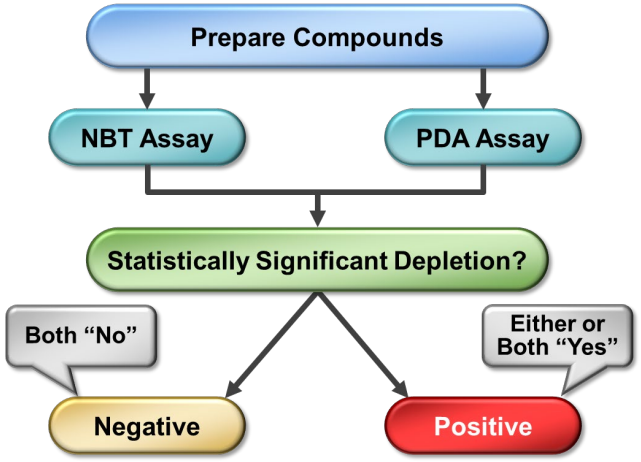


Model has been packaged for download and local implementation. The beta version is currently available for testing and evaluation upon request (email Emily.reinke@inotivco.com for access)

Electrophilic Allergen Screening Assay (EASA)

- Addresses KE1 in the Skin Sensitization AOP
- In chemico plate-based assay
  - Measures protein reactivity of a chemical via fluorescent or colorimetric probes
- Multi-lab validation study
  - Participating labs: U.S. FDA, DoD, CPSC/NIST, BRT, Inc.
  - Utilize 2019 OECD* Performance Standards for KE1-based assays for validation study
  - Peer Review of validation study underway
- Accepted on to 2024 OECD workplan for inclusion in TG 442C

Lab #	Balanced Accuracy	Sensitivity	Specificity	Within Lab Reproducibility	Between Lab Reproducibility
1	76%	85%	67%	94%	96%
2	82%	92%	71%	100%	
3	84%	85%	83%	97%	
4	84%	85%	83%	94%	
Mean	**82%**	**87%**	**76%**	**96%**	



*No. 303; Series on Testing and Assessment https://www.oecd.org/chemicalsafety/testing/performance-standards.htm

DAs for Predicting Eye Irritation Classifications

NICEATM, PETA Science Consortium International, and EPA Office of Pesticide Programs collaborated to test agrochemical formulations in a multi-phase study using a common set of in vitro test methods.

EPA

- Developed two DAs involving:
  - BCOP with histopathology
  - EO + BCOP with histopathology
- Compared predictions (and associated personal protective equipment requirements) of the DAs and in vivo data orthogonally, rather than evaluating direct concordance.
  - Good alignment with many discrepancies corrected if only considering personal protective equipment.
- Weight of evidence evaluation
  - Suggests both DAs are as or more fit-for-purpose, reliable, and relevant than the in vivo test.
  - Overall high confidence in use of DAs for assessing eye irritation potential of agrochemical formulations.
- Publication: van der Zalm et al. 2024 https://doi.org/10.1080/15569527.2023.2275029

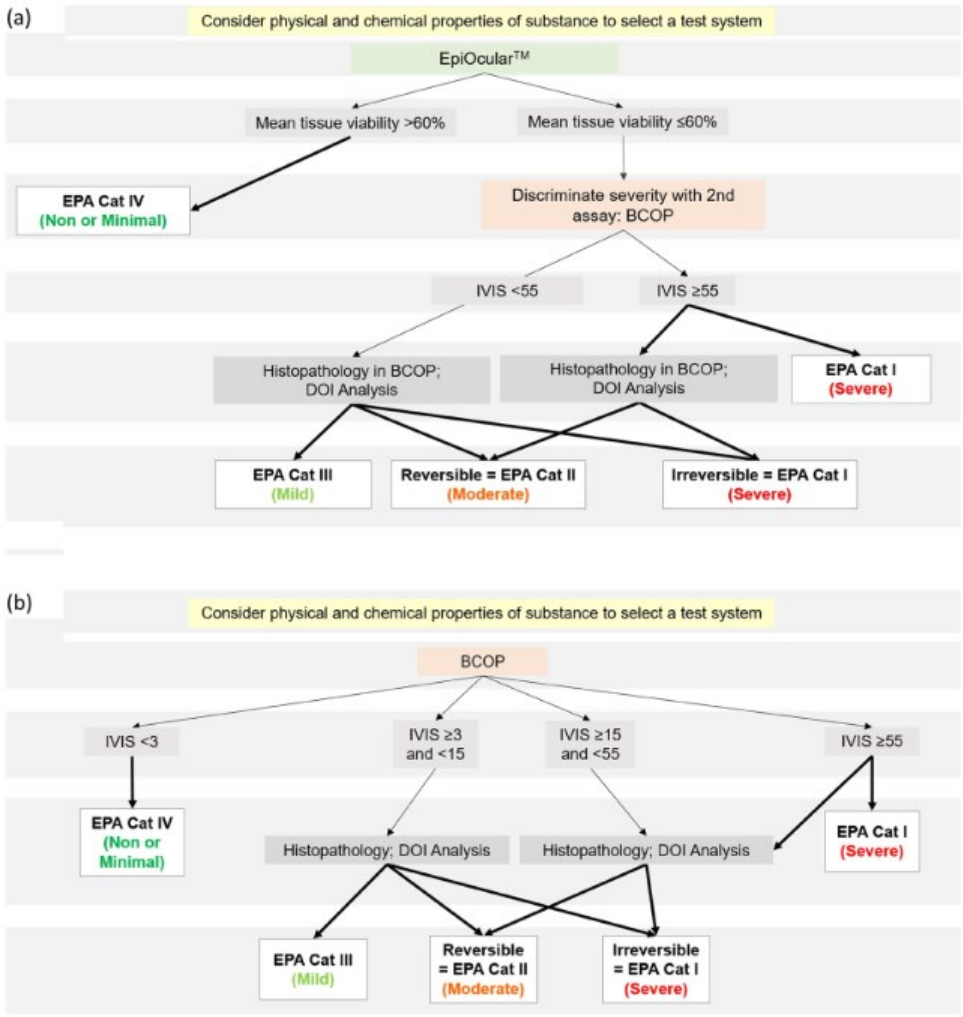
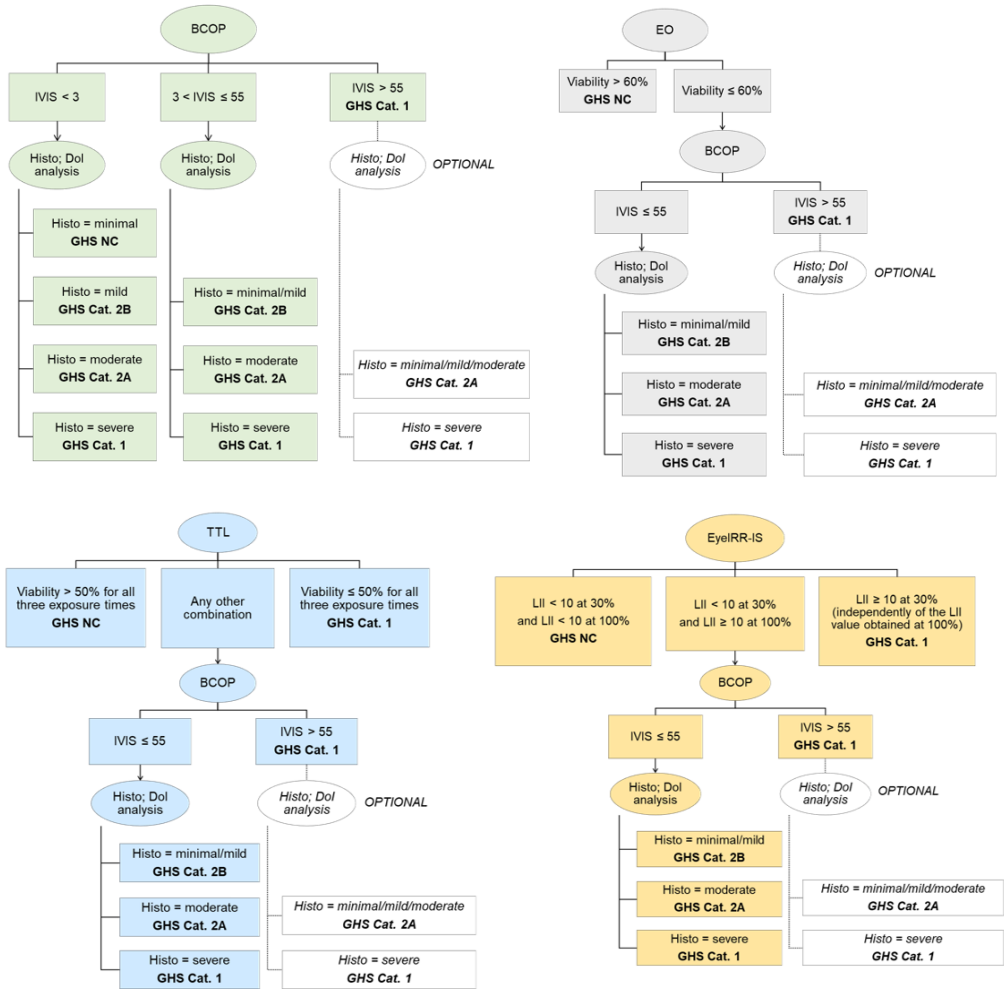


Figure 2
van der Zalm et al. 2024

DAs for Predicting Eye Irritation Classifications

GHS

- Preliminary assessment of results to determine consensus predictions for each formulation (i.e., majority agreement on classification among in vitro methods and historical in vivo data).
  - Consensus prediction achieved for 27 of 29 formulations.
- Developed four DAs:
  - BCOP with histopathology (DA-BCOP+)
  - EO + BCOP with histopathology (DA-EO+)
  - TTL+ BCOP with histopathology (DA-TTL+)
  - EyeIRR-IS + BCOP with histopathology (DA-EyeIRR-IS+)
- Assessed DA predictions (and associated hazard labeling) for concordance with consensus predictions, rather than direct concordance with in vivo data.
  - In vivo test concordant or no change to hazard labeling for 93% (25/27) of formulations. Remaining 7% underpredicted and underprotective.
  - All DAs performed similarly or better than the in vivo test, and generally resulted in hazard labeling that is more protective of human health.
- Manuscript in final stages of preparation (anticipate publishing in summer 2024).



Daniel et al., in preparation

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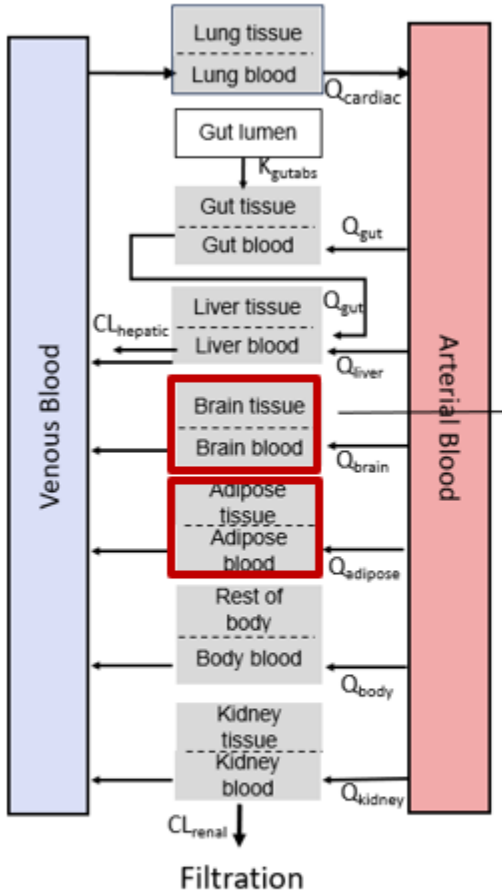
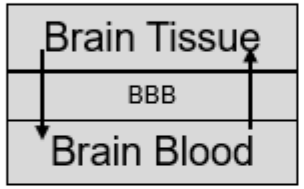
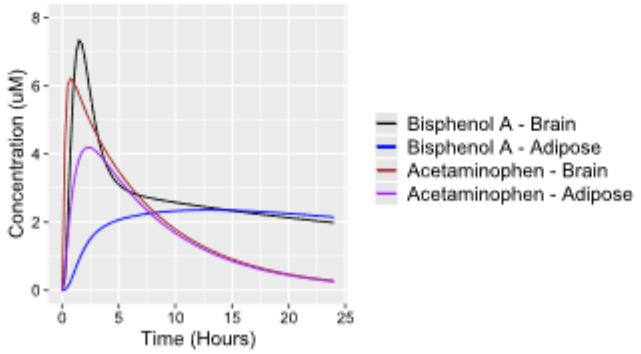
Predicting Chemical Distribution in Brain and Adipose Compartments



- Perfusion-limited model with brain and adipose compartments (Simple Model)
- Build upon generic PBPK model from EPA's httk R package (v2.2.2)



- Diffusion-Limited brain compartment considering blood brain barrier permeability (Complex Model)
- Predicts brain tissue distribution of chemicals from capillary blood

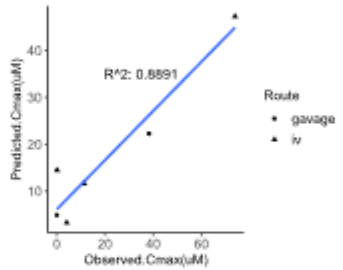


Model output includes time series concentration graphs

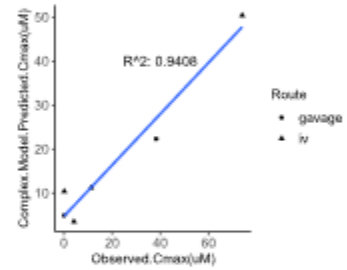
Ongoing Updates

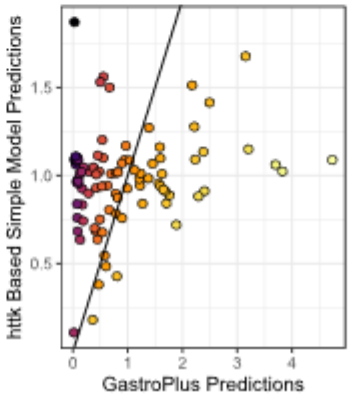
- Incorporation of predicted BBB permeability coefficient values in addition to measured.
- Exploration of additional validation criterions applied for other commercial brain models.
- Efforts for further comparisons using pharmacokinetic time series data from additional chemicals to provide greater confidence in these models.

Simple Model Predicted Brain Cmax Vs Observed Data

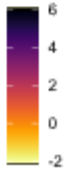


Complex Model Predicted Brain Cmax Vs Observed Data

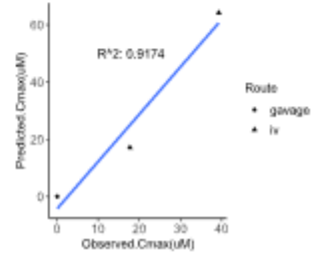




Fold Change



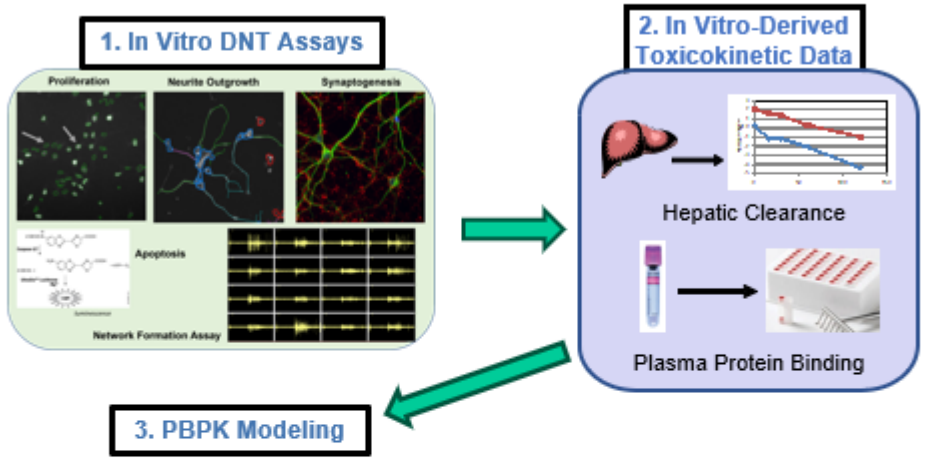
Simple Model Predicted Adipose Cmax Vs Observed Data

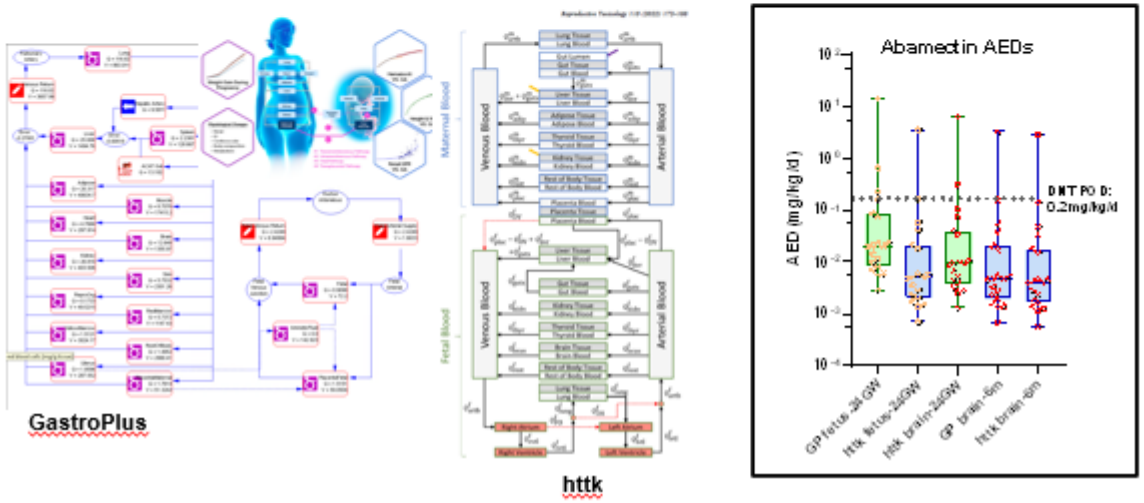


In Vitro to In Vivo Extrapolation (IVIVE) for Developmental Neurotoxicity

A Comparison of Physiologically Based Pharmacokinetic Models

- Physiologically-based pharmacokinetic (PBPK) models compared for DNT-IVIVE approach
- Chemicals bioactive in DNT NAMs from EPA with experimental toxicokinetic data
- Findings
  - Chemicals preferentially partition into the brain
  - In vivo DNT points of departure fall within the range of human administered equivalent dosages (AEDs) for bioactive endpoints for both programs, showing the concordance of in vitro-derived, DNT-IVIVE predictions with in vivo data
  - GastroPlus & httk perform similarly, though httk provides somewhat more conservative estimates

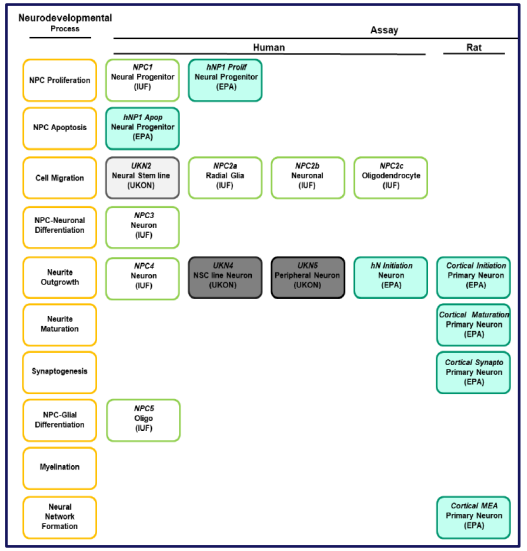


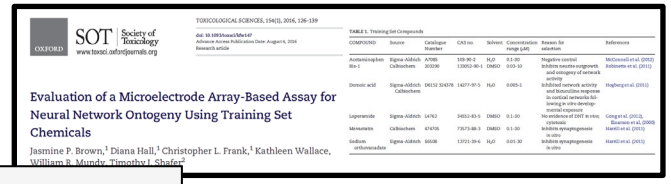


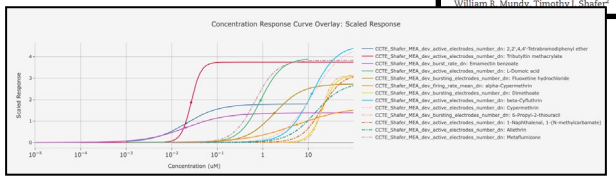
Transferability of the DNT in vitro battery

Identification of training set chemicals

- Developmental Neurotoxicity (DNT) in vitro battery (IVB)
  - 17 assays
  - Endorsement & initial recommendations provided by OECD in 2023
- Training set chemicals are needed for assay transferability
  - Initial lists were provided here
    - Assay-developed recommendations- original publications & OECD guidance
    - Data-driven recommendations- selective activity identified in ToxCast
    - Negative compounds
- Lists are being provided to OECD this month







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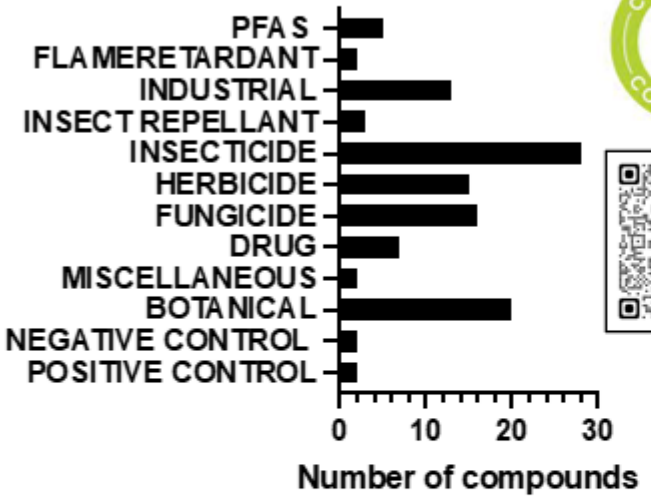
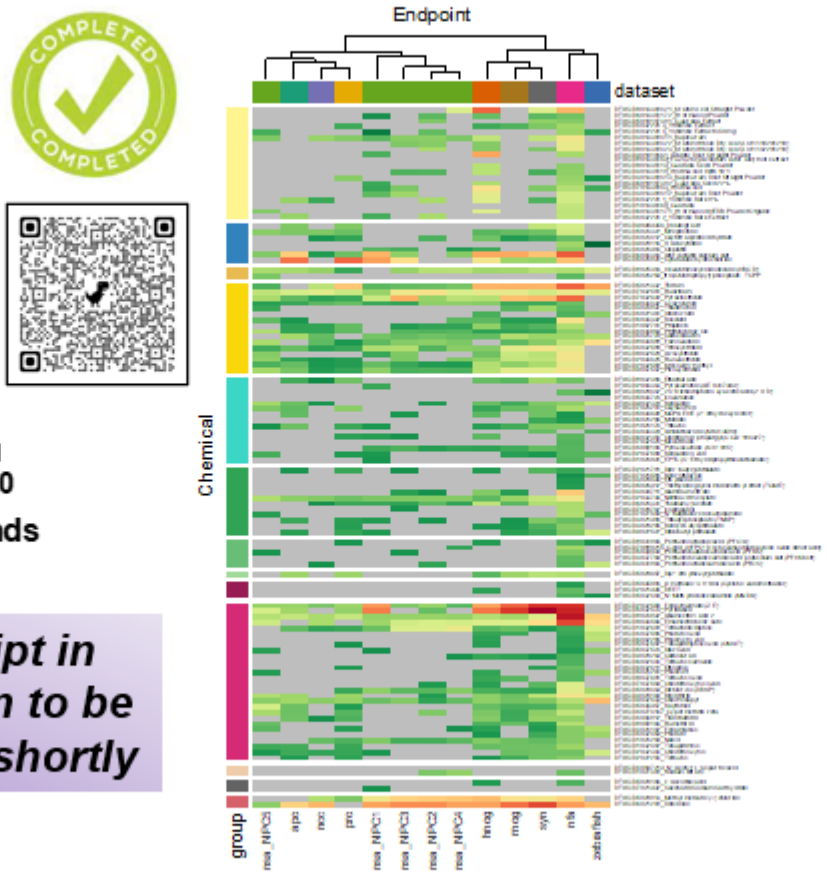
DNT Health Effect Innovation (HEI) Program

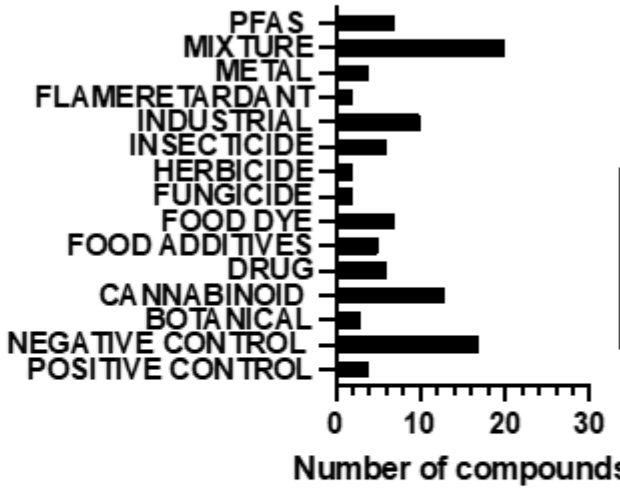
Supporting screening efforts in the OECD DNT IVB

Phase I: 115 chemicals





Phase II: 108 chemicals



Manuscript in preparation to be submitted shortly

Testing projected to be finalized late summer

Phase III: ~120 chemicals

Selection process in final stage, projected to be finalized this summer

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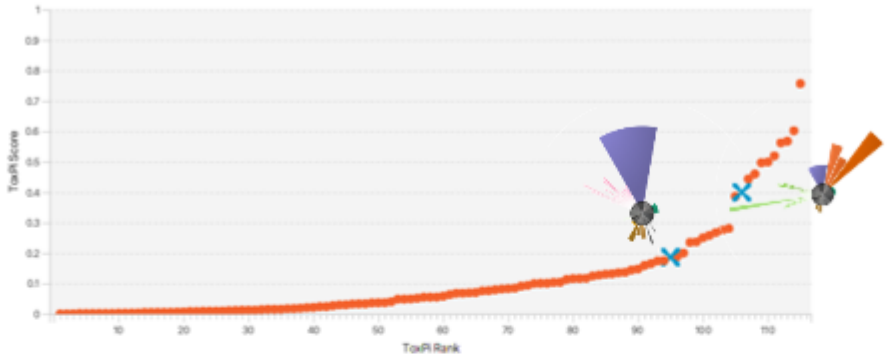
Integrated Approach to Testing and assessment (IATA) for DNT

Selected Compounds Based on Prioritization



Mifepristone (RU486)
Negative in OECD guidance document but considered unfavorable after further evaluation

Pyraclostrobin
Known MoA (inhibiting mitochondrial respiration) known to be sensitive to brain development

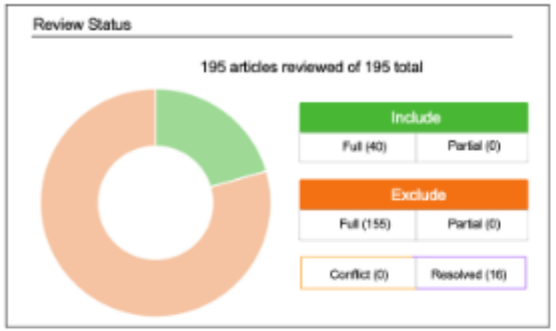
Manuscript in preparation to be submitted in the fall

Integrated Chemical Environment

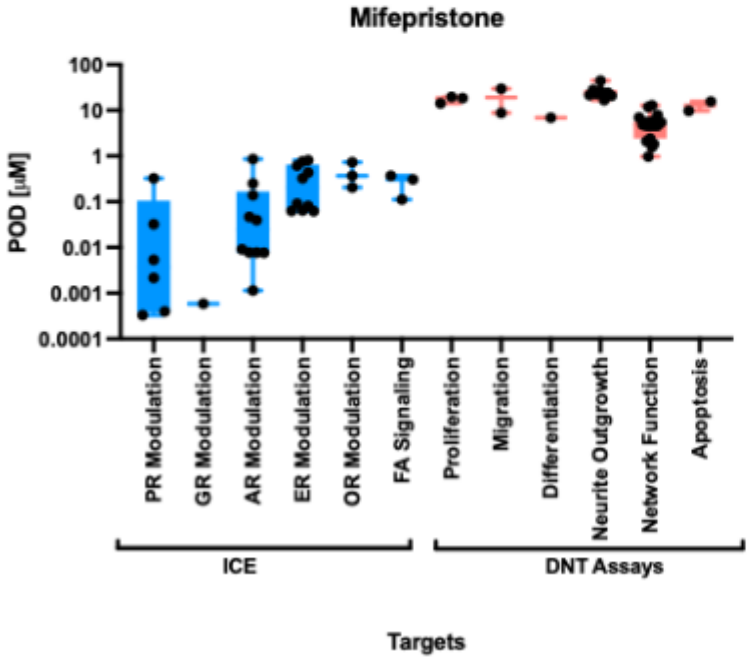
https://ice.ntp.niehs.nih.gov/

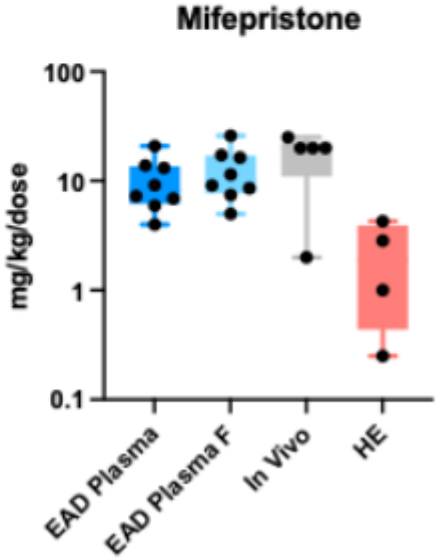
Systematic Review (EFSA protocol)

sysrev



In vitro effects: effects on proliferation and differentiation of NPCs, and on density of dendritic spines
In vivo effects: included decreased dopaminergic neurons, change in behavior, and memory impairment





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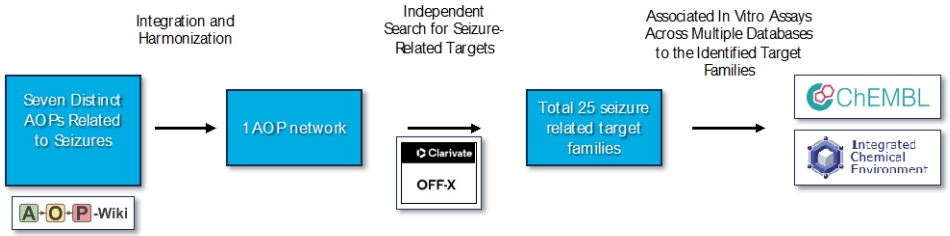
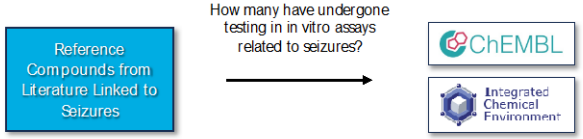
Identifying Seizure-Inducing Biological Targets

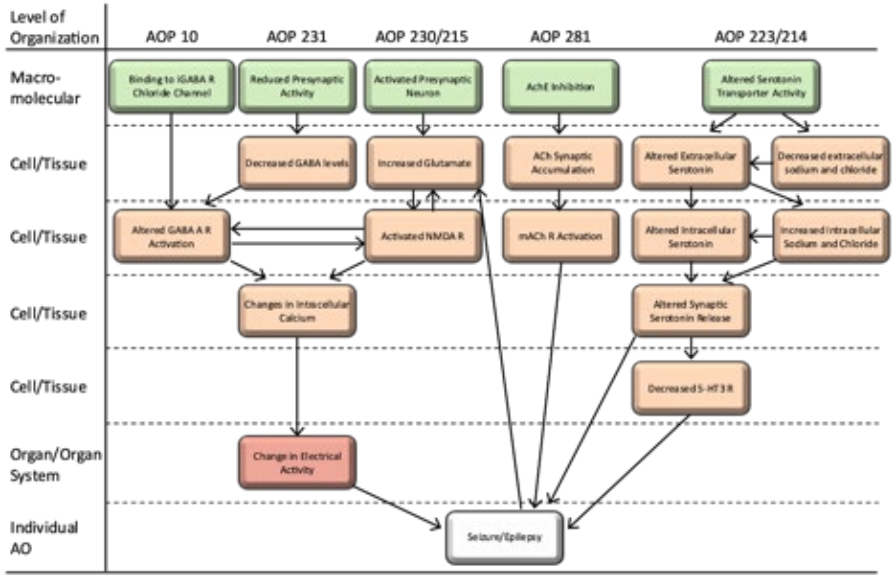
Uncovering Targets and Assays Related to Seizures



Assessing Seizure-Related Reference Compounds from Literature in Established Databases

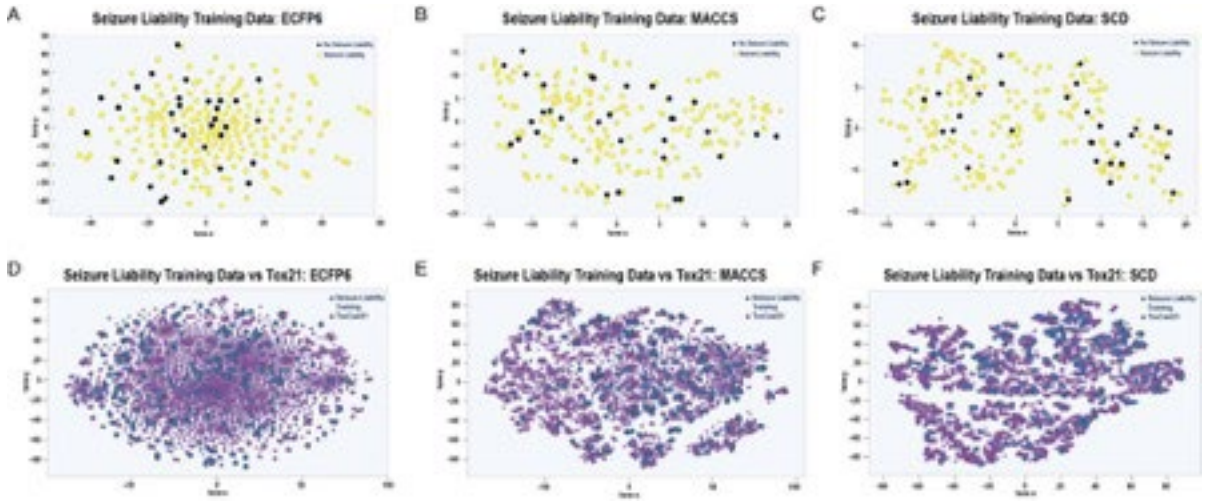


Seizure AOP Network Based on the AOP-Wiki

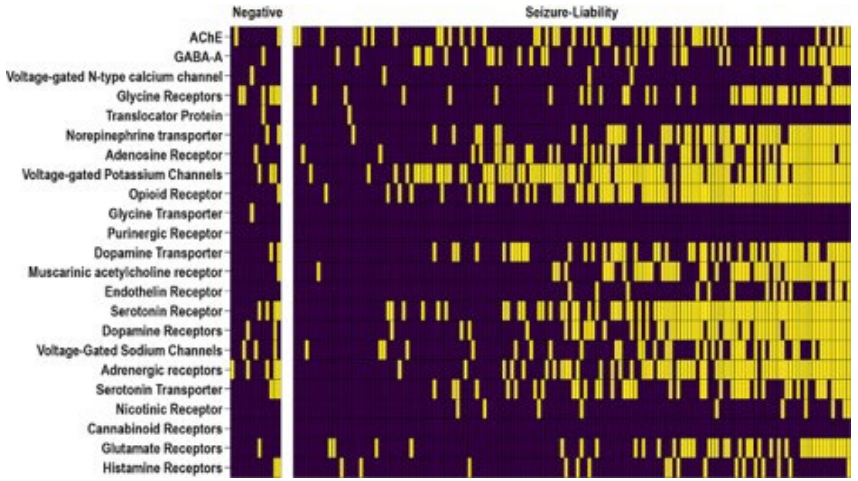


Manuscript in preparation to be submitted shortly

Chemical Diversity Among Reference Chemicals



Heatmap with Tested Chemicals in Identified Seizure Assays



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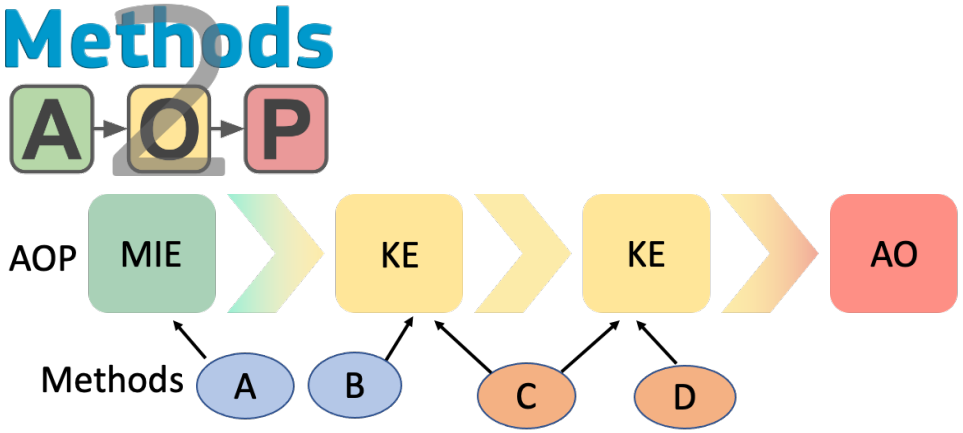
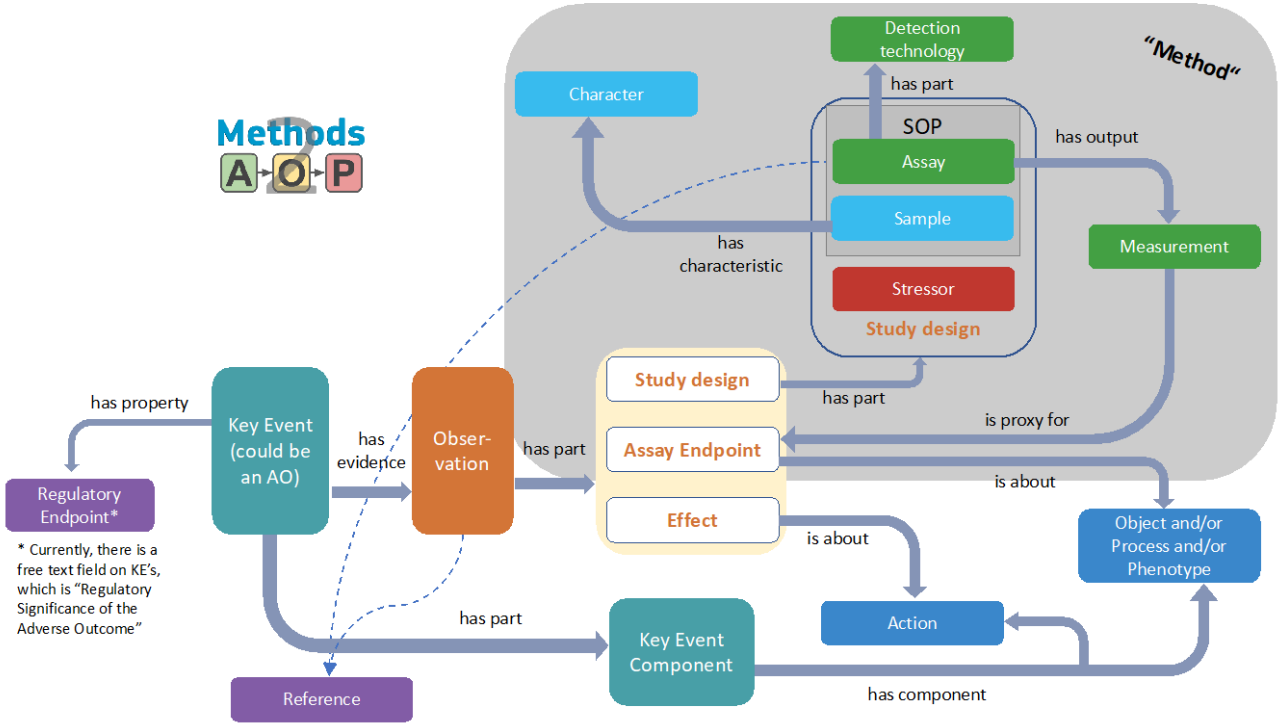
Methods2AOP International Consortium





Stakeholder feedback

SOT Society of Toxicology
Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

2023

Workshop Agenda

Topic	*Speaker/Moderator*
Welcome and introduction	**Wittwehr**, Clemens, JRC
AOPs and regulatory decisions - introduction	**Terron**, Andrea, EFSA
Real life example: AOP Applications in the US EPA Endocrine Disruptor Screening Program	**Lynn**, Scott, EPA
Q&A	moderation: **Batista**, Sofia, EFSA
Why Methods2AOP?	**Wittwehr**, Clemens, JRC
Break	
Transformations Underway in the AOP-Wiki to Advance NAMs	**Hench**, Ginnie, RTI
Case study: Aromatase inhibition leading to Reproductive Dysfunction	**Villeneuve**, Dan, EPA
Discussion, Instructions for Breakout groups	**Hogberg**, Helena, NIEHS
Breakout Groups	all
Wrap up, decisions, next steps	all

Manuscript in preparation to be submitted shortly

National Institute of Environmental Health Sciences
Division of Translational Toxicology

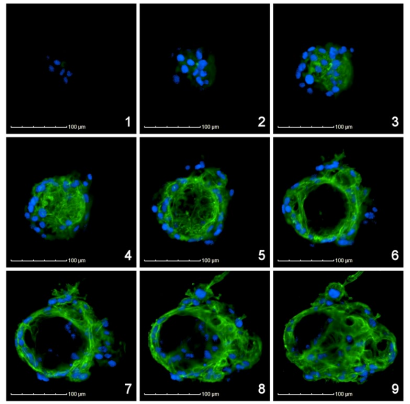
Inter-laboratory Pre-validation Study of Human Thyroid Microtissue Assay

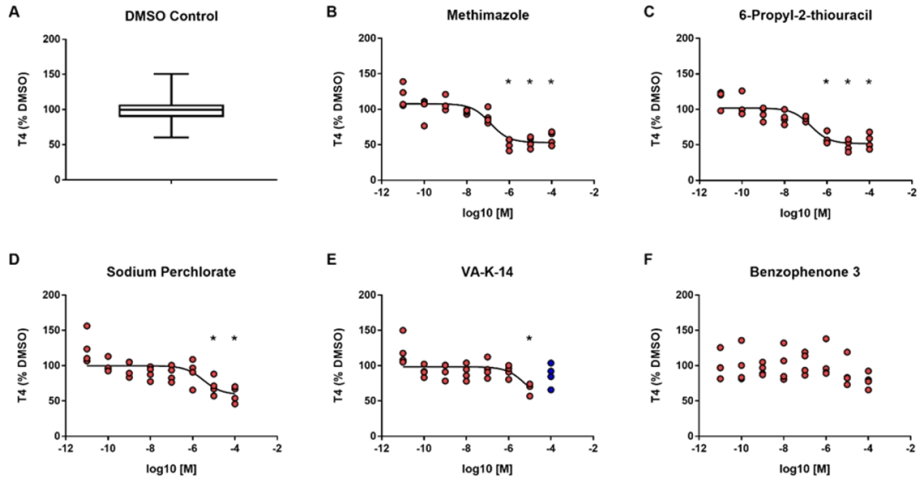
OXFORD SOT Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 2019, 1–16
doi: 10.1093/toxsci/kfz238
Advance Access Publication Date: December 6, 2019
Research Article

Development of an *In Vitro* Human Thyroid Microtissue Model for Chemical Screening

Chad Deisenroth ,*,[1] Valerie Y. Soldatow,[†] Jermaine Ford,[‡] Wendy Stewart,* Cassandra Brinkman,* Edward L. LeCluyse,[†] Denise K. MacMillan,[‡] and Russell S. Thomas *





Team Members

Coordinator: NICEATM

Method Developer
Lab 1

Lab 2

Lab 3

Lab 4

Status:

- Phase 1.2 complete (initial transfer phase, lab 2)
- Phase 1.3 underway (secondary transfer phase, labs 3 and 4)
- Phase 1.4 slated to start in summer (validation study)

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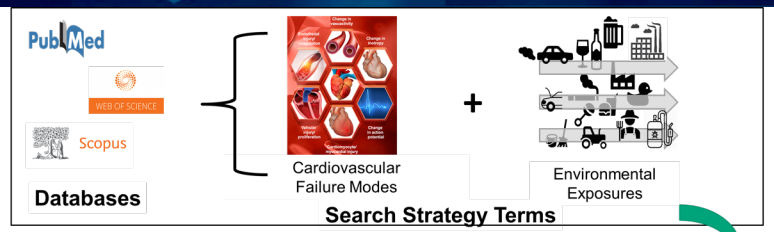
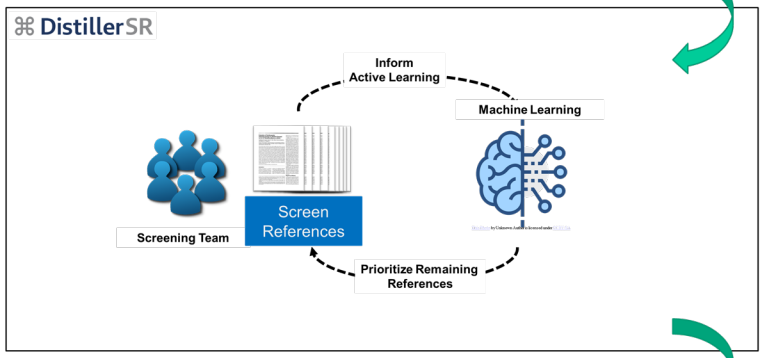
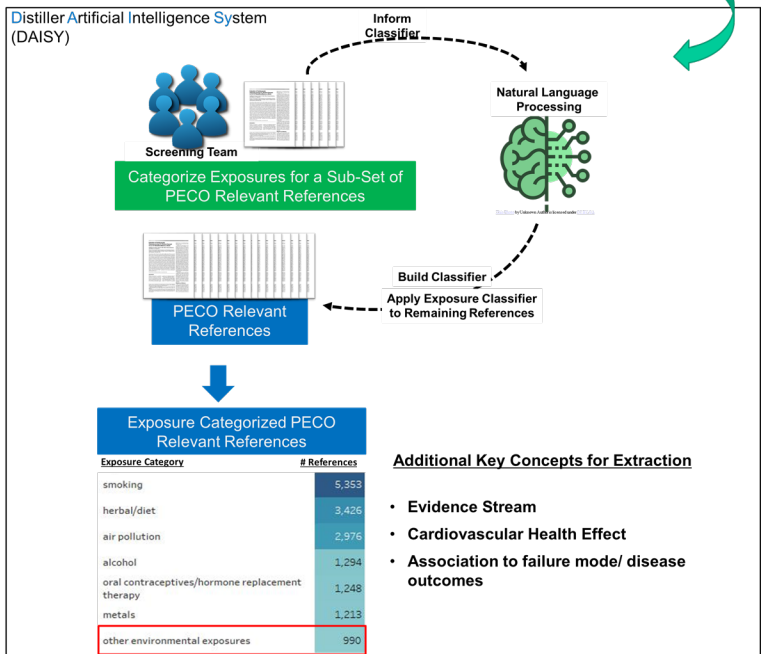
Cardiovascular (CV) Health Effect Innovation (HEI) Program

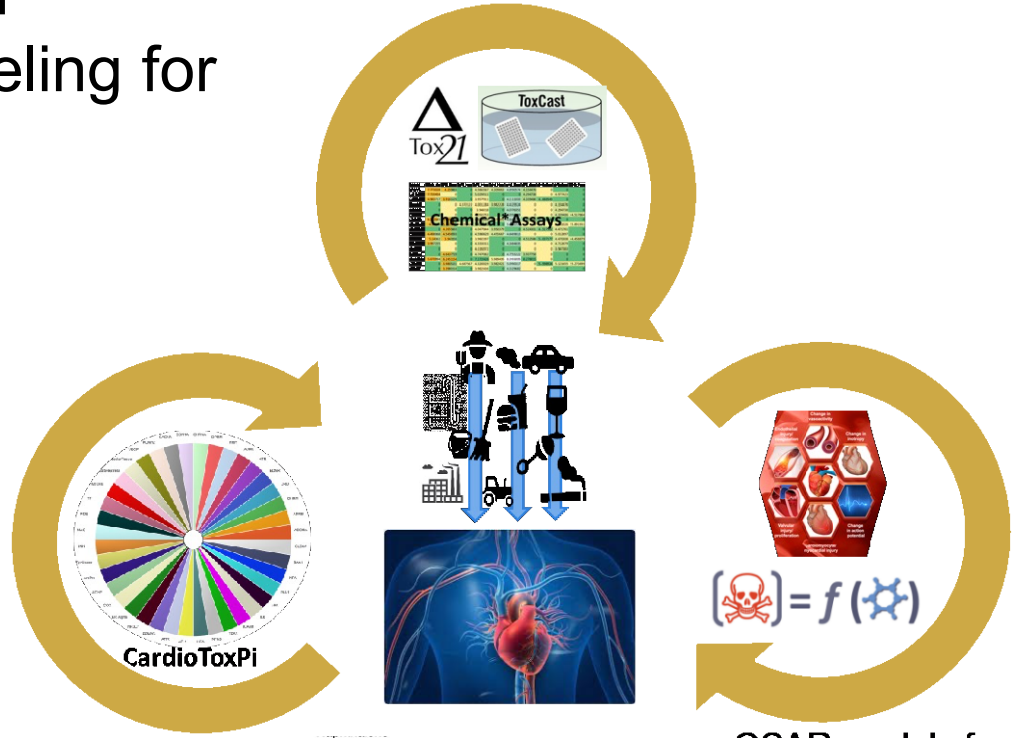






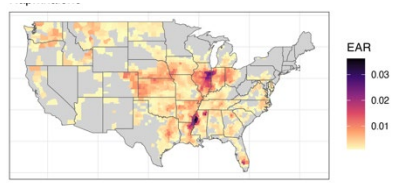
Systematic Evidence Mapping and Computational Modeling for CV Risk

Integrating HTS assay data and exposure



Identification of CV-relevant targets and endpoints

QSAR models for CardioToxPi mechanistic target groupings



Geospatial risk mapping

Krishna et al. 2024 in prep (x 2)

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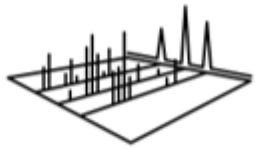
Risk Characterization of Triazole Fungicides using Human Biomonitoring and Mechanistic Data

Sampling

- Rural area — n = 140
  - Farrmers — n = 88
  - Women residents — n = 52
- Urban area — n = 50
  - Men — n = 25
  - Women — n = 25

Biomarkers



Urinary Triazoles

Internal Dose Indicator

Oxidative Stress Markers

Plasma Bile Acids

Liver Enzymes

Steroid Hormones

Cytome assay – Genotoxicity

Risk Calculations

HQ Calculation at the highest quantified value:

EDI = 6.31 µg/kg-bw/day

HQ = 2.1
Farmers

EDI = 8.77 µg/kg-bw/day

HQ = 2.9
Rural Women Residents

Unifal MG
Universidade Federal de Alfenas

SOT 2024 Poster

Marciano, et al. Regul Toxicol Pharmacol. 2024;147:105565.

Costa, et al. Chem Biol Interact. 2023;383:110689.

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Association of *in vitro* molecular targets and human biomarker alterations

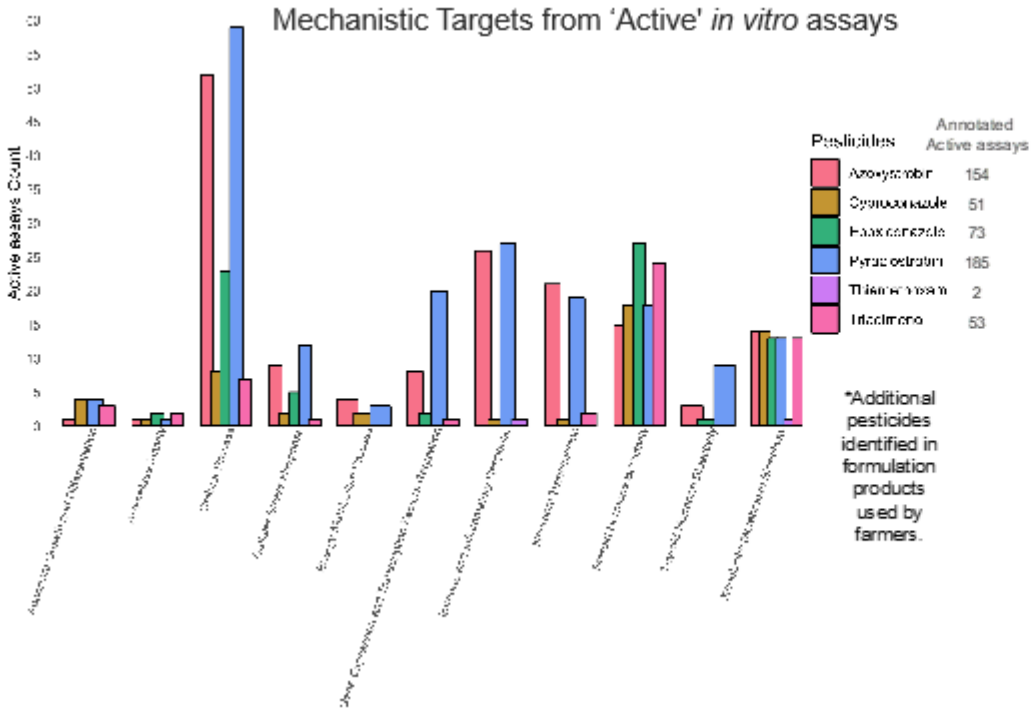
Integrated Chemical Environment v.4.0.2

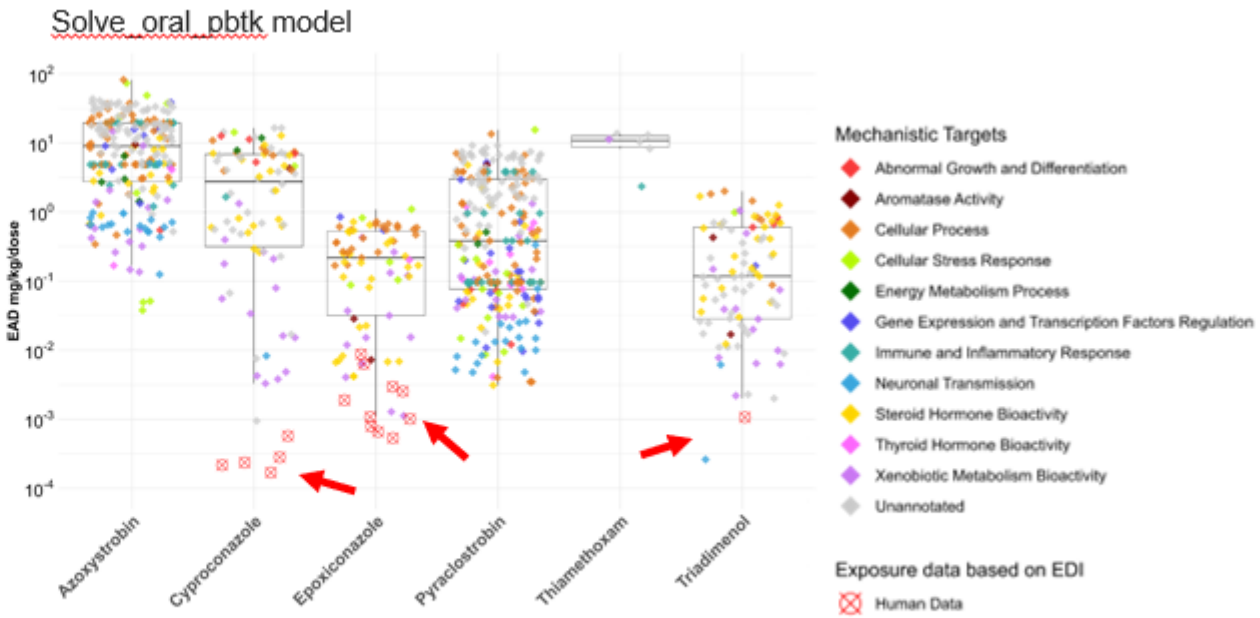
Concentration-Response Curves

- cHTS data from Tox21/ToxCast

In Vitro to *In Vivo* Extrapolation

- Calculate equivalent doses from cHTS data
- Comparison with human exposure





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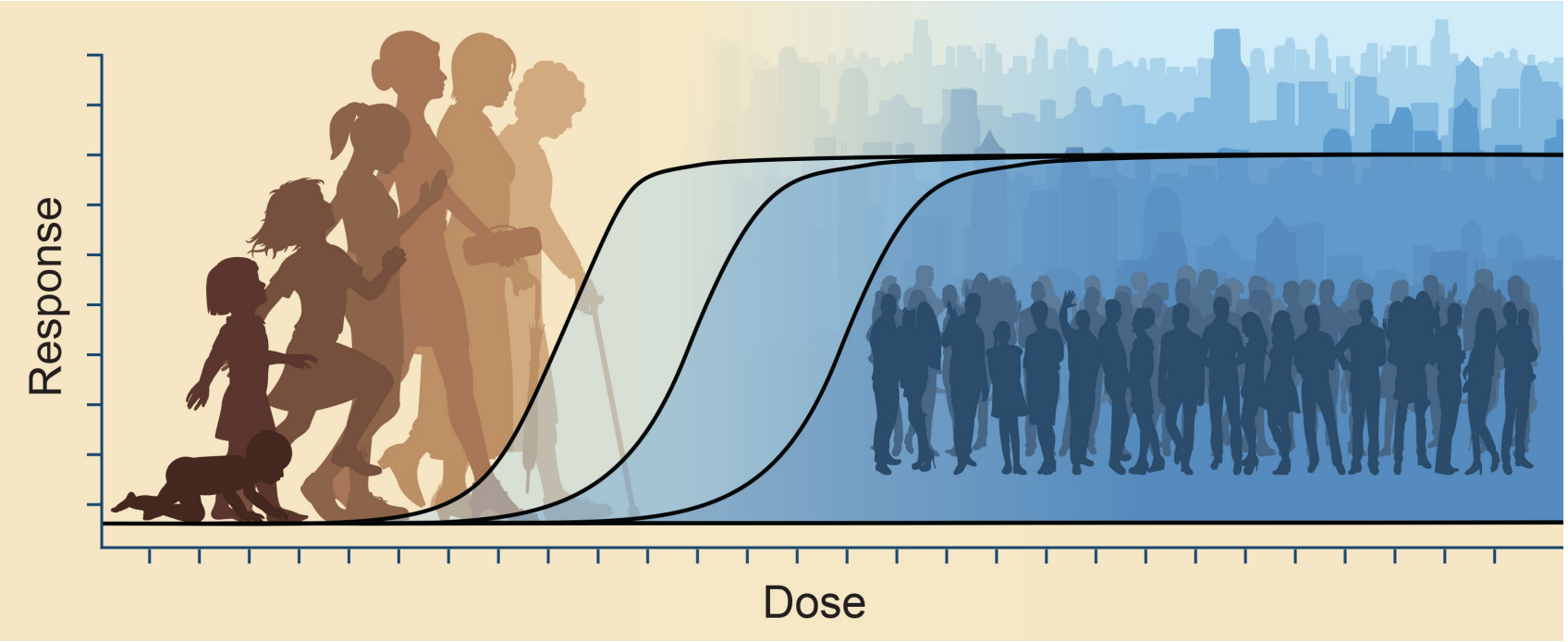
Area of Focus: NAMs to Address PopVarSusc

Using New Approach Methodologies to Address Variability and Susceptibility Across Populations



https://ntp.niehs.nih.gov/go/popvar

Workshop report in prep to be submitted to Human Genomics shortly

Human Genomics

SPRINGER NATURE GROUP
SDG Programme
supporting the Sustainable Development Goals

Human Genomics Call for Papers

New Approach Methodologies to Address Population Variability and Susceptibility in Human Risk Assessment

Guest Editors: Helena Hogberg, PhD; **Nicole Kleinstreuer**, PhD; **Kim To**, PhD

Submission Status: Open | Submission Deadline: 30 June 2024

Read more about the collection
https://www.biomedcentral.com/collections/NAMAPVS

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Clustering and Classification Workshop

Workshop report under revision at EHP

Convened international experts to discuss methods, their applications to guide toxicology research and inform hazard and risk assessment.

Accomplishments:

- Defined the concept similarity for supervised and unsupervised approaches
- Introduced different approaches, corrected some misconceptions
- Involved both NAM developers and users
- Established a consortium and a community for increasing communication and collaboration across sectors
- *Ongoing and future:* develop and share new ideas/concepts (best practices & innovation)

https://www.niehs.nih.gov/news/events/pastmtg/2022/nams2022/index.cfm

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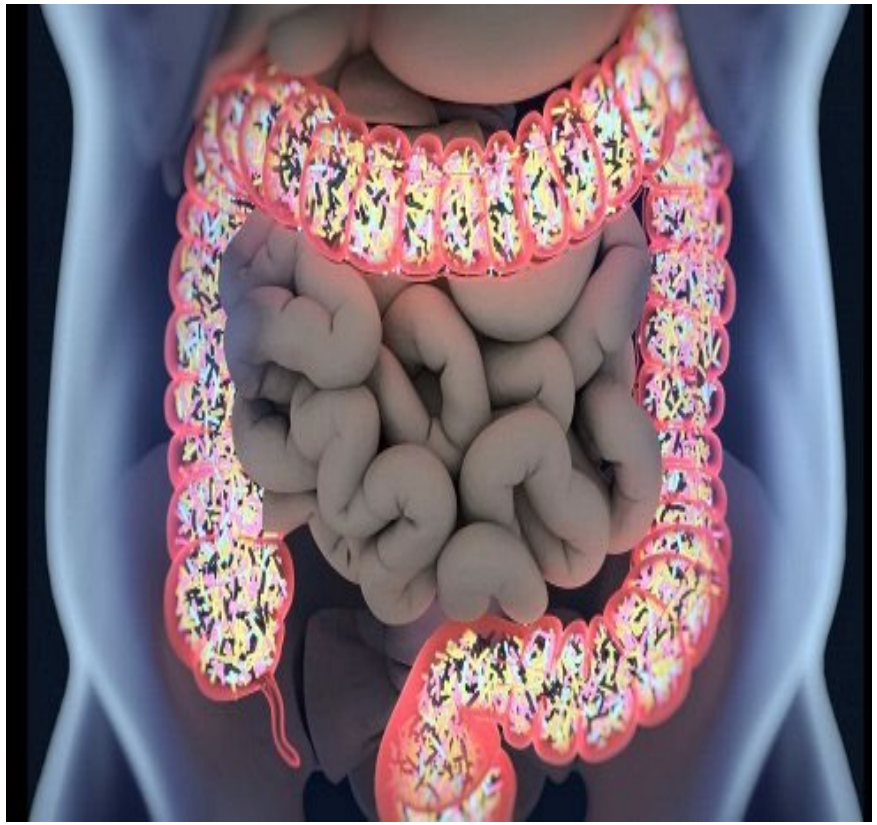
Workshop on NAMs for the Gastrointestinal Tract
October 11-12, 2023

Workshop report to be submitted to ALTEX

An in-person workshop to examine the state of the science for NAMs modeling the gastrointestinal tract and their context for regulatory consideration.

- **Focal Areas:**
  - General “state of the science” for NAM gut models
  - Models for de-risking chemicals for systemic toxicity (regulatory relevance and application)
  - Gastrointestinal toxicity
  - Systemic absorption and distribution
  - Gut allergenicity
- **A webinar series to provide background information took place prior to workshop (September 2023)**
- **In-person Day 1:** Scientific talks/state of the science
- **In-person Day 2:** Breakout groups covering the following themes:
  - Establishing confidence in existing models
  - Strengths and limitations of different model systems



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Acknowledgments

The NICEATM Group

NIEHS/DTT Contributors

UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

https://ntp.niehs.nih.gov/go/2021iccvamreport

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Integrated Chemical Environment

Coming Soon:
2022 – 2023 Biennial Report